An evidence-based approach to assess the use of opioids

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This thesis is dedicated to those silenced by chronic pain, and my great-grandfather, Lionel Arthur Kirk (1892-1946), who was sent to Balliol College, Oxford in 1917 (July 5 to October 31), to retain his commission awarded while serving on the Western Front in the Australian Imperial Force (No. 4479, 25th Battalion). At Balliol, Lionel joined the No. 6 Officer Cadet Battalion and survived all members of the 25th Battalion, which may be attested to his time in Oxford. He returned safely to his home in Queensland, Australia, where my grandfather, subsequent family, and I were born. I shall never understand what he saw or the effect the war had on him and those from his generation. Precisely 100 years later, I arrived in Oxford and have the opportunity to complete and defend my DPhil at the University of Oxford – an opportunity I shall never take for granted.

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To the most important people in my life, my family, thank you for your patience, love, and support. Many of you have taught me the determination, resilience, and optimism necessary to complete this doctorate. Having family on the other side of the world is extraordinarily difficult, particularly during a global pandemic. Still, I am grateful for the many memories and special times we have shared together in Oxford, Australia, and abroad. Finally, I acknowledge the sacrifices I have endured and the perseverance I have employed to reach this milestone; my future self will be tremendously grateful.

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Abstract

Background Since the 1990s, the prescribing of opioids has increased in England and most high-income countries. However, insufficient datasets used in previous research may have underrepresented the extent of the problem.

Aims To assess global and national use of opioids, drivers of suboptimal use, and consider strategies to prevent opioid-related deaths.

Methods I conducted two cross-sectional analyses and two retrospective observational studies, using several datasets, including controlled opioid consumption statistics from the International Narcotic Control Board, the Global Essential Medicines Database of 137 national essential medicines lists, sales of over-the-counter products containing codeine, and the Preventable Deaths Database. I performed a synthesis of pharmacological resources and a systematic review of observational studies to explore factors associated with high-dose opioids.

Results 687 million people (10% of the global population) consumed 89% of the world's controlled opioids in 2015-17. Countries included a median of 6 opioids (IQR: 5-9; range: 0-19) in national essential medicines lists; morphine (95%), fentanyl (83%), and codeine (69%) were the most common. 31.5 billion units of codeine, costing £2.55 billion, were sold over-the-counter across 31 countries in 2013-19, with 3% and 54% increases respectively. In the UK, 4.75 billion dosage units of codeine in combination with 1711 tonnes of paracetamol and 96 tonnes of ibuprofen, costing £638 million, were purchased over-the-counter in 2013-19. I identified 233 opioid drugs and created the Oxford Catalogue of Opioids (https://www.catalogueofopioids.net/).

Five factors were associated with high-dose opioids, including co-prescription of benzodiazepines, depression, Emergency Department visits, unemployment, and being male. There were 176 opioid-related Prevention of Future Deaths reports in 2013-19, with a 262% increase. I created the Preventable Deaths Tracker (https://preventabledeathstracker.net/) and launched the Coroners' Concerns to Prevent Harms series in BMJ Evidence-Based Medicine.

Conclusions There are persistent disparities and variations in the use of and access to prescribed and non-prescribed opioids. While opioids can be overused or underused, and can cause fatal and non-fatal harms, they still have a place in modern medicine in the right patient, at the right dosage regimen, and for the right reasons. I have outlined future research to serve patient safety, reduce avoidable harms, and improve evidence-based decision-making in clinical practice and policy.

Statement of Contributions

I certify that this thesis contains my work. In instances where others have contributed to my work, their initials are used and summarised below:

- In chapters 5 and 8, Dr Jeffrey K. Aronson (JKA) conducted the dual search of pharmacology sources, was consulted when the eligibility criteria for inclusion or exclusion of opioids or coroner cases were unclear and checked the stems attributed to opioids.
- In chapter 5, Konrad Sitkowski (KS) preregistered the study protocol and conducted the second search to update the number of opioid drugs.
- In chapter 7, Prof Carl Heneghan (CH) helped resolve disagreements when the study's eligibility was unclear and the risk of bias assessments differed.
- In chapter 7, Dr Constantinos Koshiaris (CK) provided statistical advice.
- In chapter 7, Assoc Prof Kamal R. Mahtani (KRM) helped resolve disagreements when the study's eligibility was unclear, and the risk of bias assessments differed.
- In chapter 7, Nia Roberts (NR) reviewed the search strategy I developed for my systematic review.
- In chapter 7, Tonny B. Muthee (TBM) was the second title and abstract screener and data extractor.
- In chapter 8, Dr Maja K. Bilip (MKB) conducted the dual-screen for opioid-related deaths.
- In chapter 8, Ali Ains (AA) and Grace Anthony (GC) are mentioned in ongoing research.
- In chapter 7 and 8, Nicholas J. DeVito (NJD) was the second full-text screener and data extractor for factors in my review, and he helped design and troubleshot the web scraper.
- Amadea Turk (AT) was the scribe during my PPI discussion group in December 2019 and provided me with support and feedback.
- Jacqueline Walumbe (JW) was in attendance during my PPI meeting, answered questions from patients, and provided me with support and helpful feedback.

Chapter 1

1 Overview and structure of thesis

1.1 Rationale of thesis

Failures to find a balance between appropriate therapeutic use and misuse of opioids, distinguishing concepts of licit and illicit use, and finding a regulatory framework in which patients medical needs can be adequately met have resulted in many problems across the world. In most of Africa, Asia, and Latin America, the access, availability and use of opioids to treat pain are limited and controversial (1). While in the USA, 222 lives are lost every day to opioid overdoses (2).

In England, various studies have confirmed that the prescribing of opioids has increased (3–7). Yet, these studies have significant limitations that may be unrepresentative of the problem due to insufficient access to data (8). Previous studies have investigated a subset of opioids, conditions and geographies; most data are several years out of date at the time of publication, very few correct for opioid strength or separately analyse high-dose prescriptions, and few include non-prescribed opioids (e.g. those purchased over-the-counter). Instead, research efforts are disproportionately focusing on initiatives to reduce the use of opioids (9–14). While reducing the overuse of opioids is important, these interventions are resource-intensive, less scalable, and are failing to have a widespread impact on patient care and safety. Therefore, an adequate assessment of the problems are needed. My thesis addresses these limitations to develop a better understanding of the problems, which are required before governments and clinicians can implement scalable and effective interventions and policies to prevent an opioid crisis in the UK.

1.1.1 Overarching hypothesis

The use of opioids is suboptimal, which may be associated with overuse, underuse, and direct patient harm.

1.1.2 Overall aim of thesis

To assess global and national use of opioids, and drivers of suboptimal use, and consider prevention strategies to avert opioid-related deaths.

1.2 Thesis structure

The structure of my thesis is outlined in Figure 1.1.

1.2.1 Chapter 2: Background

In chapter 2, I summarised the pharmacology and history of opioids, evaluated previous research on the use of opioids, and described observations from the opioid deprescribing clinic in Oxford and the patient and public involvement (PPI) used in my research.

1.2.2 Chapter 3: Analysis of controlled opioids consumed globally, 2015-2017

In chapter 3, I conducted a cross-sectional study using narcotic consumption statistics from the International Narcotics Control Board (INCB). I analysed global, regional, and national consumption of controlled opioids in 214 countries, states, and territories. My findings are published in the *British Journal of Pain* and available as a preprint (15,16).

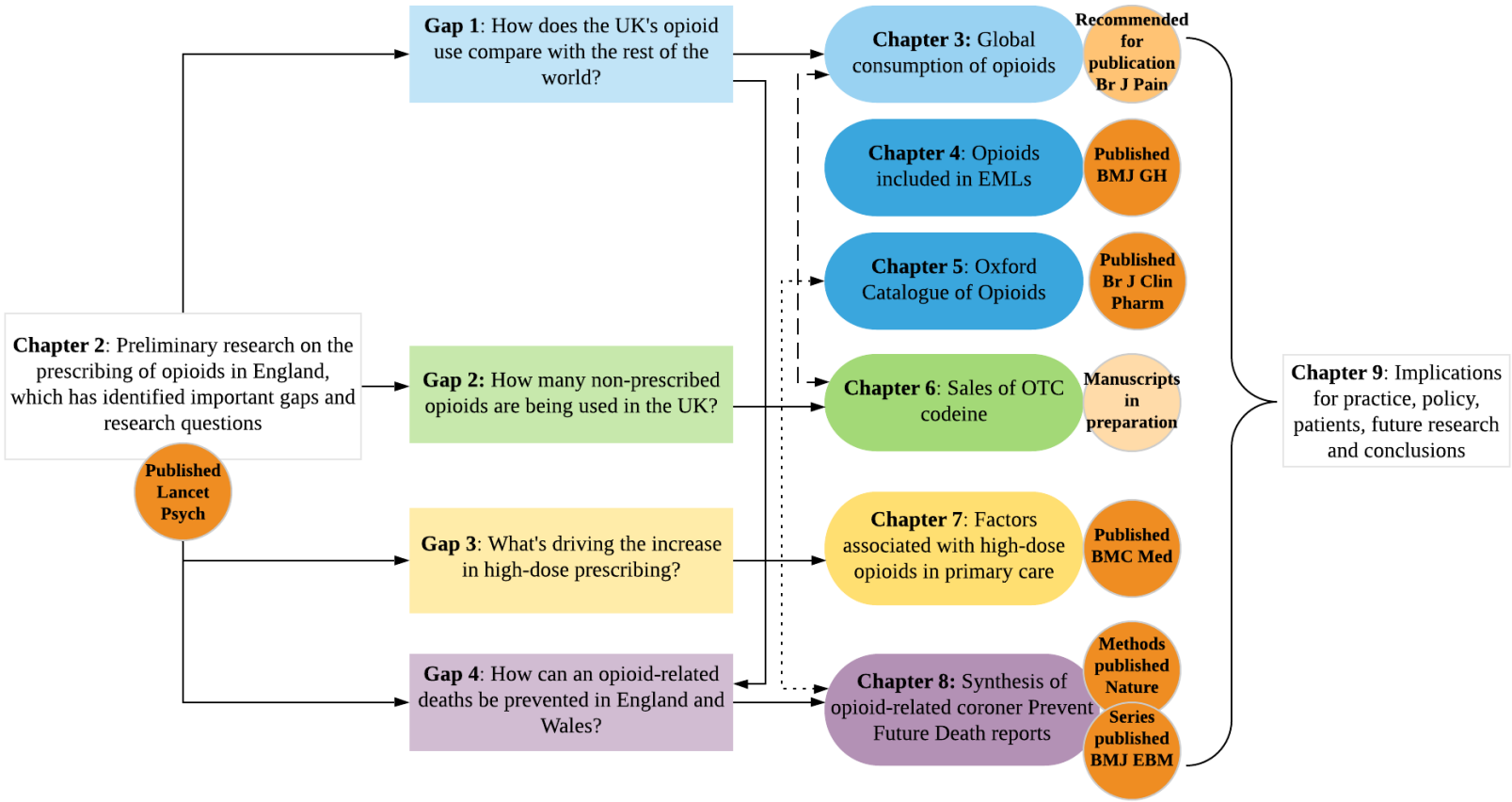


Figure 1.1: Flow chart of the four key gaps (rectangles) I address in six results chapters (rectangular ovals), which form the basis of my DPhil thesis. Orange circles indicate the publication status of each chapter.

1.2.3 Chapter 4: Analysis of opioids included in national essential medicines lists

In chapter 4, I conducted a cross-sectional analysis of the numbers and types of opioids included in 137 national essential medicines lists (EMLs) using the Global Essential Medicines database. This research is published in *BMJ Global Health* (17), and has 724 abstract, 723 full, and 172 PDF downloads as of 5 January 2021. I presented this research to members of the WHO's Expert Committee on the Selection and Use of Essential Medicines as an invited keynote speaker at the inaugural Global Essential Medicines Meeting in Toronto (November 20-21, 2019). My abstract was also accepted for a poster presentation at the IASP 18th World Congress on Pain, which was cancelled due to the covid-19 pandemic.

1.2.4 Chapter 5: Systematic development of the Oxford Catalogue of Opioids

In chapter 5, I conducted a systematic search of seven pharmacology sources to determine the number of opioid drugs developed and created an online resource, the Oxford Catalogue of Opioids (https://www.catalogueofopioids.net/). This research is published in the *British Journal of Clinical Pharmacology* (18).

1.2.5 Chapter 6: Analysis of over-the-counter sales of codeine-containing products in 31 countries, 2013-2019

In chapter 6, I conducted a retrospective observational study using six years of consumer electronic point of sales data to determine the volume, expenditure, and trends of OTC codeine-containing products sold in 31 countries, including the UK. My findings on the sales in 31 countries is under peer review at *Addiction* and is available as a pre-print (19), the other manuscript on UK sales is in preparation. I presented the protocol for this study as a poster at the 6th Preventing Overdiagnosis conference (August 20-22, 2018) in Copenhagen, Denmark (20).

1.2.6 Chapter 7: Systematic review of factors associated with prescribing of high-dose opioids in high-income primary care settings

In chapter 7, I conducted a systematic review of observational research to explore factors associated with the prescribing high-dose of opioids in primary care. This chapter is published in *BMC Medicine* (21). As of 5 January 2021, the publication is in the 96th percentile of a similar age in all journals. I wrote the findings for The Conversation (22) and presented the results as a poster at Pharmacology 2019 in Edinburgh (December 16), which the committee selected for publication in the *British Journal of Clinical Pharmacology* (23). I presented the protocol for this research at the Clinical Pharmacology Colloquium in Bangor, Wales (May 12, 2018), and as a poster at the Rotary District 1090 Conference in Portsmouth (March 09, 2019), and the EBM Live conference in Oxford, which was also published in *BMJ Evidence Based Medicine* (24).

1.2.7 Chapter 8: Systematic synthesis of coroner reports to prevent opioid-related deaths in England and Wales, 2013-2019: preliminary findings

In chapter 8, I used a computer program to scrape the Courts and Tribunal Judiciary website and save over 3,000 coroner Prevent Future Death (PFD) reports and their responses to create the Preventable Deaths Database. I systematically screened the reports for opioid-related deaths, assessed trends over time, and developed the Preventable Deaths Tracker (https://preventabledeathstracker.net/). I co-authored a publication in *Nature,* discussing the data collection methods used in this chapter (25). I launched a monthly series in *BMJ Evidence Based Medicine* titled 'Coroners' Concerns to Prevent Harms' to disseminate key learnings from the Database to serve patient safety and educate the public, clinicians, and policymakers (26–30).

1.2.8 Chapter 9: Discussion and conclusion

In chapter 9, I summarised the findings from my six results chapters, discussed how they add to the existing literature, and the strengths and limitations of my research. I also considered the implications of my research and the required future research.

1.3 Personal motivation for conducting this thesis on opioids

In the Summer of 2012, I started a part-time job as a Pharmacy Assistant. I had just completed the first academic year of a BSc in Biomedical Sciences. Pharmacology was my major, so working in a pharmacy was a perfect opportunity to gain practical insights. The number one sale each day was *Nurofen Plus*, a combination of 15mg of codeine and 500mg of paracetamol per tablet, which was available over-the-counter (OTC) at the discretion of the Pharmacist. As I started building rapport with customers, many confided in me about their pain and need for pain medicines.

After a year in the Pharmacy, I did a study abroad programme at the University of Florida in the USA. Here I took classes in immunology, developmental neurobiology, bioethics, and addictive disorders, all of which was relevant to pain and opioids. But most importantly, I learnt about the US opioid crisis, the flaws of the American healthcare system, and experienced the power of pharmaceutical marketing. I returned to Australia and graduated with a BSc, receiving an Advancement Grant from my university to volunteer at Nakornping Hospital in Chiang Mai, Thailand. The hospital was public and delivered universal care through the “30 baht” project (equivalent to $1 USD). I spent time in paediatrics, surgery and women’s health. Most patients I saw presented with late-stage disease, and severe pain was the driver for visiting the hospital.

The most common presentations were motorbike accidents, infections, and terminal cancers, all of which caused pain. A case I will never forget was a woman aged 35 who presented with extreme pain under her left armpit; she was later diagnosed with Stage III breast cancer and was terminal. She was given no pain relief.

The next month, I started an Honours in Pharmacology – a 12 month independently driven research project. For this project, I wanted to explore my interest in opioids and chronic pain. I reached out to Emeritus Professor Jenny Strong, a leading Occupational Therapist and academic specialising in chronic pain. Together, we created a multi-disciplinary team of academics, pain consultants, pharmacologists and a clinical psychologist. I recruited 40 participants with chronic low-back pain from a tertiary care pain clinic and 20 healthy controls, collected blood samples for cytokine analyses, administered cognitive tests and pain questionnaires. I published my findings in *Pain Reports* (31) and presented a poster at the International Association for the Study of Pain (IASP) 16th World Congress on Pain in 2016. My time in the pain clinics where opioids were often prescribed contrasted with the literature that showcased the harms and uncertainties for opioids in people with chronic pain. This disparity between clinical practice and evidence sparked my interest in evidence-based medicine. I started following the research of the Centre for Evidence-Based Medicine at the University of Oxford.

After Honours, I commenced a Research Assistant position to work on a qualitative study of contemporary military veterans experience transitioning from service to civilisation. From speaking with many veterans and their partners, I learnt most had pain from injuries and general 'wear-and-tear' from their time in the military, with some using opioids to manage their pain.

After an unsuccessful grant to investigate chronic pain and the use of opioids in military veterans, a colleague recommended I apply for the Australian Women's Weekly and QANTAS *Women of the Future Award* – an advertisement she found while flicking through magazines at her local hair salon. I hesitated at applying for such a competition, but after great encouragement, I applied. I was interviewed, short-listed, and flown to Sydney for my first (and probably last!) magazine photoshoot. I was awarded the Judge's Choice Winner at a luncheon in Sydney surrounded by 100 leading Australian women and celebrities – a day I will never forget. The award provided a travel grant that I used to attend scientific conferences, visit Cochrane UK, and Oxford's Centre for Evidence-Based Medicine. But most importantly, my two-page spread in the Women's Weekly magazine gave a voice to people with chronic pain, a condition that sufferers often describe as being "invisible" to others. The Women's Weekly is the most read magazine in Australia, with 2.49 million readers (32) – more readers than I'll ever receive for any study published in an academic journal.

The combination of my experiences working in the pharmacy, studying in the US, visiting hospitals in Thailand, and conducting research in private pain clinics, strengthened my resolve to undertake this DPhil on the use of opioids – a topic I am wholly passionate about.

1.4 Key accomplishments, training, and dissemination of research

1.4.1 Publications

Since commencing this DPhil in October 2017, I have published 21 articles in peer-review journals (3,17,18,21,25–27,31,33–41); one is reported in chapter 2 (3), chapter 3 (16), chapter 4 (17), chapter 5 (18), chapter 7 (21), and four in chapter 8 (26–29). I also have nine manuscripts

under peer-review and five manuscripts in process as of June 2021. Appendix 1.1 outlines my list of publications.

1.4.2 Conferences and public engagement

I have presented six posters and five presentations at national and international conferences during my DPhil (Appendix 1.2). I have been an invited speaker at 18 public engagement and scientific events, including being the keynote speaker at the Rotary District 1090 Paul Harris Fellows Awards Luncheon (23 Feb 2020) - a prestigious event in the Rotary International calendar, and the Royal Society of Medicine's Spotlight On Opioids event (23 Apr 2020 – postponed due to covid-19). Appendix 1.2 outlines my conference posters, presentations, and keynote speaking events I have completed during my DPhil.

1.4.3 Other dissemination activities

I have authored ten blogs on my research and collaborative projects (Appendix 1.3), including writing the findings of my systematic review in chapter 7 for *The Conversation* (22), in which a patient contributor, Sean Jennings, provided his personal story for the article. I presented the findings from chapter 3 and 4 to members of the WHO's Expert Committee on the Selection and Use of Essential Medicines at the inaugural Global Essential Medicines Meeting in Toronto (20-21 November 2019). I created two websites to disseminate the findings from chapter 5 (https://www.catalogueofopioids.net/) and chapter 8 (https://preventabledeathstracker.net/), which are still being developed. The first article I wrote for the Coroners' Concerns to Prevent Harms series (27), which described two deaths from ingesting alcohol-based hand sanitisers, was press released by *The BMJ* and picked up by several news outlets, including the Daily Mail (42), and I was interviewed by BBC Radio Oxford and BBC Radio 5 Live Breakfast. An extraordinary

learning opportunity for my DPhil and future dissemination activities. I was invited to write an EBM Verdict on tramadol for *BMJ Evidence Based Medicine,* and following its publication (34), I was invited to speak on *The BMJ* Talk Evidence podcast (43). The episode has had over 14,800 views as of 9 January 2021. I also spoke on the CEBM podcast about reporting biases following the publication of an entry to the Catalogue of Bias resource (44,45).

1.4.4 Teaching and supervision

I have had the opportunity to develop teaching skills through the Centre for Evidence-Based Medicine, Oxford's Department of Continuity Education, and Oxford's Learning Institute's *Developing Learning and Teaching* programme. I facilitated on the Practice of Evidence Based Healthcare module for the MSc in Evidence-Based Health Care in October 2018, April 2019, and January 2020. I assessed Year 4 undergraduate medical students from the Oxford University Medical School for their critical appraisal assessments in 2018. In Trinity Term 2019, I obtained the Staff and Educational Development Association (SEDA) Award for Teaching following the successful submission of my teaching portfolio to the Oxford Learning Institute (Appendix 1.4).

I have supervised and co-supervised eight Oxford medical students and two junior doctors to conduct various research projects during my DPhil. I co-supervised four undergraduate and postgraduate Oxford medical students for their Special Study Module (SSM) in Hilary Term 2020. This project was an audit of the highest-ranking medical and health journal policies to determine their transparency and openness requirements using the Centre for Open Science (COS) Transparency and Openness Promotion (TOP) guidelines. The study protocol was preregistered (46), and the findings are being written for publication. In Michaelmas Term 2020, I supervised four undergraduate Oxford medical students for their Final Honours Scheme (FHS)

research theses. Two of the students used the Preventable Deaths Database (chapter 8) to investigate deaths from cardiovascular diseases involving anticoagulants (47) and suicides involving medicaments (48). The third student (KS) conducted phase two of the research mentioned in chapter 5, updating the search of pharmacology sources and extracting pharmacological properties of opioid drugs (49). The fourth student conducted a systematic review of case reports and case series to determine the extent of harm from ingesting alcohol-based hand sanitisers (50), following the first article in the Coroners' Concerns to Prevent Harms series (27). I am supervising two Foundation Year 1 doctors to conduct two systematic reviews; one on the effectiveness of artificial intelligence (AI) in traumatic brain injuries (51) and the other on the prevalence of paediatric traumatic brain injury in low- and middle-income countries (52).

1.4.5 Formal training and skill development

As a recipient of the NIHR SPCR Studentship, I have had the opportunity to attend various training days, workshops, and three annual Trainee Events. The SPCR also provided additional support to participate in the Practice of Evidence Based Healthcare module (January 2018), four Stata courses at Oxford IT Learning Centre (March 2018), a Biostatistics course run by the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (October 2019), and the Overview of Data Science course run by Oxford's Department of Continuing Education (Hilary 2020). I attended training at the Science Media Centre in London (October 2019) and received media training from Rotary (January 2019), which have improved my confidence when engaging with the media to disseminate my research. In September 2019, I attended the Oxford-Berlin Summer School for Open Research, which progressed my theoretical and technical open science skills (see section 1.4.6).

I have developed skills in evidence synthesis, with four published systematic reviews that synthesised observational studies (21,39), diagnostic accuracy studies (37), and mixed methods with qualitative and quantitative studies (41). I have five reviews in progress, with three that synthesise both trials and observational studies (51,52), one that synthesises case reports and case series (50), and a narrative review on AI's role in optimising the use of opioids. I have designed a range of observational studies that have used various datasets, including population-level prescribing data (3); global consumption of narcotics (15); essential medicines lists (17); commercial sales data; death data from coroner reports; dispensed prescriptions from private prescribers; and adverse drug reactions reported to MHRA's yellow card scheme. I have used innovative methods to collect and obtain data, such as Freedom of Information (FOI) requests (53) and web scraping (25). I developed programming skills and a basic understanding of Python in Jupyter Notebooks using pandas, seaborn, and matplotlib. I have a basic knowledge of Git, virtual environments, and web scraping. I taught myself HTML, JavaScript, and CSS to create a website that integrates the web scrape from chapter 8 (https://preventabledeathstracker.net/). The rest of this thesis should outline the remaining professional, methodological, and scholarly skills I have developed.

1.4.6 Open science practices

Open science, also known as open research or open scholarship, is the sharing of information to increase the transparency, replicability, and reproducibility of research. It is a process that involves all members of the research ecosystem, including researchers, universities, publishers, funders, and commercial companies involved in the research. Six principles have been proposed, including open access, open data, open education resources, open methods, open peer review, and open source (54). I created an Open Science Checklist to highlight how I have used open

science practices in my DPhil (Appendix 1.5). For all chapters, I wrote a study protocol, shared my study materials and my statistical code. For two-thirds of my chapters, I preregistered the study protocols, and where possible (83% of chapters), I made the data available. It was not possible to share the data for chapter 6 on OTC codeine sales owing to the contractual agreements with IQVIA. I have used a pre-print server to share the findings of two chapters. I am still in the final stages of writing publications, blogs, and other dissemination activities to share the results of my research. In my results chapters (chapters 3-8) I have used the checklist to highlight the links to repositories that openly share the protocols, data, and other study materials.

1.4.7 Grants and funding disclosures

My DPhil was primarily funded by the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) Studentship. I also successfully obtained scholarships from the Naji Foundation and the Rotary Foundation to cover the additional expenses of being an international student studying abroad. I received a small grant (£10,000) from the Primary Care Research Trust of Birmingham and Midlands Research Practices Consortium to purchase the OTC sales data (chapter 6). I received an Engagement and Dissemination Grant (£795) from the SPCR to develop the Preventable Deaths Tracker (chapter 8). The SPCR provided the funds for the article processing charges of my systematic review published in BMC Medicine (chapter 7) and the development of the Oxford Catalogue of Opioids manuscript in the British Journal of Clinical Pharmacology (chapter 5). Dr Nav Persaud from the University of Toronto and the Li Ka Shing Knowledge Institute at St Michael's Hospital covered the article processing charges for my open access publication in BMJ Global Health (chapter 4). I received a travel grant to attend the 6th Preventing Overdiagnosis Conference in Copenhagen and two Research Support Grants from Kellogg College, Oxford. The SPCR funded my travel to the 10th Royal Marsden Pain and

Opioid conference in London, the Clinical Pharmacology Colloquium in Bangor, and Pharmacology 2019 in Edinburgh. The Centre for Evidence-Based Medicine funded my travel to the 4E's Forum in Erice, Sicily. The Canadian Institutes of Health Research, Ontario SPOR Support Unit, St Michael's Hospital Foundation and Oxford's Nuffield Department of Primary Care Health Sciences funded my travel to the Global Essential Medicines meeting in Toronto. The Nuffield Department of Primary Care Health Sciences provided funding for a Stata software licence.

I also obtained an NIHR SPCR Partnership Grant (£20,000) for the study titled "Long-term impact of surgical mesh devices in UK primary care: a 20-year retrospective case-control study" (55), which is being written for publication.

1.4.8 Other achievements and extracurricular activities

I got involved in various committees and projects outside of my DPhil, which enriched my experience and developed my leadership skills. I am most proud of establishing the Doug Altman Scholarships to build capacity and bring together early-career researchers (ECRs) and medical students worldwide to attend EBMLive in Oxford. The idea for this scholarship came after I attended my first EBMLive conference in June 2018 and was disappointed at the level of engagement from ECRs and medical students. As a fellow ECR, I knew the most significant barrier to attending conferences were the lack of financial support and the lack of ECR appeal in conference programmes. After discussions with Prof Carl Heneghan, Dr Peter Gill, and Ruth Davis, I put together a business plan and a funding application. We successfully secured funding from the McCall MacBain Foundation for 14 students to travel from Brazil, Denmark, Egypt, Germany, India, New Zealand, Nigeria, the USA, and across the UK, to provide accommodation

and attendance to the conference. I co-created events and sessions dedicated to ECRs, and seminars for ECRs to present their research. I wrote a first-author editorial published in *The BMJ* to promote the scholarship (38), and blogs for BMJ opinion (56) and the EBMLive website (57). Following the conference, I co-worked with the 14 scholars to write and publish outputs from the discussion we had during the sessions (35,36).

We also created a panel of judges, including Prof Heneghan, Dr Helen MacDonald, Sir Iain Chalmers, Dr Gill, and myself, to select the winner of the Doug Altman Award from the 14 scholars. We graded the students on their presentations and engagement during the conference. During the meeting's final session, following the keynote address by Prof John Ioannidis, I addressed the conference with Mrs Sue Altman to announce the Doug Altman Award winner, Dr Stephen Bradley. Dr Bradley won the award for his "Oxford Declaration", which has now developed into the "Declaration to Improve Health Research" (https://www.improvehealthresearch.com/). The Declaration has been signed by over 80 people and three organisations and led to a critical overview of the problems in medical research, which I co-authored and was published in the *Journal of the Royal Society of Medicine* (40). The Declaration team has been involved in various engagement activities, including poster presentations, lightning talks, blogs, and the translation of the declaration into German, Portuguese, and Arabic, summarised here (https://twitter.com/TA_Declaration/status/1339974233154330624). There are plans to continue this work, including a hackathon co-run with the Centre for Open Science, to write to journals about incorporating Registered Reports, which I chaired the event.

In 2018, I joined a network called OPeRA, *Open Pain Research Advocacy and Appraisal*, a group of 10 ECRs, academics, and clinicians working collaboratively to improve the transparency and openness of pain research (https://osf.io/h239s/). We conducted an audit of the highest-ranking pain journal policies to determine their openness and transparency using the TOP guidelines. We published the findings in *BMJ Evidence Based Medicine* (33), and I wrote a blog for *BMJ EBM Spotlight* (58), and I presented this research at the launch event for Reproducible Research Oxford - RROx (January 13, 2020).

In 2018 and 2019, I sat on the NIHR SPCR Trainee committee to co-organise the Annual Trainees' Events programmes. I collaborated with members from the nine partner universities to organise tailored training for SPCR Trainees. In 2018, I organised the biannual Clinical Pharmacology Colloquium (November 23, 2018) at Green Templeton College in Oxford.

In 2019, I organised and chaired the scientific committee for the 4E's Forum in Erice, Italy, to "Improve the Detection, Analysis and Reporting of Harms in Healthcare". The forum was a collaboration between the CEBM in Oxford and the Uppsala Monitoring Centre in Sweden. I developed the programme, led various sessions during the conference, presented at the meeting, and co-developed a report following the conference (59).

In 2019, I joined *BMJ Evidence Based Medicine* as the Editorial Registrar, and I am continuing as an Associate Editor in 2021. The editorial roles have provided important insight into academic publishing.

In 2019, I co-founded the Rotary Partnership for Education (RP4E) scholarship, which provides mentorship and financial support to disadvantaged young people in low-income countries to continue their education by attending college or university in their home countries. Thus far, we have supported eleven students (eight to attend college and three to attend university) from the Home for Rescue of the Afflicted Children (HORAC) in Kathmandu, Nepal. In 2021, we launched the Ghana Girls Education project with Action Through Enterprise, which funded five Ghanaian girls to attend their local high school. We have 18 sponsors and mentors and will grow this in the coming years.

In 2019, I represented the cohort of DPhil students (approximately 30 students) at the university's departmental and divisional levels, reporting to the Senior Management Committee and sitting on the teaching and research boards. While rep, I had a structured training programme approved and developed for DPhil students.

In 2020, I led and co-ran the Oxford Primary Care *ReproducibiliTea* Journal Club in our department to teach and advocate for the uptake of open science practices. We held weekly face-to-face meetings during the Hilary term, and collaborated with the broader ReproducibiliTea community, and contributed to the work of Reproducible Research Oxford (RROx), the local network of the UK Reproducibility Network (UKRN). In Michaelmas 2020, we joined with the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and the Department of Psychiatry to create the Clinical *ReproducibiliTea* Journal Club, which was open to all members of Oxford's Medical Sciences Division and run online. In recognition of this work, RROx invited me to be a Fellow (60).

Chapter 2

"*You have to know the past to understand the present.*"
Dr Carl Sagan, 1980

2 Background

2.1 Aim and methods

The aim of chapter 2 is to illustrate the rationale for conducting this thesis. I used a multifaceted search strategy, including a structured search of the Cochrane Library and Medline via the PubMed interface, opportunistic sampling from the years I have been researching opioids, and forward and backward citation searches of relevant literature. I also searched for and included seminal reports from public health organisations and regulatory agencies, legislation, and clinical practice guidelines.

2.2 Definitions of key terms

The Oxford English Dictionary (OED) defines an opioid as "*any synthetic narcotic drug derived from or having properties similar to those of morphine*." (61) Others have defined opioids as "all compounds that work at the opioid receptors" (62). For this thesis, I define opioids as medicaments that target or have an effect or co-effect at one or more opioid receptors, including mu (MOP), delta (DOP), or kappa (KOP) receptors, or the nociceptin receptor (NOP). These may be naturally occurring compounds (alkaloids), or synthetic or semi-synthetic compounds. Using this definition, I exclude endogenous opioids but include opioid antagonists (e.g. naloxone) and opioids used as antidiarrheals (e.g. loperamide) and cough suppressants (e.g.

dextromethorphan). This is important, as most previous research has focused on opioid analgesics.

The OED defines an opiate as "*any drug derived from opium, esp. morphine and codeine*" (61). It is important to distinguish between 'opioids' and 'opiates', as this affects data collection and categorisation that ultimately impacts policy. There is also a small number of opiates compared with opioids, which I shall investigate in chapter 5. The Office for National Statistics (ONS) collects data on deaths related to drug poisonings (63). In their annual report, they display deaths involving "any opiate", "heroin or morphine", and "methadone", rather than all opioids, owing to variation in reported data (64).

The OED defines a narcotic as "*A drug which when swallowed, inhaled, or injected into the system induces drowsiness, stupor, or insensibility, according to its strength and the amount taken; esp. an opiate.*" (61) The term narcotic is a legal term for drugs that are abused and so also includes non-opioid substances, such as cannabis and cocaine. The International Narcotic Control Board (INCB), which regulates 136 narcotic drugs and collects global narcotic consumption statistics, also includes raw materials for the manufacturing of narcotics (65). Therefore, throughout this thesis, I primarily refer to 'opioids', as defined above, unless otherwise stated.

2.3 Pharmacology of opioids: a brief summary

Opioids exert their effects on metabotropic opioid receptors, including MOP, KOP, and DOP receptors, and the more recently discovered NOP receptor (62). MOP, DOP, and KOP are considered conventional opioid receptors, while NOP receptors are considered opioid-related

receptors (66). This is because NOP receptors have distinct pharmacology, while also exhibiting a high degree of structural homology to conventional opioid receptors (67). All four receptors are G-protein coupled receptors (GPCRs), the largest class of membrane proteins in the human genome (66). GPCRs exert their effects by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP) and modifying the permeability of ion channels, causing downstream effects (62). In humans, opioid receptors are widespread in the central and peripheral nervous systems. There are also endogenous opioids, such as enkephalins, endorphins, and dynorphins (68), but these will not be discussed in this thesis.

Opioids are categorised depending on their receptor binding and affinity, including full agonists, partial agonists, mixed agonists, inverse agonists, and antagonists. Agonists interact with opioid receptors, usually MOPs, to elicit a graded response (e.g. analgesia following the administration of morphine) (69). Substances that bind to opioid receptors but have no agonist activity and prevent the effects of opioid agonists are known as opioid receptor antagonists. Some drugs have both agonist and antagonist effects (partial agonists). Opioids are also classified based on their mode of synthesis, including alkaloids and synthetic and semi-synthetic compounds (69). Extracts from *Papaver somniferum*, or the opium poppy, contain opioid alkaloids (e.g. morphine and codeine). Modifications of morphine-like alkaloid derivatives led to the production of semi-synthetic opioids (e.g. heroin and oxycodone). Later, fully synthetic opioids were derived from morphinan (e.g. levorphanol), diphenylheptane (e.g. methadone), benzomorphan (e.g. pentazocine), and phenylpiperidine (e.g. fentanyl) (69). Opioids are also classified based on their legal "schedules" (62). But this varies by country, and in some cases individual states, so it will

not be discussed in this thesis. Opioids are occasionally categorised based on their perceived potencies, including "strong" and "weak" opioids.

2.4 History of opioids: a contemporary overview

Opioids have been used for millennia by cultivating the opium poppy, *Papaver somniferum* (69). Some propose that opium was cultivated in 3400 BC in Mesopotamia (62). Others who have mapped the diffusion of the opium poppy in western Europe have found its presence in the Mediterranean from at least the middle of the sixth millennium (70). The medical use of opioids was accelerated by isolation of morphine in the early 1800s, which is credited to the German apothecary Friedrich Wilhelm Adam Sertürner (1783-1841), and the development of the hypodermic needle in the 1850s by Charles-Gabriel Pravaz (1791–1853) and Alexander Wood (1817–1884) (71). Key events in the contemporary history of opioids are outlined in Table 2.1.

Over the past 150 years, there have been several "wars on drugs" related to opioids that have shaped regulations and the use of opioids today. These started with the opium wars (1839-1842 and 1856-1860) and the use of opium, morphine, and heroin during and after the World Wars and Civil Wars (72). This led to an increase in addiction, regulations, and "opiophobia" in clinical medicine. Internationally, the Single Convention on Narcotic Drugs of 1961, which was expanded and strengthened by the 1972 Protocol, came into effect to control the production and supply of narcotics. The International Narcotics Control Board (INCB) was established as an independent body to oversee compliance with the regulations and to collect estimates and statistics from Governments on the quantities of drugs required, manufactured, used, and seized by police and customs officers (73). In the UK, the Misuse of Drugs Act 1971, still in force,

classified and restricted opioids, while the Misuse of Drugs Regulations 2001 allow doctors, independent prescribers, and supplementary prescribers to provide opioids (74,75).

Table 2.1: Brief timeline of select events in the contemporary history of opioids

Year	Event
1805-1817	Morphine is isolated from opium by Friedrich Sertürner in Germany with the help of J.L. Gay-Lussac (71)
1850s	The hypodermic needle is invented by Charles-Gabriel Pravaz and Alexander Wood (71)
1890s	Bayer & Co. markets diacetylmorphine (diamorphine, heroin) (76)
1914	The Harrison Anti-Narcotic Act comes into effect in the USA (77)
1953	The first comprehensive textbook on pain treatment is published, The Management of Pain, written by Dr John J. Bonica (78)
1961	The Single Convention on Narcotics Drugs is established as the framework for international control of narcotic drugs (79)
1967	The first modern hospice, St Christopher's Hospice, is opened in South West London, pioneered by Dame Cicely Saunders (80)
1971	The Misuse of Drugs Act 1971 is enacted in the UK (74)
1972	On March 25, amendments are made to the Single Convention on Narcotic Drugs in Geneva, named the ‘1972 Protocol' (79)
1974	On May 9, the International Association for the Study of Pain (IASP) is established
1977	The WHO publishes the first Model List of Essential Medicines (81)
1980	The NEJM publishes a letter by Porter and Jick stating that addiction is rare in people treated with opioids (82)
1985	The WHO analgesic ladder for cancer pain is proposed (83)
1995	The FDA approves OxyContin (oxycodone controlled-release) (84)
1996	The American Pain Society institutes "pain as the 5th vital sign" (85)
2001	The Misuse of Drugs Regulations 2001 are enacted in the UK (75)
2002	In July, the first report (death disguised) of the Shipman Inquiry is published (86)

2003	In July, the second (police investigation) and third (death certification investigation) Shipman Inquiry reports are published (87)
	In July, the fourth report (regulation of controlled drugs in the community) of the Shipman Inquiry is published (86)
2004	In December, the fifth report (safeguarding patients) of the Shipman Inquiry is published (86)
	The first lawsuit against Purdue Pharma (88)
2005	In January, the sixth and final report of the Shipman Inquiry is published (86)
2006	The Health Act 2006 is enacted in the UK (89)
2015	Life expectancy in the US drops for the first time since the First World War, attributed to increasing opioid-related deaths (90)
	UK drug-driving laws enact the legal limit for prescription opioids of 220 mg of OME (i.e. blood limits of 80 µg/L of morphine) (91).
2016	The CDC publishes its guideline for prescribing opioids for chronic pain (92)
	The 2017 Canadian guideline for opioids for chronic non-cancer pain is published (93)
2017	In March, the BMA publishes a report on "Chronic pain: supporting safer prescribing of analgesics" in the UK (94)
	On October 13, *The Lancet* Commission publishes the series on "Alleviating the access abyss in palliative care and pain relief" (95)
	On October 26, President Donald Trump declares the opioid crisis a national public health emergency under federal law (96)
2018	In June, the Gosport Independent Panel publishes their report (97)
	In December, Matt Hancock orders a review of overprescribing in the NHS, to be led by NHS England Chief Pharmaceutical Officer Dr Keith Ridge (98)
	In February, the MHRA's Opioid Expert Working Groups hold their first meeting (99)
2019	In June, the OECD publishes a report on "Addressing problematic opioid use in OECD countries" (100)
	In September, PHE publishes a 'landmark' review into drugs of dependence (101)
	In October, *The Lancet* publishes the series on drug use (102)

2020	In January, police open a new criminal investigation into the opioid-related deaths at Gosport War Memorial Hospital (103)
	On August 3, NICE publishes a draft for consultation on the first guideline for "Chronic pain in over 16s: assessment and management" (104)
	In September, the MHRA announces that stronger warnings about the risks of dependence will be added to patient information leaflets and discussed with patients (105)
	In November, Purdue Pharma and the Sackler family resolve all federal criminal and civil charges against them (106)
2021	In February, McKinsey & Company settles an agreement of nearly $600 million for involvement in the US opioid crisis (107)
	On April 7, NICE is expected to publish the complete guideline for chronic pain in over 16s (108)

BMA: British Medical Association; CDC: Centre for Disease Control and Prevention; FDA: Food and Drug Administration; MHRA: Medicines and Healthcare products Regulatory Agency; NEJM: New England Journal of Medicine; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; PHE: Public Health England; WHO: World Health Organization.

Opioids were put back on the medical map during the modern hospice movement in the UK in the 1960s, pioneered by Dame Cicely Saunders (1918-2005) (80). In the 1970s, chronic pain started to be recognised as a condition, and training programmes for pain medicine and multidisciplinary pain clinics were established in the USA, led by Dr John J. Bonica (1917-1994) (78,109). In the 1980s, the WHO proposed the analgesic ladder for cancer pain, and by the 1990s it was heavily supported by medical societies and incorporated into guidelines across the world (83). The WHO analgesic ladder has three steps: 1) non-opioid analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) for mild pain; 2) weak opioids (e.g. codeine) with or without non-opioid analgesics for moderate pain; and 3) potent opioids (e.g. morphine and fentanyl) for severe pain. It promoted "titrate to effect", which meant no recommended ceiling dose for prescribing opioids.

In the 1990s, the American Pain Society instituted "pain as the 5th vital sign" (85), which led to widespread use of numeric pain scales. At the outset, these initiatives were well-intentioned, to improve pain management. However, they had unintended consequences. The WHO's analgesic ladder started being applied to non-cancer pain and the 5th vital sign encouraged administration of opioids in response to self-reported pain scores (110,111). This coincided with the development of synthetic and semi-synthetic opioids and the growth of pharmaceutical companies and the "business of pain".

The US opioid crisis, also referred to as the opioid epidemic, ensued. It can be categorised into three waves (112,113):

1. overprescription of opioids, which began in the late 1990s, predominantly affecting Baby Boomers (those born in 1945-1964);
2. increased availability of heroin, which started in 2010, mainly affecting Gen X (those born in 1965-1980); and
3. cheap manufacturing of synthetic "street" fentanyl, which began in 2013, affecting both Gen X and Millennials (those born in 1981-1990).

During the first wave, oxycodone, in particular Purdue Pharma's OxyContin, was the primary opioid being promoted and oversupplied. Purdue Pharma, owned primarily by members of the Sackler family, used several techniques to persuade doctors and the public that their opioids were safe. A letter published in the *New England Journal of Medicine* claiming that the risk of developing addiction was less than 1% (82) was used as strong evidence in marketing their drugs (114). Many factors contributed to the crisis waves, including the characteristics of the US health system, financial conflicts of interests and financial influences, socio-economic trends, and

policies that restricted access to prescribed opioids in the second and third waves. In the mid-2000s, legal settlements against Purdue Pharma began (88), and opioid litigation victories made history as the largest settlements with drug companies.

In 2015, the crisis was suggested to have reduced life expectancy in the USA for the first time in 100 years (90). In 2017, more people died from opioid overdoses than from HIV- or AIDS-related illnesses at the peak of the AIDS epidemic in the USA (90). This compelled the then US President, Donald Trump, to officially declare the opioid crisis a national public health emergency under federal law in October 2017 (115). In 2019, Purdue was found to have influenced two WHO guidelines, which were retracted (116). In November 2020, all federal criminal and civil charges against Purdue Pharma and the Sackler family were resolved and settled in court (106). The US opioid crisis has influenced prescribing and use of opioids around the world.

Two high profile cases in the UK, the Shipman Inquiry (2002-2005) and the report of the Gosport Independent Panel (2018), have also revealed misconduct involving opioids (87,97). Harold Fredrick Shipman was an English GP, who was sentenced to life imprisonment for murdering an estimated 250 of his patients with fatal doses of diamorphine (heroin) between 1975 and 1998 (86,117). The Shipman Inquiry, led by Dame Janet Smith, published six reports (86), and led to the Health Act 2006, which requires all healthcare organisations that use controlled drugs in the UK to have an "accountable officer" to monitor the use of controlled drugs (89). The Gosport tragedy involved more than 450 deaths from prescribing high doses of opioids outside of accepted practice by GP Dr Jane Barton between 1987 and 2001. The Gosport

report highlighted vital lessons for the NHS and patient safety, but the implications of the report's findings are not yet clear. In January 2020, police opened a new criminal investigation into the deaths (103). Today, the problems of prescribed and non-prescribed opioids remain widespread, affecting individuals, healthcare professionals, health systems, regulators, governments, businesses, and livelihoods.

2.5 Overview of the literature and seminal reports

The volume of opioid research has significantly increased in the last three decades, from 1414 publications in 1990 to 3838 in 2010 and 10019 in 2020 (Figure 2.1). To stay up to date with most opioid publications in 2020, I would need to read 193 publications each week (27 per day).

In 2017, three Cochrane overviews of systematic reviews were published on the benefits and harms of opioids in cancer and chronic non-cancer pain (118–120). In the overview of cancer pain, nine reviews were included, with 152 studies including 13,524 participants (118). The quality of evidence was low for all outcomes according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Overall, 19 out of 20 people with moderate or severe pain who are provided opioids for cancer pain should have pain reduced to mild or no pain within 14 days (118). Most people will have adverse events, including constipation and nausea, with between one to two in ten people will find the adverse events intolerable, requiring a change in treatment (118). The overview on high-dose opioids (defined as ≥200 mg morphine equivalent daily) for chronic non-cancer pain did not identify any reviews or studies that met the inclusion criteria (119).

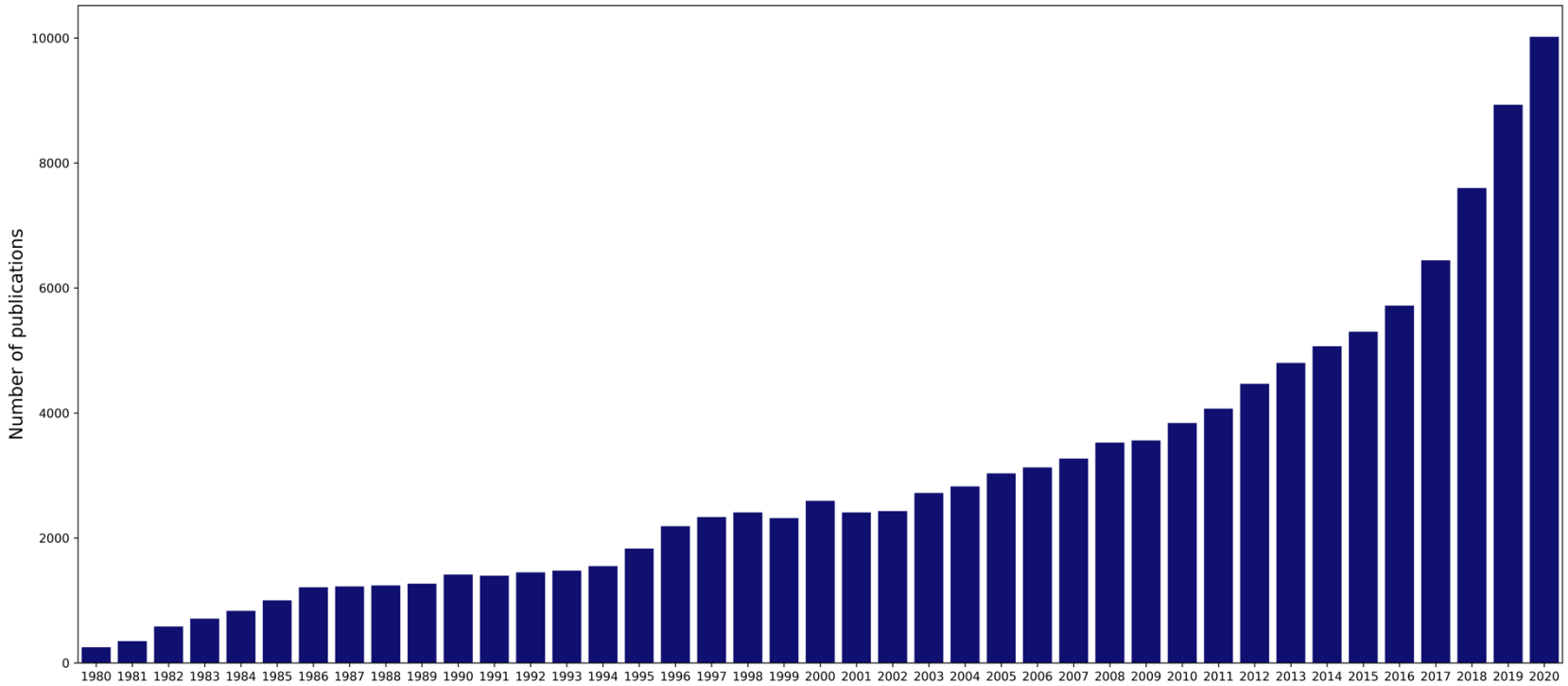


Figure 2.1: Bibliometric analysis of opioid research indexed in PubMed between 1980 and 2020. I used "(opioid*[Title/Abstract]) OR ("Analgesics, Opioid"[Mesh])" search terms. There were 115,408 publications in total between 1946 and 4 March 2021.

The other overview of Cochrane systematic reviews assessed adverse events associated with medium- and long-term use of opioids. It identified 14 reviews with quantitative data that investigated 14 different opioids (120). There were 61 studies included in the overview, with 18,679 participants. The included studies' duration was between two weeks and 13 months long, with most between 6 and 16 weeks. For generic adverse event outcomes, the quality of the evidence was very low to moderate according to GRADE, but this was downgraded for specific adverse events (120). Overall, when opioids were compared with placebo, there was a significantly increased risk of any adverse event (RR: 1.42; 95% CI: 1.22-1.66) and a serious adverse event (RR: 2.75; 95% CI: 2.06-3.67). When comparing opioids with placebo for specific adverse events, risk ratios were significant for constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting (120). When comparing opioids with a non-opioid active drug, the risk of an adverse event remained (RR: 1.21; 95% CI: 1.10-1.33). The overview found no data for several prespecified adverse events of interest, including addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine dysfunction, respiratory depression, sexual dysfunction, and sleep apnoea or sleep-disordered breathing.

I conducted an overview of Cochrane systematic reviews to identify the types of conditions and age groups investigated in Cochrane reviews involving opioids. There were 48 Cochrane reviews specific to opioids (Table 2.2). Together, the reviews included 695 trials with 9,1841 participants. Cochrane reviews have investigated 20 conditions; most (85%, 41 of 48 reviews) were in adults, two were in neonates, five in children and adolescents, and none in elderly people.

The distinction between acute and chronic pain is important, as the treatment and management strategies differ. Acute pain and, for similar reasons, cancer pain extending into most end-of-life pain, is a response to tissue damage that responds well to analgesia and has the potential to improve as the disease resolves. In contrast, chronic pain persists beyond the duration of expected tissue healing and represents a dysfunction of the pain system (121). The cause of chronic pain is complex and involves interplay of biological, psychological, and social factors. While acute pain represents a useful (and essential) biological response, the persistent pain signalling in chronic pain has no biological advantage.

Table 2.2: Conditions investigated in opioid-related Cochrane systematic reviews from inception to December 2018, ordered by the number of reviews and study participants

Indication	No. of reviews	No. of trials included	No. of participants
Cancer pain	8	127	11,575
Neuropathic pain	8	52	3,055
Illicit opioid dependence	5	70	13,859
Postoperative pain	4	127	4,263
Opioid withdrawal	3	59	6,160
Chronic non-cancer pain	3	58	5,074
Osteoarthritis	2	33	18,588
Maternal labour pain	2	90	13,408
Acute pain	2	16	1,818
Chronic low-back pain	1	15	5,540
Chronic musculoskeletal pain	1	4	4,094

Acute renal colic	1	20	1,613
Pharmaceutical opioid dependence	1	6	1,613
Rheumatoid arthritis	1	11	672
Restless legs syndrome	1	1	276
Acute pancreatitis pain	1	5	227
Chronic lung disease	1	1	6
Fibromyalgia	1	0	0
Chronic cough	1	0	0
Agitation in dementia	1	0	0
Total	**48**	**695**	**91,841**

A misunderstanding and lack of education of the different types of pain may contribute to prescription of opioids outside of their indications. Pain is subjective, self-reported, and difficult to measure. It is mostly regarded as a symptom or comorbidity of conditions, which has implications for how pain and opioid use is coded and accounted for in clinical practice and research. Opioids have an important role in the treatment of cancer pain, during palliative care, and for managing acute pain (e.g. postoperative or trauma pain). Conversely, opioids are neither beneficial nor safe for most people with chronic non-cancer pain, in whom it can persist for months, years, or even decades. Most clinical trials on the effects of opioids are conducted over short durations, use placebo comparators (rather than paracetamol, physical, or psychological therapies), and exclude people at high risk of serious adverse events, including the elderly, limiting the generalisability to clinical practice (120,122). The goal of chronic pain management is to improve quality of life and daily function. Paradoxically, opioids do the opposite in people

with chronic pain (123–125); they increase the severity of pain, negatively affect the quality of life, and reduce the ability to function.

Each year the Global Burden of Diseases studies consistently highlight the disability of pain worldwide (126). For those aged 10-49 years, road injuries (ranked first), low back pain (fourth), headache disorders (fifth), and depressive disorders (sixth) were among the top ten causes of reduced disability-adjusted life-years (DALYs). A systematic review of population studies published in 2016 reported the prevalence of chronic pain in the UK (127). It pooled prevalence estimates and reported that chronic pain affects between one-third and one-half of the UK population (pooled estimate: 43.5%; 95% CI: 38.4% to 48.6%), based on data from the best available published studies. They found that prevalence increases with age, from 14.3% in those aged 18–25 years to 62% in those over 75 years; across all types of chronic pain, it was more prevalent in females (127).

Clinical practice guidelines have been developed to assist clinicians in managing people for whom opioids are prescribed for chronic pain. The most prominent guideline was published in 2016 by the US Centers for Disease Control and Prevention (CDC), which provided 12 recommendations for primary care clinicians managing adults with chronic non-cancer pain (92). The recommendations promote non-opioid therapies. If the benefits of opioids outweigh the harms for an individual patient, they recommend that the lowest effective dose should be prescribed, and that concurrent benzodiazepines should be avoided (92). The CDC guideline recommends avoiding doses that exceed 90 mg of oral morphine equivalents (OME) per day. In 2014, a systematic review of opioid prescribing guidelines for chronic pain was published, which

found that most of the 13 guidelines recommended that doses over 90-200 mg of OME/day should be avoided (128). But most recommendations were supported by observational studies or expert consensus, owing to limited high-quality evidence. The Canadian guideline for opioid therapy and chronic non-cancer pain published in 2017 and recommended that dosages of 100 mg of OME/day should be avoided (93). The Faculty of Pain Medicine (FPM), in collaboration with Public Health England (PHE), published the Opioids Aware guidance, which recommends a maximum dosage of 120 mg OME/day (129). However, in the UK the legal limit for driving while taking opioids is 220 mg OME (i.e. blood limits of 80 µg/L of morphine or 500 µg/L of methadone) (91). Official NICE guidance in the UK has been slow to emerge. On 3 August 2020, NICE published draft guidelines for consultation on chronic pain in those over 16 years (104). The draft guidance strongly recommends against prescribing any opioids to manage chronic pain, which has caused some concern among prescribers and patients. The complete guideline is expected for publication on 7 April 2021 (108). Overall, dosage recommendations vary between countries and reviews (Table 2.3). At present, there is no official WHO guideline to standardise such variation, owing to retraction of their opioid guidelines because of pharmaceutical industry influence.

Table 2.3: Definitions of high-dose oral morphine equivalent (OME) dosages in clinical guidelines and seminal reviews, descending by dose

Source	Dosage, OME (mg/day)
Cochrane review, 2017 (119)	200
PHE Opioids Aware, 2018 (129)	120
Canadian guideline, 2017 (93)	100

CDC, 2016 (92)	90
Review of opioid guidelines, 2014 (128)	90-200

CDC: Centers for Disease Control and Prevention; PHE: Public Health England

Measurement of opioid use varies which has implications for research, practice, and policy. In studies investigating trends of opioid use, some studies use the number of prescriptions or items, costs, physical quantity (e.g. kg), OME per day or over a specified period, or defined daily doses (DDDs). The DDD is a technical measure, created by the WHO that is assigned to most medicines with an anatomical therapeutic chemical (ATC) code, defined as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" (130). A DDD does not correspond to the recommended prescribed daily dose. It is intended to provide an statistical estimate of consumption rather than the actual use of a drug. It allows different drugs in the same group to be compared or trends in drug use in populations over time to be studied. Various pharmacoepidemiological studies investigating trends of opioids have compared these multiple metrics (131–136) and concluded that OME is the advised unit for opioid research, as it best represents clinical use. While it is important to standardise doses for consistency and comparisons in research, it can also limit the ways in which research findings are translated into policy and clinical practice and has significant implications for patient safety.

In countries with prescribing data, many studies have investigated the trends in opioid use. Since the early 2000s, the rate of prescribing has increased in most countries. The Organisation for Economic Co-operation and Development (OECD) published a report in 2019, evaluating the "problematic" use of opioids in 25 OECD countries (100). They analysed opioid-related deaths

and found an increase of more than 20% between 2011 and 2016; the most significant increases were in the USA, Canada, Estonia, Sweden, Norway, Ireland, and England and Wales. The report concluded with four key areas to consider for improving the use of opioids and reducing harms: 1) better prescribing and opioid-related literacy; 2) better care expanding access to treatment and harm minimisation interventions; 3) better approaches across the health, social, and criminal justice systems; and 4) better knowledge and research for supporting decision-making at all levels (100). *The Lancet* has published two series: palliative care and pain relief in 2017 (95) and drug use in 2019 (102). One report estimated that $145 million would close the global gap in morphine need for palliative care, but highlighted many barriers that limit access to opioids in low- and middle-income countries (137). One of the studies evaluated patterns of opioid use and dependence globally (138). The authors estimated that in 2017 alone, 40.5 million people were dependent on opioids and 109,500 people died from an opioid overdose (138). They recommended that alternative policies incorporating human rights and public health should be adopted, with frameworks that do not criminalise drug use and reduce drug-related harm at the population level.

In the UK, various datasets are available for pharmacoepidemiological research. Initial studies on opioid use were conducted using the Clinical Practice Research Datalink (CPRD) (5,139–141). However, these studies focused on either a subgroup of opioids (e.g. morphine, fentanyl, oxycodone, and buprenorphine (5)) or an individual condition (e.g. musculoskeletal pain (140)). The UK biobank has similarly been used to investigate the use of opioids (142). Between 2006 and 2010, 5.5% of people reported regular use of opioids and 87% of users reported chronic pain. The use of opioids increased with age and was most common in females (142). However,

these datasets only included a sample of the population, limiting the generalisability of the findings on national opioid use.

In 2018, I was involved in a collaborative project with Oxford's DataLab and Pain Consultant, Dr Jane Quinlan, to conduct a retrospective observational study to assess the national use of opioids. We used data from NHS Digital through the OpenPrescribing.net platform to examine opioid prescribing trends and geographical variation in England between 1998 and 2016, using the annual number of items dispensed, OME (mg), and cost per 1000 of the population. We found that the total number of items for all opioid-containing formulations increased by 34%, from 568 items per 1000 in 1998 to 761 in 2016 respectively. After correcting for OME, the trend increased by 127%, from 190,000 mg per 1000 population in 1998 to 431,000 mg in 2016). We also investigated trends in the use of high-dose long-acting opioids (defined as >120 mg OME), which increased by 581% for items and 457% for OME, from 3 items per 1000 in 1998 to 23 items in 2016, and 17,800 mg in 1998 to 99,300 mg in 2016. Across England, the total OME differed almost eight-fold, from 52,700 mg per 1000 registered patients to 416,000 mg per 1000 registered patients. The lowest prescribers of opioids were generally around the Greater London regions, with high prescribers in northern and coastal areas of England. Between 2016 and 2017, there was a 3.5% decline in items and a 10.5% decline in OME prescribed. The DataLab turned our findings into new measures on OpenPrescribing (https://openprescribing.net/measure/?tags=opioids). The conclusions of this research were published in The *Lancet Psychiatry* (3), and I presented these results in a seminar at the Royal College of General Practitioners (RCGP) Conference in Glasgow, Scotland (4 October 2018). This study has important implications for my thesis and informed the rationale and design of

subsequent studies in this thesis, including chapter 6 (OTC sales of codeine) and chapter 7 (systematic review of factors associated with high-dose use).

In September 2019, Public Health England (PHE) released a "landmark" report into medicines associated with dependence, including opioids (143). They found that 5.6 million people (10% of the population) in England were dispensed at least one opioid in 2017-2018 (144). They also found that the number of people taking opioids fell by 3.9% between 2015 and 2018. But half of all people for whom opioids were prescribed in March 2018 continuously took opioids for at least 12 months, which had increased since April 2016. The PHE report provided some recommendations, including expanding the availability of prescribing data, enhancing clinical guidance, improving information for patients and carers, and improving the support available to patients. In October 2015, a similar report was published by the British Medical Association (BMA), which concluded with three similar policy recommendations: 1) a national helpline for people for whom drugs of dependence were prescribed; 2) an increase in specialist support services; and 3) revised guidelines on safe prescribing, management, and withdrawal of prescription drugs (145). However, none of the BMA's 2015 recommendations has been actioned to date.

From my review and critical appraisal of the evidence, I identified four gaps that I address in this thesis:

1. How does the UK's use of opioids compare with the rest of the world?
2. How many non-prescribed opioids are being used in the UK, and abroad?
3. What is driving the increase in high-dose prescribing of opioids?

4. How can opioid-related deaths be prevented in England and Wales?

2.6 Observations from the opioid deprescribing clinics in Oxford

Dr Jane Quinlan, Consultant in Anaesthesia and Pain Management, invited me to attend her monthly opioid deprescribing clinics at the Churchill Hospital when we met while collaborating on the Curtis et al. study (3), discussed in section 2.5. Dr Quinlan was the Oxford University Hospitals NHS Foundation Trust Lead for Pain and created the Oxford PainGuide App, resources for GPs managing patients on opioids, and leaflets for patients (146). The resources include an 'opioid calculator' to calculate the patient's daily OME dose and templates to tailor opioid reduction plans (146), based on the FPM Opioids Aware guidance (129). I observed 29 patients over 18 months, from June 2018 to December 2019.

Using questionnaires administered during her consultations, Dr Quinlan and her team conducted a mixed methods study, which described the profiles and outcomes of 60 patients who attended the clinic between 2017-2019 (147). 52% of patients identified as women and patients had a median age of 53 years (range: 23-76 years), a BMI of 28 (range: 18-57), and daily median OME doses of 180 mg (range: 13-1200 mg/day), with 63% taking doses above the FPM's maximum recommended dose of 120 mg/day of OME. As noted in the article, the patient taking 13 mg/day was "referred for their concerning behaviour" of accessing OTC codeine products (147). Over 80% of patients described symptoms of clinical depression, and 63% reported clinically significant anxiety. Despite taking opioids, most patients reported severe pain, had high scores for pain interference and psychological distress, and had low scores for self-efficacy beliefs, strikingly similar findings to my Honours research conducted in private pain clinics in Australia

(31). All of the 29 patients I observed in the clinic have unique stories that have informed the research in my thesis. I share three cases for context:

> A woman took 280 mg/day of OME for nerve pain, including 40 mg of long-acting oxycodone in the morning and evening and a daily average of six "swigs" of Oramorph (Figure 2.2). She was also taking antidepressants and the highest dose of gabapentin. She had previously taken fentanyl lozenges as part of her drug regimen. The taper of the fentanyl lozenges was not only safer for the patient, but it reduced the annual cost of her drugs by more than £8000.
>
> A man who took 10 mg of morphine suppositories eight times a day and oral tramadol for breakthrough pain for chronic pancreatitis and persistent post-surgical pain. He had been using morphine suppositories for 18 years and asserted that he could not tolerate oral morphine despite successfully taking tramadol orally.
>
> A man with a long history of operations and infections resulting in chronic post-surgical pain, after an operation on a gangrenous toe 29 years before. He was taking 960 mg/day of OME in the form of four 100 microgram fentanyl patches. He described two overdoses: the first while sunbathing on holidays abroad and the second in the UK.

OPIOID CALCULATOR

for calculation of oral Morphine Equivalent Daily Dose (MED) in mg/day

British Pain Society maximum recommended dose in chronic pain is 120mg MED per day*

(this limit does NOT apply in acute or palliative pain)

insert the dose of the drug under the name, and the number of doses per day for each drug used

(these conversion doses are approximate and assume long term use)

MORPHINE									
Morphine modified release (mg)	doses/day	MED	**Morphine liquid immediate release** (mg)	doses/day	MED	**Morphine tablets immediate release** (mg)	doses/day	MED	subtotal MED
		0	20	6	120			0	120
OXYCODONE / HYDROMORPHONE									
Oxycodone modified release (mg)	doses/day	MED	**Oxycodone immediate release** (mg)	doses/day	MED	**Hydromorphone** (mg)	doses/day	MED	subtotal MED
40	2	160			0			0	160
FENTANYL **									
Fentanyl patch (micrograms/hour)		MED	**Actiq®** (micrograms)	doses/day	MED	**There are no safe conversion directions available for transmucosal fentanyl products. This a calculation based on Actiq bioavailability and is ONLY AN APPROXIMATE GUIDE to morphine equivalence			
		0			0				
WEAK OPIOIDS									
Tramadol (mg)	doses/day	MED	**Codeine** (mg)	doses/day	MED	**Dihydrocodeine** (mg)	doses/day	MED	subtotal MED
		0			0			0	0
BUPRENORPHINE									
BuTrans® patch (micrograms/hour)		MED	**Transtec® patch** (micrograms/hour)		MED	**sublingual tablet** (micrograms)	doses/day	MED	subtotal MED
		0			0			0	0
			TOTAL ORAL MORPHINE EQUIVALENT DOSE in mg/day						**280**

Figure 2.2: Screenshot of the opioid calculated created by Dr Quinlan that was used with patients. This example shows a total oral morphine equivalent (OME) dose of 280 mg.

Reflecting on my time in the clinic, there were patterns I noticed. Each month there were always one or two patients who did not attend for their appointment, and on one occasion no patients attended. It is difficult to ascertain the reasons for this, but patients were aware that this clinic was to reduce their opioids, which made many highly anxious. Some had blame towards others for their pain; for some, this was directed at doctors (e.g. repeated failed operations); for others, it was the perceived perpetrator of an accident (e.g. motorcar crashes). Often, patients would report other forms of addiction, including tobacco and alcohol. One patient reported drinking ten cans of diet coke daily, and another was addicted to video games. Most were unemployed, described poor sleep, and had mental health comorbidities and past traumas. Many patients were hoping they would receive a "new" pill that would "cure" their pain, and some asked about the possibility of medical cannabis.

People were taking opioids for a variety of pain conditions. Common origins of pain included failed and/or repeated operations that led to persistent post-surgical pain, nerve damage, infections, ulcers, and chronic pancreatitis. Less common origins were gout, multiple sclerosis, scoliosis, Ehlers-Danlos syndrome, neurofibromatosis, and a case of chronic regional pain syndrome (CRPS) from an infected cat bite.

I learnt about patients' knowledge of and relationship with opioids. Most patients had a "*spare supply*" of opioids "*just in case*". I discovered some unsafe and risky behaviours of using opioids, including "swigging" from bottles of Oramorph, cutting fentanyl patches to taper dosages, and one patient had been adding an extra fentanyl patch for breakthrough pain. Many patients described withdrawal symptoms and how their lives revolved around their next opioid dose. One stated, "*my body didn't want it, my mind did. It was the opioids talking*". One patient, who had previously been a nurse, described his contrasting experience of locking up opioids in the controlled drugs cabinets in the hospital with his GP's behaviour, who "*dished*" out opioids "*as if they were Smarties*".

To encourage opioid reduction, Dr Quinlan often set goals or discussed potential incentives for deprescribing. Some patients were referred because they needed to lower their dosage and tolerance to opioids in preparation for surgery. For patients who were able to drive, Dr Quinlan used the drug-driving laws to encourage dosage reduction.

Over the 18 months, I experienced both successful and unsuccessful cases of opioid tapering. One patient had used a motorised wheelchair for 10-15 years and had transitioned to crutches since reducing his opioid dose. On reflection, there is no clear marker that predicted successful tapering. It is difficult to know how a patient will respond and the potential consequences of opioid deprescribing. Those that were successful were keen to share their story and help others do the same. Many said that it had taken six months after tapering to feel "normal" again. Their pain had not gone away. Instead, they developed better ways for managing their pain that did not involve opioids.

All patients had clear medical reasons for initiating opioids. But these drugs had been titrated to higher doses over prolonged periods with no other management strategies. Attending the clinics provided an appreciation of the complexities of having chronic pain, taking high doses of opioids, and the conundrums for prescribers and healthcare professionals, and the challenges of managing patients' expectations. While my time at the opioid clinic cannot be classified as formal patient and public involvement (PPI), it shaped and enriched many aspects of my research.

2.7 Patient and public involvement in my research

In December 2019, I held a discussion group with three patients, to receive input on three studies in this thesis (chapters 3, 6, and 7). These studies were chosen as they were my active projects at the time of the meeting, and I had key questions:

1. What were the most important outcomes of my research, which matter to patients?
2. How could this research affect or benefit you/patients?
3. How would you interpret these findings?

4. How should this research be presented and disseminated?
5. What are the take-home messages?
6. Knowing this result, what would you want to be done about it?

I created a Google Form to recruit patients and advertised for contributors via our departmental PPI network, social media, and pain advocacy groups. I received 19 responses to my advertisement. I recruited three people to attend the in-person meeting because of the limitations associated with travelling. On reflection, this could have been resolved using online means to facilitate input and discussions with patients, which I will consider in my future research.

On the day, I facilitated the meeting with the three patients with two department members, who had experience conducting PPI, in attendance. One acted as my scribe (AT), and the other helped answer clinical or challenging questions that arose (JW). This was my first PPI session, so their help, support, expertise, and feedback were incredibly valuable. I obtained input from patients by generating group discussion and receiving written information about my research. I also gathered written feedback about the session from patients, which I will use when designing my next PPI event. Overall, this PPI activity helped shape what findings I emphasised, how I presented and displayed my results, the implications I discussed, and methods for dissemination. Of note, one of these patients allowed me to share their personal story and contributed to my article in The Conversation (22) to disseminate the findings from my systematic review (chapter 7).

2.8 Chapter summary

- Opioids are naturally occurring or synthetic or semi-synthetic substances that have morphine-like activity.
- In the past 150 years, several events have occurred that have shaped current regulations and the use of opioids today.
- The US opioid crisis, which began in the late 1990s, involved three waves: overprescription of opioids, increased supply of heroin, and cheap illicit fentanyls.
- A large volume of opioid research is being published, which is growing each year.
- I conducted a critical overview of the literature and seminal reports on the use of opioids that identified the four gaps I investigate in this thesis.
- I observed 29 patients attending the opioid deprescribing clinics in Oxford, which increased my knowledge of opioid use and informed aspects of my research.
- I used PPI for the work described in chapters 3, 6, and 7, which shaped my analysis, presentation, and dissemination of my research.

Chapter 3

"Monitoring access to opioid medicines is essential to ensure that pain and suffering, especially among the poorest populations, is neither ignored nor neglected."
Knaul et al. 2021 (148)

*This chapter is based on my first-author manuscript published in the *British Journal of Pain,* entitled "*Global, regional and national consumption of controlled opioids: a cross-sectional study of 214 countries and non-metropolitan territorie*s" (16). I presented some of the finding from this research at the Inaugural Global Essential Medicines (GEM) Meeting in Toronto, Canada (November 20-21, 2019).

3 Analysis of controlled opioids consumed globally, 2015-2017

3.1 Chapter rationale

In chapter 2, section 2.5, I examined the volume of opioids dispensed in England (3), and thus the first research question of my DPhil was, how did England's use of opioids compare with the rest of the world. Previous studies and reports comparing the consumption of opioids globally have used data from the International Narcotic Control Board (INCB) (1,138,149–152). The INCB are an independent body of the United Nations (UN) that monitor the implementation of international drug control conventions, including the Single Convention on Narcotic Drugs of 1961, which requires governments from all countries and non-metropolitan territories regardless of whether or not they are signatories to the convention, to report annual statistics on narcotic

consumption relating to controlled drugs (153). When designing this study, the most up to date data published were from 2011-2013, which may not represent current patterns of use. I, therefore, provide an up-to-date analysis of opioid consumption patterns across the world.

3.2 Introduction and Aims

The consumption of opioids has increased globally since the 1990s, particularly in the Americas, Europe, and Oceania, but with substantial disparities in most of Africa and Asia (1,138,149–152). Several observational studies have examined long-term consumption trends globally and evaluated barriers to access (1,154–159). These studies showed that complex interactions between historical, social, cultural, economic, and political decisions limit medical access to opioids. However, there are several limitations to previous studies:

- At the time of publication, the data are several years out of date.
- Consumption has been calculated using a technical measure, Defined Daily Doses (DDD), which does not accurately represent volume or prescribing in a clinical setting, which would use milligrams (mg) or oral morphine equivalents (OME) (132,133).
- Most studies include a subset of opioids focusing on cancer pain and palliative care (150,151,160,161).

To the best of my knowledge, no studies have simultaneously analysed the consumption of all types of opioids, including anaesthetics, analgesics, antidiarrheals, opioid substitution therapies, and cough suppressants. In this chapter, I, therefore, aim to provide an up to date analysis of global, regional, and national opioid consumption, measured using weight (mg) distributed for medical purposes at the retail level, adjusting for country population, and including all types of controlled opioids.

3.3 Objectives

1. to determine the global, regional and national consumption of opioids in 2015-2017;
2. to rank the consumption and types of opioids consumed in the UK; and
3. to assess the types of opioids consumed globally and nationally in 2015-2017.

3.4 Methods

3.4.1 Study design and data sources

I designed and conducted a cross-sectional study using the most up-to-date INCB data (2015-2017) as of August 2019 (162). To obtain the data, I emailed researchers who had previously used the data in published research and acquired the email address of the Chief of the Narcotics Control and Estimates Section of the INCB, who later shared the required data via email in an excel sheet. Consumption refers to the total amount of a narcotic that has left the wholesaler and has been distributed for medical purposes at the retail level (e.g. to hospitals or pharmacies). I received data in kilograms (kg) and removed 27 non-opioid substances (e.g. cannabis, coca leaf, and cocaine) to create a dataset of all reported opioids under international control. The substances I included and excluded are listed in Appendix 3.1.

3.4.2 Global, regional, and national consumption of opioids

I used all available data for countries and territories (n=214) as defined by the INCB's "Index of names of countries and non-metropolitan territories" (163). I converted total consumption from kg to tonnes to report the total global consumption between 2015 and 2017. I created an annual rate in mg/person by converting kg to mg, calculating the three-year mean, and dividing this by 2016 population data from the WHO Global Health Observatory (164); Appendix 3.2 has sample

calculations. INCB recommend using a three-year mean to account for annual variations in reporting data, and published studies have used this metric (165). I calculated the median and interquartile range (IQR) for national consumption. I categorised countries into deciles and calculated the percentage of opioids consumed and the population's percentage in each decile. I visualised the spread of consumption using bar graphs and a choropleth map with a colour spectrum representing the deciles.

3.4.3 Consumption of opioids in the UK

I ranked all countries by their mean annual consumption in mg/person to determine the UK's rank. I compared the UK's consumption with the median consumption of opioids and determined the UK's total consumption percentage. I also calculated the UK's total consumption for each type of opioid in mg/person using 2016 population data from the WHO Global Health Observatory (164).

3.4.4 Types of opioids consumed

I categorised opioids by their Anatomical Therapeutic Classification (ATC) index subgroups. I calculated the mean annual consumption by type of opioid globally in kg and mg/person for each country and ATC index subgroup.

3.4.5 Statistical software and open science practices

I used Stata v16 for all statistical analyses and pandas (166) and plotly modules in Jupyter Notebooks, with Python v3.7 for choropleth maps. I shared my study protocol, materials, data, and statistical code on the OSF and GitHub (Table 3.1).

Table 3.1: Open Science Checklist for Chapter 3 on global opioid consumption

Principles		Links
Open methods	Protocol	https://osf.io/6kfs9/
	Preregistration	No
	Materials	https://osf.io/6nzds/
	Statistical code	https://github.com/georgiarichards/opioid_emls_maps
Open data	Data	https://osf.io/6nzds/
Open access	Pre-print	https://osf.io/fs74k/
	Publication	https://doi.org/10.1177/20494637211013052
	Blog	To be written post-publication
	Tool	No, as others have created the Opioid Atlas with this data (https://krisrs1128.github.io/OpioidAtlas/), but the data is out of date.

3.5 Results

3.5.1 Global, regional, and national consumption of opioids

Globally, over 700 tonnes (710,043 kg) of opioids were consumed in 2015-17, an average of 32 mg/person each year. Regionally, the Americas (144 mg/person) were the greatest consumers, followed by Oceania (132 mg/person), Europe (98 mg/person), Asia (3.5 mg/person), and Africa (1.4 mg/person), see Figure 3.1.

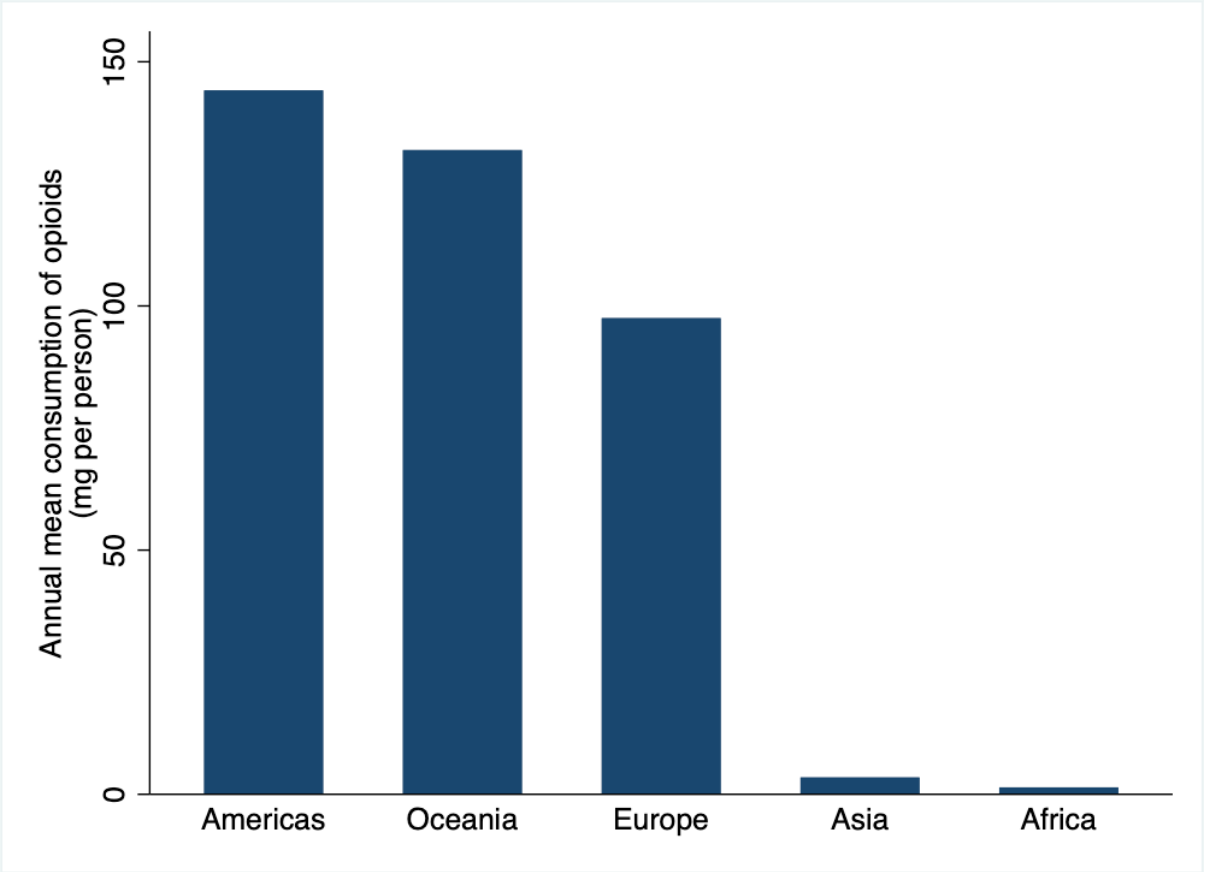


Figure 3.1: Annual mean consumption of opioids in mg/person in 2015 to 2017

Nationally, countries consumed a median of 3.3 mg/person (IQR: 0.24-14.8, range: 0-480). But consumption was skewed across the world; see Figure 3.2. Germany had the greatest consumption of opioids (480 mg/person), followed by Iceland (428 mg/person), the USA (398 mg/person) and Canada (333 mg/person), see Figure 3.3 and Appendix 3.3 for consumption data. There were 21 countries in the top decile of consumption; they consumed 89% (630 tonnes) of the world's opioids, although they accounted for only 9.7% of the world's population (687 million of 7.1 billion people in 2016), see Table 3.2. Deciles that accounted for larger percentages of the population, decile 6 (24% of the population), decile 3 (21% of the population) and decile 4 (13% of the population), consumed only 2.7%, 0.28%, and 0.32% of the world's

opioids respectively (Table 3.2). Thirty-five countries, accounting for 3.1% of the population, reported no consumption of opioids to the INCB.

Table 3.2: Deciles of opioid consumption

Decile	No. of countries	Range of consumption (mg/person)	% of consumption	% of population
10	21	62-480	88.75	9.7
9	21	18-56	3.260	2.9
8	22	10.3-17.7	3.256	7.7
7	21	5.6-10.2	0.979	5.1
6	22	3.32-5.54	2.709	23.5
5	21	1.6-3.3	0.437	6.5
4	21	0.54-1.55	0.319	13.0
3	22	0.049-0.527	0.282	20.9
2	8	0.002-0.037	0.005	7.7
1	35	0-0	-	3.1

3.5.2 Consumption of opioids in the UK

The UK consumed a mean of 124 mg/person of opioids and ranked 11th globally (Figure 3.3). The UK consumed 38-fold more than the median consumption, accounting for 3.5% of all opioids globally. Methadone had the greatest consumption (127 mg/person), followed by morphine (88 mg/person), dihydrocodeine (79 mg/person), and oxycodone (58 mg/person) (Figure 3.4). No data were reported to the INCB by the UK for trimeperidine, tilidine, piritramide, difenoxin, and codeine.

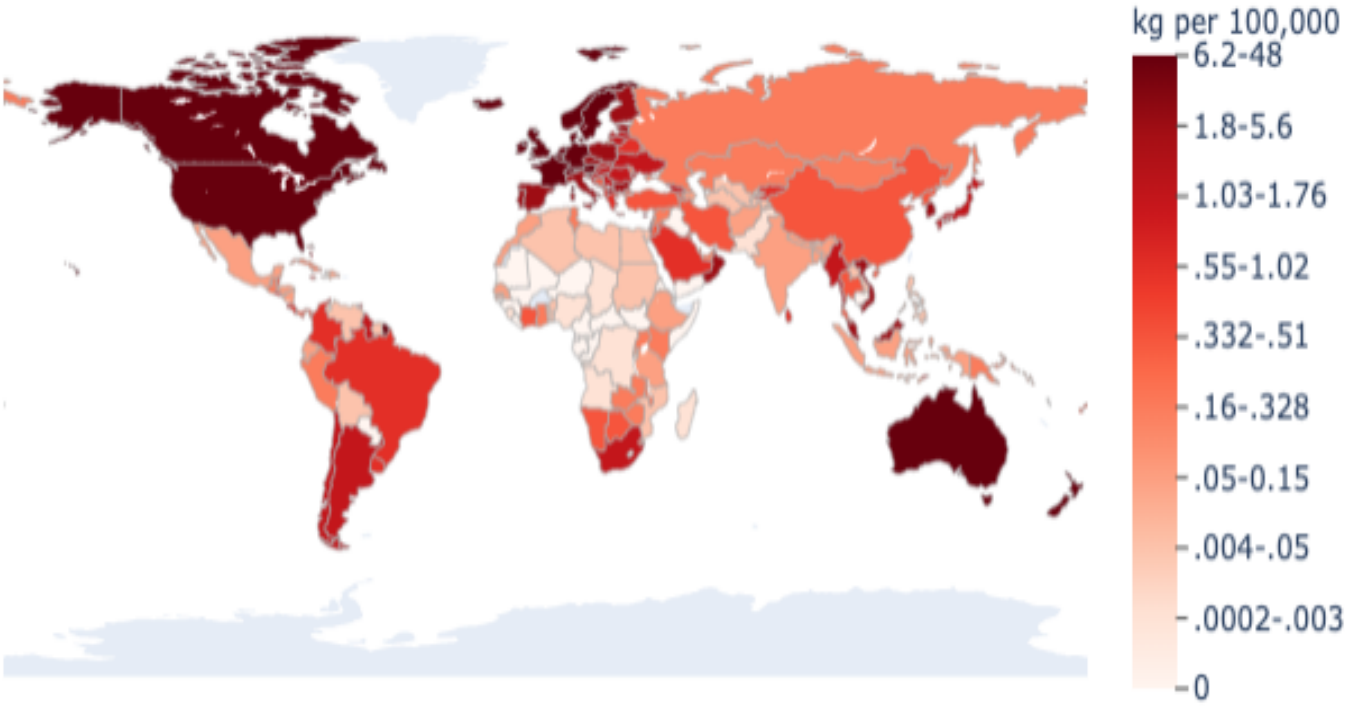


Figure 3.2: Annual mean consumption of opioids for 2015-17 grouped by deciles.

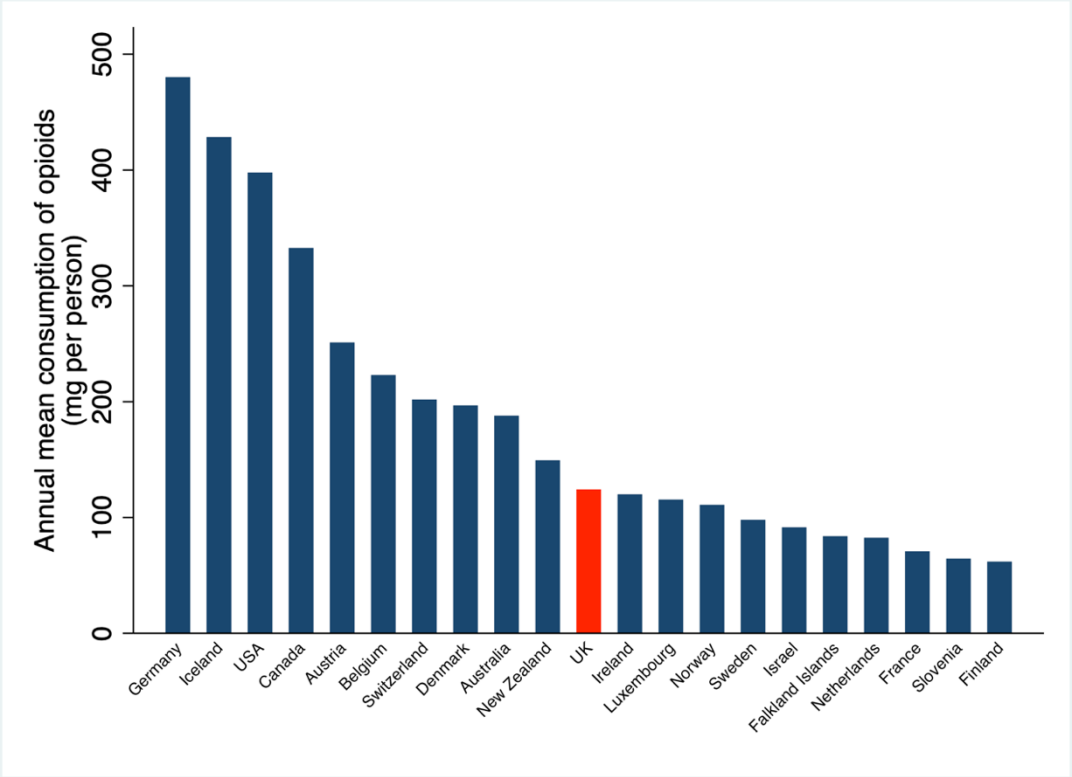


Figure 3.3: Countries in the top decile (n=21) of opioid consumption (mg per person). The UK was ranked 11th of 214 countries and non-metropolitan territories.

3.5.3 Types of opioids consumed

Countries reported data for 225 different opioid substances detailed in Appendix 3.1. Globally, oxycodone was the most heavily consumed, accounting for one-third of all opioids (249 of 710 tonnes), followed by morphine (15.9%, 124 of 710 tonnes), methadone (15.8%, 123 of 710 tonnes), and tilidine (13.9%, 109 of 710 tonnes), see Figure 3.5 and Appendix 3.4. Analgesics (492,810 kg, n=12) were the most common ATC category of opioids consumed, followed by opioid substitution therapies (113,850 kg, n=2), cough suppressants (95,486 kg, n=2), anaesthetics (300 kgs, n=3), and antidiarrheals (68 kgs, n=2).

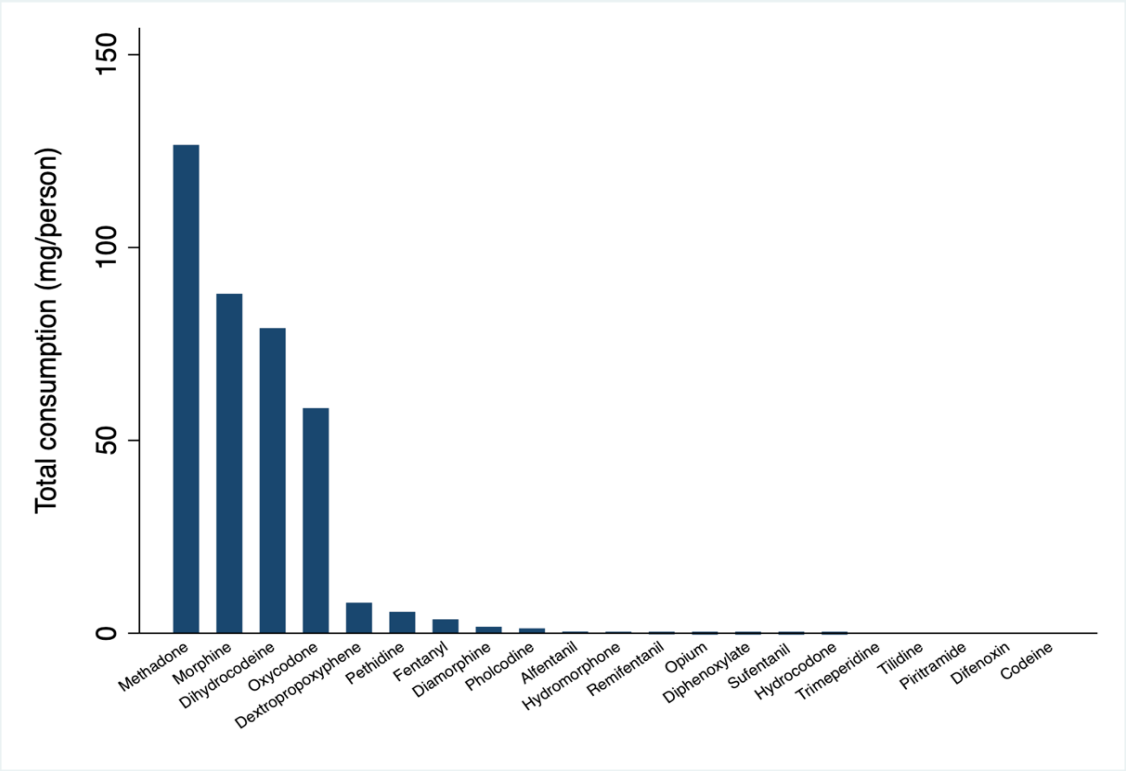


Figure 3.4: The UK's consumption of opioids in 2015-2017 (mg/person) by opioid type.

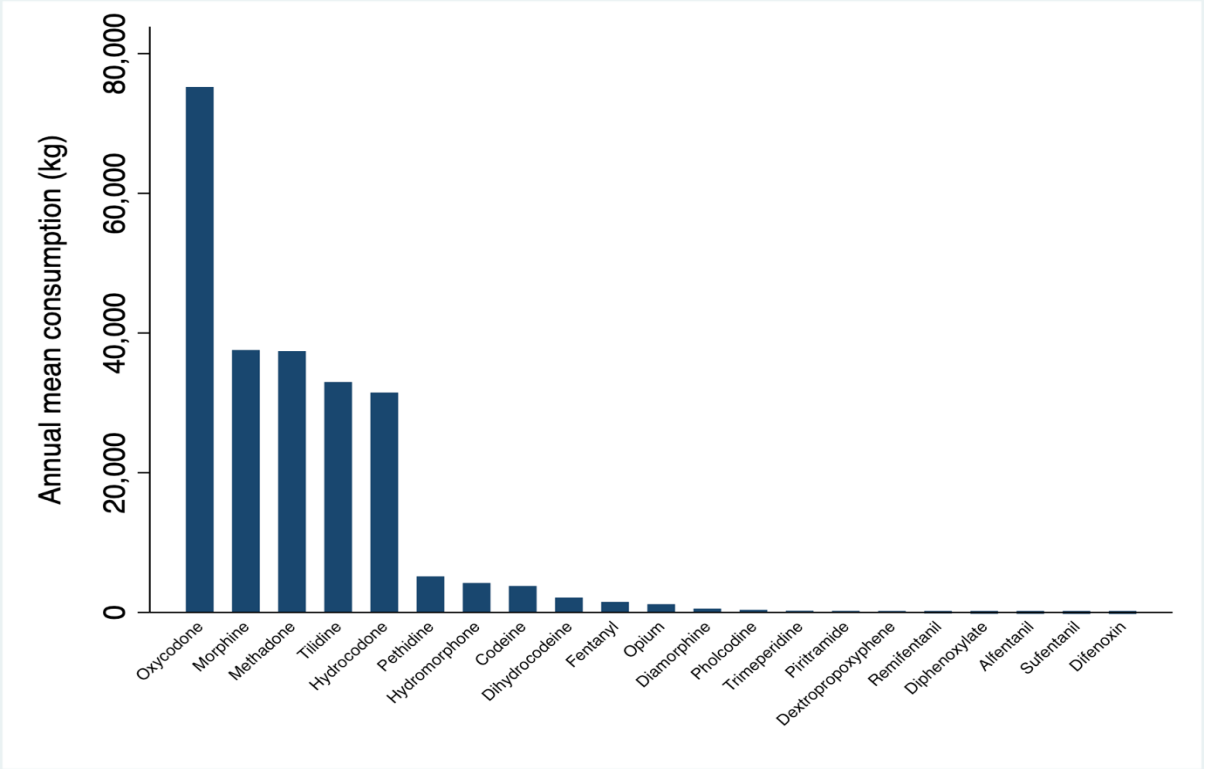


Figure 3.5: Global annual mean consumption in 2015-2017 by type of opioid.

After adjusting for population, opioids grouped by type, were consumed most by the following countries and territories:

- Australia of diphenoxylate (1 mg/person);
- Austria of morphine (644 mg/person);
- Barbados of pethidine (73 mg/person);
- Canada of hydromorphone (109 mg/person);
- Denmark of remifentanil (0.5 mg/person)
- Germany were the largest consumers of tilidine (1139 mg/person) and sufentanil (0.03 mg/person);
- Iceland were the largest consumers of codeine (1090 mg/person);
- Italy of pholcodine (15 mg/person);
- Latvia of trimeperidine (5 mg/person);
- Luxembourg of piritramide (6 mg/person);
- New Zealand of methadone (196 mg/person);
- Norfolk Island of fentanyl (12 mg/person);
- Switzerland of diamorphine (5 mg/person);
- the UK of dihydrocodeine (79 mg/person), dextropropoxyphene (8 mg/person), and alfentanil (0.4 mg/person);
- the USA of oxycodone (506 mg/person) and hydrocodone (291 mg/person), and the only consumers of difenoxin (0.01 mg/person); and
- Wallis & Futuna Islands of opium (133 mg/person).

3.6 Discussion

3.6.1 Summary of findings

An average of 32 mg per person of opioids was consumed globally between 2015 and 2017. However, consumption was disproportionately distributed across the world, as 6.4 billion people (90% of the global population) had little or no consumption of essential opioid medicines. Consumption in Oceania surpassed Europe, and the Americas consumed 41-fold more than Asia and 103-fold more than Africa. Nationally, Germany and Iceland's consumption exceeded the USA and Canada, a stark difference to previous years (1). The UK consumed 3.5% of all opioids, ranking 11th out of 214 countries and territories. Opioid analgesics (morphine, dihydrocodeine and oxycodone) and opioid substitution therapy (methadone) were more commonly consumed in the UK and globally than cough suppressants (e.g. pholcodine), anaesthetics (e.g. alfentanil), and antidiarrheals (e.g. diphenoxylate). Globally, oxycodone accounted for one-third of all opioids consumed, although 72% of this consumption occurred in the USA.

3.6.2 Strengths and limitations

This chapter provides an up-to-date overview of controlled opioid substances consumed globally between 2015 and 2017. The findings are representative of the global population between 2015 and 2017. Compared with previous research, I included all types of available opioids rather than focusing on analgesics or a subset of opioids (150,151,160,161). The limitations of INCB data have been well documented, including the possibility that countries and territories report their data late or inaccurately or that they do not report any consumption statistics (160,162). I found 35 countries and territories that reported consuming no controlled opioids, which may not

represent their actual consumption during this time. Governments are not required to report consumption statistics to the INCB for opioids that are not regulated as internationally controlled substances (e.g. tramadol and buprenorphine). Thus, my analysis represents the consumption of controlled opioids rather than total consumption. It is not clear what proportion of people consumed or received opioids, and therefore I used the 2016 population data for all age groups, which assumes opioids were consumed by individuals of all ages, including children. I categorised each type of opioid using the ATC index; however, opioids such as fentanyl may be used as analgesics and anaesthetics, which I did not consider when categorising opioids. The effects of different types of opioids vary by dose (e.g. 10 mg of morphine will have a greater effect than 10 mg of codeine), which conversion to oral morphine equivalents (OME) accounts for. I measured consumption using weight in mg, adjusted for population, as conversion factors for OME and DDDs are not available for all 225 substances included in my analysis. Thus, my findings may not be easily comparable to most previous studies, which included a subset of opioids and measured consumption in DDDs.

3.6.3 Implications

3.6.3.1 Implications for policy

The WHO deems opioids as essential medicines (167), and recommends all governments provide access. Previous research has found many barriers to accessing opioids, including the absence of training; fear of dependence and diversion; problems with sourcing; regulation complexities of opioids as internationally controlled substances; costs; and cultural and social attitudes towards pain and opioids (1,154,155,168). My findings question whether much has been achieved to overcome these barriers, as disparities in consumption persist across most countries. Using this data alone, it is impossible to determine which countries require access to more or less controlled

opioids. For countries with low consumption, governments can use this data to review their policies to ensure a sufficient volume of opioids are available, which meet the populations need for managing pain and opioid dependence.

The shift to greater consumption in Germany over Canada and the USA may be attributed to mitigation strategies in North America, which are reducing medical access to opioids (e.g. prescription monitoring programs and pill mill laws) (169–171). However, these restrictions have had devastating consequences. Opioid-dependent patients without access to opioid substitution therapy, such as methadone, have moved to illicit sources of opioids, and deaths from unintended overdoses have rapidly increased (172). Lessons from the North American opioid crisis must be considered by all governments when designing strategies and clinical guidelines that improve access to opioids while limiting dependence and harm. In the UK, there are no NICE guidelines for prescribing opioids (NICE published draft guidelines on chronic pain for consultation in August 2020, which warns against using any opioid (104)), and the WHO recently retracted its two main guidelines for opioid use, because of interference by opioid manufacturers (116). Thus, a coordinated effort is needed across all countries to develop evidence-based guidelines that promote the appropriate use of opioids, warn against the significant harms of opioids, and support non-pharmaceutical approaches to managing chronic pain.

3.6.3.2 Implications for patients, the public, and clinical practice

Maintaining access to opioids for acute pain, palliative care, cancer pain, and opioid dependence while limiting the harms from opioids remains a global public health challenge. Despite disparities in opioid consumption globally, advocating for a balanced approach, and increasing

education on opioids is essential. Continuing professional education in pain management and opioid pharmacology is needed to ensure opioids are being prescribed to the 'right' patient, at the 'right' dose and formulation, for the 'right' duration, and an appropriate indication.

There is also a need to educate the public and prescribers globally about the impact of financial and non-financial conflicts of interests. In low- and middle-income countries, there is a growing concern that pharmaceutical companies are infiltrating (173,174), including evidence that opioid manufacturers interfered with two WHO opioid guidelines (116). To prevent a repetition of the North American opioid crisis in other countries, the public and prescribers must be prepared for biased marketing campaigns and pharmaceutical influences.

In December 2019, I presented the results of this chapter to my PPI contributors. They were shocked to learn that most of the world did not have access to opioids, with one commenting, "everyone should know this data". When I speak at Rotary events or other keynote addresses, I use Figure 3.2 to highlight the "other" opioid crisis and the importance of ensuring access to pain medicines. The statistic that 90% of the world's population has limited access to pain relief often results in shock from the audience. In response to seeing this data, a PPI contributor commented, "people in affluent countries expect more." What they may have been alluding to is that in many high-income countries, people expect to receive a prescription when visiting doctors (175,176), particularly if they are in pain. A qualitative study of people dying from cancer in Scotland and Kenya showed the differences are primarily driven by needs and cultural contexts (177). For example, in Scotland, the primary concern of patients with cancer was the emotional pain of facing death. In Kenya, the physical pain and financial burden dominated due to the accessibility

and affordability of analgesia, equipment, food, and care assistance (177). In India, opioid misperceptions, bureaucratic hurdles, and sociocultural/infrastructure challenges were barriers to cancer pain management and opioid availability (178). Thus, there may be many macro- and micro-level factors driving the wide variations in opioid consumption that may be country- and cultural-dependent, which should be investigated and used to tailor interventions that ensure opioids are received by those most in need.

3.6.4 Implications for future research

Understanding the barriers experienced by the 35 countries, states, and territories that did not submit data to the INCB could help remedy incomplete reporting. The INCB could trial technologies to streamline data submissions, which may increase governments willingness to submit data, and improve the timeliness of accessing such data. I emailed a member of the INCB and received the data in an excel spreadsheet. An open and accessible platform, such as the Opioid Atlas, which was last updated in 2016 and has data from 1989 to 2013 (179,180), could be used to share the data as soon as updates are available. Better estimates on the prevalence of pain and opioid dependence would improve our understanding of the need for opioids in each country, which could benchmark and monitor overuse and underuse. While access to electronic health records remains fragmented, the INCB's data is the most useful to compare opioid use globally.

3.7 Conclusion

According to the data collected by the INCB, the consumption of controlled opioids is low in most countries while extremely high in a few countries, including the UK. The INCB and governments should use technologies to improve the accuracy and speed of reporting opioid

consumption to the INCB and sharing such data in the public domain. Governments and international bodies should work together to update and develop policies and clinical guidelines that promote access to opioids for acute and cancer pain, palliative care, and opioid dependence while implementing strategies to improve education, reduce harms, and influences of vested pharmaceutical company interests.

3.8 Chapter summary

- I assessed global, regional, and national consumption of controlled opioids from 2015 to 2017 using data from the INCB.
- I included data from 214 countries and non-metropolitan territories and combined data on 225 opioid substances categorised as anaesthetics, analgesics, antidiarrheals, opioid substitution therapies, and cough suppressants.
- An average of 32 mg/person was consumed globally from 2015 to 2017, but this was not equally distributed worldwide.
- 90% of the world's population consumed only 11% of the world's opioids.
- The UK was ranked 11th and consumed 3.5% of the world's opioids.
- Oxycodone is the most consumed opioid globally.

Chapter 4

"It is a list of the most important, effective drugs that should be available to everyone and all."
Nicola Magrini, 2017 (181)

*This chapter is based on my first-author publication in *BMJ Global Health* titled "*Relation of opioid consumption to the inclusion of opioids in 137 national Essential Medicines Lists*" (17). I presented these findings at the Inaugural Global Essential Medicines (GEM) Meeting in Toronto, Canada (November 20-21, 2019).

4 Analysis of opioids included in national essential medicines lists

4.1 Chapter rationale

In Chapter 3, I found the majority of countries had low or no consumption of opioids. Yet, the WHO deems opioids as essential medicines and recommends listing opioids in national essential medicines lists (EMLs). This led to the questions of what countries with EMLs include opioids, how many opioids do they have, and what types of opioids are included?

4.2 Introduction and Aim

An essential medicine is defined as "those that satisfy the priority health care needs of the population." (182) Since the first Model List of Essential Medicines in 1977, the WHO has included opioids as essential medicines (81). Drugs are selected based on disease prevalence, public health relevance, clinical efficacy, safety and cost-effectiveness (182). The advantages of establishing a central list of drugs include a reduction in the number of pharmaceutical products

to be purchased, stored, analysed, and distributed; improvement in the quality of drug utilisation, management, information, and monitoring; stimulation of local pharmaceutical industries; and to extend primary health care provisions and access to high-priority drug programmes (81). The WHO, therefore, encourages governments to adopt and adapt the WHO's Model List to meet the needs of their populations.

As of June 2017, 137 countries (70% of 195 countries) serving more than 5 billion people have EMLs (183). Countries that implement the WHO's EMLs policies have improved the quality of use of medicines (184). However, studies have highlighted considerable variation in the numbers and types of medicines included in EMLs (185,186). Researchers have evaluated the inclusion of drugs for neuropathic pain in national EMLs (186), which included four opioids (i.e. tramadol, morphine, methadone, and oxycodone) and focused on 117 developing countries. Another study that analysed national EMLs for opioids only included ten low- and middle-income countries and focused on morphine (187). Using the Global Essential Medicines (GEM) database of all national EMLs, the full extent of opioids included in lists can be evaluated.

It is now recognised that adopting a list of essential medicines could be beneficial in high-income countries, reduce suboptimal prescribing and improve the affordability of essential medicines (188,189). However, national lists in high-, middle-, and low-income countries have not been investigated to determine the numbers and types of all opioids included. Therefore, this study aimed to determine what countries include opioids in their EMLs and quantify the numbers and types of opioids included in lists for comparison with the WHO's Model List of Essential Medicines.

4.3 Objectives

1. to determine what countries list opioids in their national EMLs;
2. to quantify the numbers of opioids included in national EMLs in comparison with the WHO's Model List;
3. to assess the types of opioids included in national EMLs in comparison with the WHO's Model List.

4.4 Methods

4.4.1 Study design and data sources

I conducted a cross-sectional study using data from the GEM database (190). Persaud and colleagues developed the GEM database in June 2017 by extracting all medicines listed by all countries with a national EML (n=137, 70% of 195 countries) from the WHO repository, as previously described (185). The medicines included in the database are indexed using the ATC index. I independently searched the ATC index to create a list of opioids. JKA also independently searched the ATC index to develop a list of opioids. I compared our lists of opioids, discussed discrepancies, and created a master list of ATC codes for opioids; see Appendix 4.1. I used the drug names and ATC codes in the master list to search for opioids in the GEM database and created a refined database of opioids. I used the 20th edition of the WHO's Model List of Essential Medicines (167) as it was the current list when this study began, but no changes or additions to opioids were found in the 21st edition of the WHO's Model List of Essential Medicines (191).

4.4.2 Data analysis

I determined the number and type of opioids included in the WHO's Model List and summed the numbers of opioids in each national list to determine the numbers of countries with and without opioids in their EMLs. I determined the median number of opioids in lists, the IQR, and range. I grouped countries into nine quantiles and used a colour spectrum and choropleth map to visualise the data. I calculated the percentage of opioids listed as a total of all included drugs and compared the percentage on each country's lists with the WHO's Model List using a one-sample z-test and a significance level of 0.05.

I determined the types of opioid drugs in the lists and calculated the percentage of lists that reported each type of opioid. I grouped opioids into ATC subgroups (i.e. anaesthetics, analgesics, antidiarrheals, opioid substitution therapies, and cough suppressants) to determine the most commonly listed groups of opioids. For each country, I calculated the percentage of opioids that were the same as in the WHO Model List (where 100% indicates that all five opioids are included in a list) and the number of additional opioids included in lists.

4.4.3 Statistical software and open science practices

I used Stata v16 for all statistical analyses and Python v3 in Jupyter Notebooks with pandas (166) and plotly modules for choropleth maps. I shared my study protocol, materials, data, and statistical code on the OSF and GitHub (Table 4.1).

Table 4.1: Open Science Checklist for Chapter 4 on opioids included in national EMLs

Principles		Links
Open methods	Protocol	https://osf.io/6kfs9/
	Preregistration	No
	Materials	https://osf.io/385hx/
	Statistical code	https://github.com/georgiarichards/opioid_emls_maps
Open data	Data	https://osf.io/385hx/
Open access	Pre-print	No
	Publication	https://gh.bmj.com/content/5/11/e003563
	Blog	No
	Tool	Yes, but created by Dr Persaud: https://global.essentialmeds.org/dashboard/medicines

4.5 Results

4.5.1 Opioids listed in the WHO's Model List of Essential Medicines

The 20th edition of the WHO's Model List of Essential Medicines included five opioids: codeine, fentanyl, loperamide, methadone, and morphine (Table 4.2). The included opioids accounted for 1.4% of all drugs listed in the WHO's Model List.

Table 4.2: Opioids in the 20th edition of the WHO Model List of Essential Medicines

Drug	Dose & route of administration	Additional notes
Anaesthetics, preoperative medicines & medical gases: preoperative medication & sedation for short-term procedures		
morphine	Injection: 10 mg (sulfate or hydrochloride) in 1 mL ampoule	

Medicines for pain and palliative care: opioid analgesics		
codeine	Tablet: 30 mg (phosphate)	
fentanyl	Transdermal patch: 12 µg/hr; 25 µg/hr; 50 µg/hr; 75 µg/hr; 100 µg/hr	cancer pain
methadone	Tablet: 5 mg; 10 mg (as hydrochloride); Oral liquid: 5mg/5mL; 10mg/5mL (as hydrochloride); Concentrate for oral liquid: 5 mg/mL; 10mg/mL (as hydrochloride)	complementary* list; cancer pain
morphine	Granules (slow-release; to mix with water): 20 mg to 200 mg (morphine sulfate); Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule; Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 mL; Tablet (slow release): 10 mg to 200 mg (morphine hydrochloride or morphine sulfate); Tablet (immediate release): 10 mg (morphine sulfate).	Alternatives limited to hydromorphone and oxycodone.
Medicines for pain and palliative care: medicines for other common symptoms in palliative care		
loperamide	Solid oral dosage form: 2 mg	
Medicines for mental and behavioural disorders: medicines for disorders due to psychoactive substances		
methadone	Concentrate for oral liquid: 5 mg/mL; 10 mg/mL (hydrochloride). Oral liquid: 5 mg/5 mL; 10 mg/5 mL (hydrochloride).	complementary* list; buprenorphine is an alternative; should only be used alongside an established support programme

*complementary list: presents essential medicines for priority diseases, for which specialised diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings.

4.5.2 Countries with opioids in their national EMLs

There were 137 countries with national EMLs, of which 99% (n=136) included one or more opioid in their list. Cambodia was the only country that did not include any opioids. Fifty-eight countries did not have a national EML (Appendix 4.2). The median date of EMLs was 2011 (IQR: 2009-2013, range: 2001-2017), see Figure 4.1.

4.5.3 Numbers of opioids in EMLs

There was a median of six opioids (IQR: 5-9; range 0-19) included in EMLs. Slovakia included the most (n=19), and Angola, Bulgaria, and Somalia had the least (n=1) opioids. Figure 4.2 maps the variation in opioids listed, and Appendix 4.3 includes the tabulated data by quantiles.

4.5.4 Types of opioids in EMLs

There were 33 unique opioids included in the lists (Table 4.3). Analgesics were the most common form of opioids listed (99% of lists), followed by antidiarrheals (64%), opioid substitution therapies (52%), anaesthetics (26%), and cough suppressants (25%). Morphine (95%), fentanyl (83%), codeine (69%), pethidine (65%), and tramadol (62%) were the most common types of opioids included, which does not directly align with the five opioids in the WHO's Model List (i.e. codeine, fentanyl, loperamide, methadone, and morphine).

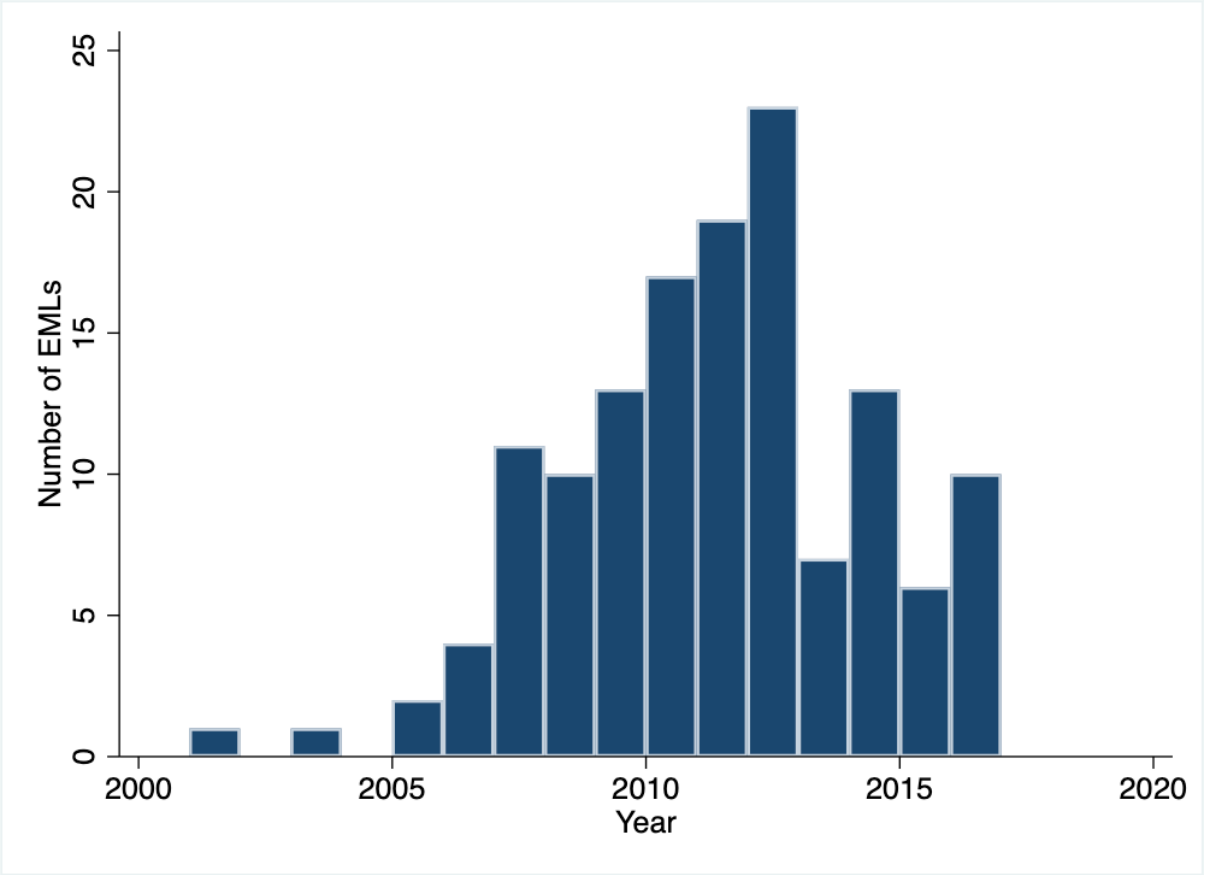


Figure 4.1: Publication year of the 137 essential medicines lists (EMLs)

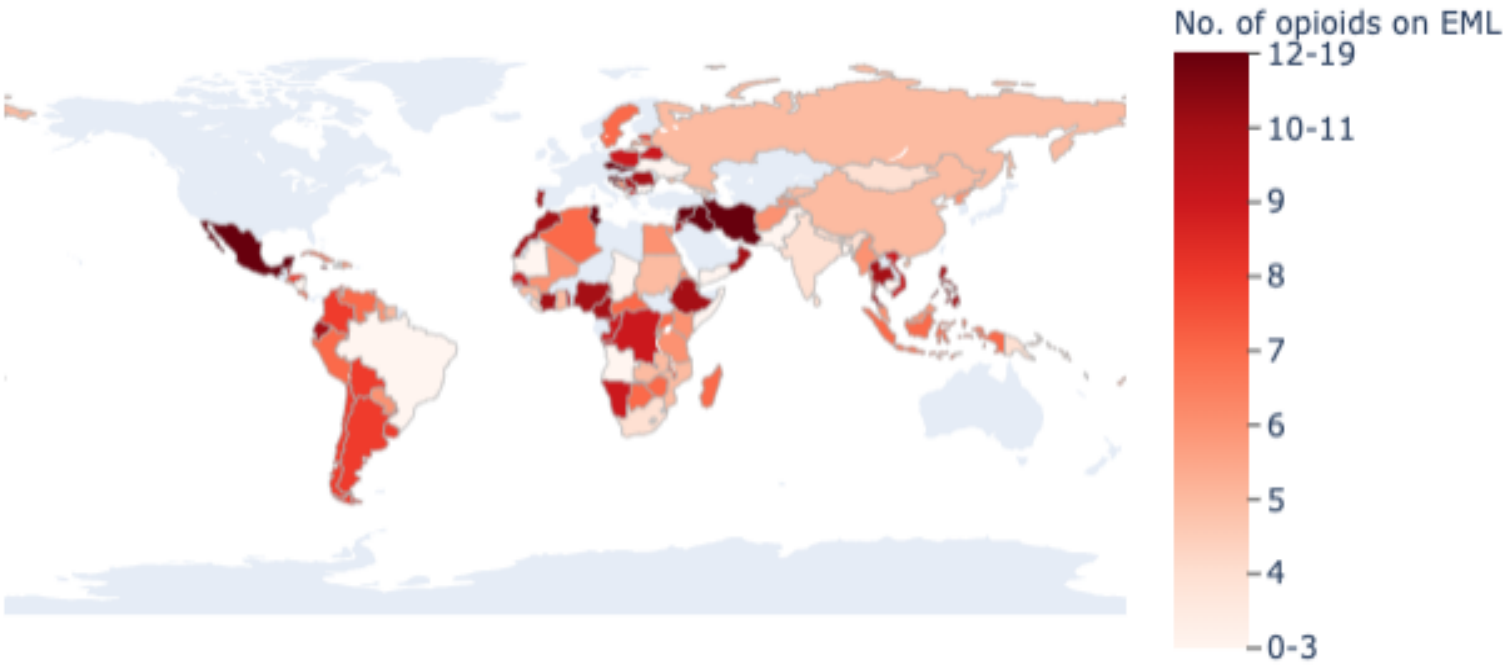


Figure 4.2: Numbers of opioids included in national essential medicines lists (EMLs) grouped by nine quantiles. There were 137 countries with EMLs, countries in light grey (n=58) did not have an EML.

Table 4.3: Types of opioids (n=33) included in national essential medicines lists by Anatomical Therapeutic Classification (ATC) subgroup in descending order

Opioids	No. of countries listed, n=137 (%)
Analgesics	**136 (99%)**
Morphine	130 (94.9)
Fentanyl	113 (82.5)
Codeine	94 (68.6)
Pethidine	89 (65.0)
Tramadol	85 (62.0)
Oxycodone	22 (16.1)
Dihydrocodeine	18 (13.1)
Pentazocine	16 (11.7)
Dextropropoxyphene	11 (8.0)
Nalbuphine	11 (8.0)
Trimeperidine	8 (5.8)
Opium	7 (5.1)
Papaveretum	3 (2.2)
Tapentadol	3 (2.2)
Piritramide	2 (1.5)
Butorphanol	2 (1.5)
Pargeverine	2 (1.5)
Tilidine	2 (1.5)
Hydrocodone	2 (1.5)
Antidiarrheals	**87 (64%)**
Loperamide	83 (60.6)
Diphenoxylate	15 (11.0)
Eluxadoline	1 (0.7)
Difenoxin	1 (0.7)
Opioid substitution therapies	**71 (52%)**
Methadone	56 (40.9)
Buprenorphine	34 (24.8)
Diamorphine	1 (0.7)
Anaesthetics	**36 (26%)**

Remifentanil	22 (16.1)
Sufentanil	19 (13.9)
Alfentanil	16 (11.7)
Cough suppressants	**34 (25%)**
Dextromethorphan	40 (29.2)
Hydromorphone	14 (10.2)
Pholcodine	12 (8.8)
Noscapine	5 (3.7)

4.5.5 Comparison of national EMLs with the WHO's Model List

Countries included significantly ($z = 6.33$, $P<0.05$) more opioids than the WHO's Model List as a percentage of all drugs listed (mean: 1.9% of all drugs, standard deviation: 1.0%). Ninety-five per cent of countries included morphine, 83% listed fentanyl, 69% codeine, 61% loperamide, and 41% methadone (Figure 4.3). Most countries (98.5%, n=135) included at least one opioid recommended by the WHO, except for Cambodia, which listed no opioids, and Somalia, which only listed pethidine. Eighteen percent of countries (25 of 137) included all five opioids from the WHO's Model List. There were also many opioids included in national EMLs that were not included in the WHO's Model List (Figure 4.4).

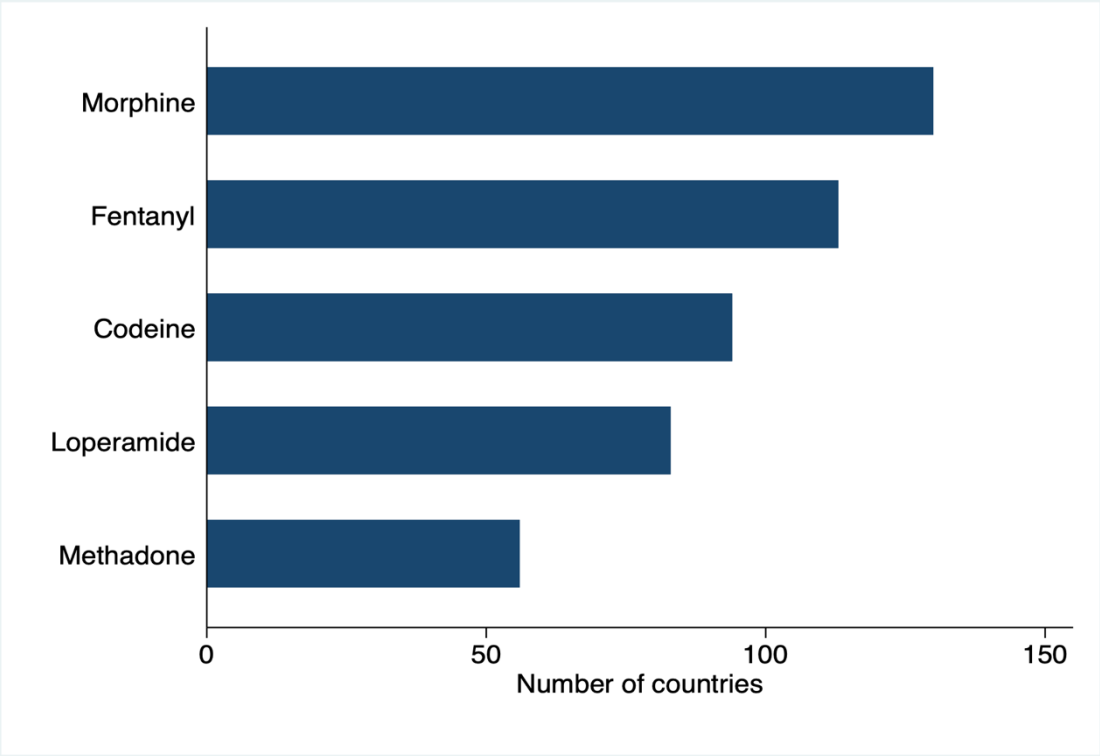


Figure 4.3: Five opioids in the WHO's Model List of Essential Medicines and the number of countries that included each opioid in their national essential medicines lists

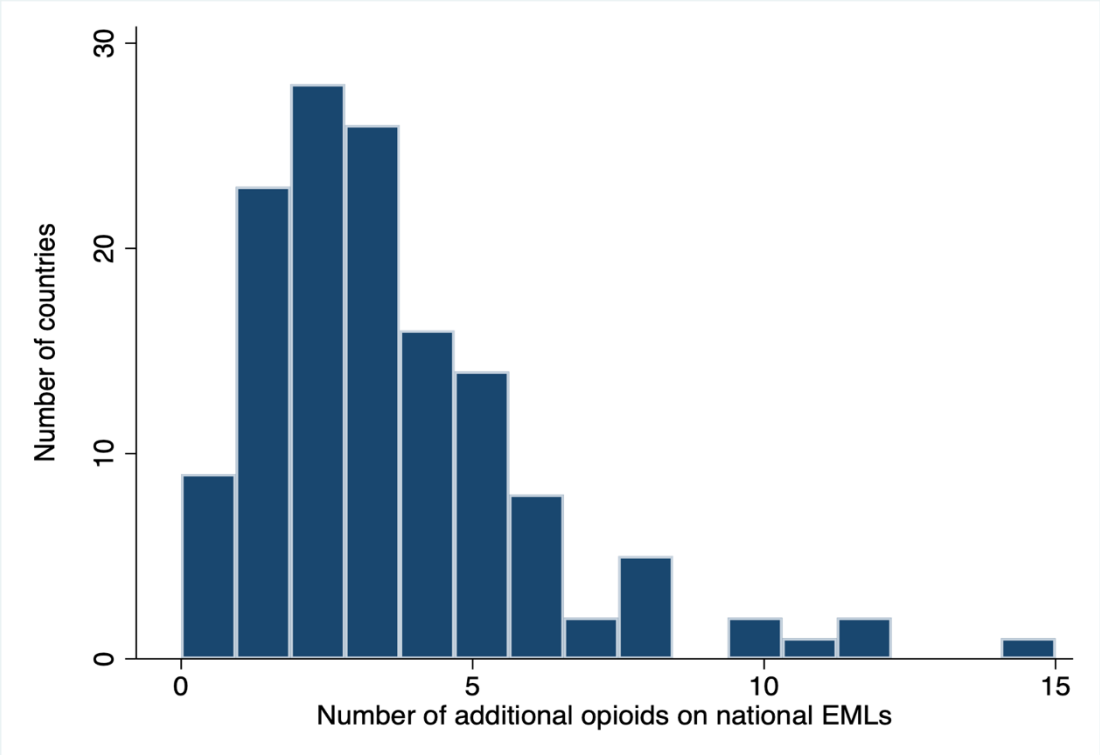


Figure 4.4: Number of additional opioids included in national essential medicines lists (EMLs) compared with the opioids included in WHO's Model List

4.6 Discussion

4.6.1 Summary of findings

All countries with national EMLs included one or more opioid, except Cambodia. The WHO recommends including five opioids: morphine for anaesthesia; codeine, fentanyl, methadone, and morphine for pain and palliative care; loperamide for diarrheal symptoms; and methadone for opioid use disorders. Countries included significantly more opioids in national EMLs than the five opioids in the WHO's Model List of Essential Medicines. There were variations in the numbers and types of opioids included in EMLs. Analgesics (i.e. morphine, fentanyl, and codeine) were the most commonly included opioids in EMLs.

4.6.2 Strengths and limitations

To the best of my knowledge, this is the first analysis of all opioids included in 137 national EMLs. Drugs included in lists indicate nominal drug availability. Thus, it is not possible to elucidate the clinical use, consumption or accessibility of opioids in lists. I classified opioids using the ATC index as I did in Chapter 3, which allocates codes for drugs based on their indications. However, some opioids, such as methadone, have multiple indications, which I did not account for when categorising types of opioids. I also did not include opioid antagonists, which may be essential for countries experiencing high rates of opioid dependence. Persaud and colleagues extracted data in the GEM database from the WHO's web portal in June 2017, and some countries may have updated their list since. However, most EMLs were already several years out of date and had not been updated for some time.

4.6.3 Implications

4.6.3.1 Implications for policy

After developing the first Model List of Essential Medicines, the WHO encouraged countries to select medicines that meet their populations' health priorities (81). Therefore, variations between countries were expected. However, including 19 different opioids, all with complex pharmacology, as found in Slovakia's EML, or not including any opioids found in Cambodia's EML, may not adequately reflect the different health needs of those populations. Notably, Cambodia has experienced recent outbreaks of HIV due to the unsafe use of recreational opioids (192). It is a major transit route for exporting heroin (193), which may impact policies, access to pharmaceutical opioids, and health services in these regions. Differences from the WHO Model List may be driven by other factors, such as cost implications imposed by EMLs, patchy implementation of lists, pharmaceutical interests that push more drugs into EMLs, and restraints in healthcare systems on where and how opioids are prescribed, and by whom (194,195).

The WHO encourages countries with EMLs to continually revisit their drug selections by considering changing public health priorities, epidemiological conditions, progress in pharmacological and pharmacovigilance systems (81). I found many lists that were several years out of date. Thus, revision of current EMLs to reflect such changes would be timely. A fundamental principle for establishing an EML is that drugs are included if they have proven efficacy and safety with adequate scientific data from controlled studies (81). Therefore, governments could provide explanations for medicines they have decided to add, and the WHO could give feedback to countries updating their lists to highlight specific opioids for inclusion or removal based on systematic evidence synthesis.

In 2004, the WHO stated that the lack of access to essential medicines remains one of the most serious global public health problems (196). As countries move towards universal health coverage, as part of achieving sustainable development goals, the importance of essential medicines lists will perhaps increase (197). Adopting a refined list of medicines is also being recognised as a tool to reduce suboptimal prescribing and improve the affordability of essential medicines in high-income countries (184,188,198). Thus, the 55 countries without EMLs could investigate the feasibility of implementing a list to help prescribers identify effective treatments with minimal harms to prevent overuse and reduce healthcare expenditure.

4.6.3.2 Implications for patients, the public, and clinical practice

Access to medicines is widely recognised as a human right (199), although many people may be prevented from accessing essential opioid medicines because they are not included in their country's EML. Suppose lists were up to date, and governments simply shared data, prescribers and the public could use tools such as the Global Essential Medicines dashboard (https://global.essentialmeds.org/dashboard/medicines) to determine nominal drug availability in real-time. The pharmacology of opioids are complex; different types of opioids produce different effects, which is often not taught in medical schools (200,201). In the UK, the teaching of clinical pharmacology and therapeutics varies, and the performance of prescribing is infrequently assessed (202,203). In Europe, most medical schools reported that their students were not well prepared for prescribing (204). National EMLs, or the WHO's Model List for countries without EMLs, could be used in medical schools' curriculum to ensure students have a baseline knowledge of the pharmacology of essential medicines.

4.6.4 Implications for future research

Future research should focus on understanding the function of EMLs in enabling access to essential medicines like opioids in practice. Others can adopt my methods to investigate the numbers and types of opioid antagonists (e.g. naloxone or naltrexone) and non-opioid alternatives (e.g. paracetamol, ibuprofen, and ketamine) in EMLs, as well as other classes of drugs. The processes for creating and updating lists should be explored. The significant differences from the WHO's Model List and the differences between countries should be further studied. Whether specific opioids should be added or removed from particular EMLs based on systematic evidence synthesis should be prioritised. These investigations may help identify opportunities to improve EMLs and promote the appropriate use of opioids.

4.7 Conclusion

There were variations in the numbers and types of opioids included in national EMLs. Governments with national EMLs should consider revising the opioids included in their EMLs to reflect their changing population health needs and the best available evidence on opioids. Countries without lists could consider developing a refined list of medicines that ensures universal access to essential drugs like opioids while promoting appropriate use and preventing overuse and harms.

4.8 Chapter summary

- 136 of the 137 countries with an EML included one or more opioid in their list.
- There were 55 countries without EMLs.
- The WHO included five opioids in their 20th Model List of Essential Medicines: codeine, fentanyl, loperamide, methadone, and morphine.
- Countries included 0-19 opioids (median 6; IQR: 5-9) in their lists, significantly more than in the WHO's Model List.
- There were 33 different types of opioids included in the lists.
- Morphine (95%), fentanyl (83%), and codeine (69%) were the most commonly included opioids in lists.

Chapter 5

"If the names are unknown, knowledge of the things also perishes."
– Carolus Linnaeus (205)*, 1751*

*This chapter is based on my first-author manuscript published in the *British Journal of Clinical Pharmacology* (18), titled "*The Oxford Catalogue of Opioids: a systematic synthesis of opioid drug names and their pharmacology*".

5 Systematic development of the Oxford Catalogue of Opioids

5.1 Chapter rationale

In Chapter 4, I identified 33 different types of opioids included in 137 national Essential Medicines Lists (EMLs). However, the UK does not have an EML. Instead, it has the British National Formulary (BNF), which lists drugs approved in the UK with information about using and prescribing such drugs. Yet, it is not clear how many opioids have been developed and how the 33 opioids in EMLs compare with those in the BNF. As opioids are widely prescribed, cause harm, and have varying pharmacology, an online catalogue of opioids would centralise this information for researchers, prescribers, and the public.

5.2 Introduction and Aim

Thus far, I have illustrated the growth of opioid prescribing in England (3) (i.e. Chapter 2, section 2.5) and the variation in consumption of opioids across the globe (Chapter 3). This growing demand for analgesia, coupled with the US opioid crisis, and the need to treat and manage opioid dependence and overdose have incentivised new and potentially less addictive

formulations of opioids and alternatives (206–208). Some estimate that thousands of opioids have been synthesised for their various analgesic, antidiarrheal, antitussive and dependence-producing properties (209). However, the number of opioids is unknown, and there is no central repository that outlines their names, types, and pharmacological effects.

Several organisations and authorities have developed systems to name, classify, and index drugs (Table 5.1). City pharmacopoeias were the first to standardise and publish drug names, with information on available formulations, including opium. These were later unified into national pharmacopoeias, such as the British Pharmacopoeia, followed by national formularies, such as the BNF, and International pharmacopoeias. Drug nomenclature systems followed, including chemical names (e.g. the International Union of Pure and Applied Chemistry (IUPAC) names); non-proprietary or generic names (e.g. International Nonproprietary Names (INNs)); and manufacturers' proprietary or brand names. Drug indexes and classification systems followed, including the World Health Organization (WHO) Anatomical Therapeutic Classification (ATC) index and the International Union of Basic and Clinical Pharmacology/British Pharmacology Society (IUPHAR/BPS) Guide to Pharmacology (Table 5.1).

Table 5.1: Timeline of selected drug nomenclature, classification systems, and indexes

Year	Event
1618	London Pharmacopoeia first published
1820	United States Pharmacopoeia first published
1864	British Pharmacopoeia first published (merging the London, Edinburgh, and Dublin Pharmacopoeias)
1883	Martindale's Extra Pharmacopoeia first published
1886	Japanese Pharmacopoeia first published
1889	The Merck Index first published
1907	British Pharmaceutical Codex first published
1919	IUPAC established
1949	The BNF first published
1951	The International Pharmacopoeia first published
1953	The first list of INNs for pharmaceutical substances published and becomes operational
	The Pharmacopoeia of the People's Republic of China first published
	The BAN system created
1961	USAN Council began
1969	European Pharmacopoeia first published
1977	WHO publishes the first Model List of Essential Medicines
1981	The ATC/DDD system recommended by WHO as the international standard for drug utilisation studies
1996	Dictionary of Pharmacological Agents first published
1999	Concise Dictionary of Pharmacological Agents first published
2003	IUPHAR & BPS develop the Guide to Pharmacology

ATC: Anatomical Therapeutic Classification; BAN: British Approved Name; BNF: British National Formulary; BPS: British Pharmacology Society; DDD: defined daily dose; INN: International Nonproprietary Names; IUPAC: International Union of Pure and Applied Chemistry; IUPHAR: International Union of Basic and Clinical Pharmacology; USAN: United States Adopted Name; WHO: World Health Organization.

Onomastics is the study of names, and in this chapter, I will use it in combination with evidence synthesis to investigate the drug nomenclature of opioids. Nomenclature, derived from Latin *nōmen* (name) and *calāre* (to call) (210), uses a set of rules and conventions to form a list of names. Nomenclature is a branch of taxonomy concerned with applying scientific names to taxa,

based on a classification scheme in accordance with agreed international rules and conventions. The best-known taxonomy, created by the Swedish botanist, zoologist and physician, Carolus Linnaeus (211), is binomial nomenclature, which revolutionised how species were named and communicated by scientists across the world. The formation of a taxonomy involves two parts; classification and nomenclature. The classification process determines what group or groups are included, while nomenclature defines such groups' names. My classification group is "opioids". But a single drug can have multiple names, including:

1. a chemical name (e.g., IUPAC);
2. a non-proprietary or generic name (e.g. INN); and
3. a proprietary or brand name.

Most drugs are named by the combination of their primary target (e.g. opioid receptors) and either their observed effect (e.g. agonist) or coeffect with another ligand (e.g. antagonist) (212). Chemical names are based on the molecular structure of a drug; they are typically very long and complex and can vary. The IUPAC is an internationally recognised authority that develops recommendations to establish unambiguous, uniform, and consistent nomenclature and terminology. However, chemical names are not often used in clinical practice. Nonproprietary names are applied for by pharmaceutical companies during regulatory approval, either via country-specific agencies (i.e. a BAN through the MHRA) or through the WHO (INNs). This type of naming is most useful, as the stems (prefixes, suffixes and infixes) used to define the name can help determine the class and show chemical relationships. For example, drugs whose names end in -*vastatin* are hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins; however, this naming system has its imperfections (213). The names of

combination products are generally indicated by joining the non-proprietary names using hyphens or slashes; unique to the UK or in countries that use BANs, a combination product with two or more drugs in a single dose form may have a *co-* prefix. For example, co-codamol is a codeine-paracetamol combination product. Pharmaceutical companies create proprietary or brand names for drugs that make it through to regulatory approval and are the company's exclusive property. For example, OxyContin is Purdue Pharma's proprietary name for oxycodone. Thus, a single drug will have multiple proprietary names depending on the country or company marketing or manufacturing the drug.

The ubiquitous use and increased development of novel opioids may not be reflected in the confidence of prescribers or the knowledge of the public. Studies in primary care have shown that providers often report inadequate training of opioid prescribing for chronic non-cancer pain (214–216). Others have found that poor public knowledge of opioids is a barrier to observational research and may drive over- and under-reporting of opioid use and misuse (217,218). How a drug is named and classified determines how it is used; thus, misnaming a drug or a lack of knowledge of such names can cause confusion (212). A catalogue of opioid drug names and their pharmacology could help bridge the public's knowledge gap, aid prescribers when choosing an opioid, and centralise information for those developing the next generation of opioids and their alternatives. The aim of this chapter was to systematically search relevant databases to create a robust list of opioid drug names.

5.3 Objectives

1. to compare the 33 opioids listed in national EMLs with the opioids listed in the BNF;
2. to compare the opioids included in the BNF with those listed by the WHO Model List of Essential Medicines; and
3. to quantify the number of opioids developed and synthesis their nomenclature.

5.4 Methods

5.4.1 Opioids in national EMLs compared with the BNF

I used the list of 33 opioids in EMLs to search the OpenPrescribing website (https://openprescribing.net/chemical/) and the BNF website (https://bnf.nice.org.uk/) to note which opioids were and were not available. I also hand-searched sections in the BNF (e.g. section 4.7.2 for opioid analgesics). I did not include opioid antagonists in this analysis as these opioids were excluded from the EMLs analysis in Chapter 4. I compared the lists of opioids for similarities and differences and displayed the findings in a table.

5.4.2 Opioids in the BNF compared with the WHO Model List

Using the 20th edition of the WHO's Model List of Essential Medicines as in Chapter 4 section 4.4.2, I compared the five listed opioids with the opioids included in the BNF as identified following the search conducted in section 5.4.1. I calculated the percentage of opioids that were the same as the WHO Model List (where 100% indicates that all five opioids are included in the BNF) and the number of additional opioids included in the BNF.

5.4.3 List of opioid drug names

This research involves three phases, as displayed in Figure 5.1: Development of the list of opioid drugs, cataloguing the drugs based on their pharmacology, and developing an online resource. In this chapter, I focus on phase one.

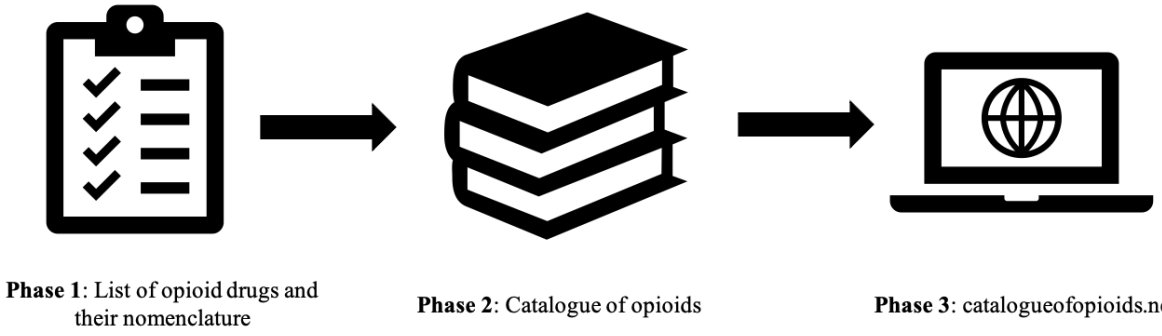


Figure 5.1: Three phases of research to develop the Oxford Catalogue of Opioids. This chapter outlines phase one, which creates the list of opioid drugs and synthesises their nomenclature.

5.4.4 Study design and data sources

I designed and conducted a systematic search of openly available pharmacology data sources across two time periods. I independently conducted the first search of four databases in January 2019, which was duplicated independently by an experienced clinical pharmacologist (JKA). The four databases included:

1. the ATC classification system (https://www.whocc.no/atc_ddd_index/);
2. the INCB Index of Names of Narcotic Drugs, using the most up-to-date (2017) report at the time of my search (pages 15-17 from https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2017/Narcotic_drugs_technical_publication_2017.pdf);

3. Martindale's Extra Pharmacopoeia (https://www.medicinescomplete.com/#/browse/martindale); and
4. the Merck Index Online (https://www.rsc.org/Merck-Index/).

I combined the lists of opioids generated from the two independent searches and removed duplicates. I compared the lists for discrepancies, and a single list of opioid drugs was created through consensus. The second search was conducted in November 2020 by an Oxford University medical student (KS) whom I supervised for their Final Honours Scheme (FHS) research in Michaelmas Term (October-December) 2020. The second search included seven data sources:

1. the ATC classification system (https://www.whocc.no/atc_ddd_index/);
2. the BNF (https://openprescribing.net/bnf/);
3. the IUPHAR/BPS Guide to Pharmacology (https://www.guidetopharmacology.org/);
4. the INCB Index of Names of Narcotic Drugs, using the updated (2019) version (https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2019/Narcotic_Drugs_Technical_Publication_2019_web.pdf);
5. the WHO MedNet service for INNs (https://mednet-communities.net/inn/login);
6. Martindale's Extra Pharmacopoeia (https://www.medicinescomplete.com/#/browse/martindale); and
7. the Merck Index Online (https://www.rsc.org/Merck-Index/).

Since then, opioids were added ad hoc, as discovered or identified in the published literature.

5.4.5 Search terms and eligibility criteria

For both searches, I used "opioid", "opiate", and "narcotic" search terms, as well as stems of common opioids to identify derivatives such as "-fentanyl" and "-orphine". I included opioids if

they were defined as a medicament and targeted or had an effect or coeffect at one or more opioid receptors, including mu (MOP), delta (DOP), or kappa (KOP) receptors, or the nociceptin receptor (NOP). I excluded medicaments that did not have an IUPAC name (i.e. opium). Endogenous opioids or opioids that were metabolites, peptides, intermediates, analogues, or raw opioid-related materials were also excluded from the list unless they were synthesised as a medicament. During the second search, I consulted an experienced clinical pharmacologist (JKA) when the eligibility criteria for inclusion or exclusion were unclear.

5.4.6 Extraction and analysis

For each drug name, the data source in which it was identified, the chemical name (IUPAC from PubChem (219)), and the non-proprietary names (BANs, USANs, and INNs from the WHO's MedNet service (220)) were extracted into a Google Sheet and ordered alphabetically. For opioids listed in the BNF, I also extracted proprietary name examples for the UK by searching the IUPHAR/BPS Guide to Pharmacology, UpToDate (https://www.uptodate.com/home), and the NHS Medicines A to Z website (https://www.nhs.uk/medicines/). I used non-proprietary names (i.e. INNs) as index names for the catalogue because of their use in prescribing. If no INN was available, I selected the BAN or the name reported in the BNF; otherwise, I used the next most familiar name. For example, diacetylmorphine (heroin) does not have an INN but is listed as diamorphine in the BNF, so I selected diamorphine as the index name. I extracted the stem of each opioid (suffix or prefix) from the WHO's Stem Book 2018 (221), which was also validated by experienced clinical pharmacology (JKA) following extraction. I used the stem to group drugs and calculated the percentage occurrence for each stem group. I created a flow diagram, bar graphs, and calculated medians and IQRs where appropriate.

5.4.7 Opioid vignettes and ongoing research

Phase two (as per Figure 5.1) is not described in this chapter as it was conducted by an FHS student (KS), and phase three will require funding and further support. In phase two, pharmacological data, including the molecular formula; molecular weight (g/mol); receptor targets (i.e. MOP, DOP, KOP, or NOP); actions at opioid receptors (i.e. agonist, partial agonist, and antagonist, or mixed); and class based on their origin of discovery or development (i.e. alkaloids, semisynthetic, or synthetic) were extracted for each opioid to catalogue the drugs based on their pharmacological properties, rather than solely nomenclature, as discussed in this chapter. For phase three, I used WIX.com to create a resource in the form of a website to share the database of drugs and centralise and dissemination information that may assist researchers, prescribers and the public. Future research will use the data extracted in phase two to catalogue the opioids by their pharmacology properties and publish drug vignettes on opioids, starting with the opioids included in the BNF. The opioid vignettes will have the following structure:

- name of the drug with details relating to its discovery and development;
- structure of the drug;
- mechanism of action;
- indications for licensed formulations and regulatory status (MHRA and FDA);
- pharmacokinetic properties;
- pharmacodynamic properties;
- known contraindications and warnings in licensed use;
- known adverse effects and adverse reactions;
- drug-drug interactions; and
- links to biomedical and clinical trials databases.

5.4.8 Statistical software and open science practices

I preregistered the study protocol on the OSF (49) and shared all data, code, and figures openly at GitHub and the OSF project page (Table 5.2). I used Python v3 in Jupyter Notebooks with pandas (166), seaborn (222), and matplotlib (223) modules for analysis and to create figures.

Table 5.2: Open Science Checklist for Chapter 5 on the Oxford Catalogue of Opioids

Principles		Links
Open methods	Protocol	https://osf.io/4fu7b
	Preregistration	Yes: https://osf.io/4fu7b
	Materials	https://osf.io/2ph6c/
	Statistical code	https://github.com/georgiarichards/CatalogueofOpioids
Open data	Data	https://osf.io/edks3/
Open access	Pre-print	No
	Publication	https://doi.org/10.1111/bcp.14786
	Blog	https://www.catalogueofopioids.net/post/welcome-to-the-oxford-catalogue-of-opioids
	Tool	https://www.catalogueofopioids.net/the-catalogue

5.5 Results

5.5.1 Opioids in national EMLs compared with the BNF

Of the 33 opioids listed in EMLs, 72% (n=24) were also included in the BNF (Table 5.3). The BNF included two additional opioids, dipipanone and meptazinol, while EMLs included nine additional opioids, butorphanol, difenoxin, hydrocodone, noscapine, pargeverine, piritramide, sufentanil, tilidine, and trimeperidine.

Table 5.3: Comparison of opioids in the British National Formulary with the 33 opioids listed in 137 national Essential Medicines Lists.

	Similarities	Differences	
Opioids*	**In both**	**BNF only**	**EMLs only**
alfentanil	●		
buprenorphine	●		
butorphanol			●
codeine	●		
dextromethorphan	●		
dextropropoxyphene	●		
diamorphine	●		
difenoxin			●
dihydrocodeine	●		
diphenoxylate	●		
dipipanone		●	
eluxadoline	●		
fentanyl	●		
hydrocodone			●
hydromorphone	●		
loperamide	●		
meptazinol		●	
methadone	●		
morphine	●		
nalbuphine	●		
noscapine			●
opium	●		
oxycodone	●		
papaveretum	●		
pargeverine			●
pentazocine	●		
pethidine	●		
pholcodine	●		

	piritramide			●
	remifentanil	●		
	sufentanil			●
	tapentadol	●		
	tilidine			●
	tramadol	●		
	trimeperidine			●
Totals	**35**	**24**	**2**	**9**

BNF: British National Formulary; EML: Essential Medicines Lists; *this table does not include opioid antagonists included in the BNF as the EML analysis in Chapter 4 did not include opioid antagonists. Opioids in **bold** were included in the WHO's Model List of Essential Medicines.

5.5.2 Opioids in the BNF compared with the WHO Model List of Essential Medicines

There were 32 opioids listed in the BNF, including six opioid receptor antagonists (i.e. methylnaltrexone, naldemedine, nalmefene, naloxegol, naloxone, and naltrexone). All five opioids (100%) included in the WHO Model List were listed in the BNF.

5.5.3 List of opioid drug names

I identified 158 opioids after the first search of four sources in 2019 (Figure 5.2). The updated search using seven sources, and the published literature in 2020 identified 233 opioids (Figure 5.2). Of the 75 drugs added to the list, 56% (n=42) were identified from the literature, 27% (n=20) from the WHO MedNet database of INNs, 11% (n=8) from the Guide to Pharmacology, 8% (n=6) from the updated (2019) INCB technical report, and 3% (n=2) from Wikipedia. For all 233 opioids, the sources contained a median of 68 opioids (IQR: 61–115), and I identified each drug in a median of two data sources (IQR: 1 to 4 sources). The WHO MedNet database of INNs contained the most (73%), followed by the INCB report (52%), the Merck Index (47%), Martindale (29%), the Guide to Pharmacology (28%), the ATC index (24%), and the BNF (13%) (Figure 5.3).

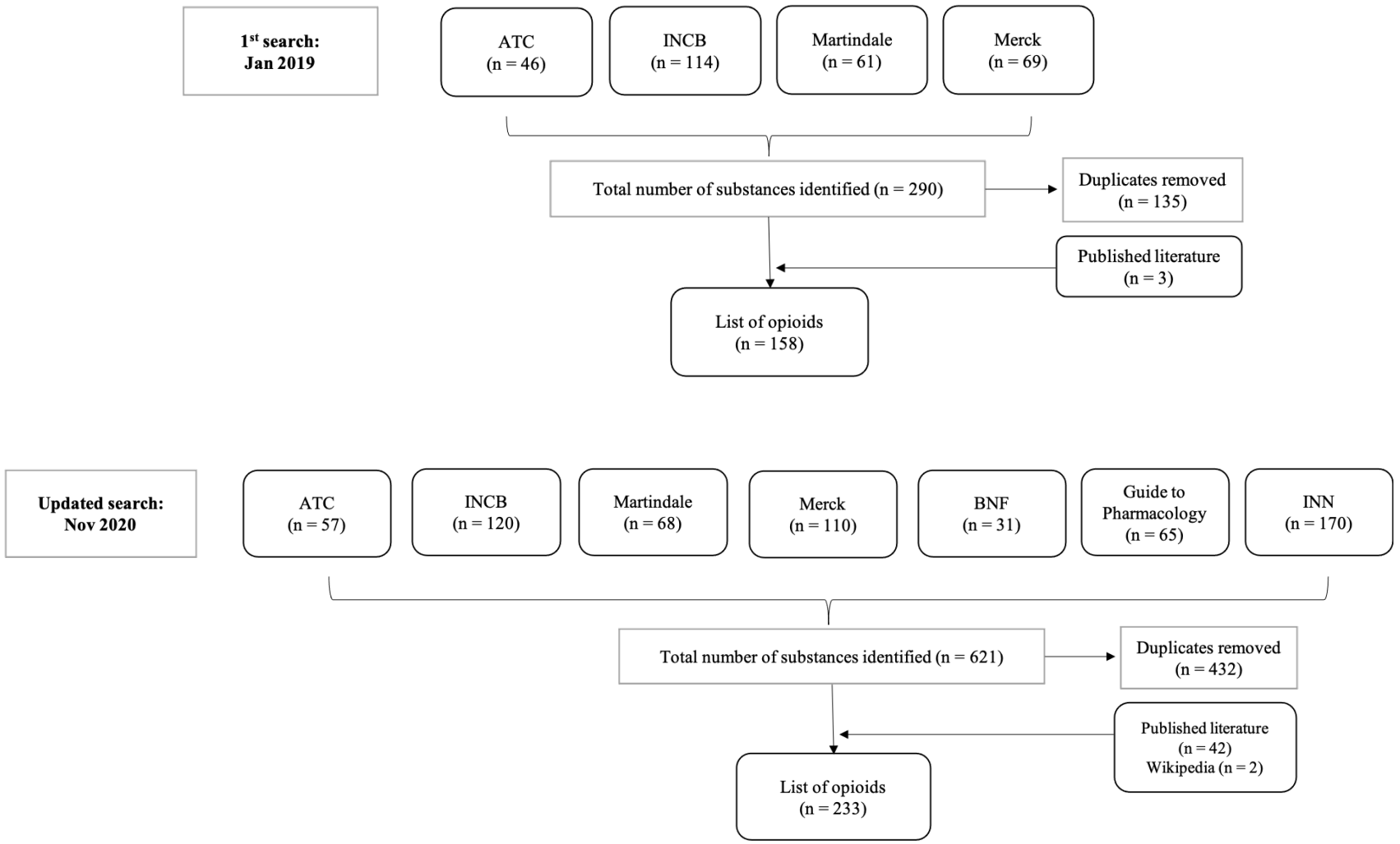


Figure 5.2: Flow-diagrams of the searches conducted to identify opioid drugs

There were ten unique drug stems, *"-fentanil"* (26%), "*-orphine*" (18%), "*-adol*" (14%), and "*-eridine*" (12%) being the most common (Figure 5.4). Fifty drugs (21.5%) could not be assigned a WHO stem (Table 5.4). The complete list of 233 drugs in the Oxford Catalogue of Opioids, and their chemical names, is presented in Appendix 5.1. For opioids in the BNF (Table 5.5), 90% (n=28) had INNs, 77% (n=24) had BANs, 68% (n=21) had USANs, and two drugs (i.e. diamorphine and papaveretum) did not have proprietary names.

5.5.4 Opioid vignettes and ongoing research

The online resource (https://www.catalogueofopioids.net/) and OSF project page (https://osf.io/2ph6c/) is updated in real-time and will illustrate the opioid vignettes, blogs, and the status of current research.

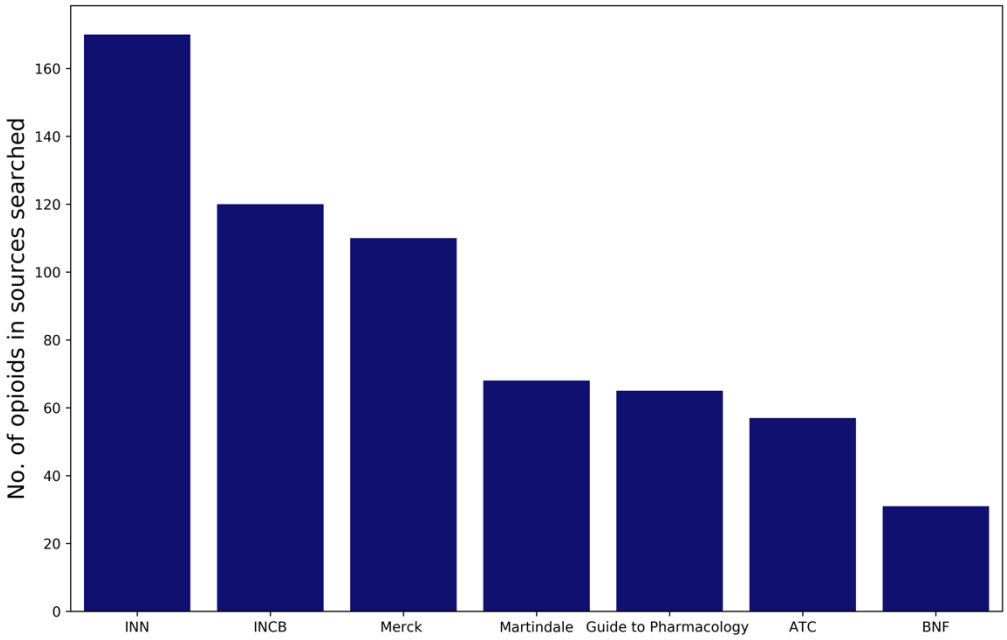


Figure 5.3: The number of opioid drugs identified in the seven sources searched to create phase one of the Oxford Catalogue of Opioids.

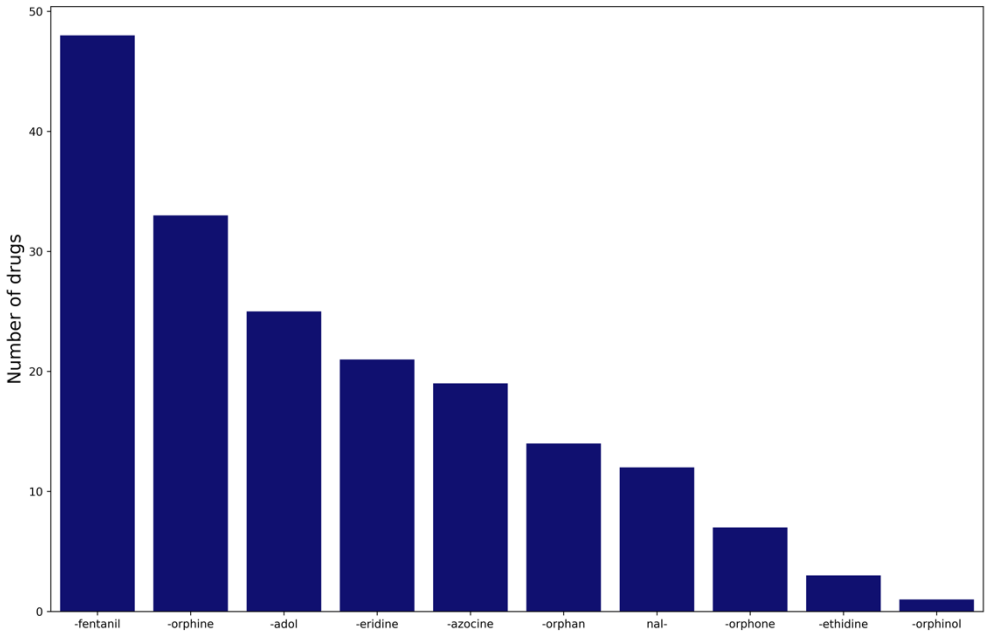


Figure 5.4: Ten stems of the drugs in the Oxford Catalogue of Opioids according to the WHO's Stem Book 2018

Table 5.4: Stems of drugs in the Oxford Catalogue of Opioids in alphabetical order

WHO stem	Description	Frequency (%)	Examples
-adol	analgesics	25 (13.7)	acetylmethadol
-azocine	narcotic antagonists/agonists related to 6,7-benzomorphan	19 (10.4)	anazocine
-eridine -ethidine	pethidine derivatives	21 (11.5) 3 (1.6)	carperidine; benzethidine
-fentanil	opioid receptor agonists, analgesics, fentanyl derivatives	48 (26.2)	alfentanil
nal-	opioid receptor antagonists/agonists related to normorphine	12 (6.6)	methylnaltrexone
-orphan -orphine -orphinol -orphone	opioid receptor antagonists/agonists, morphinan derivatives	14 (7.7) 33 (18.0) 1 (0.5) 7 (3.8)	butorphanol; acetorphine; hydromorphinol; oxymorphone
no stems	–	50 (21.5)	alphaprodine; clonitazene

Table 5.5: Opioids listed in the BNF from the Oxford Catalogue of Opioids for opioids. All 233 opioids are listed in Appendix 5.1.

Nonproprietary names			Chemical name	Examples of UK proprietary names
INN/index name	**BAN**	**USAN**	**IUPAC**	
alfentanil	alfentanil	alfentanil hydrochloride	N-[1-[2-(4-ethyl-5-oxotetrazol-1-yl)ethyl]-4-(methoxymethyl) piperidin-4-yl]-N-phenylpropanamide	Rapifen
buprenorphine	buprenorphine	buprenorphine hydrochloride	(1S,2S,6R,14R,15R,16R)-5-(cyclopropylmethyl)-16-[(2S)-2-hydroxy-3,3-dimethylbutan-2-yl]-15-methoxy-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11-trien-11-ol	Subutex; Transtec; Suboxone
codeine*	co-codamol; co-codaprin	-	(4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro [3,2-e] isoquinolin-7-ol	Codeine Linctus; Galcodine; Kaodene
dextromethorphan	dextromethorphan	dextromethorphan polistirex	(1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo [7.5.3.01,10.02,7] heptadeca-2(7),3,5-triene	Robitussin Dry Cough
dextropropoxyphene	dextropropoxyphene; co-proxamol;	propoxyphene hydrochloride; propoxyphene napsylate	[(2S,3R)-4-(dimethylamino)-3-methyl-1,2-diphenylbutan-2-yl] propanoate	Distalgesic; Cosalgesic; Dolgesic
diamorphine*	-	-	[(4R,4aR,7S,7aR,12bS)-9-acetyloxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] acetate	-
dihydrocodeine	co-dydramol	-	(4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1H-4,12-methanobenzofuro [3,2-e]isoquinolin-7-ol	Paramol; Remedeine; DHC Continus
diphenoxylate	diphenoxylate; co-phenotrope	-	ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate	Lomotil
dipipanone	dipipanone	-	4,4-diphenyl-6-piperidin-1-ylheptan-3-one	Diconal
eluxadoline	eluxadoline	eluxadoline	5-[[[(2S)-2-amino-3-(4-carbamoyl-2,6-dimethylphenyl) propanoyl]-[(1S)-1-(5-phenyl-1H-imidazol-2-yl) ethyl]amino]methyl]-2-methoxybenzoic acid	Truberzi

fentanyl	fentanyl	fentanyl citrate	N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] propanamide	Actiq; Durogesic; Matrifen
hydromorphone	hydromorphone	-	(4R,4aR,7aR,12bS)-9-hydroxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one	Dilaudid; Palladone
loperamide	loperamide	loperamide; loperamide hydrochloride	4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-N,N-dimethyl-2,2-diphenylbutanamide	Fortasec; Imodium; Dioralez
meptazinol	meptazinol	meptazinol hydrochloride	3-(3-ethyl-1-methylazepan-3-yl) phenol	Meptid
methadone	methadone	-	6-(dimethylamino)-4,4-diphenylheptan-3-one	Dolophine HCL; Methadose; Physeptone
methylnaltrexone	methylnaltrexone bromide	methylnaltrexone bromide	(4R,4aS,7aR,12bS)-3-(cyclopropylmethyl)-4a,9-dihydroxy-3-methyl-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-3-ium-7-one	Relistor
morphine	-	-	(4R,4aR,7S,7aR,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e] isoquinoline-7,9-diol	MST Continus; Oramorph; Zomorph; Sevredol
nalbuphine	-	nalbuphine hydrochloride	(4R,4aS,7S,7aR,12bS)-3-(cyclobutylmethyl)-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e] isoquinoline-4a,7,9-triol	Nubain
naldemedine	-	naldemedine	(4R,4aS,7aR,12bS)-3-(cyclopropylmethyl)-4a,7,9-trihydroxy-N-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-1,2,4,5,7a,13-hexahydro-4,12-methanobenzofuro[3,2-e]isoquinoline-6-carboxamide	Rizmoic
nalmefene	nalmefene	nalmefene	(4R,4aS,7aS,12bS)-3-(cyclopropylmethyl)-7-methylidene-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e] isoquinoline-4a,9-diol	Selincro
naloxegol	naloxegol	naloxegol	(4R,4aS,7S,7aR,12bS)-7-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]-3-prop-2-enyl-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinoline-4a,9-diol	Moventig

naloxone	naloxone	naloxone hydrochloride	(4R,4aS,7aR,12bS)-4a,9-dihydroxy-3-prop-2-enyl-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one	Narcan; Nyxoid; Prenoxad
naltrexone	naltrexone	naltrexone; naltrexone hydroxhloride	(4R,4aS,7aR,12bS)-3-(cyclopropylmethyl)-4a,9-dihydroxy-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one	Adepend; Nalorex; Opizone
oxycodone	oxycodone	oxycodone	(4R,4aS,7aR,12bS)-4a-hydroxy-9-methoxy-3-methyl-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one	Lynlor; OxyContin; Oxynorm;
papaveretum*	-	-	(4R,4aR,7S,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol;(4R,4aR,7S,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol;1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline; hydrochloride	-
pentazocine	pentazocine	pentazocine; pentazocine hydrochloride; pentazocine lactate	(1R,9R,13R)-1,13-dimethyl-10-(3-methylbut-2-enyl)-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol	Fortral
pethidine	-	meperidine	ethyl 1-methyl-4-phenylpiperidine-4-carboxylate	Demerol
pholcodine	pholcodine	-	(4R,4aR,7S,7aR,12bS)-3-methyl-9-(2-morpholin-4-ylethoxy)-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e] isoquinolin-7-ol	Galenphol; Pavacol-D
remifentanil	remifentanil	remifentanil hydrochloride	methyl 1-(3-methoxy-3-oxopropyl)-4-(N-propanoylanilino)piperidine-4-carboxylate	Ultiva
tapentadol	-	tapentadol	3-[(2R,3R)-1-(dimethylamino)-2-methylpentan-3-yl]phenol	Palexia
tramadol	tramadol	tramadol hydrochloride	(1R,2R)-2-[(dimethylamino)methyl]-1-(3-	Mabron; Oldaram; Zydol

			methoxyphenyl)cyclohexan-1-ol	

BAN: British Approved Name; INN: International Nonproprietary Names; IUPAC: International Union of Pure and Applied Chemistry; USAN: United States Adopted Name. *drugs that do not have an INN or alterative.

5.6 Discussion

5.6.1 Summary of findings

I identified 233 opioid drugs from seven sources and created an online resource to disseminate the Oxford Catalogue of Opioids (https://www.catalogueofopioids.net/), published in the *British Journal of Clinical Pharmacology* (18). There were variations in the numbers of opioids identified from each source: the WHO's MedNet service of INNs included the most drugs, and the BNF had the fewest. This variation can be attributed to the type and purpose of each source. There were ten unique drug stems, just over a quarter representing "-fentanil". For opioids in the BNF, most had non-proprietary and proprietary names. There were more similarities than differences in opioids listed in the BNF compared with the opioids in national EMLs. The BNF included all five opioids recommended by the WHO's Model List of Essential Medicines.

5.6.2 Strengths and limitations

A review of opioid pharmacology in 1983 estimated that thousands of opioids have been synthesised and investigated for their various properties (209). However, to the best of my knowledge, this is the first study to systematically determine the number of opioid medicaments and assess opioid nomenclature. One peer reviewer described my project as "*a Hercules task*" and that "*The authors ought to be complimented... This catalogue can indeed be of importance*

for both scientists and prescribers. I do hope, in the interest of prescribers, that it shall be expanded with the strength of different opioids in phase 3."

I named opioids using non-proprietary drug names (e.g. INNs where possible), which have more therapeutic utility and reduce the risk of medication errors (224,225). I searched a range of pharmacology resources, including general databases (the Merck Index and Guide to Pharmacology), a pharmacopoeia (Martindale), a formulary (the BNF), drug classification systems (ATC and INNs), and an index of internationally controlled drugs (the INCB report). I used systematic methods to search various sources, conducted in duplicate, and checked by an experienced clinical pharmacologist (JKA), who has been on the UK's Nomenclature & Taxonomy Advisory Group for more than ten years. The second peer reviewer acknowledged the robustness of my research, stating, "*Overall I found this study topical and of good quality for publication… opioids were identified through a systematic search and categorised by drug name and pharmacological properties to create a classification system. The study is very topical in the context of growing concern in opioid misuse and harm, and original given that there is no central repository including novel opioids as explained in the introduction. A major strength of this study is that the catalogue of opioids developed would be of significant value to various fields, including clinical practice, research and drug development, and public health. Potential implications of the opioid catalogue in these fields are comprehensively discussed in the manuscript. Graphs and tables are easy to comprehend and aids understanding of the results. The method of identifying opioids through the search of sources is clearly stated. Other activities, such as consulting experienced pharmacologist and performing a search through published literature, enhance the robustness of the research method. Reasons for the inclusion*

and exclusion of opioids are justified. The method of cataloguing opioids is also easy to follow, and no major flaw was identified."

Despite using systematic methods, there may be other opioids that were not identified from my searches, owing to reporting biases. Various limitations, such as spelling variants, look-alike and sound-alike names, the use of different nomenclature for a single drug, drug abbreviations, and the implications of chemical salts (225–228), were considered but may have resulted in opioids being omitted from the outputs of my searches. I used manual methods to search the sources, and despite updating the search in November 2020, methods are needed to be developed to automatically and efficiently update the catalogue to reflect discoveries and progress in opioid pharmacology.

5.6.3 Implications

5.6.3.1 Implications for policy

The comparison of opioids listed in the BNF with those in national EMLs and the WHO's Model List should prompt governments and medicine regulators without EMLs to examine the numbers and types of opioids being approved and prescribed. In a collaborative study with McMaster University and the University of Toronto, I contributed to a cross-sectional study that found that the numbers of full opioid agonists approved by regulators in Australia, Canada, the UK, and the US were associated with the numbers of opioid-related deaths in those countries (229). While the BNF contains all five opioids recommended by the WHO's Model List, the MHRA could review the additional opioids in the BNF to determine the extent of their clinical use, effectiveness, harms and involvement in opioid-related deaths. The centralised list of 233 drugs may also be

useful for law enforcement agencies in increasing their knowledge and testing capacity for novel opioids being illegally purchased and sold for recreational use.

5.6.3.2 Implications for patients, the public, and clinical practice

When doctors prescribe unfamiliar medicines, and when patients take them, more errors are likely to occur (230). My catalogue of opioids could assist GPs when prescribing opioids to patients and when communicating about opioids to patients and carers and other healthcare professionals (e.g. pharmacists and nurses) and consultants managing patients across all levels of the healthcare system. Reflecting on my time in the opioid clinics, the main form of communication between the pain consultant and the prescribing doctor were letters, emailed, faxed, or posted. In most cases, the pain consultant would provide a robust plan tailored to the patient to taper the dose of opioids slowly. But in some cases, this would first require a switch from one opioid or formulation to another for safety reasons. For example, if a patient showed evidence or confessed to "swigging" Oramorph from the bottle, the consultant would recommend rotating Oramorph (morphine liquid/syrup) to morphine tablets to stabilise their dosage. Changes such as this may induce anxiety and confusion for patients and carers. As soon as the consultant explained Oramorph and morphine tablets contained the same active drug, patients appeared at ease. This example highlights the importance of using non-proprietary drug names, the index name in my catalogue, when prescribing and communication about medicines (231–233). While further research is required to develop, tailor, and test my catalogue's usefulness, it could supply vital information for prescribers, dispensers, and users of opioids.

Inconsistent drug names can put patients and the public at risk of harms (218,234). The rise in new SARS-CoV2 variants further highlights the importance of nomenclature for communication and advancing science (235). While there are national and international standards for drug nomenclature, authorities and organisations (e.g. IUPAC and the WHO), and regulatory bodies to approve such names, all opioids in my list may not have been through such processes, owing to their maturity or infancy. For example, morphine was first marketed by Merck in 1827, long before drug nomenclature standards existed, and various novel opioids are being identified on the black market, such as the rise in fentanyl analogues (236). Many countries still use a mixture of proprietary and non-proprietary names, which can cause confusion (232). On February 01, 2021, Australia updated their national legislation to mandate prescriptions are written using their active ingredient, the non-proprietary drug name (237). A consolidated list of opioid drugs with their chemical and pharmacological properties could therefore harmonise discrepancies and standardise nomenclature across countries, which has been found to reduce confusion, medication errors, and unwarranted variation, as well as improve medication knowledge, adherence, training, and communication (225,238–240). The better patients can understand their medications, the fewer the errors, and the greater the autonomy and involvement in their health.

There is also the possibility that the Catalogue of Opioids can be used as a teaching and training resource by medical schools or pharmacology departments. As I continue to develop the catalogue and write opioid vignettes, I will engage with students and early-career researchers and offer them a chance to get involved with writing and disseminating the work of the catalogue.

5.6.4 Implications for future research

Varying drug nomenclature can affect the ability and quality of evidence synthesis and knowledge generation. My list of opioid names can be used in the design and conduct of research to streamline the identification of studies or prescribing data. For example, in Chapter 4, instead of only searching the ATC index to create a list of opioids (section 4.4.1), I could have used this list of opioids to search the GEM database immediately. For systematic reviews, this list of opioids could be used to create search terms that include chemical, proprietary, and non-proprietary drug names, instead of the methods I used to generate search terms in Chapter 7. For drug utilisation studies, the list could be used to design product code lists for databases such as CPRD or QResearch. My list of opioids may also assist researchers in developing novel opioids, in comparing and contrasting former drugs, and assist pharmaceutical companies in creating proprietary names.

Ongoing and future research will be required to develop phase three of the catalogue (https://www.catalogueofopioids.net/). The purpose of the online resource is to create a visual platform that will aid prescribers and inform patients, carers, and the public about the properties of opioids to improve safety. The Bandolier project's previous work led to creating the "Oxford league table of analgesics in acute pain", which became a useful resource for prescribing clinicians (241). Future research could use this list of 233 opioids to systematically extract the number needed to treat (NNT) from RCTs to create a league table of opioids and dose-response curves to improve OMEs calculations. Maintaining and updating and the catalogue will be an ongoing process, which involving the pharmaceutical industry may help identify novel opioids and accelerate the process. Future research will need patient and public involvement and

engagement (PPIE) with key stakeholders (e.g. patients and prescribers) to ensure the catalogue meets the target audiences' needs and effectively improves knowledge, and promotes the safe use of opioids.

5.7 Conclusion

In Chapter 5, I systematically identified 233 opioid drugs, synthesised their drug nomenclature, and launched the Oxford Catalogue of Opioids. Consistent drug nomenclature is essential for improving the safety and communication of medicines. Current and future research will catalogue opioids based on their pharmacological properties and provide information to assist prescribers, researchers, and regulators, to improve the knowledge and safety of opioids.

5.8 Chapter summary

- Phase one of the Oxford Catalogue of Opioids systematically identified 233 opioid drugs from seven sources and the published literature to create a list of opioid drugs.
- The identified opioids had ten unique drug stems, with *"-fentanil"*, "*-orphine*", "*-adol*", and "*-eridine*" being the most common.
- The BNF included 32 opioids and listed all five opioids recommended in the WHO's Model List of Essential Medicines.
- Opioids included in the BNF were similar to those included in the 137 national EMLs.
- I created an online resource (https://www.catalogueofopioids.net/) that will catalogue opioids, improve access to information, simplify the language of opioids, and promote safe use.

Chapter 6

"My generation sippin' cough syrup like it's water."
Kendrick Lamar, A.D.H.D, 2011

*This chapter is being prepared as two manuscripts; the first entitled "*Sales of over-the-counter codeine-containing products in 31 countries, 2013-2019*" is under peer review at *Addiction* (ADD-21-0446) and openly available as a preprint (19), the other entitled "*Over-the-counter codeine-containing medicines purchased in the UK, 2013-2019*" is in preparation. I received a Travel Grant from Kellogg College to present the protocol for this chapter as a poster at the 6th Preventing Overdiagnosis conference in Copenhagen, Denmark (August 20-22, 2018), and the abstract was published in *BMJ Evidence Based Medicine* (20).

6 Analysis of over-the-counter sales of codeine-containing products in 31 countries, 2013-2019

6.1 Chapter rationale

Efforts have been made to understand the consumption of prescribed and dispensed opioids (3,136,242,243). However, in many countries, including the UK, opioids such as analgesics containing codeine can be purchased over-the-counter (OTC) without a prescription or consultation with a doctor or other prescriber. However, it is not known whether opioids purchased without a prescription are following similar trends to prescribed opioids. On 1 February 2018, codeine was reclassified to prescription-only in Australia (244). This stimulated conversations about the status of OTC codeine-containing products in the UK (245–247) and was the catalyst for my determination to obtain data on OTC sales of codeine.

6.2 Introduction and Aim

Codeine (3-methylmorphine) is a naturally occurring opium alkaloid acting as an agonist on MOP receptors, first isolated in 1833 (248). It is considered a "weak" opioid and has a potency ratio to morphine of 1:10 (249,250). Codeine is principally metabolised in the liver by *O*-demethylation to morphine and morphine-6-glucuronide (Figure 6.1) via the cytochrome P450 enzyme CYP2D6. This enzyme activity varies widely from one person to another, owing to significant genetic polymorphisms (251–254). People can be classified as ultrarapid, extensive, intermediate, or poor metabolisers. Ultrarapid metabolisers, who constitute about 3% of Caucasians in northern Europe, 5-10% in southern Europe (255), and 10-30% in Arabian and northeast African countries (256), have CYP2D6 gene duplication, resulting in exaggerated and potentially dangerous opioidergic effects (257). Poor metabolisers, who constitute 7-10% of Caucasians (258), do not express functional CYP2D6 and thus experience little benefit from codeine. A defect in CYP2DE is an autosomal recessive trait, and more than 70 allelic variants have been described (259). Therefore, CYP2DE polymorphisms in individuals using codeine are important to consider.

Codeine (Table 6.1) is used for its analgesic, antidiarrheal, and antitussive effects (260–262). It is often combined with other analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. These combinations have greater efficacy, or a lower number needed to treat (NNT), than codeine alone (Table 6.2). But most clinical trials testing the efficacy of codeine have used high doses (25-90 mg), which are not available OTC.

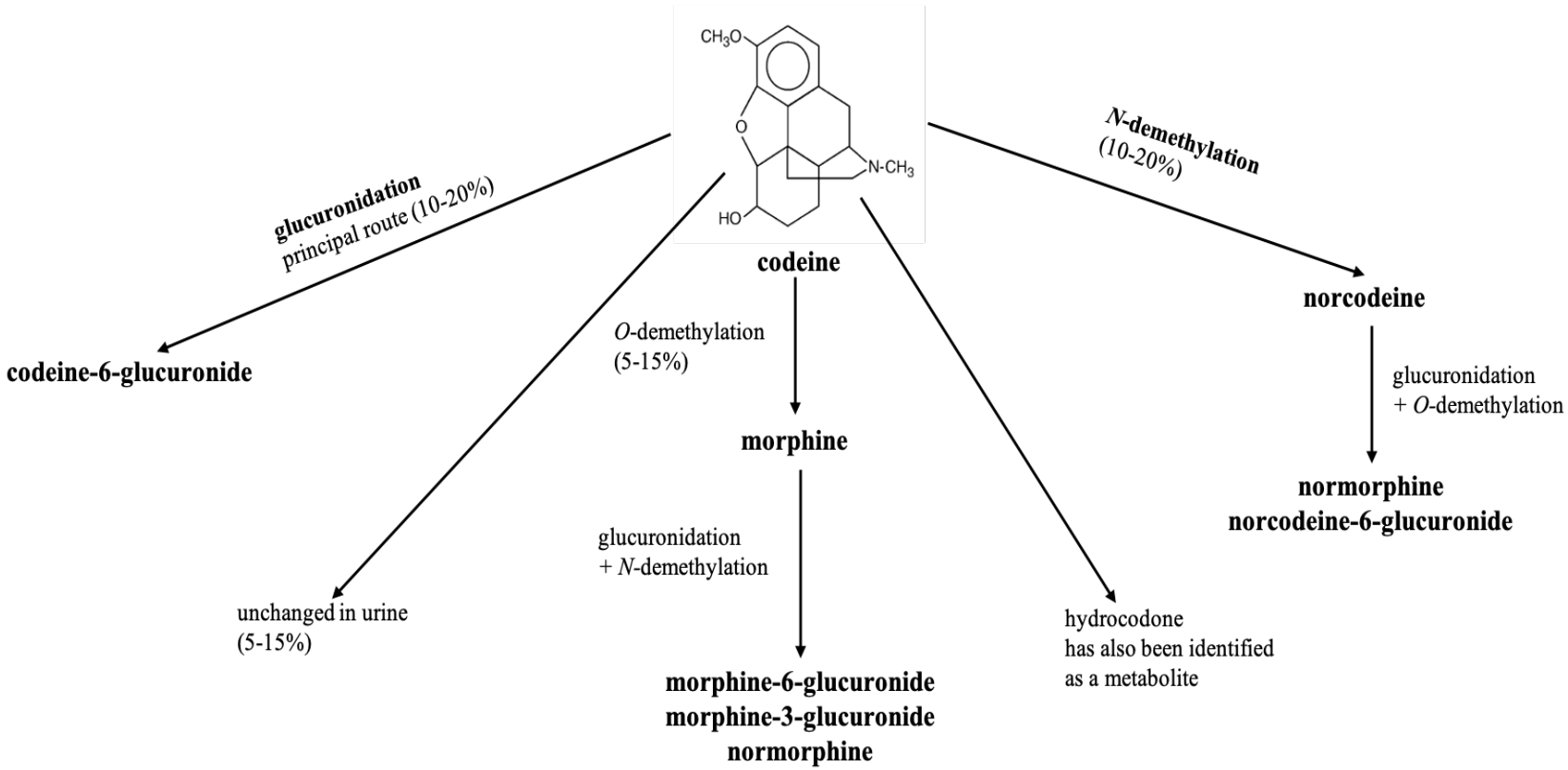


Figure 6.1: Metabolism of codeine, adapted from Williams et al. 2001 (248)

Table 6.1: Properties of codeine and clinical information from the BNF (48–52) and the Oxford Catalogue of Opioids (Chapter 5).

IUPAC name	(4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
Molecular formula	$C_{18}H_{21}NO_3$
Molecular weight (g/mol)	299.4
Indications for use	Codeine-paracetamol combination (i.e. co-codamol): 1. mild to moderate pain (adults only; doses 15/500) 2. moderate pain (adults only; doses 8/500 or 15/500) 3. moderate to severe pain (adults only; doses 30/500) 4. short-term treatment of acute moderate pain (child 12-17 yrs, doses 8/500, 15/500 or 30/500); Codeine-aspirin combination: 1. mild to moderate pain (adults only) Codeine phosphate: 1. acute diarrhoea (child 12-17 yrs & adults); 2. mild to moderate pain (adults only) where other analgesics such as paracetamol or ibuprofen have proved ineffective; 3. short-term treatment of acute moderate pain (child 12-17 yrs); 4. dry or painful cough (adults only).
Adverse effects	**General, frequencies unknown:** biliary spasm; hypothermia; mood altered; sexual dysfunction; ureteral spasm. **Specific, with oral use, frequencies unknown:** abdominal cramps or pain; addiction; agranulocytosis; appetite decreased; blood disorder; depression; drug reaction with eosinophilia and systemic symptoms (DRESS); dyskinesia; dyspnoea; face oedema; fatigue; fever; hyperglycaemia; hypersensitivity; intracranial pressure increased; irritability; lymphadenopathy; malaise; muscle rigidity (with high doses); nightmare; pancreatitis; restlessness; seizure; severe cutaneous adverse reactions (SCARS); splenomegaly; thrombocytopenia; urinary disorders; vision disorders. **Specific, with parenteral use, frequency unknown:** dysuria
Contraindications	1. all children and adolescents (under 18 years) who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea; 2. ultra-rapid metabolisers (CYP2D6) of codeine; 3. in children (≤12 years) for cough and cold; 4. breast-feeding mothers; 5. acute ulcerative colitis;

	6. antibiotic-associated colitis; 7. conditions where abdominal distension develops; and 8. conditions where inhibition of peristalsis should be avoided.
Not recommended in	all children and adolescents (under 18 years) who have breathing problems, including those with neuromuscular disorders, severe cardiac or respiratory conditions, respiratory infections, multiple trauma or extensive surgical procedures
Cautions	acute abdomen; cardiac arrhythmias; gallstones; alcohol dependence; chronic alcoholism; avoid abrupt withdrawal after long-term treatment; chronic dehydration; chronic malnutrition; convulsive disorders; and hepatocellular insufficiency.

Table 6.2: Numbers needed to treat (NNT) for codeine in adults published in Cochrane systematic reviews

Reference	Condition	Intervention	No. of participants	No. of studies	NNT* (95% CI)
Derry et al. 2010 (22)	acute postsurgical pain	codeine 60 mg as a single agent	2411	33	12 (8.4-18)
	dental surgery		1146	15	21 (12-96)
Derry et al. 2015 (53)	acute postoperative pain	400 mg ibuprofen & 25.6-60 mg codeine	443	4	2.2 (1.8-2.6)
		ibuprofen & codeine (any dose)	204	3	1.3 (1-1.6)
Toms et al. 2009 (54)	postoperative pain	800-1000mg paracetamol & 60 mg codeine	2295	26	2.2 (1.8-2.9)
		600-650 mg paracetamol & 60 mg codeine			3.9 (2.9-4.5)
		300 mg paracetamol			6.9 (4.8-12)

		& 30 mg codeine			

*at least 50% of pain relief over 4 to 6 hours compared to placebo

The authors of a Cochrane overview of systematic reviews published in 2015 on oral OTC analgesics for acute pain found no studies or insufficient information on combinations of analgesics with low doses of codeine (263). A non-Cochrane systematic review published in 2019 on the efficacy and safety of low-dose (≤30 mg) codeine included ten RCTs (264). It showed low- to moderate-quality evidence that combination products of low-dose codeine (15-30 mg) provided small to moderate pain relief for acute and chronic pain conditions in the immediate short term (264). But data on the safety and longer-term use of low-dose codeine are limited.

Prescription monitoring programmes and pharmacoepidemiological studies have successfully examined the use of opioids (3,136,242,243,265). However, codeine sold OTC has not been accounted for because, in many countries, it does not require a prescription or consultation with a prescriber. Previous research on the use of non-prescribed codeine has therefore relied on case reports (266–268), self-reported questionnaires (269–276), qualitative studies (277–280), and data from poisons centres, hospital admissions, or coronial systems (281–285). These observational studies have highlighted several safety concerns and harms associated with OTC codeine, including dependence, misuse, collateral toxicity from combinations with paracetamol and ibuprofen, and death. They have also shown that females were more likely to purchase codeine OTC than males (269,273,276,282); chronic pain was the most common indication for use (269,271,281); and depression, anxiety, and gastrointestinal disturbances were reported as adverse effects of OTC codeine use (271,285).

Access to codeine without a prescription bolsters the perception of safety, and in some settings, abuse of OTC codeine is normalised and encouraged. The mixing of codeine cough syrup with alcohol and or soft drinks has been popularised in rap music and by American athletes, who make a drink called "purple drank" from codeine syrup and soda (286). OTC codeine has been used to manufacture illicit morphine and heroin and create a cheap heroin substitute called "krokodil" (287,288). The use of "Krok" has been reported in Russia, Europe, the UK, and North America, and its adverse effects include damage to blood vessels, skin, muscles, bones, multiorgan failure, and death (287,289). Thus, the full picture of the growing opioid problem will not be known until data on prescription and OTC opioids are evaluated.

Regulation of codeine-containing products varies across the world, making it difficult to estimate how much they are used (290). Under the 1961 Single Convention on Narcotic Drugs, codeine is a Schedule III drug (291). Drugs in this Schedule are said to be "not liable to abuse and cannot produce ill effects", and thus reporting data on their consumption to the INCB is not mandatory. In a report presented at the WHO's Expert Committee on Drug Dependence in October 2019 reviewing codeine formulations listed in Schedule III, the INCB reported a 64% increase in demand for codeine in the last decade, an all-time high of 269 tonnes in 2011 compared with 164 tonnes in 1992 (290). But this information is nearly ten years out of date. As I reported in Chapter 3, 11.3 tonnes of codeine were consumed globally between 2015 and 2017 (15), which is a 96% decrease in codeine consumption since 2011. As discussed in section 3.6.2 of Chapter 3, there are many limitations of these data, owing to codeine's Schedule. Thus, it is not clear whether there has been an actual decrease in codeine consumption or a reduction in the number of countries reporting data on codeine to the INCB (e.g. the UK did not report codeine

consumption to the INCB in 2015-2017). Values of sales of all OTC medicines in the UK have been reported by category on the data platform *Statista* (292). In 2019, the "pain relief" category had the greatest value at £628.6 million (GBP), followed by the cough, cold, and sore throat category (£478.7), and the vitamins and minerals category (£431.5) (292). But access to and publication of granular data on OTC sales of products containing codeine has been limited, owing to variation in regulations, trade exemptions, and disclosures of commercial interests (290).

Governments can mandate their regulations of controlled substances. A study published in 2015 reviewed OTC codeine regulations in the European Union (as of March-August 2014) and found more than half (54%, n=15/28) of member countries did not permit the sale of codeine OTC (293). In the UK, codeine is available without a prescription in pharmacies as a combination product (deemed a pharmacy medicine, P), usually as 8 mg codeine with 500 mg paracetamol (e.g. Co-Codamol). It is classed as a controlled substance (Class B) under the Misuse of Drugs Act 1971 (or Class A when prepared for injection) and Schedule 5 when in OTC formulations under the Misuse of Drugs Regulations 2001 (or Schedule 2 when prepared for injection, without another active or inert ingredient, when containing >100 mg per dosage unit or a total concentration of >2.5%) (294). There were 49 authorised products in the UK containing codeine and available from pharmacies as of 2009; 36 were combined with paracetamol, two with ibuprofen, and four with aspirin (295).

While there is still access to OTC codeine-containing products in the UK (as of January 2021), tighter measures are slowly being implemented (Table 6.3). In 2013, the MHRA restricted the

use of codeine in children (<12 years) and contraindicated its use in all children and adolescents (<18 years) who undergo a tonsillectomy, adenoidectomy, both, or any other procedure for obstructive sleep apnoea (296). In 2019, the MHRA created the Opioid Expert Working Group (EWG) of the Commission on Human Medicines (CHM) to review the evidence and provide recommendations to the MHRA (297), including an assessment of the use of OTC opioids and risk minimisation measures. On September 23, 2020, the MHRA's Opioid EWG published a press release stating that they will be adding "stronger warnings" to patient information leaflets and "will consider" reclassifying "all opioid-based painkillers" to be prescription-only "as necessary" (105). Thus, my aim to describe the sales and public expenditure of OTC products containing codeine purchased in the UK and 30 other countries in this chapter is timely.

Table 6.3: Brief timeline of key events relating to OTC codeine in the UK and abroad. Reclassification events are highlighted in grey.

Year	Event
1833	Codeine is isolated from opium by French chemist Pierre-Jean Robiquet (248)
1961	On March 30, the Single Convention on Narcotic Drugs is published, which classifies codeine as Schedule III
1968	Medicines Act 1968 in the UK
1971	In the UK, codeine is categorised as a Class B controlled substance or a Class A drug when prepared for injection under the Misuse of Drugs Act 1971
1977	Codeine is included on the WHO's List of Essential Medicines (81)
1986	Codeine is placed on "step 2" of WHO's "pain ladder" for cancer pain (298)
2005	In February, the Committee on Safety of Medicines (CHM's predecessor) considers the risk of addiction to OTC medicines containing codeine and dihydrocodeine in the UK. Following this review, they added warnings to product information and reduce pack sizes (max 32 tablets) (295)
2009	In January, the UK's All-Party Parliamentary Group on Drug Misuse published a report on physical dependence and addiction to OTC and prescribed medicines (299)
	In September, MHRA/CHM announced new warnings and tighter controls on the sales of OTC medicines containing codeine, including changes to indications, labels and leaflets, pack sizes (<32 tablets), and advertising (295)
2013	In July, MHRA/CHM restricted codeine for analgesia in children (≤12 years) due to reports of morphine toxicity (296)

	On July 30, the State of Minnesota in the US reclassified some codeine preparations from Schedule V to Schedule II controlled substances (300)
2015	On April 29, MHRA/CHM restricted codeine for cough and cold in children (≤12 years) due to risks of respiratory side effects (301)
2016	On February 01, codeine becomes prescription-only in Manitoba, Canada (302)
	On March 14, cough medicine containing codeine is banned in India, but pharmaceutical companies pressure the government to release the ban and offer temporary relief to Pfizer and Abbott Laboratories (303)
	In July, Health Canada issued new safety measures stating codeine is contraindicated in patients under 18 years to treat pain after surgery to remove tonsils or adenoids (304), and Canada's Minister of Health proposed changes to low-dose codeine that would require a prescription for all products (305)
2017	On 20 April, the FDA contraindicated codeine in children (≤12 years) and added a warning for adolescents (12-18 years) who are obese or have conditions that increase the risk of serious breathing problems (such as obstructive sleep apnoea or severe lung disease) and mothers who are breastfeeding (306)
	In July, codeine becomes prescription-only in France, along with ethylmorphine and dextromethorphan (307)
2018	On February 01, codeine becomes prescription-only in Australia (244)
2018	Nigeria bans the manufacture and import of codeine-containing cough syrup (308)
2019	On February 13, MHRA announce the Opioid Expert Working Group following their first meeting (99)
	On May 07, an open letter is submitted to Health Canada from the Canadian Pharmacists Association to request all products containing codeine be made prescription-only (309)
	In September, Public Health England published a report entitled "Dependence and withdrawal associated with some prescribing medicines: an evidence review" (101), which recommends the CHM examines the evidence and guidance on OTC opioid medicines, including those containing low-dose codeine, and reconsider options for reducing access to them (144)
	In October, a pre-review report on codeine preparations listed in Schedule III of the Single Convention is presented at the WHO's Expert Committee on Drug Dependence, 42nd meeting in Geneva (290)
2020	In August, MHRA announced it "will consider" reclassification of "all opioid-based painkillers" as prescription-only (105)
	In October, New Zealand announced it would reclassify all codeine-containing medicines to prescription-only, but the response to the COVID-19 pandemic has delayed its implementation (310)
2019-2021	The government of Canada proposes changes to the scheduling of OTC codeine to make all products containing codeine prescription-only (311)

CHM: Commission on Human Medicines; MHRA: Medical Health Regulatory Agency; WHO: World Health Organization

6.3 Objectives

1. to review the status and availability of codeine in 31 countries;
2. to determine the volume of OTC codeine-containing products purchased nationally each year, adjusted for population, and assess trends between 2013 and 2019;
3. to determine public expenditure (in £ sterling as of 20/09/2019) of OTC codeine-containing products purchased each year nationally, adjusted for population, and to assess trends between 2013 and 2019; and
4. to evaluate the sales of OTC codeine-containing products in the UK.

6.4 Methods

6.4.1 Rapid policy review of the status of codeine

I conducted a rapid review of policies, reports, and studies that discussed the availability and status of codeine products. I first searched PubMed using "codeine" and "over-the-counter" key words for relevant studies. I then searched Google for reports and country specific legislation for the 31 countries included in this study that had provided data to IQVIA. I extracted whether codeine was available OTC or prescription only for each country. If available OTC, I also extracted the maximum dosage. If codeine was not available OTC and there had been a regulation change, I extracted the date of such change. I summarised the findings in a table and reported the percentage of countries with and without access to OTC codeine.

6.4.2 Study design and data sources

I designed and conducted a retrospective observational study using consumer health sales data purchased from the human data science company *IQVIA* (312), formerly Quintiles and IMS

Health. The data included products containing codeine in the "adult pain relief" category, which are collected using scan track barcodes from electronic point-of-sale (EPoS) store data. This is commercial information, which requires a fee to access. So the Primary Care Research Trust of Birmingham and Midlands Research Practices Consortium provided a grant (£10,000) to purchase the data.

Before I obtained the data from *IQVIA*, I spent many months investigating whether such data on OTC codeine sales were available. To the best of my knowledge, no published studies have used such data. I found two reports that summarised the OTC medicine market in Britain (292,313), which led to negotiations with two market research companies, *IRi* (314) and *Nielsen* (315). These companies appeared to be unfamiliar with the ecosystem of academic publishing. They would not guarantee that I could publish my findings in a journal, owing to their contractual agreement restrictions, which they were not prepared to amend. I identified *IQVIA* as a company that might have such data on OTC codeine sales from MHRA's response to my Freedom of Information (FOI) request (316), where I had asked for a copy of a "review" mentioned in a Drug Safety Update, dated September 2009, but published on 11 December 2014 (295). The MHRA responded to my FOI request (316), stating:

> "*I can confirm that we do not hold the information that you have requested. The MHRA did not perform a formal review of sales data and ADR reports at 6 and 12 months after amendment of the Marketing Authorisations (MAs) as planned. This was because it took longer than anticipated for the updated product information to reach pharmacies, due to the number of products affected. However, in 2014 the MHRA reviewed usage data and relevant spontaneously-reported cases before and after 2009, to assess the impact of the*

updates to product information (rather than the impact of the article in the Sept edition of Drug Safety Update specifically) … A copy of the main body of the 2014 assessment is provided as this is relevant to your request. ***The usage data considered in 2014 has been redacted from the report as this information is exempt from release under Section 41****, Information provided in confidence: information provided to us in confidence, with the expectation that it will not be released, is exempt from disclosure under the FOI Act … The MHRA has requested permission to release these data from the data provider. However, you should be able to obtain these data directly from* ***IQVIA*** *subject to payment of their usual fee for provision of usage data*." (see Appendix 6.1)

I obtained quotes from *IRi*, *IQVIA*, and *Nielsen*. I selected *IQVIA* because their data are widely published (317–320), including three studies that examined codeine (321–323): one on the consumption of OTC cough syrup containing codeine in Taiwan (322) and two in Australia before and after the rescheduling of codeine to prescription-only (321,323). *IQVIA* could also provide six years of data in 31 countries (within the financial restrictions of my grant), had previously worked with academic institutions, and would allow publication of my findings following approvals.

The data were extracted on 16 September 2019 and provided quarterly from 1 April 2013 to 31 March 2019. *IQVIA*'s sample of data is based on audits and covers a median of 73% (IQR: 58-86%) of pharmaceutical markets (Table 6.4). The database provided by *IQVIA* contained the following variables: country (e.g. UK); source (e.g. UK OTC Pharm); CHC3 (e.g. general pain relief, dry cough products, cold or flu remedies); CHC4 (e.g. effervescent, caps/tabs);

combination (e.g. codeine-paracetamol); pack info (e.g. caps 8/500 8 mg 31); price to the wholesaler; price to the chemist; price to the public; units (i.e. the number of packs sold); counting units (i.e. the number of individual tablets/items or mL of liquid sold); and standard units (i.e. *IQVIA*'s standardisation of liquids and tablets). I also extracted annual population statistics in calendar years (2013 to 2018) from the World Bank for the 31 countries (324) and the Office of National Statistics (ONS) for the UK (325).

6.4.3 Volume and trends of OTC codeine-containing products in 31 countries

I calculated descriptive statistics to determine the numbers and types of products, formulations, substances in combinations, pack sizes, and dosages. Owing to missing data for dose, I used *IQVIA*'s variable of "standard units", which they calculated to standardise data for liquid and solid dosage forms. I calculated the total volume of sales over the six-year study period, and I summed quarters to create annual totals (e.g. from quarter two in 2013 to quarter one in 2014). For each country, I determined the mean volume of sales over six years, adjusted for population, and created an annual rate of units sold per 1000 of each year's population. I plotted the data and calculated the change in trends over time.

Table 6.4: Coverage of *IQVIA*'s data by country in alphabetical order

country	% of the total market
Argentina	73
Belgium	71
Brazil	53
Bulgaria	85
Canada	87
Croatia	67
Estonia	88
Finland	73
France	79
Germany	86
Greece	60

Ireland	80
Italy	37
Japan	56
Latvia	92
Lithuania	92
Mexico	61
Netherlands	58
Poland	75
Portugal	58
Romania	85
Russia	65
Serbia	100
Slovakia	85
Slovenia	97
Spain	48
South Africa	86
Switzerland	75
Thailand	22
UK	67
USA	47

6.4.4 Public expenditure on OTC codeine-containing products in 31 countries

I used *IQVIA*'s variable, "price to the public", to calculate total public expenditure on OTC codeine-containing products. This variable was chosen as in most countries, like the UK, the public pays for OTC products rather than the costs being subsidised or charged to healthcare budgets and governments. Data were converted to GBP (£ sterling) for each country by *IQVIA* on extraction (16 September 2019). I determined the mean public expenditure for each country, adjusting for population. I summed quarters to create annual totals and rates of public expenditure (£) per 1000 of each country's population. I plotted the data and calculated the change in trends over time. I compared trends in sales and public expenditure for each country.

6.4.5 OTC codeine-containing products sold in the UK

I conducted descriptive statistics to determine the numbers and types of products, formulations, dosages, substances in combinations, and the sizes of packs and bottles sold OTC. I used *IQVIA*'s "units" and "CHC4" variables to determine the volume of packs and bottles sold, adjusting for the UK population. I used the "pack info" and "counting units" variables to calculate the volume of codeine sold in kilograms (kg) for solids and kilolitres (kL) for liquids and the volume of paracetamol and ibuprofen sold in kg, adjusting for population. If dosage was not provided in the "pack info" variable, I searched for the product on the electronic medicines compendium (emc) (326). I converted the volume of codeine in kg to oral morphine equivalents (OME), using the Faculty of Pain Medicine's (FPM) equianalgesic potency ratio of 0.1 (327). I did not convert liquid codeine to OME, as there is limited research on the bioavailability of codeine from different oral formulations (328). Instead of using *IQVIA*'s "standard unit" variable, I had all dosage data to calculate "dosage units" of codeine to standardise the volumes of liquid and solid dosage forms. For liquids, one unit was 12 mL of codeine, and for solids, this was dependent on the dosage of codeine. For example, for the 44 products with a dose of 8 mg of codeine, one unit was 8 mg of codeine.

I determined the total volume of dosage units of codeine purchased and the total public expenditure (GBP, £) for the six-year study period, adjusting for population. I summed quarters to determine the annual rate of sales in dosage units per UK resident and calculated the percentage change over time. I repeated this for public expenditure, using IQVIA's "price to public" variable, and adjusting for population. I calculated the mean price per dosage unit and determined whether this had changed over the study period. Trends were plotted.

6.4.6 Statistical software and open science practices

I preregistered my study protocols on the OSF for the two analyses; 31 countries (329) and the UK (330). I shared my statistical code and study materials openly at GitHub and the OSF (Table 6.5), but owing to contractual agreements with *IQVIA*, I cannot openly share the data. I used Stata v16 and Python v3 in Jupyter Notebooks with pandas (166), seaborn (222), and matplotlib (223) libraries for analysis and to create figures.

Table 6.5: Open Science Checklist for Chapter 6 on OTC codeine sales

Principles		Links
Open methods	Protocols	https://osf.io/ay4mc; https://osf.io/d6tbh; https://ebm.bmj.com/content/23/Suppl_2/A63.2.abstract
	Preregistration	
	Materials	https://osf.io/yt6bf/
	Statistical code	https://github.com/georgiarichards/otc_codeine
Open data	Data	not possible – purchasable directly from *IQVIA*
Open access	Pre-print	https://www.medrxiv.org/content/10.1101/2021.04.21.21255888v1
	Publication	Under review at Addiction (ADD-21-0446)
	Blog	will prepare post-publication
	Tools	no funding could be sought for a "codeine policy tracker" as discussed in section 6.6

6.5 Results

6.5.1 Rapid review of codeine policies

Codeine was available OTC in 42% of countries (13/31), with Canada and the USA having variable access and 3 countries (i.e. Brazil, Mexico, and Serbia) where no sources could be identified to validate the status of codeine (Table 6.6).

Table 6.6: Codeine regulations in the 31 countries included in this chapter

Country	available OTC	max dose OTC (mg)	date of change	notes and references
31 countries included in this chapter				
Argentina	**X**			(331)
Belgium	**X**			(293)
Brazil				no sources identified
Bulgaria	•	30		(293)
Canada, not including Manitoba	•	8 20mg/ 30mL		sold in combination with paracetamol as Tylenol Number 1 (T1s) (290,332)
Canada, Manitoba only	**X**		01/02/2016	prescription-only (302)
Croatia	**X**			(293)
Estonia	•	8		(293)
Finland	**X**		1973	(293,333)
France	**X**		2017	prescription-only; they were previously available with a max dose of 20 mg (293)
Germany	**X**			(293)
Greece	**X**			codeine is an "illegal" drug; it is available by prescription as Lonarid-N or Lonalgal (290,293)
Ireland	•	12.8; 15mg/5 ml		(270,293) in 2017, no longer visible for selection (334)
Italy	**X**			prescription-only (290,293)
Japan	•			(290)
Latvia	•	8; 3 mg/5 ml		(293)
Lithuania	•	8		(293)
Mexico				no sources identified
Netherlands	•	2.5mg/5ml		available as cough linctus only (293); since 2013, codeine-paracetamol combinations are no longer reimbursed (335)
Poland	•	15		(293)
Portugal	**X**			(293)
Romania	•	12.5		codeine (Farmacod) requires a prescription; doses cannot exceed 15 mg (290,293,336)
Russia	**X**		2012	(337)
Serbia				no sources identified
Slovakia	**X**			(293)

Slovenia	●	10		(293)
Spain	**X**			(293)
South Africa	●	20; 10mg/5mL		(270,290)
Switzerland	●			cough syrups containing codeine are available at the discretion of the pharmacist (290,338)
Thailand				no sources identified
UK	●	12.8		permitted with at least one other active or inactive ingredient (290,293)
USA	~			codeine is a Schedule II controlled substance when used in products for pain-relief (alone or >80 mg per dosage unit). Cough syrups are classed as Schedule III, IV or V, depending on the formulation (290). In the State of Minnesota, for example, some codeine preparations were reclassified from Schedule V to Schedule II controlled substances in 2013 (300)

OTC: over-the-counter; ●: yes; **X**: no; ~: status varies

6.5.2 Volume and trends of OTC codeine-containing products in 31 countries

There were 569 products and 12 formulations sold across 31 countries. Tablets were the most common formulations sold, followed by syrups, soluble tablets, and coated tablets (Figure 6.2). Dosages of codeine were available for only 17% of products (98 of 569) in 15 countries, so I could not calculate dosage units and oral morphine equivalents (OME). The products contained a median of 3 substances per combination (IQR: 2-4, range: 1-16); three countries (Bulgaria, Portugal and Romania) sold products containing phenacetin.

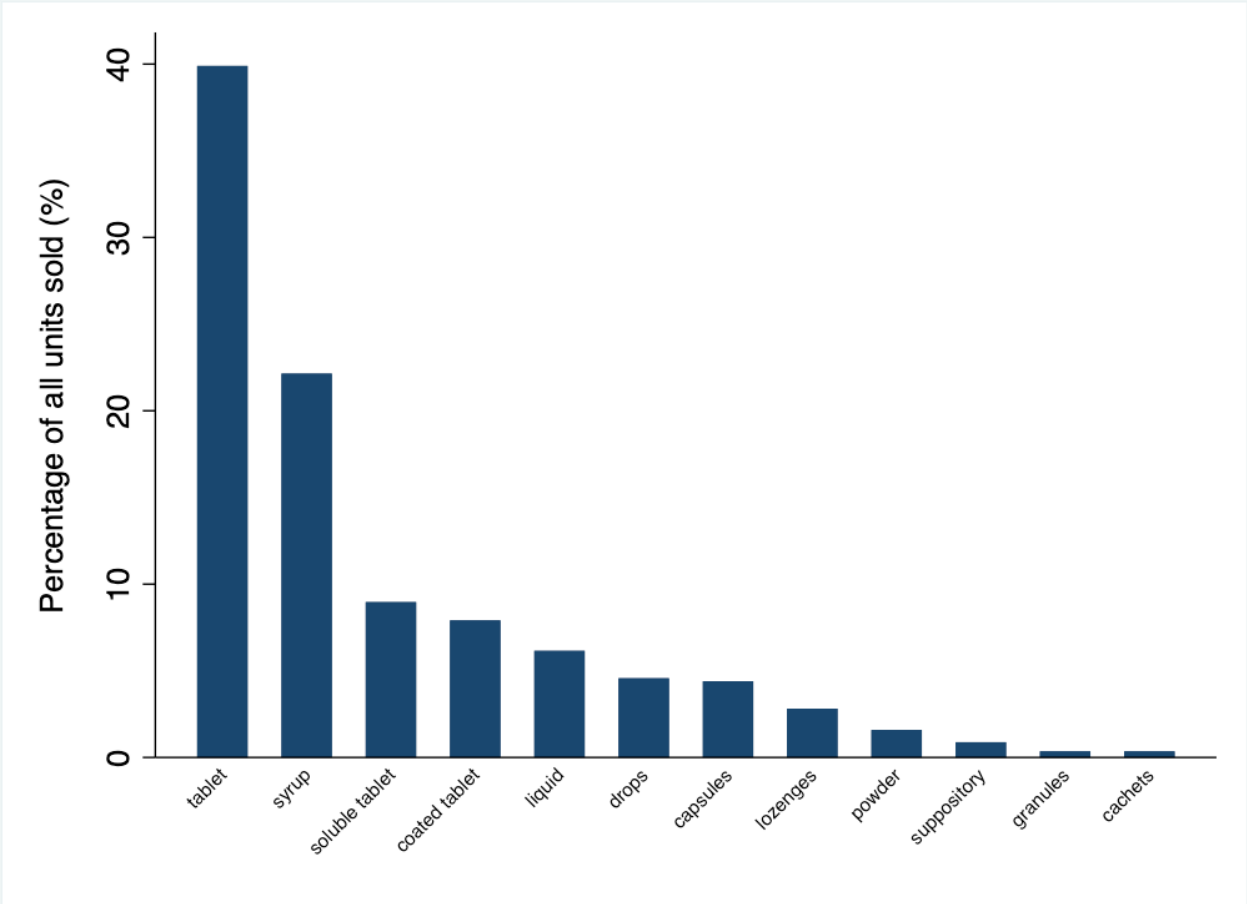


Figure 6.2: Percentage of all OTC codeine-containing products sold by formulation for 31 countries over six years (April 2013 to March 2019).

Over the study period (April 2013 to March 2019), 31.5 billion units of codeine were sold across 31 countries. The total sales volume increased by 2.8%, from 3025 units per 1000 in 2013-14 to 3111 units per 1000 in 2018-19. The distribution of sales between countries was not uniform, with five countries representing 90% of all OTC codeine sales. South Africa accounted for the greatest volume of sales (34%), followed by France (20%), Japan (17%), the UK (15%), and Poland (5%). South Africa had the greatest mean volume of OTC codeine sales (31 units/person), followed by Ireland (mean of 24 units/person), France (mean of 16 units/person),

Latvia (mean of 15 units/person), and the UK (mean of 12 units/person), see Figure 6.3 and Table 6.7.

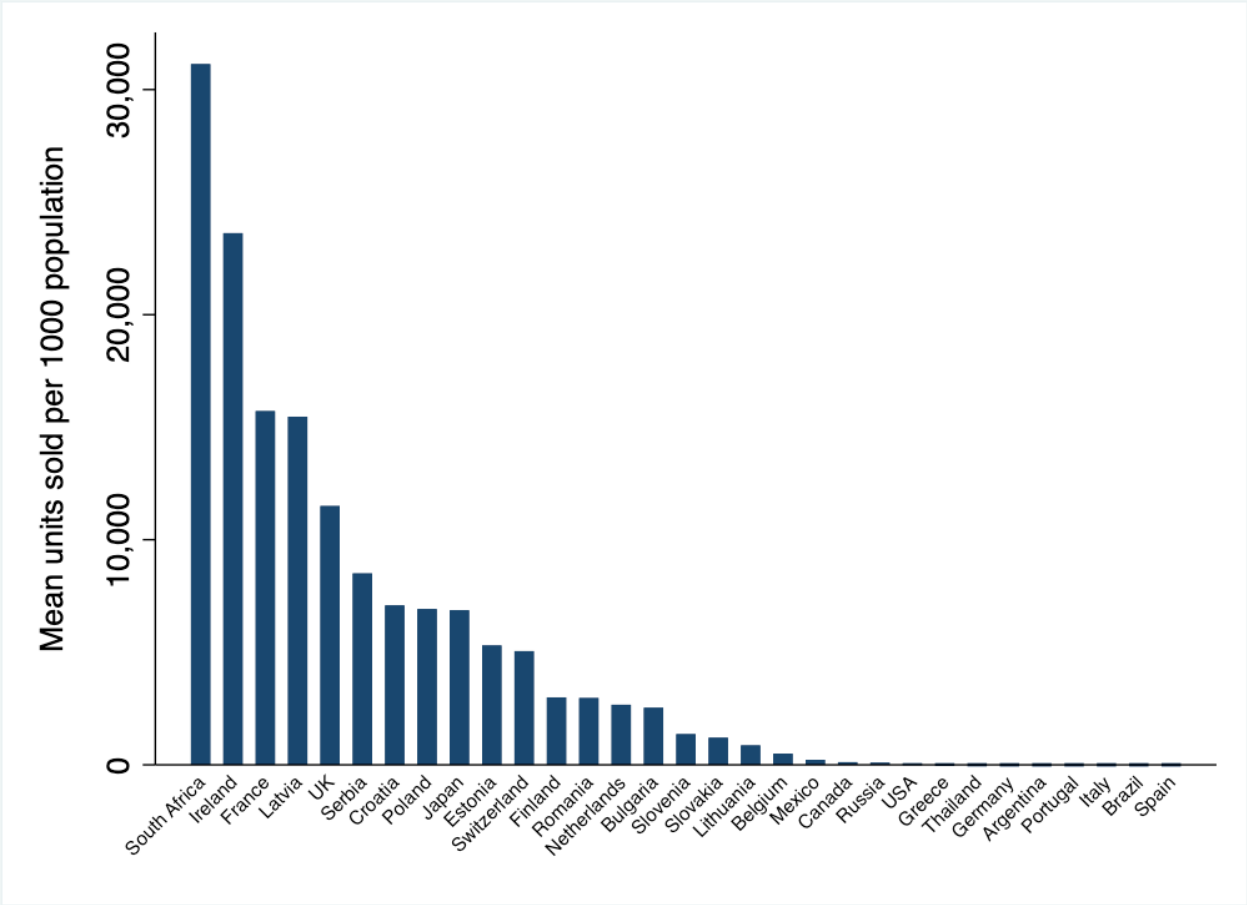


Figure 6.3: Mean volume of OTC codeine-containing units sold over six years in 31 countries with available data, ranked by countries with the greatest to least volume of sales

Table 6.7: Volume of OTC codeine-containing products sold between April 2013 and March 2019 in 31 countries

Country	**mean** units **sold per 1000 (SD)**	units **sold per 1000 in 2018-19**
Argentina	0.111 (0.19)	0
Belgium	497 (849)	144
Brazil	0.0018 (0.003)	0.0006

Bulgaria	2537 (163)	2674
Canada	117 (44)	177
Croatia	7084 (469)	6407
Estonia	5305 (1081)	6658
Finland	2996 (310)	2575
France	15717 (10558)	313
Germany	0.770 (0.18)	1
Greece	27 (16)	11
Ireland	23621 (2566)	22860
Italy	0.0068 (0.013)	0
Japan	6870 (4780)	10655
Latvia	15468 (682)	15544
Lithuania	865 (169)	1091
Mexico	221 (89)	341
Netherlands	2668 (299)	2290
Poland	6921 (598)	6893
Portugal	0.007 (0.01)	0
Romania	2969 (191)	3151
Russia	96 (41)	112
Serbia	8505 (451)	7921
Slovakia	1205 (74)	1214
Slovenia	1364 (93)	1274
South Africa	31133 (3154)	37775
Spain	0.0015 (0.004)	0
Switzerland	5051 (1473)	3494
Thailand	6 (3)	6
UK	11500 (333)	11157
USA	57 (26)	26

OTC: over-the-counter; SD: standard deviation.

In the most recent year of data (April 2018-March 2019), South Africa had the greatest volume of sales (38 units/person), followed by Ireland (23 units/person), Latvia (16 units/person), the UK (11 units/person), and Japan (10.7 units/person), see Table 6.7.

Over time, 48% of countries (15/31) had an increase in sales. For countries in the top quartile with the greatest sales volumes (top 8, Figure 6.4A), trends increased for South Africa (30%), Ireland (8%), Latvia (11%), and Poland (19%). Sales decreased for France (99%), the UK (7%), Serbia (4%), and Croatia (17%). For countries in the second-largest quartile for sales (Figure 6.4B), trends increased in Japan (1219%), Estonia (65%), Romania (10%), and Bulgaria (18%). Sales decreased in Switzerland (50%), Finland (22%), Netherlands (16%), and Slovenia (16%). Trends for countries in the bottom two quartiles are in Appendix 6.2 and Appendix 6.3.

6.5.3 Public expenditure on OTC codeine-containing products

Total public expenditure on OTC codeine-containing products in 31 countries over six years was £2.55 billion. During this time, public expenditure increased by 54%, from £196 per 1000 in 2013-14 to £301 per 1000 in 2018-19. Ireland had the greatest mean public expenditure of £5.70 per person, followed by the UK (mean of £1.60/person), South Africa (mean of £1.26/person), Croatia (mean of £1.25/person), and Estonia (mean of £1/person), see Figure 6.5 and Table 6.8. In the most recent year of data (April 2018-March 2019), Ireland continued to have the greatest public expenditure (£6.60/person), followed by South Africa (£1.637/person), the UK (£1.636/person), Japan (£1.47/person) and Estonia (£1.41), see Table 6.8. Over time, 58% of countries (18/31) had increased public expenditure. All countries in the top quartile of sales increased public expenditure over the six years, except France, in which sales fell by 97%

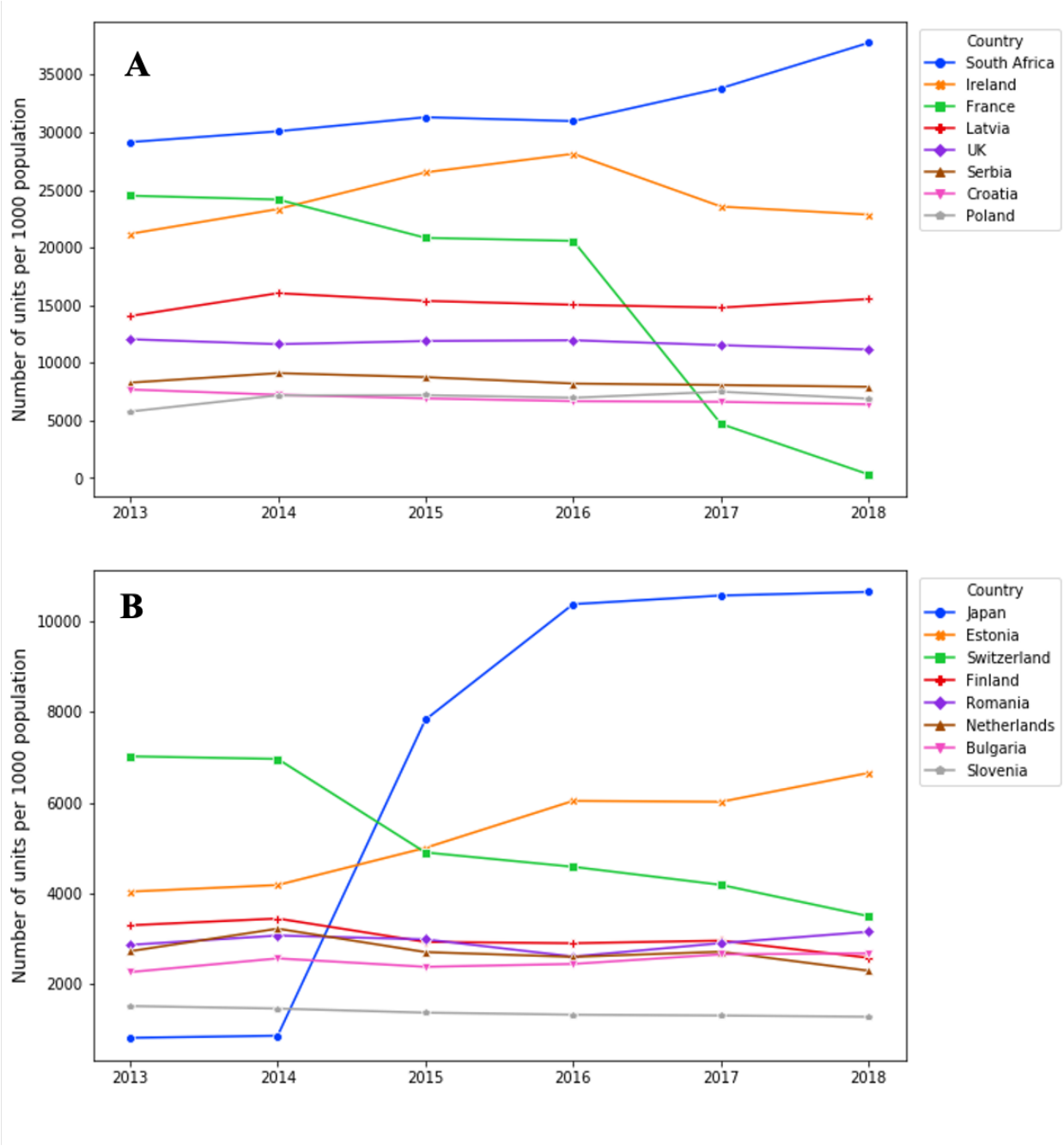


Figure 6.4: Sales of over-the-counter products containing codeine per 1000 of the population starting in April 2013-March 2014, ending in April 2018-March 2019, for countries in the top quartile of sales (A) and second quartile of sales (B).

(Figure 6.6). In South Africa, expenditure increased by 47%; in Ireland by 25%, Latvia 77%, the UK 12%, Serbia 27%, Croatia 1.5%, and Poland 51%.

In most countries, both sales and expenditure simultaneously either increased (45%, 14/31) or decreased (39%, 12/31), while in other countries (16%, 5/31), there was a discordance in the direction of the percentage changes (Figure 6.7).

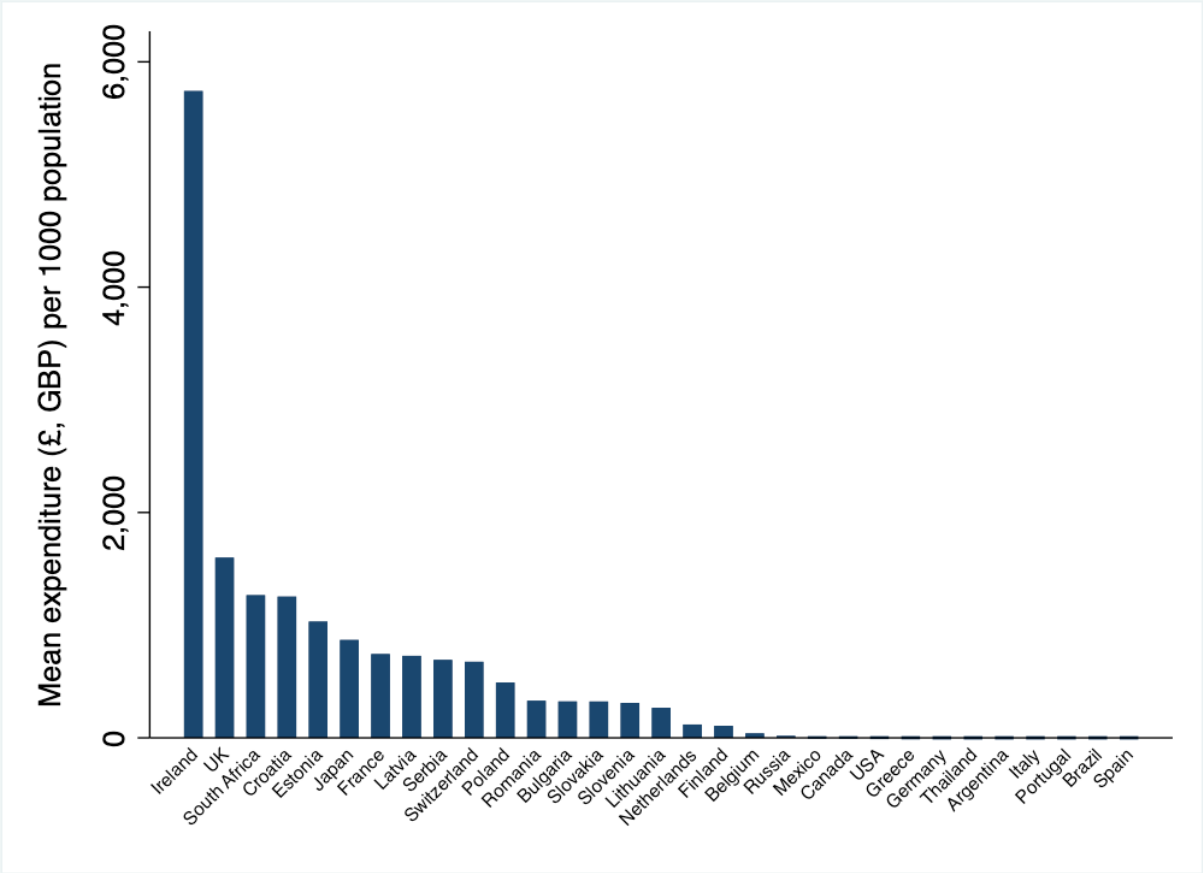


Figure 6.5: Mean public expenditure on OTC codeine-containing products sold over six years in 31 countries with available data, ranked by countries with the greatest to least volume of sales

Table 6.8: Public expenditure of OTC codeine-containing products sold between April 2013 and March 2019 in 31 countries.

Country	mean £ per 1000 (SD)	£ per 1000 in 2018-19
Argentina	0.002 (0.004)	0
Belgium	40 (40)	22.2
Brazil	0.0004 (0.0008)	0.0002
Bulgaria	323 (40)	373
Canada	7 (6)	4
Croatia	1254 (93)	1276
Estonia	1032 (273)	1413
Finland	106 (9)	100
France	743 (449)	31
Germany	0.136 (0.07)	0.262
Greece	1 (0.76)	0.608
Ireland	5741 (624)	6636
Italy	0.0018 (0.004)	0
Japan	869 (659)	1466
Latvia	728 (178)	994
Lithuania	266 (75)	372
Mexico	8 (3)	12
Netherlands	118 (10)	112
Poland	491 (89)	593
Portugal	0.0008 (0.001)	0
Romania	329 (63)	429
Russia	18 (8)	20
Serbia	692 (79)	794
Slovakia	323 (42)	374
Slovenia	309 (24)	307
South Africa	1266 (265)	1638

Spain	0.0001 (0.0003)	0
Switzerland	675 (80)	552
Thailand	0.117 (0.06)	0.149
UK	1599 (97)	1636
USA	4 (1)	2

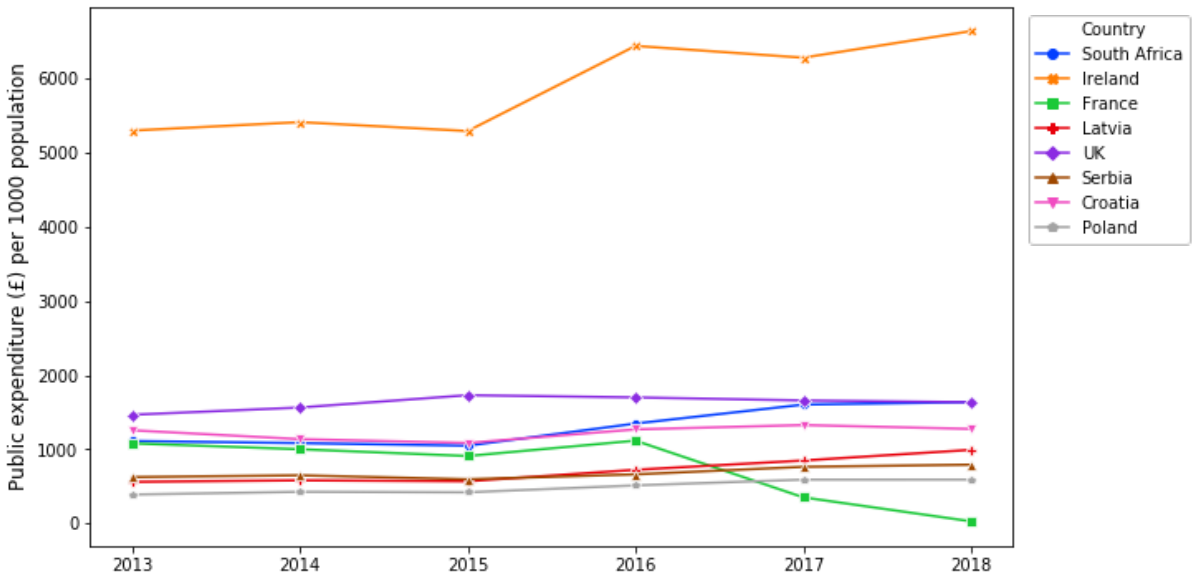


Figure 6.6: Public expenditure in GBP (£ sterling) per 1000 of the population on over-the-counter products containing codeine starting in April 2013-March 2014, and ending in April 2018-March 2019, for countries in the top quartile of sales

6.5.4 OTC codeine-containing products sold in the UK

There were 83 products containing codeine sold in the UK between April 2013 and March 2019. The UK sold codeine OTC in five formulations, with tablets (49%), effervescent tablets (20%), and liquids (13%) being the most common (Table 6.9). Products contained a median of 8 mg of codeine (IQR: 8-12.8 mg) and a median of two substances (IQR: 2-3) in their combinations, with

most (74%) containing paracetamol. Packs had a median of 30 units (IQR: 18-31 units), and liquids had a medium volume of 200 mL (IQR: 150-2000 mL).

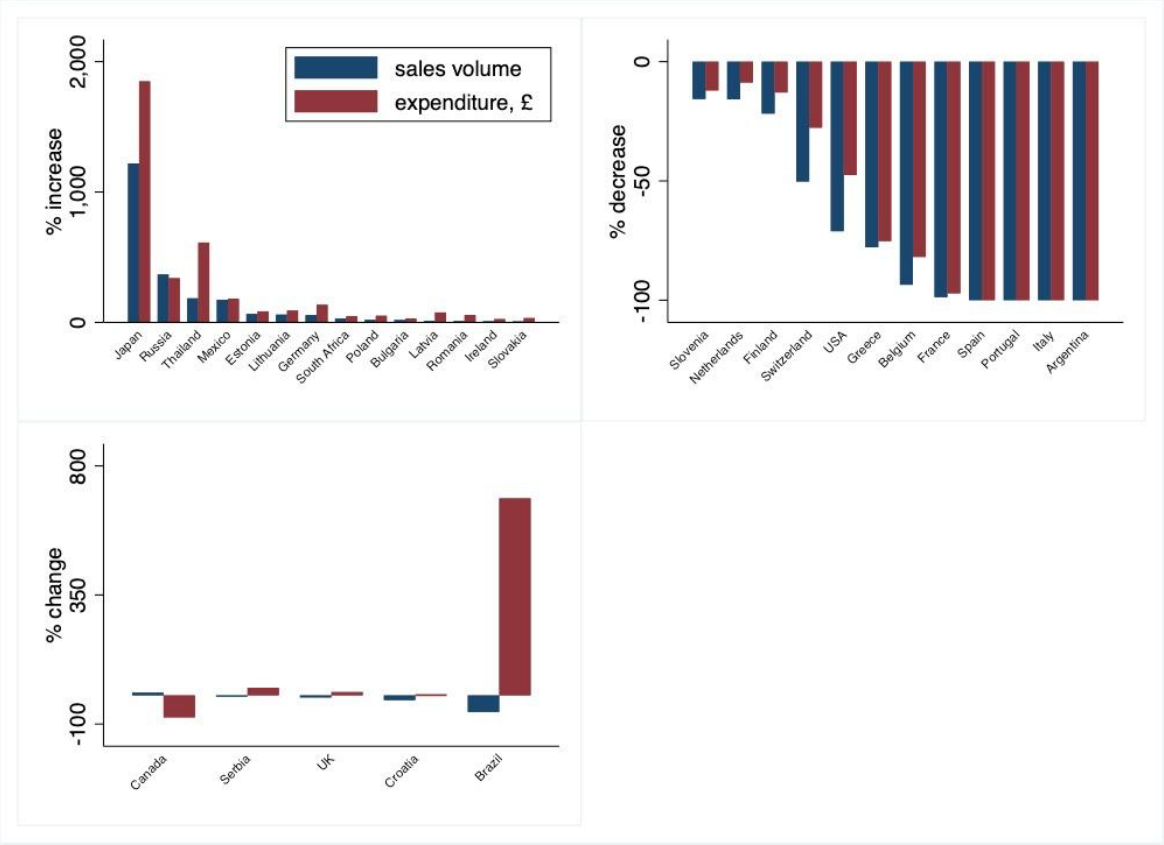


Figure 6.7: Percentage changes in sales volume (items sold per 1000 of the population) and public expenditure (£ per 1000 of the population) for products containing codeine sold OTC in all 31 countries between April 2013 and March 2019.

Over the 6-year study period, 46 tonnes of codeine (equivalent to 4.6 tonnes of morphine) and 10,046 kilolitres of codeine were sold OTC in the UK (Table 6.10). After adjusting for population, 694 mg of codeine and 19 mL of codeine for every UK resident were purchased. During this period, 1711 tonnes of paracetamol (26 g per person) and 96 tonnes of ibuprofen (1.4 g per person) were sold in combination with OTC codeine in the UK (Table 6.10).

Table 6.9: Types of products sold OTC containing codeine in the UK

	frequency (%)	median (IQR)
formulations		
tablets	41 (49.4)	-
effervescent tablets	17 (20.5)	
liquids	11 (13.3)	
capsules	7 (8.4)	
soluble tablets	7 (8.4)	
strength (mg)		
8	44 (53.0)	8 (8-12.8)
10	10 (12.1)	
12.8	15 (18.1)	
15	12 (14.5)	
30	2 (2.4)	
number of substances in combinations		
1	6 (7.2)	2 (2-3)
2	39 (47.0)	
3	27 (32.5)	
4	9 (10.8)	
6	2 (2.4)	
types of substances in combinations		
paracetamol	61 (73.5)	-
ibuprofen	9 (10.8)	
brompheniramine/pseudoephedrine	3 (3.6)	
aspirin	2 (2.4)	
expectorant	1 (1.2)	
inorganic acid	1 (1.2)	
size of packs (number of units)		
10	5 (6.9)	30 (18-32)
12	7 (9.7)	
16	6 (8.3)	
20	5 (6.9)	
24	12 (16.7)	
30	9 (12.5)	
32	17 (23.6)	
60	3 (4.2)	
100	8 (11.1)	
size of bottles (mL)		
90	1 (9.1)	200 (150-2000)
100	1 (9.1)	
150	1 (9.1)	
200	5 (45.5)	
2000	3 (27.3)	

Table 6.10: Volume of products containing codeine sold OTC in the UK over six years, starting in April 2013 and ending in March 2019, for solids and liquids

	6-year total	April 2018–March 2019
	solids	
amount of codeine (kg)	46108	7970
rate of codeine use (mg/person)	694	120
OME (kg)	4611	797
OME (mg/person)	69	12
no. of packs	108 million	17.5 million
packs/person	1.6	0.3
amount of paracetamol (kg)	1710956	280810
rate of paracetamol use (mg/person)	25739	4230
amount of ibuprofen (kg)	96020	18388
rate of ibuprofen use (mg/person)	1445	277
	liquids	
volume of codeine (kL)	10046	1291
rate of codeine use (mL/person)	151	19
no. of bottles	2649039	336677
bottles per 100 population	4.0	0.5
	dosage unit*	
total units of codeine	4.75 billion	763 million
total units per person	72	11.5

OME: oral morphine equivalent, calculated using a potency ratio of 0.1 (113).
*dosage units standardise volumes of liquid and solid dosage forms so they can be combined. For liquids, one unit was 12 mL of codeine, and for solids, this depended on the dosage of codeine in the product.

Over the study period, 4.75 billion dosage units of codeine were sold OTC (72 units per UK resident). Sales of OTC codeine fell by 8%, from 12.5 units per resident in April 2013-March 2014 to 11.5 units per resident in April 2018-March 2019 (Figure 6.8). The public spent £638 million (£9.6 per person) on OTC codeine-containing products, which increased by 12%, from £1.47 per person in April 2013-March 2014 to £1.64 in April 2018-March 2019 (Figure 6.9). One unit of codeine cost an average of £0.13 per dose (SD: 0.01), which increased by 22%, from £0.12 per dosage unit of codeine in April 2013-March 2014 to £0.14 per dosage unit of codeine in April 2018-March 2019.

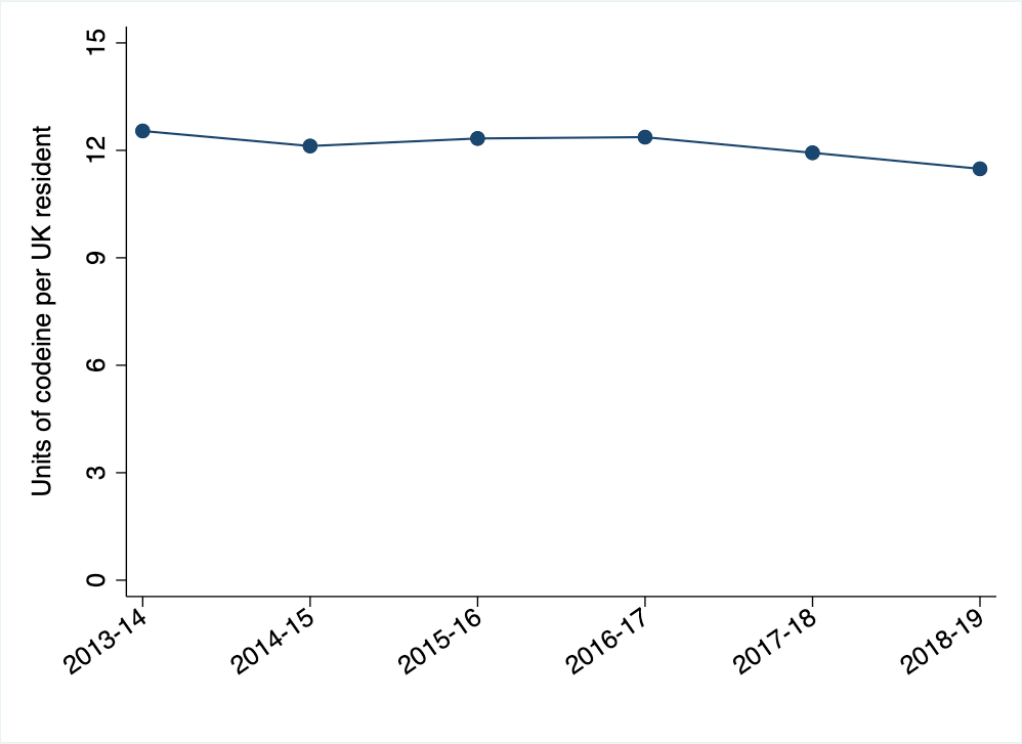


Figure 6.8: OTC products containing codeine sold in the UK

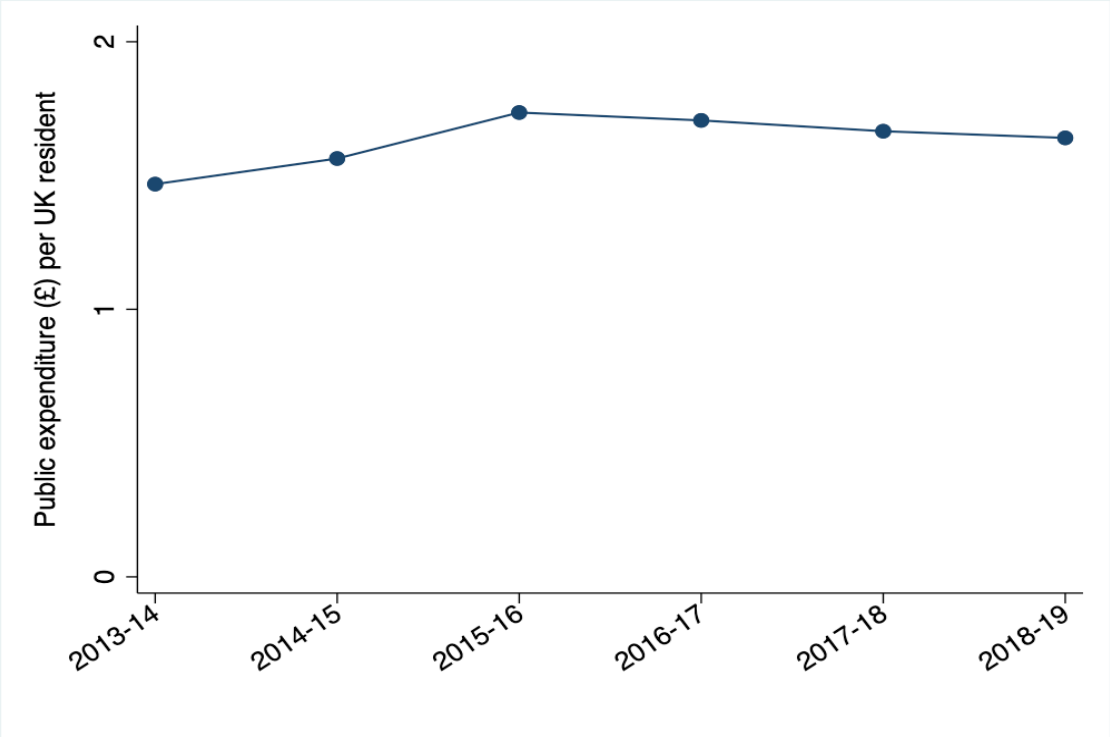


Figure 6.9: Public expenditure (£ per UK resident) on OTC codeine products in the UK

6.6 Discussion

6.6.1 Summary of findings

Between April 2013 and March 2019, 31.5 billion units of codeine, costing £2.55 billion, were sold OTC in 31 countries. Total sales and public expenditure across all countries increased by 3% and 54% respectively during this time. Five countries accounted for most of the sales (90%). South Africa, Ireland, and France had the greatest mean volume of OTC codeine sales per person. Ireland, the UK, and South Africa had the greatest mean public expenditure per person. Most countries (52%) had a decrease in sales volume over the six years but increased public expenditure. Sales of OTC codeine in the UK accounted for nearly one-sixth (15%) of the total volume; 4.75 billion units of codeine were purchased without a prescription, costing the public £638 million over the study period. In combination with codeine, 1711 tonnes of paracetamol and 96 tonnes of ibuprofen were purchased. Sales fell by 8% in the UK, but public expenditure increased by 12%. Across all countries, various products, formulations, combinations, dosages, and pack sizes of codeine were sold OTC.

6.6.2 Strengths and limitations

This chapter presents the first analysis of OTC sales of products containing codeine in the UK and abroad to the best of my knowledge. I used *IQVIA*'s "standard units" to analyse 31 countries and standardised UK sales to "dosage units" so that liquids and solids could be combined. But the availability of dosage data for all products sold in the UK allowed a more detailed analysis of the volumes of codeine, paracetamol, and ibuprofen and conversion of codeine to OME for solids. I did not convert liquids to OME, as there were limited data on the bioavailability of codeine from different oral formulations. A study of seven healthy adults following rectal or oral

administration of codeine showed no difference in bioavailability (328). This is useful, as Belgium, France, and Switzerland sold five products of codeine OTC as suppositories. However, for the 12 other oral formulations, I could not identify any evidence. I, therefore, assumed that all oral formulations of codeine (i.e. cachets, capsules, coated tablets, drops, effervescent tablets, granules, liquids, lozenges, powder, soluble tablets, syrups, and tablets) were bioequivalent.

My analysis included all countries with available data from *IQVIA,* which covered more than 70% of the pharmaceutical market for most countries; this was 67% for the UK. The skewed distribution of sales (90% of sales in five countries) may be attributed to the variation in *IQVIA*'s coverage for some countries, but it is more likely affected by regulatory changes and the accessibility and availability of codeine. For example, drug shortages are increasingly common in the UK and globally, increasing the costs of drugs (230,339,340). *IQVIA* converted expenditure to GBP for all countries, which may not accurately represent each country's currency's value overtime. I calculated rates using population statistics for all age groups, even though the data represented "adult" pain relief. Most codeine products were contraindicated in children and adolescents over the study period. Codeine-containing products may also be purchased from online pharmacies or the black market in large quantities (341), which were not captured in these data. The figures represent population-level sales and expenditure, providing a proxy for actual use. Thus, it is not possible to estimate the prevalence of use or associated harms. If codeine was reclassified to prescription-only in the UK, electronic health records could monitor the prevalence of use, misuse, and dependence on codeine.

6.6.3 Implications

6.6.3.1 Implications for policy

Codeine is listed in the WHO's Model List of Essential Medicines for pain and palliative care at 30 mg. It is included in 69% of national EMLs, see Chapter 4 (17), and is a Schedule III drug, deeming it "not liable to abuse and cannot produce ill effects" by the 1961 Single Convention on Narcotic Drugs (291). It is highly likely that regulations, such as the Single Convention, affect sales volumes and the types of products available. I found a wide range of products, formulations, dosages, pack sizes, and types of substances sold in combination with codeine, which may be attributed to variation in countries' policies. For example, in Bulgaria, Portugal, and Romania, five products contained phenacetin, an acetamide used for pain relief and fever, which was withdrawn from the market in the 1970s following increased reporting of urological diseases and cancers (342). However, access to and use of codeine has greatly increased across the globe since 1961, and our knowledge of codeine, its varying metabolism, associated harms, and lack of effectiveness at low doses is established (263,267,273,283). Some suggest that "if codeine had been discovered today, it would not have made it as far as the pharmacy shelves." (248) This accumulation of evidence questions whether codeine should be rescheduled in the Single Convention and by governments worldwide.

The WHO recommends weak opioids, such as codeine and tramadol (290,343), remain at their current schedules to reduce barriers and ensure access to pain relief for people in low- and middle-income countries, which I highlighted and discussed in Chapter 3 (15). Unlike the US opioid crisis, codeine misuse and abuse are not restricted to high-income countries (274,344,345). South Africa had the highest volume of OTC codeine sales over the study period

consistently. A study of opioid dependence in South Africa in 2008 showed that 5-8% of people in addiction treatment facilities reported problems with OTC codeine medications and cough mixtures as their primary or secondary drug of choice (345). But this has probably increased since 2008. The availability of non-prescribed codeine may also have ramifications for neighbouring countries that restrict access. For example, there are reports in Zimbabwe, which outlawed in 2015 OTC codeine syrups, that codeine-containing cough syrup called "BronCleer" is being illegally smuggled across borders from South Africa and sold on the streets (346). Governments in South Africa, Canada, Switzerland, and the UK are considering reclassifying codeine-containing products to prescription-only (105,311,338,347). Thus, my findings could be used by these governments to inform future regulatory changes.

Minnesota (July 2013), Manitoba (February 2016), France (July 2017), and Australia (February 2018) have reclassified codeine to prescription-only (244,300,302,307). My results show the effect of France's regulatory changes. France had the third highest mean volume of OTC codeine sales, but sales fell by 77% between 2016 and 2017 and by a further 93% in 2018. The impact of their regulatory change has not been evaluated in France. But studies in Australia showed a reduction in all codeine-related poisonings and no change in calls to poisons centres or sales for high-strength (>15 mg) codeine following reclassification (321,348). Regulatory changes in Manitoba, Canada, have also been effective in reducing the sales of codeine and had no significant effect on the rate of prescribed codeine (349). The Health Canada's 2016 announcement of proposed changes to reclassify OTC codeine did not significantly affect purchasing, but their 60-day public comment period on the proposed changes in September 2017 was associated with a 44% reduction in codeine purchased OTC (349). This Canadian study was

conducted following a meeting I arranged with Dr Tara Gomes while attending the Toronto GEM meeting. Dr Gomes is the Principal Investigator of Ontario's Drug Policy Research Network (ODPRN), and her research has been influential in researching the North American opioid crisis. I informed Dr Gomes of my success in obtaining data on OTC codeine sales in the UK, which led to her team acquiring OTC data for Canada from *IQVIA*. They also provided ODPRN with data by province, so geographical variation in purchasing was also assessed in our study, which was not possible in my UK analysis. The consistency of findings in Australia and Manitoba suggests that reclassifying OTC codeine in the UK might reduce the unsafe use of these products.

People seeking access to codeine in the UK have described current policies to restrict supplies as ineffective and consider that it is "easier" to obtain supplies from multiple pharmacies (277). Reducing pack sizes of OTC codeine and increasing warnings in patient information leaflets, as proposed by MHRA's Opioid EWG (105), were ineffective in reducing codeine misuse in Australia and are seen as inadequate measures for those already dependent on OTC codeine (277,284,350). Since MHRA's 2009 review (295), I identified 34 additional products containing codeine sold OTC in the UK. But the sheer volume of codeine, paracetamol, and ibuprofen being purchased in the UK should be considered by MHRA's Opioid EWG and lessons from other countries that have reclassified codeine to prescription-only should be investigated in the UK context.

There were opposing views when the Therapeutic Goods Administration (TGA) announced plans to up-schedule codeine in Australia. Consumers and pharmacists mostly questioned the

proposal, while GPs encouraged the changes (351). If codeine became prescription-only in the UK, people experiencing problems with OTC codeine could be identified and benefit from increased medical support or referral to pain or addiction services (352). But access to these resources can vary or be non-existent in some regions. The need for a consultation and prescription would increase workload and costs to the NHS. An evaluation before codeine was reclassified in Australia showed 99 admissions for OTC codeine-related complications in one tertiary teaching hospital, costing over $1 million AUD (285). Since codeine is a relatively cheap drug, managing codeine dependence and prescribing in primary care may be more cost-effective and may reduce the burden in the broader healthcare system. Pharmaceutical companies might also use regulatory change as an opportunity to increase costs for prescribed codeine, and my analysis showed that the cost per dosage unit has increased by 22% in the UK. Thus, economic evaluations are required, and procurement costs of codeine should be monitored.

If the reclassification of codeine to prescription-only were implemented in the UK, clear public health campaigns would be required to educate the public and prescribers. In the lead up to the ban in Australia, there were anecdotal reports of panic buying of OTC codeine products (244) and a fear that the public might purchase more non-opioid analgesics OTC (353), which might cause further harm. There were also concerns that patients would be switched to higher strength codeine products or more potent opioids (244,351), as these products are more effective and cost less than low doses of codeine on prescription. Before reclassification in Australia, a real-time monitoring programme, similar to the one they use for pseudoephedrine sales, called project STOP (354,355), was implemented in pharmacies to track purchasing OTC codeine (244). This required a customer to show identification to check their recent codeine purchases. If no changes

are made to the status of codeine in the UK, my findings still support the need for further education on the appropriate use of codeine and the need for real-time monitoring of OTC codeine sales and their harms.

6.6.3.2 Implications for patients, the public, and clinical practice

Self-care and self-medication practices are essential components of any healthcare system. Access to OTC products empowers patients to be active participants in their health and manage self-limiting conditions without consulting a GP. In December 2017, the Royal College of General Practitioners (RCGP) in the UK launched the '*3 before GP'* campaign to combat winter workload pressures (356). However, not all medicines available OTC are of low risk, and there are often misconceptions among the public that medicines without a prescription are relatively safe (277). While my findings show that there are probably many people worldwide purchasing and consuming codeine from OTC products, the prevalence of codeine misuse, abuse, and dependence is unclear. In the UK, 2.2% of people in drug treatment in 2013/14 reported codeine as a primary or secondary drug of abuse (357). However, those affected by codeine misuse and dependence are reportedly hard to reach and do not engage with formal treatment services (278). A survey of adults in the UK and Ireland who used OTC codeine found that respondents were more likely to seek advice on how to control their codeine use from the internet than from their GP (273). One-third of participants in a Northern Ireland survey reported having personally encountered cases of OTC abuse (358). Thus, it is likely that the misuse of OTC codeine is under-reported and often unreported.

GPs have raised concerns over identifying codeine use and the ramifications if codeine became prescription-only in the UK. In a qualitative study with medical professionals, one British GP participant stated, "*It is very difficult to control patients' codeine use, as they may use multiple pharmacies, buy from friends or online. I don't think we have fully woken up to the scale of the problem of opiate dependence."* (139). In response to MHRA's Opioid EWG announcement considering reclassifying codeine in 2020, a GP partner indicated it would have "significant implications" for workload, and added, while it "may be the right thing to do", agencies must "coordinate" over an opioid strategy so that patients are not left "in the lurch" (245). In the meantime, clinicians should ask patients about non-prescription medications when taking a medication history and consider OTC codeine misuse in patients who present with NSAIDs or paracetamol-related morbidity. Patients, caregivers, and the public should be informed on how to recognise the signs of morphine toxicity, which may include reduced levels of consciousness; lack of appetite; somnolence; constipation; respiratory depression; pin-point pupils; or nausea and vomiting, and that medical attention should be sought immediately if these signs or symptoms appear.

Selling and prescribing codeine requires at least as much vigilance as morphine, despite their reputation and regulatory differences. Studies that have analysed public posts on Instagram, lyrics of hip-hop music, and US hip-hop artists' deaths (360–362), which promote abuse of low-dose codeine products. One study showed that drug-related messages in music predicted substance misuse in young adults aged 16-25 years and that drug-related slang was nearly 19 times more common in 2017 than in 2007 (362). A scoping review on the non-medical use of pharmaceuticals identified several ways in which codeine was reportedly abused, including

mixtures with alcohol or soft drinks (e.g. “purple drank”), with kratom leaves (e.g. “kratom cocktails”), and in the production of home-made opiates (e.g. “krokodil”) (363). Public health interventions using a multidisciplinary approach that integrates regulation, enforcement, health surveillance, and service delivery are therefore needed to prevent “pharmacy shopping”. But these should be tailored to counteract the glamourisation of codeine misuse in young adults. The hip-hop song entitled “1-800-273-8255”, the US suicide hotline, by rapper Logic significantly increased public awareness of the National Suicide Prevention Lifeline (364). Thus, hip-hop music can also be used to prevent rather than promote a generation from “*sippin' cough syrup like it’s water*”.

6.6.4 Implications for future research

A €2.04 million grant was provided under the FP7 Marie Curie Industry-Academia Partnerships and Pathways strand in 2015 to the CODEMISUSED collaboration to quantify the extent of codeine use, misuse, and dependence in the UK, Ireland, and South Africa (365). But questions and gaps in the evidence-base remained. My chapter fills one of these gaps and illustrates that it is possible to obtain data on OTC codeine sales in the UK and abroad. Future research can therefore use my methods and purchase such data to monitor the sales of OTC codeine in other countries, as we conducted in Canada, and test the effectiveness and implementation of regulatory changes and measures. If codeine remains available OTC in the UK, real-time monitoring systems could be implemented to reduce pharmacy shopping (354,355). Pharmacovigilance databases should be explored, such as hospital admissions data and the MHRA’s Yellow Card Scheme, to identify the impact of regulatory changes and monitor the extent of the codeine problem in the UK. Systematic methods described previously (20,293)

could be used to update my rapid review of policies on OTC codeine globally. As these policies are rapidly changing, funding could be sought to create a "codeine policy tracker" to map and update regulatory changes in real-time, as constructed during the COVID-19 pandemic (366,367). Future research could also assess the impact of Brexit and the COVID-19 pandemic on OTC codeine sales in the UK.

6.7 Conclusion

Codeine is one of the most widely accessible and most widely used opioids worldwide. However, monitoring its use and preventing its misuse is a public health challenge. This chapter illustrates that sales of OTC codeine can be assessed, filling a critical evidence gap. Overall, sales and expenditure on OTC codeine products have increased. However, purchasing has fallen slightly in the UK, in line with recent opioid prescribing trends in England. Nevertheless, the total volume of products containing codeine being sold in the UK is significant. These findings illustrate that measures are needed to identify and prevent codeine misuse, increase awareness and education of codeine, and review policies to ensure optimal safety. When regulating the level of access to OTC codeine, interindividual pharmacogenetic variability, lack of information on efficacy and safety at low doses, and harms reported in observational studies should be wholly considered.

6.8 Chapter summary

- I evaluated sales and public expenditure on products containing codeine sold OTC over the six years between April 2013 and March 2019.
- I sourced OTC sales data for the UK and 30 other countries from the human data science company *IQVIA*.
- 31.5 billion units of codeine, costing £2.55 billion, were sold OTC across 31 countries in 6 years, with 3% and 54% respective increases during that time.
- 4.75 billion dosage units of codeine in combination with 1711 tonnes of paracetamol and 96 tonnes of ibuprofen were purchased OTC in the UK over six years, costing the UK public £638 million.
- In the UK, sales of OTC codeine-containing products fell by 8%, and public expenditure increased by 12%.
- These data can be used to monitor regulatory changes and should be used by governments to improve the safety of codeine products and prevent their misuse and abuse.

Chapter 7

"*All things are poison, and nothing is without poison; the dosage alone makes it, so a thing is not a poison*."
Paracelsus, 1538

*This chapter is based on my first-author publication in *BMC Medicine* (21) which was disseminated in The Conversation (22). I presented the protocol for this study as a poster at the 6th EBMLive conference in Oxford (June 18-20, 2018) and the Rotary District 1090 annual conference in Portsmouth (March 9, 2019). The abstract from EBMLive was published in *BMJ Evidence Based Medicine* (24). I presented preliminary findings at the Clinical Pharmacology Colloquium in Bangor, Wales (May 12, 2018) and a poster of the complete results at the British Pharmacology Society's "Pharmacology 2019" conference in Edinburgh, Scotland (December 15-17, 2019), which was selected for publication in the *British Journal of Clinical Pharmacology* (23).

7 Systematic review of factors associated with prescribing of high-dose opioids in high-income primary care settings

7.1 Chapter rationale

In this chapter, I aim to address the third key knowledge gap of "what is driving the increase in high-dose prescribing of opioids?" and assess drivers of suboptimal use. In chapter 2, section 2.5, I reported a 6.7-fold increase in prescribing high-dose opioids in England, from 3 prescriptions per 1000 of the population in 1998 to 23 prescriptions in 2016 (3). Other high-income countries, including Australia, Canada, and the USA, have found similar increases in prescribing high-dose

opioids (368–370). Yet little is known about what leads to high-dose prescribing, and observational studies exploring this have not been synthesised.

7.2 Introduction and Aim

High dosages of opioids are indicated in palliative care and cancer pain (118). However, there is little evidence on the effectiveness and safety of opioids at high doses for people with chronic pain. A Cochrane overview of systematic reviews on high-dose opioids for chronic non-cancer pain found no studies or data that could be included or extracted (119). Thus, clinical guidelines caution against prescribing high doses and recommend reducing or withdrawing opioids when the risk of harm outweighs the chance of benefit (92,93,129). In August 2020, NICE published their draft guidelines for chronic pain in over 16s, which advised against prescribing opioids all together (104). However, the adoption of strict guidelines may prevent patients from seeking care and limit the willingness of primary care clinics to prescribe, which could lead to unintended consequences, such as conversion to illicit opiates, and reduce the management of comorbidities such as depression (371,372).

Most people with chronic pain are managed in primary care (373). However, most primary care physicians perceive chronic non-cancer pain to be the most challenging condition to treat (214,215). While primary care remains the ideal setting for identifying and managing such patients, there is little evidence on best practices for managing people taking high doses of opioids (12). Thus, understanding who is taking high doses and driving high-dose prescribing would help reduce such uncertainties. Therefore, this study aimed to systematically synthesise patient-level observational data to explore drivers of high-dose opioid use in high-income primary care settings.

7.3 Objectives

1. to determine the number of people receiving high-dose opioids in primary care; and
2. to explore factors associated with the prescribing of high-dose opioids.

7.4 Methods

I designed this systematic review using the Cochrane Handbook for Systematic Reviews of Interventions (374), adapting it for observational studies.

7.4.1 Search strategy

I developed the search strategy for Medline (Ovid) and adapted the search strategy for Embase (Ovid) and Web of Science Core Collection (excluding Chemical Indexes), which was reviewed by an information specialist (NR). I used the terms "opioid*", "prescri*", "factor*", "primary healthcare", and variations of these terms (Appendix 7.1). I included proprietary and non-proprietary drug names for high-income countries by searching the UpToDate database in January 2018 to generate a list of opioids (Appendix 7.2). I searched from database inception to February 12 2018, and updated the search on April 5 2019.

7.4.2 Study selection

I exported the searches to Endnote X8 and removed duplicates. I screened titles and abstracts, and full texts for eligibility independently to my second reviewers (TBM; NJD). When inclusion could not be confirmed, I contacted the authors of the studies by electronic mail for clarification. I resolved disagreements by consensus or with a third study author (KRM; CH). I hand searched forward citations and reference lists of included studies. I used conference proceedings to capture

potentially eligible studies, but abstracts were not included unless a complete manuscript with data was published.

7.4.3 Eligibility criteria

I included quantitative observational studies if they

1. were conducted in primary care, defined as the first point of contact for care that can provide continuity of care, including general practice, family medicine, community pharmacy, and dental and optometry services (375);
2. were conducted in a high-income country defined by the World Bank (376);
3. included adults (≥18 years old) for whom opioids had been prescribed, stratified by oral morphine equivalents (OME) in milligrams per day (mg/day), with one or more group(s) receiving high doses. I defined high dose as ≥90 OME mg/day, as this is the lowest high-dose threshold recommended by guidelines (92,128);
4. presented summarised patient-level data; and
5. reported any factor or factors stratified by high-dose and low-dose opioid groups. I considered all languages.

I excluded studies if

1. they were conducted in nursing homes, emergency departments, out-of-hours clinics, outpatient clinics, secondary or tertiary care, or a combination of these (i.e. mixed care settings);
2. opioids were measured using a different metric to OME mg/day (e.g. defined daily dose or prescription rate per 1000 population) because OME best reflects prescribing in clinical practice (133); and

3. the study wholly focused on palliative care, cancer pain, pregnancy or labour pain, opioid-related misuse, overdose and/or death, illicit or non-prescribed opioids, opioid receptor antagonists, and non-community dwelling adults (e.g. prisoners and military personnel).

7.4.4 Data extraction

I extracted data independently from a second study author (TBM) using a predeveloped data extraction spreadsheet. This included: 1) general information and study characteristics: year of publication, geographical location, specific primary care setting, study design, data source, included and excluded populations, and sample size; 2) exposures: high-dose and low-dose thresholds, duration of dose, methods for calculating doses, and morphine equivalent conversion factors; and 3) factors reported by each study (i.e. age, gender, measures of depression). If two or more studies reported a factor, a second author (NJD) extracted the raw data. I resolved disagreements by discussion.

7.4.5 Quality and risk of bias assessment

I assessed the quality of included studies independently to a second study author (TBM) using the National Institute of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI) *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* (377) because it assesses cohort and cross-sectional studies simultaneously. The tool evaluates the quality of the research question, reporting of the study population, participation rate, selection of participants, sample size, appropriateness of statistical analyses, time frame for associations, levels of exposures, ascertainment of the exposure, appropriateness of outcome measures, outcome blinding of assessors, loss to follow-up and adjustment for confounding, which provide an

overall rating of 'good', 'fair' or 'poor'. I resolved disagreements by discussions with a third author when required (KRM, CH). I also extracted information regarding ethical approvals, participant enrolment incentives, study sponsorship, and declarations of conflicts of interests (COIs) because of the pharmaceutical company involved in the opioid crisis (378).

7.4.6 Data synthesis and analysis

I synthesised participant data from each study to determine the total number of people taking opioids and the percentage of whom high and low doses were prescribed. Before pooling data, I sought statistical advice (CK). For factors, I pooled data using a random effects model when two or more studies reported the same outcome measured similarly. For binary outcomes, I have reported relative risks (RR) with 95% confidence intervals (CIs) and have calculated the number needed to harm (NNT_H) for outcomes that were behavioural in nature. For continuous data, I have calculated the mean differences between high-dose and low-dose groups. When the median, range, and/or interquartile range were reported, I used Wan and colleagues' method to calculate the sample mean and standard deviation (SD) (379). When a study included more than two dose groups, I combined the sample means and SDs using Cochrane's formulae for combining groups (380). When I found considerable heterogeneity, defined as $I^2 \geq 75\%$ (381), I conducted sensitivity analyses by removing outliers. Subgroup analyses were not possible, owing to the small number of included studies.

7.4.7 Statistical software and open science practices

I used Stata v16 for all statistical analyses. I prospectively registered my protocol on the International Prospective Register of Systematic Reviews database (PROSPERO registration ID: CRD42018088057) and shared my study materials, data, and statistical code (Table 7.1).

Table 7.1: Open Science Checklist for Chapter 5 on the Oxford Catalogue of Opioids

Principles		Links
Open methods	Protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=88057
	Preregistration	yes, as above
	Materials	https://osf.io/cd5a9/
	Statistical code	https://osf.io/cd5a9/
Open data	Data	https://osf.io/cd5a9/
Open access	Pre-print	no
	Publication	https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01528-7
	Blog	https://theconversation.com/high-dose-opioids-five-factors-that-increase-the-risk-of-harm-133546
	Tool	no

7.5 Results

Six studies met the eligibility criteria after screening 5292 titles and abstracts and 131 full-text articles (Figure 7.1). The characteristics of participants and included studies are summarised in Table 7.2. Included studies were from three high-income countries: Australia, the UK, and the USA.

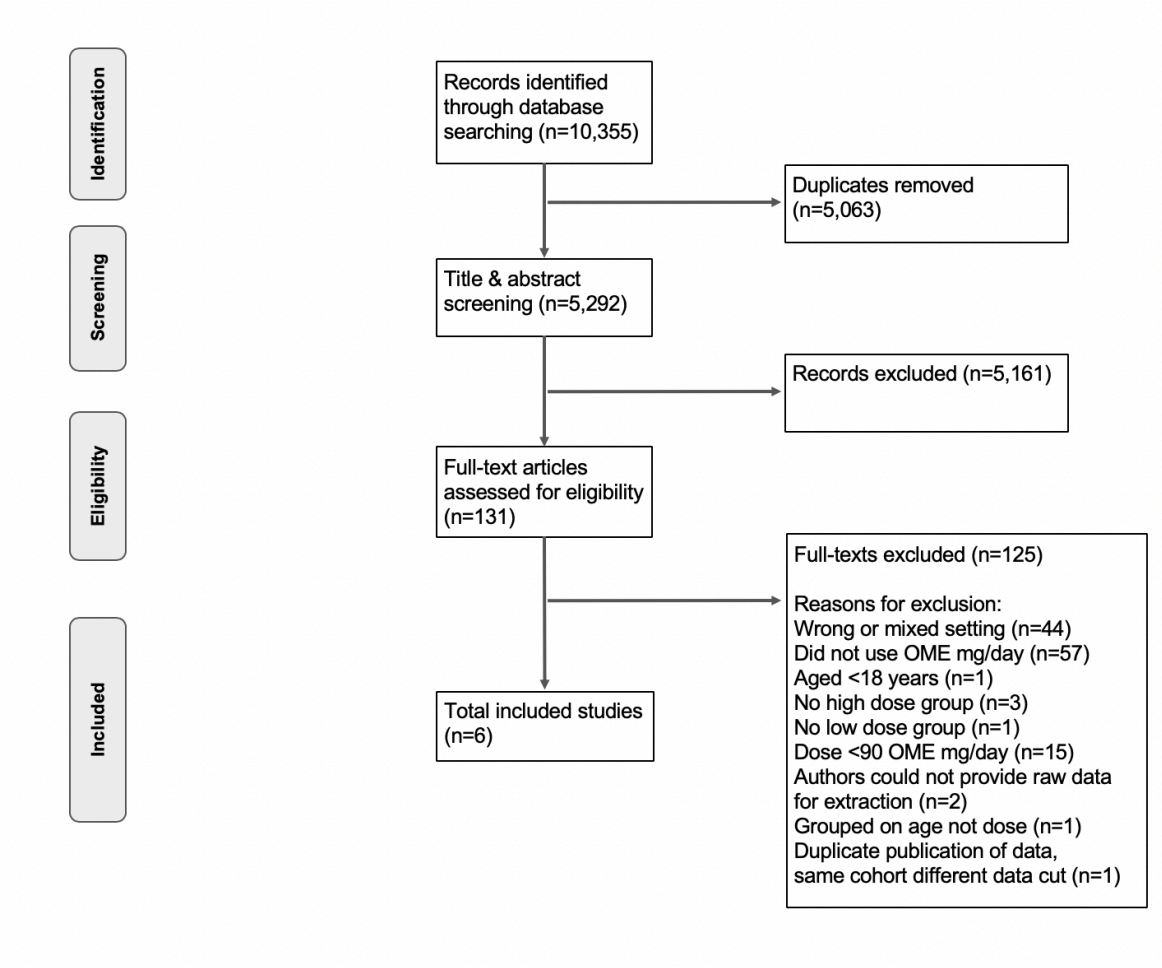


Figure 7.1: Flow diagram of the study inclusion.

7.5.1 Number of people receiving high-dose opioids in primary care

The studies included more than 4.2 million people taking opioids (n=4,248,119), of whom 3.6% (n=154,749) were using high-dose formulations. The numbers of people taking high doses were not equally distributed across studies (median: 439, IQR: 262–2778) or countries. The USA had the greatest number of people taking opioids (n=154,062) but the smallest percentage (3.6%) of participants taking high doses (Table 7.2). Australia had the highest percentage of participants taking high doses (39.2%, 425 of 1085), followed by the UK (6.5%, 262 of 4035).

Table 7.2: Characteristics of participants and included studies ordered by study design and year of publication

Study ID Country	Data source	Population	Duration to determine the opioid dose	Dose groups			
				High dose		Low dose	
Cross-sectional studies				**mg/day**	**N**	**mg/day**	**N**
Morasco, 2019 USA	Electronic medical records & self-reported measures	51 patients aged 18-70 yrs. receiving opioids for musculoskeletal pain	90-day average	≥100	17	5 – 99	34
Chang, 2018a USA	QuintilesIMS' LifeLink longitudinal prescription database linked to patient & prescriber files	4046275 patients aged ≥ 18 yrs prescribed an opioid	90-day average	>100	150814	≤100	3895461
Cohort studies				**mg/day**	**N**	**mg/day**	**N**
Chang, 2018b USA	QuintilesIMS patient-level administrative claims	191405 patients aged 18-64 years with at least one prescription opioid claim	90-day average	>100	2778	≤100	188627
Campbell, 2015 Australia	Telephone interviews, self-reported questionnaire & medication diary	1085 patients aged ≥18 yrs. with CNCP prescribed an opioid for >6 weeks	1-week average	≥91	425	1 – 90	660
Chapman, 2013 UK	CPRD	4035 patients with CNCP, ≥2 office visits & ≥1 prescription of fentanyl, hydromorphone, morphine & or oxycodone	Dose measured at each visit	>200	262	≤200	3773
Kobus, 2012 USA	Kaiser Permanente Northwest virtual data warehouse	5268 patients aged ≥18 yrs with low-back pain & > 90 consecutive days of opioid use	Last dispensed dose	≥100	453	1 – 99	4815

CNCP: chronic non-cancer pain; CPRD: Clinical practice research datalink; UK: United Kingdom; USA: United States of America

The numbers of participants in each study were also not normally distributed (median 4652, IQR: 1085–191,405). One large cross-sectional study conducted in the USA accounted for most of the participants (382). This study used a large administrative database from QuintilesIMS. Three cohort studies used databases that represent large populations - QuintilesIMS in the USA (which captures 75% of community prescriptions) (383), the Kaiser Permanente Northwest virtual data warehouse in the USA (384), and the CPRD in the UK (6). The smaller studies conducted in the USA (385) and Australia (386) actively recruited participants from primary care using self-reported questionnaires and measures.

7.5.2 Factors associated with high-dose opioids – meta-analysis

High-dose opioids were significantly associated with co-prescription of benzodiazepines (RR: 3.27, 95% CI: 1.32 to 8.13, I^2 = 99.9%, 4 studies; n=4,248,119, Figure 7.3). The high degree of heterogeneity is attributable to the two large studies that showed that participants taking high doses had respectively five- and nine-fold greater risks of having benzodiazepines co-prescribed than participants taking low doses. In a sensitivity analysis removing these studies, high doses were still significantly associated with co-prescription of benzodiazepines, with no heterogeneity (RR: 1.47, 95% CI: 1.37 to 1.59, I^2 = 0%, two studies; n=6353, Figure 7.4).

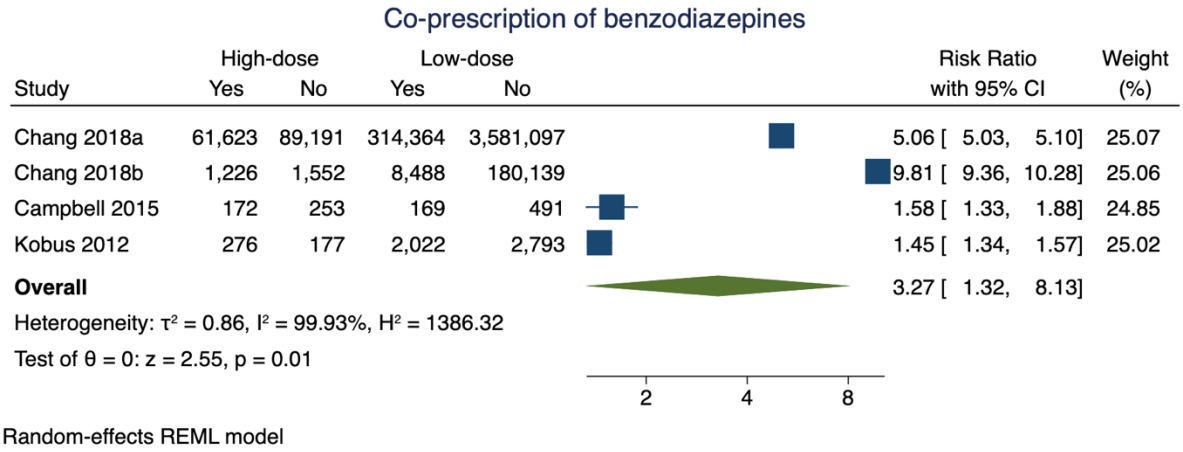


Figure 7.3: Forrest plot of studies that reported the use of benzodiazepines in people taking high and low doses of opioids in primary care

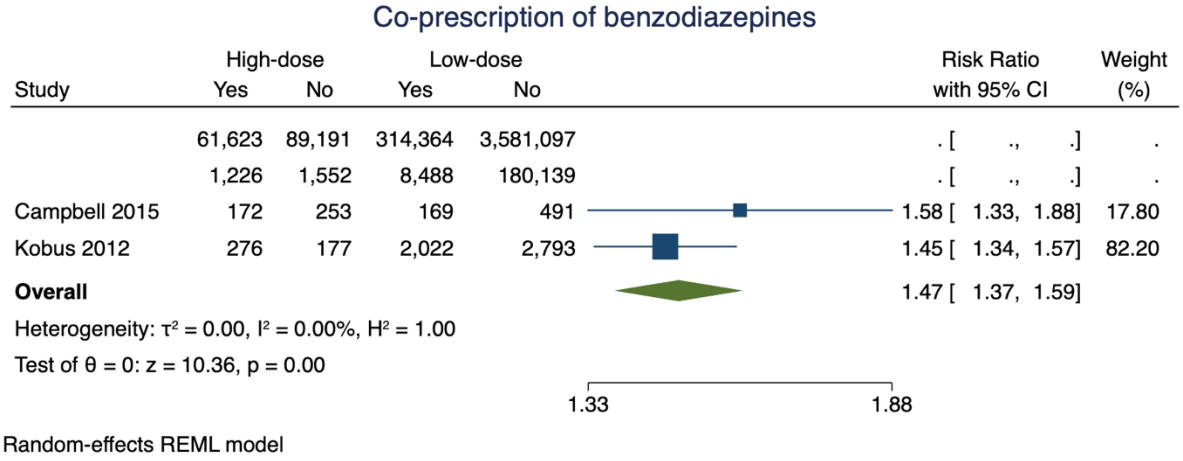
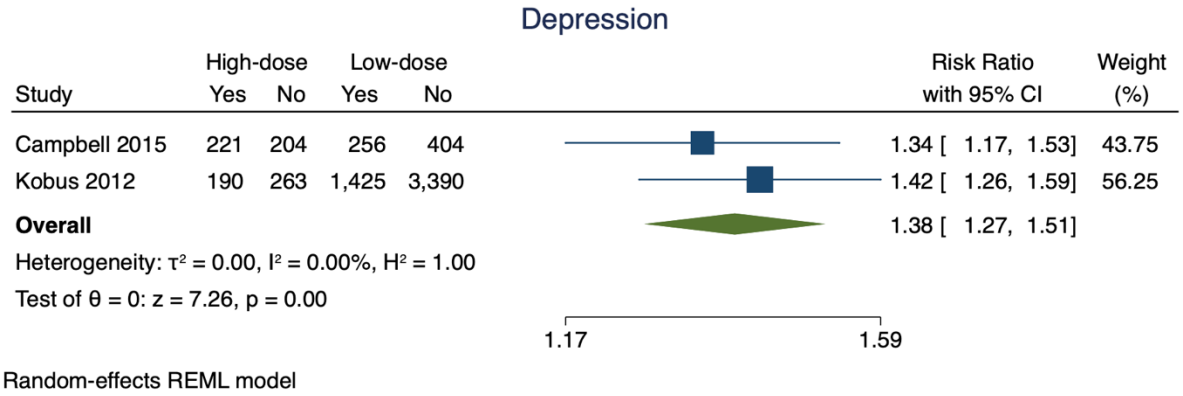


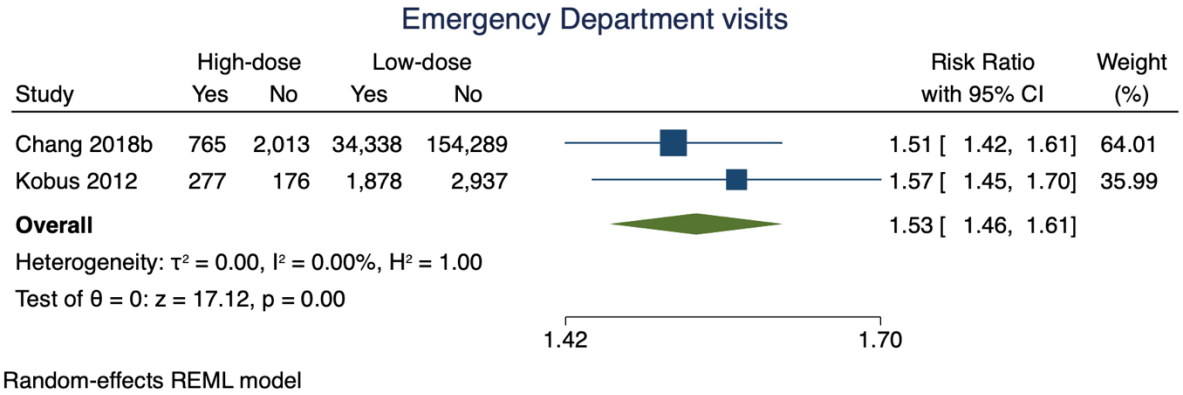
Figure 7.4: Sensitivity analysis removing two large studies that reported the use of benzodiazepines in people taking high and low doses of opioids in primary care

High-dose opioids were also significantly associated with depression (RR: 1.38, 95% CI: 1.27 to 1.51, I^2 = 0%, 2 studies; n=6353), visits to Emergency Departments (RR: 1.53, 95% CI: 1.46 to 1.61, I^2 = 0%, 2 studies; n=196673, NNT_H: 15, 95% CI: 12 to 20), unemployment (RR: 1.44, 95% CI: 1.27 to 1.63, I^2 = 0%, 2 studies; n=1136), and being male (RR 1.21, 95% CI 1.14 to 1.28, I^2 = 78.6%, 6 studies; n = 4,248,119), when compared with participants taking low doses of opioids (Figure 7.5 and Figure 7.6). In a sensitivity analysis for gender, removing Chang 2018a, participants taking high doses of opioids were still 1.2 times more likely to be males than participants taking low doses, with minimal heterogeneity (RR: 1.18, 95% CI: 1.14 to 1.22, I^2 = 0.01%, 5 studies; n=201,844, Figure 7.7).

7.5.3 Factors associated with high-dose opioids – individual studies

There were 23 factors reported by single studies that were significantly associated with high-dose opioids (Table 7.3). For example, the diagnosis of pharmaceutical opioid dependence at 12 months was significantly associated with high doses (RR: 3.11, 95% CI: 1.61 to 5.98, n=1085). Participants for whom high doses were prescribed had 29 times the risk of an opioid disorder than participants taking low doses (RR: 29, 95% CI: 26 to 32, n=191,405). For every 22 participants taking high doses, one reported tampering with their opioids (RR: 2.03, 95% CI: 1.27 to 3.25, n=1085, NNT_H: 22, 95% CI: 13 to 64). Participants taking high doses were more likely to have visited a pain clinic within six months of entering or leaving the study (RR: 2.09, 95% CI: 1.73 to 2.51, n=5268; NNT_H: 8, 95% CI: 6 to 12). High-dose opioids were also significantly associated with receiving 50% or more of one's prescriptions from a high-risk prescriber, defined as a prescriber in the top 5th percentile of opioid volume.





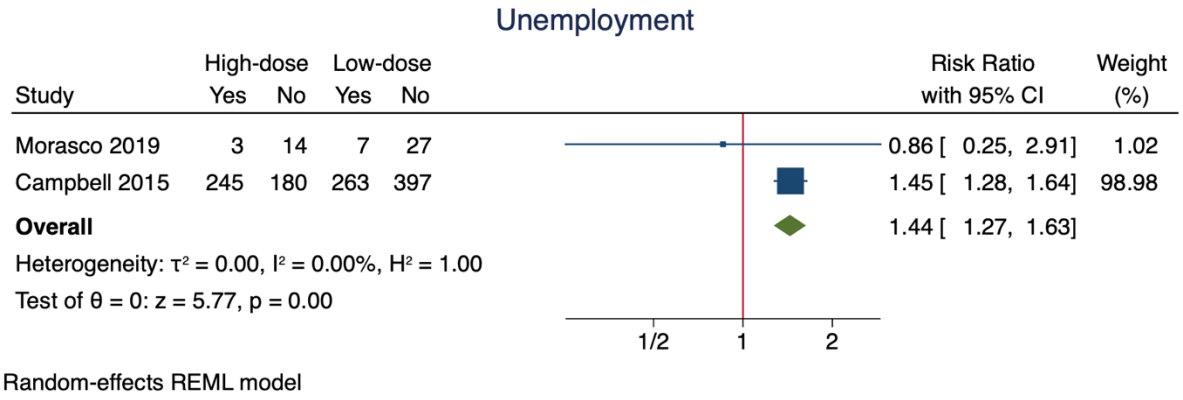


Figure 7.5: Forrest plot of studies that reported levels of depression, visits to the Emergency Department, and unemployment rates in people taking high and low doses of opioids in primary care

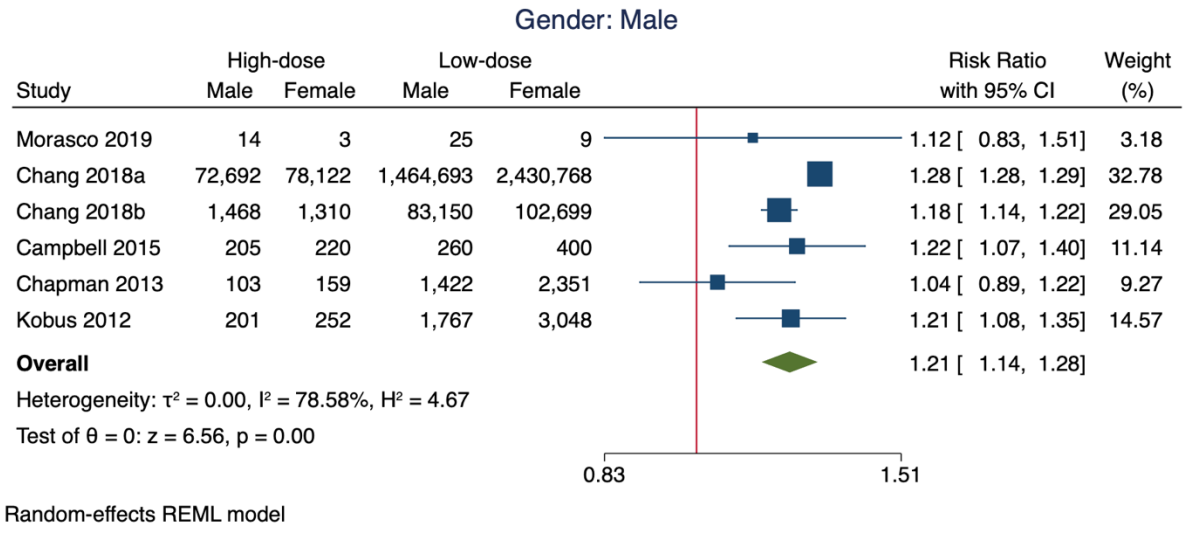


Figure 7.6: Forrest plot of studies that reported gender in people taking high and low doses of opioids in primary care

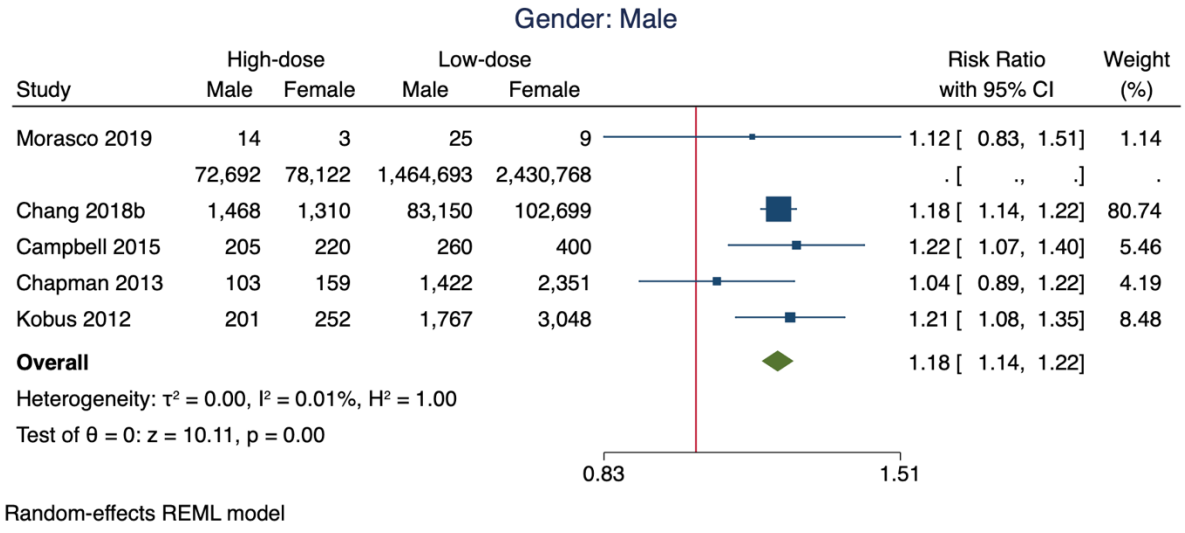


Figure 7.7: Sensitivity analysis for gender, removing Chang 2018a

Table 7.3: Factors associated with high-dose opioids reported in individual studies.

Study ID	Variable	High-dose	Low-dose	RR (95% CI)	NNT_H (95% CI)
		Count (%)	Count (%)		
Sociodemographic characteristics					
Chang, 2018a	State of residence Florida Maryland Washington	 54338 (36) 12487 (8) 15866 (11)	 1207982 (31) 250868 (6) 330335 (8)	 1.16 (1.15, 1.17) 1.29 (1.26, 1.31) 1.24 (1.22, 1.26)	NA
Kobus, 2012	Insurance coverage Medicare	 154 (34)	 1352 (28)	 1.21 (1.06, 1.39)	NA
Treatment-related factors					
Campbell, 2015	Antidepressants	246 (58)	323 (49)	1.18 (1.06, 1.32)	NA
	Type of opioid drug morphine	86 (20)	75 (11)	1.78 (1.34, 2.37)	NA
	ICD-10 lifetime pharmaceutical opioid dependence	49 (12)	28 (4)	2.72 (1.7, 4.25)	NA
	ICD-10 12-month pharmaceutical opioid dependence	26 (6)	13 (2)	3.11 (1.61, 5.98)	NA
	PODS intermediate-high (≥8)	297 (70)	367 (56)	1.26 (1.15, 1.38)	NA
	Past 3-month tampering	38 (9)	29 (4)	2.03 (1.27, 3.25)	22 (13 to 64)
	Past 3-month different drug route	7 (2)	1 (0.2)	10.87 (1.34, 88.04)	NA
Kobus, 2012	Long-acting opioids	400 (88)	1637 (34)	2.60 (2.47, 2.74)	NA
Substance use					
Chang, 2018b	Opioid disorders	530 (19)	1243 (1)	28.95 (26.3, 31.8)	NA
Campbell, 2015	Illicit drug use past 12 months	71 (17)	67 (10)	11.03 (5.8, 21.1)	NA
Kobus,	Substance use	141 (31)	1151 (24)	1.30 (1.1, 1.5)	NA

2012	disorder				
Clinical factors					
Campbell, 2015	Back or neck problems	344 (81)	484 (73)	1.10 (1.03, 1.18)	NA
	Frequent/severe headaches	134 (32)	170 (26)	1.22 (1.01, 1.48)	NA
Healthcare utilisation					
Chang, 2018a	≥4 prescribers & pharmacies in 90-days	1176 (0.78)	1948 (0.05)	15.6 (14.51, 16.76)	137 (129, 145)
Chang, 2018b	>1 Hospitalisations Concurrent 2012: Prospective 2013:	 443 (16) 396 (14)	 17061 (9) 11110 (6)	 1.76 (1.62, 1.92) 2.42 (2.21, 2.66)	 14 (12, 18) 12 (10, 14)
Kobus, 2012	Any pain clinic visits 6 months before/after index date	104 (23)	530 (11)	2.09 (1.73, 2.51)	8 (6, 12)
	Filled opioid prescription 5 days after Emergency Department visit	285 (63)	2696 (56)	1.12 (1.04, 1.21)	14 (9, 46)
Mental Health					
Kobus, 2012	PTSD diagnostic code 309.81	20 (4)	96 (2)	2.21 (1.38, 3.55)	NA
Prescribers					
		Mean (%)	**Mean (%)**	**RR (95% CI)**	
Chang, 2018a	Proportion of prescriptions from high-risk* prescribers	122159 (81)	973865 (25)	3.24 (3.23, 3.25)	NA
		Count (%)	**Count (%)**	**RR (95% CI)**	
	100% of opioid prescriptions from high-risk* prescribers	77217 (51)	572633 (15)	3.48 (3.46, 3.50)	NA
	50-99% of prescriptions from high-risk* prescribers	51277 (34)	471351 (12)	2.81 (2.79, 2.83)	NA

CI: confidence interval; ICD-10: international classification of diseases 10th revision; NNT_H : number needed to harm; PODS: Prescribed opioid difficulty scale; PTSD: post-traumatic stress disorder; RR: relative risk; *high-risk prescribers were defined as those in the top 5th percentile of opioid volume.

7.5.4 Factors not associated with high-dose opioids

Age (mean difference: -1.94, 95% CI: -4.93 to 1.04, I^2 = 94.4%, 4 studies; n=4,052,679), Caucasian ethnicity (RR: 1.09, 95% CI: 0.98 to 1.20, I^2 = 19.5%, 2 studies; n=5319), and anxiety (RR: 1.44, 95% CI: 0.87 to 2.38, I^2 = 90.7%, 2 studies; n=6353) were not associated with high-dose opioids (Figure 7.8). Several factors reported in individual studies were not associated with high-dose opioids, including the use of over-the-counter analgesics (RR: 0.95, 95% CI: 0.86 to 1.04, n=1085), a BMI greater than or equal to 30 (RR: 1.05, 95% CI: 0.95 to 1.15, n=5268), and arthritis or rheumatism pain (RR: 0.94, 95% CI: 0.85 to 1.03, n=1085). All the reported factors are listed in Appendix 7.3.

7.5.5 Quality and risk of bias assessment

Four studies were rated as being of 'good' quality (6,382–384) and two studies were rated as 'fair' (385,386) (Table 7.4). Studies rated as fair did not adequately justify their sample sizes (385) or did not report whether participants were lost to follow up and did not control for confounding (386). The included studies did not involve pharmaceutical sponsorship. However, eight authors from one included study reported conflicts involving two pharmaceutical companies who manufacture opioids (386).

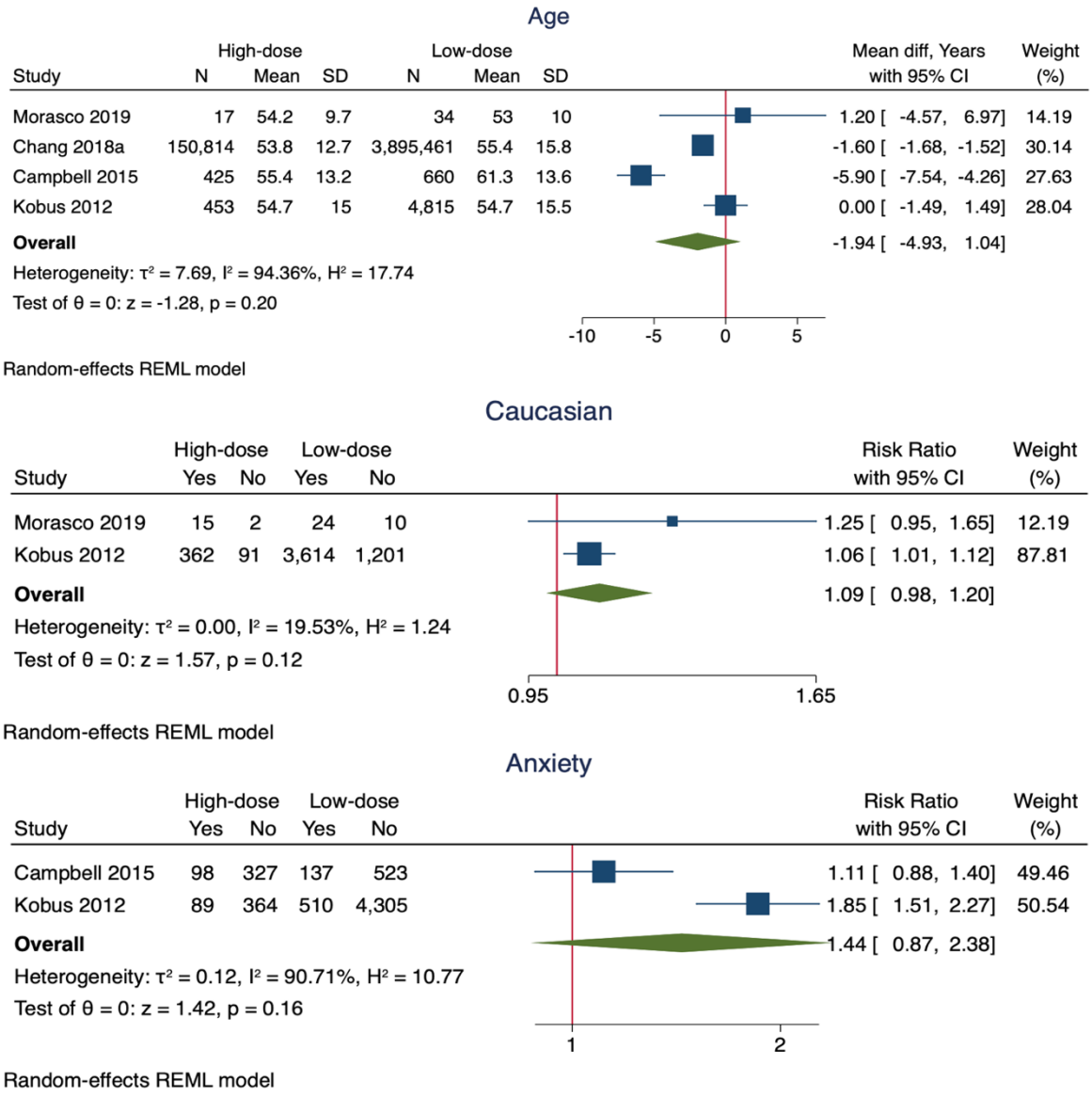


Figure 7.8: Forest plots of factors not associated with the prescribing of high-dose opioids in primary care

Table 7.4: Quality assessment of included studies, using the National Institute of Health, National Heart, Lung & Blood Institute Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies with additional data to assess risk of bias.

	NIH NHLBI Quality Assessment Tool for Observational Cohort & Cross-Sectional Studies																Additional data					
Study ID	**1**	**2**	**3**	**4**	**5a**	**5b**	**5c**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Quality rating**	**Ethical approval**	**Enrolment incentives**	**Study sponsor**	**Pharmaceutical sponsorship**	**COI declared**	**Pharmaceutical COI**
Morasco, 2019	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Fair**	NR	NR	✓	✗	✓	✗
Chang, 2018a	✓	✓	NA	✓	NA	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	NR	NA	NR	✗	✓	✗
Chang, 2018b	✓	✓	NA	✓	NA	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	Deemed not required	NA	NR	✗	✓	✗
Campbell, 2015	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✗	NR	✗	**Fair**	✓	$20 AUD to Pharmacists for referrals	✓	✗	✓	Reckitt Benckiser & Mundipharma
Chapman, 2013	✓	✓	NA	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	NA	✓	**Good**	✓	NA	✓	✗	None to report	✗
Kobus, 2012	✓	✓	NA	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✗	NA	✓	**Good**	✓	NA	✓	✗	None to report	✗

✓: yes; ✗: no; COI: conflict of interest; NA: not applicable; NR: not reported; 5a refers to sample size justification, 5b power description and 5c a measure of variance and effect estimates.

7.6 Discussion

7.6.1 Summary of findings

I found a substantial number of people taking high doses of opioids in high-income primary care settings. The USA had the most people taking high doses of opioids, followed by Australia and the UK. People taking opioids in high doses were at greater risk of harm. I found five factors associated with high-dose opioids: co-prescription of benzodiazepines, depression, increased visits to Emergency Departments, unemployment, and being male.

7.6.2 Strengths and limitations

I pooled data from over four million participants taking opioids and present the first systematic review and meta-analysis of factors associated with the prescribing of high-dose opioids in primary care. Most observational studies on the prescribing of opioids use population-level data (i.e. the number of prescriptions dispensed) (3,7,242), which were excluded from this review. I included studies that used individual patient-level data, which is important for two reasons. First, the number of people taking opioids and high-dose opioids can be determined and secondly, dosages for each patient can be calculated. There is no consensus definition of what constitutes high-dose, and thus I defined high-dose as ≥90 OME mg/day and low-dose as <90 OME mg/day, based on well-established guidelines (92,128). Therefore, I excluded studies that classified high-dose as <90 OME mg/day. I was not successful in obtaining raw data from authors of included studies to conduct subgroup analyses using alternative definitions for high-dose, which could be considered a limitation of my review. However, sharing data and practising open science is not encouraged by pain journals (33) - where most of the included studies (five of six) were published. Actual dosage exposure may be different from what is prescribed, dispensed, and self-

reported, and the dosages may also not consistently sit within my defined dosage thresholds. For example, a patient may experience less pain in one day and not consume their complete daily dose. In contrast, when pain is worse, they may exceed their daily dose. There is also no standardised equianalgesic conversion for calculating OME (387).

My systematic review did not include qualitative studies, as these studies did not address the research question. Recently, qualitative studies on patients experiences of taking opioids for chronic non-cancer pain have been systematically synthesised and published (388). The authors included 31 studies and identified five themes with an overarching theme of patients' constantly balancing' tensions between taking and not taking opioids and difficulties building a therapeutic alliance with healthcare professions (388).

I included observational studies which have inherent limitations when conducting meta-analyses, particularly when there is major heterogeneity. For the six studies included in my review, it is not possible to determine the causal or temporal relationship between factors associated with high-dose opioids. One cannot conclude, for example, whether depression was present before the participant was titrated to high doses and, if so, whether taking opioids in high doses worsened pre-existing depression. My findings do not represent all individuals in the population of included countries taking high-dose opioids. Similarly, my findings do not represent all possible factors driving or associated with high-dose opioid, owing to reporting biases in the available and published data. Four studies reported the indication for taking high doses of opioids: two for chronic non-cancer pain (6,386); one for musculoskeletal pain (385); and one for low-back pain (384), but comorbidities were poorly reported. Furthermore, most of the included studies and

participants were from the USA, and there was substantial heterogeneity between countries and studies in the percentages of participants taking high doses. Therefore, my findings are less generalisable to other high-income countries in North America, Europe, and Oceania, and the conclusions are not applicable to low- and middle-income countries. These reporting biases may significantly impact the findings as few studies were eligible for inclusion and none of the included studies had a prospective design. Ideally, access to population-wide individual patient-level data (i.e. electronic medical records) would allow better monitoring and auditing of suboptimal prescribing of high-dose opioids.

7.6.3 Implications

7.6.3.1 Implications for policy

Investment in resources and programs to effectively manage people taking high-dose opioids in primary care is warranted. Sociodemographic factors such as male gender and unemployment may be useful proxies to help identify people taking high doses and amenable to therapeutic interventions. Improved management of these patients may reduce the burden on Emergency Departments and benefit stretched healthcare systems and budgets. In the USA, the opioid crisis has cost more than $72.4 billion (389). In England, £24.8 million could be saved if every general practice prescribed high-dose opioids at the same rate as the lowest decile (i.e. 0.17 prescription units per 1000 patients per month), resulting in 543000 fewer high-dose prescriptions being dispensed (3). In December 2020, I was approached by the Oxford Academic Health Science Network (ASHN) to submit my findings from this review to NHS England's Medicines Safety Improvement Programme, which has set a target to reduce high-dose (>120 mg OME) opioid prescribing for non-cancer pain by 50% by March 2024 (390). Efforts have been made to audit the number of people taking high doses of opioids in primary care (391,392). My findings

support the extension of such audits to include population-wide real-time audit and feedback of individual patient-level data to reduce the suboptimal prescribing of opioids, monitor NHS England's reduction target, and provide safety warnings such as when high doses are co-prescribed with benzodiazepines. In March 2020, the MHRA/CHM added "important safety information" to the BNF to remind prescribers that "opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death" (393). My findings indicate such reminders could be implemented in primary care EHRs.

7.6.3.2 Implications for patients, the public and clinical practice

Factors such as the co-prescription of benzodiazepines and depression are priority areas that primary care clinicians should consider when managing patients taking opioids. In people concurrently using benzodiazepines and opioids, the rate of death is 10-fold greater than in people taking opioids alone (369). Thus, clinicians should carefully reconsider prescribing this combination of drugs and, when the combination is deemed necessary, the lowest possible doses should be given for the shortest duration (393). Continuous benzodiazepine treatment lasting two or more months should be discouraged and marked dosage increases should be avoided (394). Prescribers should also inform patients of the signs and symptoms of respiratory depression and sedation and advise them to seek urgent medical attention should these occur. For patients with depression who are taking high-dose opioids, primary care providers should exercise caution, consider a gradual taper, and offer close medical supervision and support.

My finding that people taking opioids in high doses were at greater risk of harm emphasises Swiss physician Paracelsus's proclamation that "the dose makes the poison". Previously, those

treating pain were encouraged to 'titrate to effect' using the WHO's pain ladder, meaning there was no maximum dose for opioids. This practice was evident in the patients I observed at the Opioid Clinics. The largest dosage of a patient was 990 mg OME/day. They had received this dosage for more than 20 years, which was in the form of multiple fentanyl patches titrated over many years for persistent post-surgical pain. However, the relationship between opioid dosage and harm is not linear due to other factors, including opioid tolerance, pharmacogenetics and drug metabolism, duration of dosage, and type of opioid, highlighting the complexity of managing such patients on high doses. Despite high-dose thresholds for prescribing opioids varying across the world, these recommended cut-offs must not be used as a measure of safety independently (395). Patients should be wholly informed of the potential harms of taking opioids, regardless of dosage. For patients already taking high doses of opioids, shared decision making, and patient involvement are particularly important when devising tapering programs to reduce opioid dosages.

7.6.4 Implications for future research

A coordinated international effort is needed to understand the country-specific drivers of high-dose opioid use. Improving access to patient-level data and the use of diagnostic codes for chronic non-cancer pain in primary care are needed. Future research should prospectively examine patient-level data on the prescribing of high-dose opioids in primary care to control for confounding and investigate the relationships between associated factors, indications for use, and comorbidities. Prescribers' clinical decision-making regarding dose escalation or reduction of opioids, and the associated benefits and harms of this, warrants further investigation. Standardising definitions for high- and low-dose thresholds, methods for calculating OME, developing core reporting outcomes for studies analysing the prescribing of opioids, and

improving data sharing would help facilitate evidence synthesis and understand differences between and within populations.

7.7 Conclusion

Many people are taking high doses of opioids in primary care settings worldwide, and these individuals are at risk of harm. The addition of identified factors to an already long list of harms invites a reconsideration of the merits of prescribing high-dose opioids. Monitoring the use of benzodiazepines and managing depression and visits to Emergency Departments in patients taking high doses of opioids in primary care are warranted.

7.8 Chapter summary

- I assessed drivers of high-dose opioid use in high-income primary care by conducting a systematic review of observational studies;
- I included six studies with over 4.2 million participants taking opioids in Australia, the UK, and the USA, of whom 3.6% were taking high doses;
- People taking high-dose opioids are at increased risk of harm;
- Five factors were associated with high-dose opioids, including the co-prescription of benzodiazepines, depression, Emergency Department visits, unemployment, and being male.
- Coordinated strategies and services that promote the safe prescribing of opioids are needed.

Chapter 8

"Every opioid-related death represents a missed opportunity for prevention"
Babu et al. 2019 (396)

*I co-authored a publication in *Nature* (25) describing the methods used in this chapter, and I launched a series in *BMJ Evidence Based Medicine* titled, Coroners' Concerns to Prevent Harms (26), to disseminate key lessons from this research. I presented the preliminary findings of this chapter at the 4E's Forum to Improve the Detection, Analysis, and Reporting of Harms in Healthcare in Erice, Sicily (7-9 October 2019) and at the Clinical Pharmacology Colloquium held on Zoom (8 December 2020).

8 Systematic synthesis of coroner reports to prevent opioid-related deaths in England and Wales, 2013-2019: preliminary findings

8.1 Chapter rationale

In the USA, 222 people died every day from an opioid overdose in the 12 months ending in May 2020 (2). In England and Wales in 2019, 12 people died every day from drug poisonings, and 49% of those deaths involved an opiate (63). The USA opioid crisis illustrates the urgent need to investigate and prevent such deaths from increasing in the UK. The coronial system in England and Wales has legislation that mandates coroners to write a report if they believe a death could have been prevented and communicate their reports to individuals or organisations with the power to take action. Such reports have been made openly available since July 2013 on the Courts and Tribunal Judiciary website (397). I have used innovative methods, called web

scraping, to automatically collect such data and create a database that I use in this chapter to assess preventable deaths from opioids.

8.2 Introduction and Aim

Death is the most serious outcome and marker of harm. In England and Wales, deaths from opiates have increased by 3.5-fold, of which heroin and morphine are the most frequently mentioned, from 8.4 deaths per million people in 1993 to 37.9 per million in 2019 (63). Most of these deaths are premature and preventable, and more than two-thirds are attributable to socioeconomic inequalities in England (398). A randomised trial of clinicians prescribing opioids to patients in the USA who subsequently died from overdose found that those who received notification of their patients' deaths reduced their prescribing of opioids, initiated fewer prescriptions, and prescribed fewer high-dose opioids, compared with clinicians who were provided with a safe prescribing injunction or no intervention (399). Thus, investigating and communicating about opioid-related deaths, and how they can be prevented, is critical for improving the prescribing and safety of opioids.

The case of Harold Shipman and the deaths of more than 450 people following inappropriate administration of opioids at the Gosport War Memorial Hospital are high profile cases that highlight the consequences of unsafe practices in the NHS, which resulted in cases of serious misconduct and premature deaths and put many lives at risk (87,97). If appropriate data had been available, such episodes of misconduct might have been identified earlier, and many deaths could have been prevented. Deaths related to drug poisonings in England and Wales are collected and monitored by the Office of National Statistics (ONS) (63,400–404). Previous research has also used data from the National Programme on Substance Abuse Deaths

(283,405,406), the National Drug Treatment Monitoring System and the Drug Data Warehouse linked to the ONS's mortality records (407,408), and the UK Biobank (142). However, most of this research focuses on opioid-dependent individuals and the implementation of harm reduction strategies, such as naloxone programmes and safe injection facilities. In December 2016, the Advisory Council on the Misuse of Drugs (ACMD) published a report titled "*Reducing opioid-related deaths in the UK*" (409), building on their report in 2000, "*Reducing drug-related deaths*" (410). This report's key findings were sent to the Home Secretary, who recommended expanding access to opioid substitution treatments (e.g. methadone and buprenorphine), naloxone programmes, and provision of medically-supervised consumption clinics, among other drug-related services (409). However, the report also mentioned the need to improve the processes of collecting information on opioid-related deaths and recommended that governments fund independent research to improve understanding of the causes and drivers of opioid-related deaths.

The causes of deaths are established at coroners' inquests unless a criminal court examines the cause of death. Since 1984, legislation in England and Wales has encouraged coroners to report and communicate a death "*to the person or authority who may have power to take such action*" when the "*coroner believes that action should be taken to prevent the recurrence of fatalities similar to that in respect of which the inquest is being held*…" (411). These reports, previously called Rule 43, are named Prevent Future Deaths or PFDs, were mandated under Paragraph 7 of Schedule 5 of the Coroners and Justice Act 2009, and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013 (412,413). When an individual or organisation receives a PFD

report, they are required under these regulations to respond to the coroner within 56 days of receipt to outline actions proposed or taken to address the coroner's concerns.

At the second Clinical Pharmacology Colloquium I attended (November 24, 2018), Professor Robin Ferner presented the findings of a study, which examined 500 coroners PFD reports to identify cases where a medicine caused or contributed to the death (414,415). Of the 500 cases, there were 99 reports (totalling 100 people) in which a medicine or part of the medication process or both were involved. Of the 100 deaths identified, opioids (n=17 deaths) were the second most commonly reported drug class of concern after anticoagulants (414). Ferner and colleagues suggested that the concerns raised by coroners' were of national importance, but reports were often addressed locally, and response rates were low (415). However, an analysis of all available PFD reports on the Judiciary website has not been performed. I therefore designed a study to systematically analyse all available PFD reports in which an opioid was implicated. In this chapter, I report the preliminary findings.

8.3 Objectives

1. to determine the number of PFD cases where an opioid caused or contributed to the death, and any changes over time.

8.4 Methods

8.4.1 Study design and data collection

I designed a retrospective synthesis of case reports, replicating the methods described by Ferner and colleagues (414). These initial methods involved manually screening the pages on the Courts

and Tribunal Judiciary website (397) and physically saving the corresponding portable document format (PDFs) files in a folder. There were just under 3000 entries to manually save at the time I started data collection. After doing this manual collection for months, with thousands of entries to still screen and save, I mentioned this study to colleagues in the EBM DataLab, who suggested using "web scraping". I had no prior knowledge of scraping, but with significant assistance (ND), we wrote 2051 lines of code to create the scraper (available here: https://github.com/georgiarichards/georgiarichards.github.io/blob/master/data/Website%20scraper%20-%20PDFs%20%26%20case%20info%20for%20PFD%20reports-Sep182020.ipynb).

Web scrapers are computer programs that extract or "scrape" information from websites (25). A scraper understands the Hypertext Markup Language (HTML) code used to create the website and can pull information from specific areas, including words, numbers, tables, images, or documents, for example. The article I co-authored in *Nature* describes how scraping works, how to get started, and things to consider when designing a web scrape (25). My scraper goes to each Uniform Resource Locator (URL) on the Judiciary website that hosts a case and pulls the date of the report, the case reference ID, the name of the deceased, the coroner's name, the coroner's area of jurisdiction, the category of the report, to whom the report was sent, and any PDFs available on the page. It then saves the information in a .csv file and puts the PDFs in a folder on my computer (Figure 8.1). My scrape takes approximately three hours to collect and save all of this information. The ability to automate such tasks, in relatively little time, means that I can re-run the scrape to update the .csv file and collect new PDFs that are added to the website. More importantly, I have developed a computationally reproducible data-collection workflow, which others can use and build on.

8.4.2 The Preventable Deaths Database and eligibility criteria

I used the .csv file from the web scrape to create the Preventable Deaths Database, which contains 3,037 entries, once duplicates were removed, from 2013 to 2019, as of the last web scrape on 18 September 2020. In the web scrape, each row represents a unique URL link. In the Preventable Deaths Database, each row represents a unique PFD/case as duplicates are removed.

I screened each PFD in the database to determine its eligibility for inclusion, and this work was duplicated independently (MB). I included cases if an opioid was mentioned in the report and it caused or contributed to the death, including opioids used illicitly (i.e. heroin). I excluded cases if they did not mention an opioid or mentioned an opioid that did not cause or contribute to death. If eligibility was unclear, I consulted clinical pharmacologists who have been expert witnesses in coroners' courts (RF and JKA) and a reader in clinical pharmacy and drug safety with experience screening PFDs (AC). I defined an opioid as a drug, either natural, synthetic, or semi-synthetic, which is an agonist at MOR.

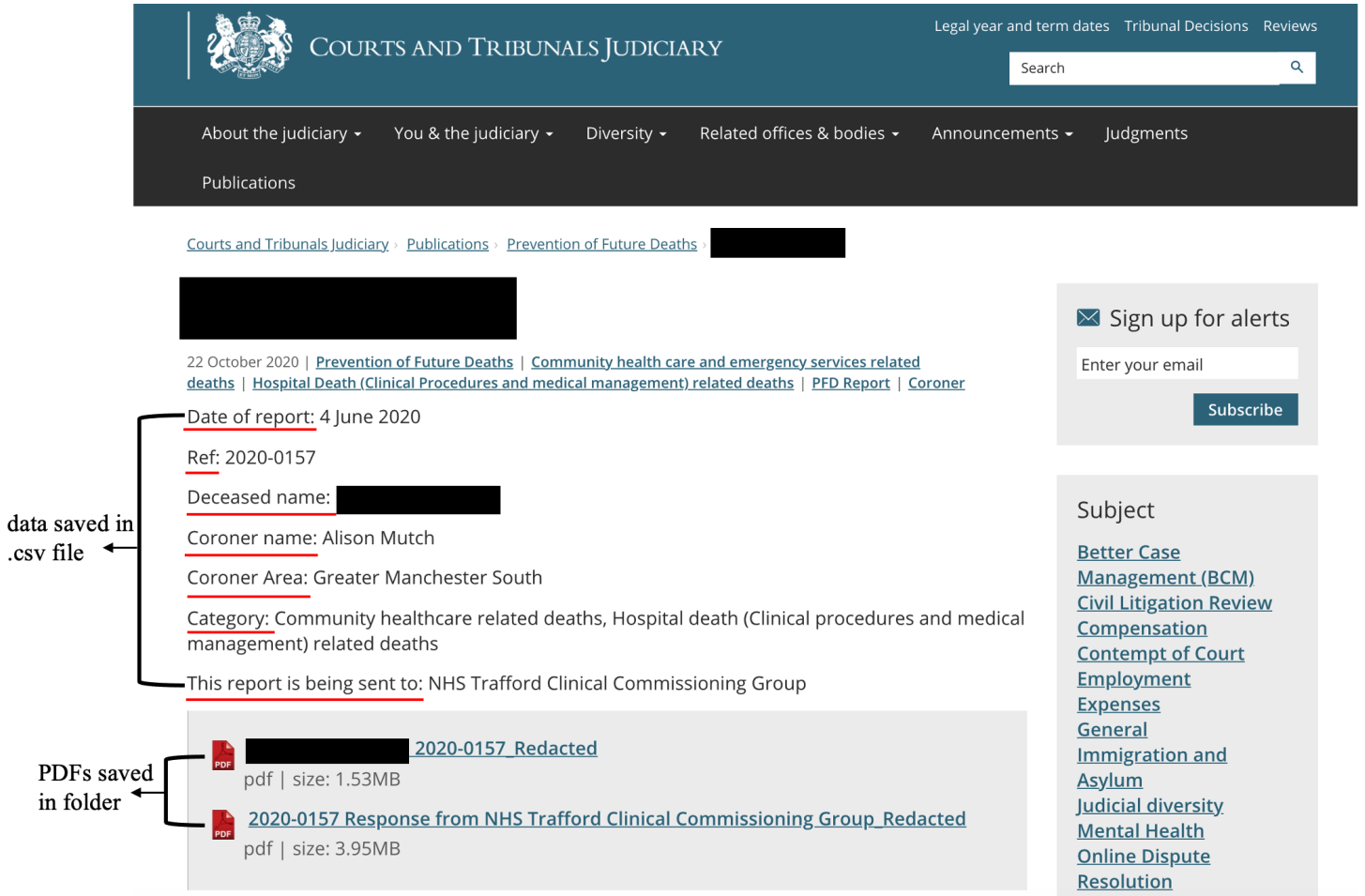


Figure 8.1: Schematic example of the elements that the web scraper extracts and saves. I have redacted the name of the deceased for this example.

8.4.3 Data extraction and analysis

I, in conjunction with others working on the Preventable Deaths Database (ET, MB, AA, GA), am manually extracting the following data from PDFs for each case:

- the number of people/organisations who were sent the report;
- the number of people/organisations who responded to the report, and the date of their response;
- the date on which the coroner mandated a response to the report (usually 56 days from the date of the report);
- the date(s) on which the inquest was opened and concluded;
- the date of death;
- the number of people deceased included in the report (e.g. in car accidents, the coroner often refers to multiple deaths in a single report);
- the age of the deceased (if reported);
- the sex of the deceased;
- the setting or location of the death;
- the coroner's conclusion from the inquest;
- the coroner's reported causes of death;
- concerns raised by the coroner;
- any actions recommended by the coroner to be taken by those being sent the report;
- any medical, mental health, or social history reported by the coroner;
- the type and number of substances or drugs involved or implicated in the death;
- the source of the substance or drug (i.e. prescribed, over-the-counter, purchased online, family or friends, illegal sources, or a mixture);

- whether the deceased was reported to have a disability (yes/no), to be a prisoner at the time of death (yes/no), military personnel (yes/no), or resident at a nursing or care home (yes/no).

For this chapter, I have descriptively analysed the number of people and cases in which an opioid caused or contributed to death. I calculated the number of opioid-related PFDs and all PFDs each year, defining the year as the date of the report. The date of death was not used, as this is missing from some PFDs. I determined the rate of opioid-related PFDs as per all PFDs annually and used this to quantify the percentage change over time, to account for coroners' behaviours in writing PFDs, and the frequency with which cases were uploaded to the Judiciary website. I summarised the age and sex profile of cases, using percentages and calculating medians and IQRs where appropriate. I used the ONS age categories (63) to examine the spread of cases for each age group. I provided examples of opioid-related PFD reports to highlight the types of concerns raised by coroners' and the lessons to be learnt from this rich source of data.

8.4.4 Ongoing research

As per my pre-registered protocol and data extraction, I shall conduct further analyses of these data. I shall examine geographical variation, assess how the Chief Coroner's Office categorised opioid-related deaths, and the median time for a coroner to issue a report after the date of death. I shall use content analysis to determine the frequency of concerns raised by coroners to assess whether reports describe a previously recognised harm, hazard, or death. I shall use thematic analysis to classify the concerns raised and actions recommended by coroners. I shall assess the types of individuals or organisations being sent opioid-related PFDs, and calculate the response rates, the median time it took addresses to respond, as well as the proportion who reported on

time (within 56 days) or late (after 56 days) or are overdue (still awaiting a response). I shall extract data from the ONS on opiate deaths to calculate the annual rate of opiate deaths with a PFD report (i.e. the rate of opiate-related deaths considered "preventable" by coroners in England and Wales), and assess changes over time. I shall write these findings for publication and work up a grant application to expand and continue this programme of research. Future research that will require funding will include a corresponding synthesis of responses to assess actions proposed or taken by addressees. If such funding is obtained, I shall assemble a panel of stakeholders to determine the suitability and relevance of the coroners' concerns and organisations' responses to identify gaps for further improvements in systems, processes, policies, training, education, monitoring or audits, and patient safety initiatives.

Once data have been extracted from all 3037 cases, I shall conduct an analysis that summarises all cases to determine the most common coroners' conclusions and causes of deaths in PFDs. I shall determine all individuals and organisations' response rates who have received a PFD report and map this geographically. As mentioned in Chapter 1, I supervised four FHS students, two of whom used the Preventable Deaths Database. One student (AA) assessed deaths from cardiovascular diseases when anticoagulants, or the absence of anticoagulants, caused or contributed to the death. Another student (GA) examined suicides in which a medicament caused or contributed to death. Both protocols have been pre-registered (47,48), and the findings will be submitted for publication following examination of the students' dissertations, which are due in week 8 of Hilary Term, 2021.

8.4.4.1 Preventable Deaths Tracker and Coroners' Concerns to Prevent Harms series

From my reading of over 3000 coroner PFD reports, two pertinent issues emerged: the low response rates to PFDs and the volume of cases providing critical lessons for healthcare professionals, public health organisations, regulators, policymakers, and the public. I discussed these issues at the 4E's Forum, which led to two ideas that are now projects in progress: The Preventable Deaths Tracker (https://preventabledeathstracker.net/) and a monthly series in *BMJ Evidence Based Medicine* titled, "Coroners' Concerns to Prevent Harms" (26). For the tracker, in a few weeks, I taught myself how to code HTML, Cascading Style Sheets (CSS), and JavaScript, as well as the basics of web development (i.e. how to purchase and link a domain name and host the webpage), and got the preventabledeathstracker.net website up and running. This involved 105 lines of code: https://github.com/georgiarichards/georgiarichards.github.io/blob/master/index.html.

8.4.5 Statistical software and open science practices

I preregistered the study protocol on the OSF and openly shared the study materials, statistical code, and data affiliated with this research (Table 8.1). I used Python v3 in Jupyter Notebooks to create the web scrape, analyse the data, and create figures using requests (416), beautifulsoup (417), pandas (166), seaborn (222), and matplotlib (223) libraries.

Table 8.1: Open Science Checklist for Chapter 8 on preventable opioid deaths

Principles		Links
Open methods	Protocol	https://osf.io/qje8a
	Preregistration	
	Materials	https://osf.io/ecz4r/
	Statistical code & data	https://github.com/georgiarichards/georgiarichards.github.io
Open data		https://github.com/georgiarichards/opioiddeaths
Open access	Pre-print	in preparation
	Publications	in preparation; methods are published in Nature, https://www.nature.com/articles/d41586-020-02558-0, and other outputs in BMJ EBM: https://ebm.bmj.com/content/early/2021/01/10/bmjebm-2020-111567; https://ebm.bmj.com/content/early/2020/12/02/bmjebm-2020-111568; and https://ebm.bmj.com/content/early/2021/02/09/bmjebm-2020-111640
	Blog	will prepare with the publication
	Tool	https://preventabledeathstracker.net/

8.5 Results

8.5.1 Opioid-related PFD reports

Of the 3037 unique cases, 176 (5.8%) of the reports involved opioids, totalling 177 people (Figure 8.2; Appendix 8.1). Each year there was a median of 27 opioid-related PFDs (IQR: 20-32; Table 8.2). The rate of opioid-related cases increased over time, from 2.3% of PFDs in 2013 and 4.9% in 2014 to 8.4% in 2019 (Figure 8.3). Two-thirds (66%) of opioid deaths involved males and the median age of death was 42 years (IQR: 32-51; range: 0.003-94; n=110 cases reporting age). Most of the deaths occurred in those aged 30-49 years (Figure 8.4).

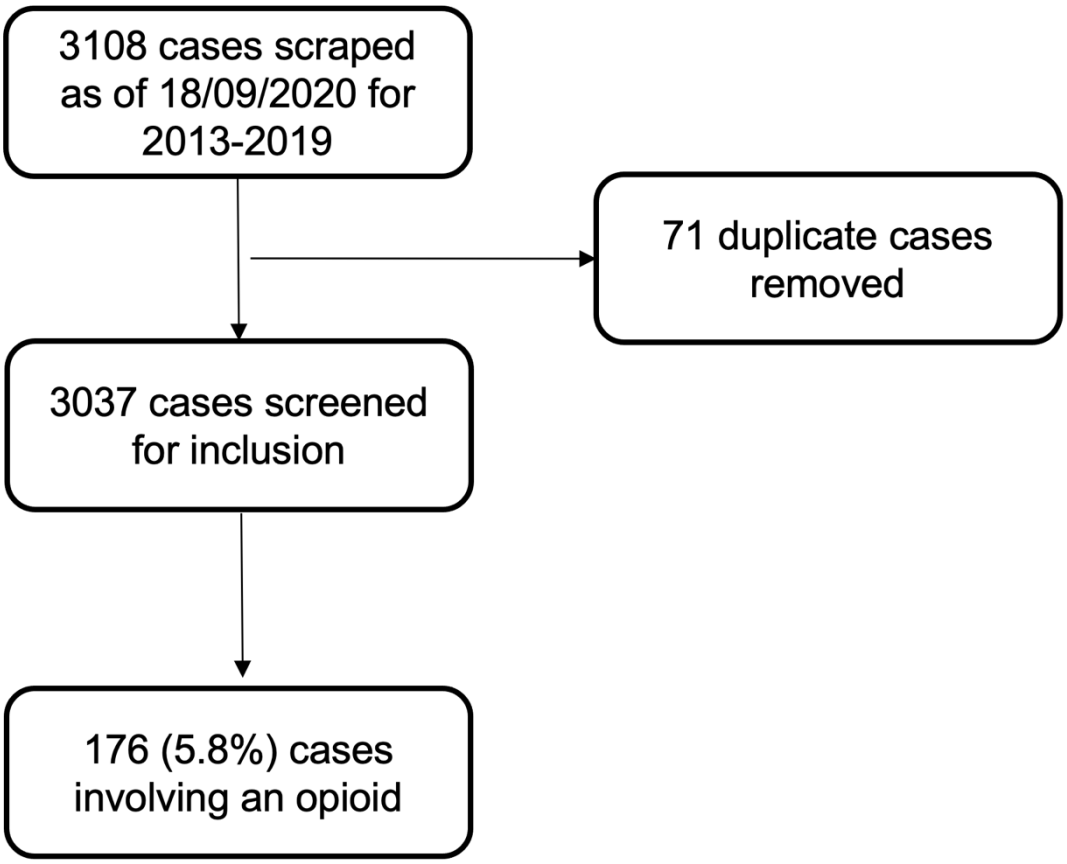


Figure 8.2: Flow diagram illustrating the number of Prevent Future Death (PFD) reports scraped and screened and the number that met the eligibility criteria for inclusion

Table 8.2: Volume of PFDs and opioid-related PFDs written between 2013 and 2019

Year*	Total number of PFDs	Number of PFDs involving an opioid (%)
2013	173	4 (2.3)
2014	555	27 (4.9)
2015	477	23 (4.8)
2016	470	16 (3.4)
2017	435	30 (6.9)
2018	413	33 (8.0)
2019	514	43 (8.4)
Median (IQR)	**470 (424-495)**	**27 (20-32)**

*year of the date of report. PFD: Prevent Future Death. %: rate of PFDs involving opioids.

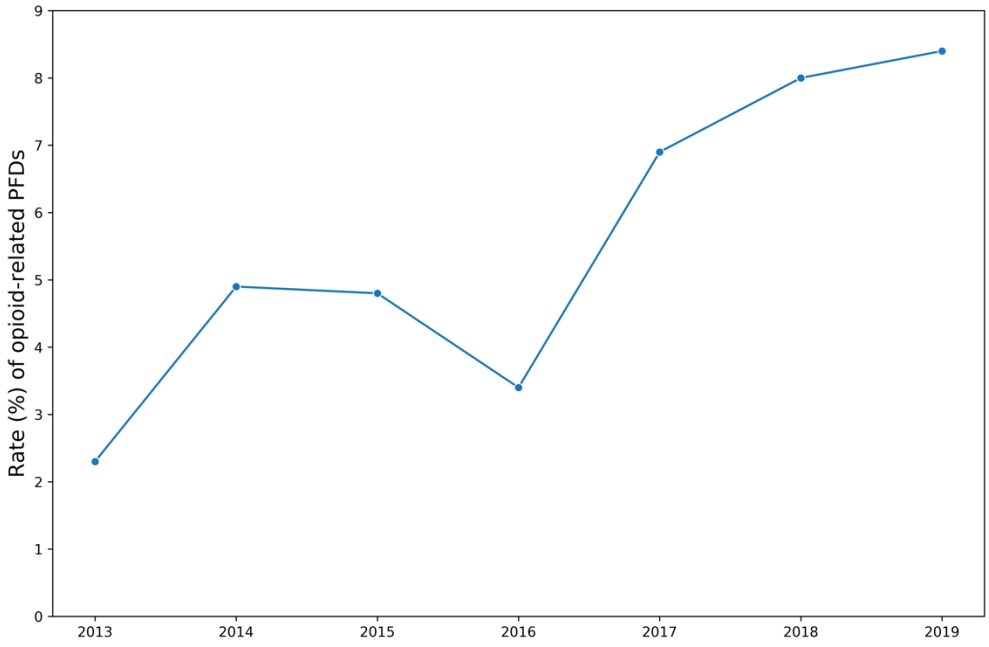


Figure 8.3: Trend of the rate of opioid-related Prevent Future Death (PFDs) reports between 2013 and 2019, where year represents the date of report

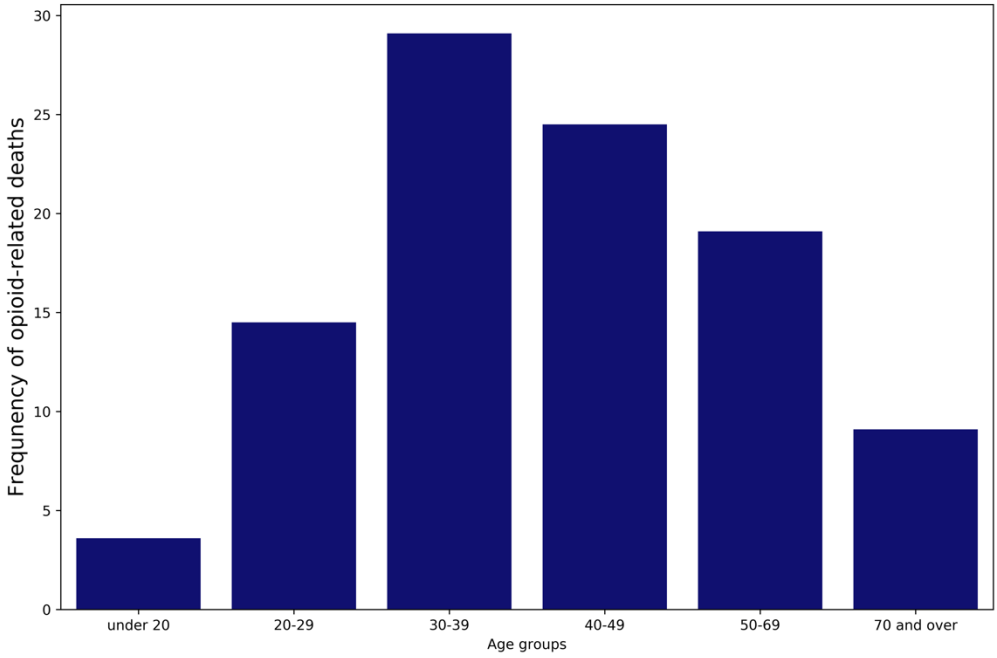


Figure 8.4: Frequency distribution of opioid-related Prevent Future Death (PFDs) reports by the ONS age groups

The four opioid-related deaths in people under 20 years of age included:

1. a neonate delivered by elective caesarean section at 36 weeks' gestation because of placenta praevia. The deceased began displaying symptoms of respiratory distress, which were not escalated, and no medical review occurred for nearly 4 hours. She was premedicated with morphine, suxamethonium, and atropine before intubation. Immediately after administering drugs, she suffered an adverse reaction to suxamethonium, which triggered a cardiac arrest (418).
2. a ten-year-old boy experiencing pain associated with cerebral palsy, for which he was given a 25-microgram patch of fentanyl while in the Emergency Department. He developed drowsiness, sickness, polydipsia, and subjective fevers and chills. He arrested two-days later while in hospital. Advanced life support was provided, but he died without regaining consciousness. Opportunities were missed for the fentanyl to cease being dispensed by the pharmacy team. If Trust procedures and guidance had been followed, and if his parents had had adequate information on how to monitor the effects of opioids, his death may have been prevented (419).
3. a 15-year-old girl took an unknown quantity of morphine tablets while at home, which had been prescribed for another family member. She had several medical and social problems under investigation, including possible epilepsy with daily seizures, and she had not attended school for a long time. There was some evidence that she had attempted self-harm, which her family denied. There were several communication problems between services, and at the time of her death, no plan for her medical care, mental health concerns, or social matters had been arranged. The coroner concluded that she had taken

her own life and that the cause of death had been acute hypoxia due to morphine overdose (420).

4. a 17-year-old boy who took a fatal dose of heroin while in his final year of school. He was attending a Grammar school, was ahead of his chronological age, and excelled academically. He began to change his approach to school, struggled with how he felt about himself and his friendships, which he disclosed to a cognitive behavioural therapy (CBT) therapist. He disclosed self-harming and had two paracetamol overdoses. He was diagnosed with Autistic Spectrum Disorder, Attention Deficit Hyperactivity Disorder, and emotional Behavioural Dysregulation. He was transferred to a state school, dropped back a year to repeat grade 10, and began working with the Autism Team. On many occasions, he was reported missing, attempted suicide, slept rough, and presented to Emergency Departments and received various assessments. He had an unsuccessful suicide attempt with heroin, which an opioid receptor antagonist reversed. The coroner gave a narrative conclusion of suicide, with a contribution from a failure of mental health services to recognise his increasing risk as he transitioned from child to adolescent mental health services and the reduced provisions and support after 16 years of age (421).

8.5.2 Other important case report examples

All cases included in this study highlight devastating premature deaths involving opioids. This chapter describes three case reports that discuss two key safety issues to demonstrate some of the lessons, which require dissemination and urgent action.

8.5.2.1 Case 1: fentanyl patches while taking a hot bath (422)

A 74-year-old woman with terminal cancer of the colon and carcinomatosis had fentanyl patches prescribed as part of her palliative care plan. She was not advised about the amount of medication she needed or the effects of the route of administration. She had a hot bath while wearing the patch and was found dead in the bath with the hot tap running. The coroner concluded misadventure with the cause of death as opiate toxicity, carcinomatosis, carcinoma colon, and ischaemic heart disease. In the patient information leaflet, there was a reference to the dangers of taking a "prolonged hot bath" while wearing the patch, but this was halfway down the eighth page of a leaflet that was several pages long with closely printed words. There was also evidence that the deceased received advice from nurses to take a bath when removing the patch to aid its removal. There were additional concerns surrounding communication between the palliative care nurses and GP practice, with "scanty" details in her electronic health records' notes. The coroner addressed the report to the GP practice and to MacMillan Cancer Care, who were responsible for the palliative care nurses, and to the pharmaceutical company responsible for manufacturing the patches.

8.5.2.2 Case 2 and Case 3: Online purchasing of acetylfentanyl (423,424)

In February 2015, a woman found her husband lying on the floor and unresponsive. He was known to abuse drugs, and there was drug paraphernalia in the room where he was found. He was confirmed dead at the scene. Post-mortem toxicology analysis found the presence of acetylfentanyl, a highly potent selective MOP agonist, which the deceased had ordered online with the view of weaning himself off heroin. The coroner gave the conclusion of "drugs related", noted this was the first known death from acetylfentanyl in the UK, and sent the PFD to the

ACMD. According to the Judiciary website (423), the ACMD is nearly six years overdue (2048 days as of 19 February 2021) in their response under Regulation 28.

In August 2015, a 29-year-old man was found unconscious in a hotel room. Paramedics attended and carried out cardiopulmonary resuscitation. He was taken to the hospital for further resuscitation, where death was confirmed. The coroner gave the conclusion of "drug related" and the cause of death as acetylfentanyl toxicity. The PFD was sent to the Secretary of State for Health to publicise the toxic effects of acetylfentanyl and circulate updated information on acetylfentanyl to the NHS and via the Coroners' Society. The coroner also asked for a report on the number of known fatalities from acetylfentanyl toxicity from 2014 to "date" (January 2016). According to the Judiciary website (424), the Secretary of State's response is nearly five years overdue (1778 days as of 19 February 2021). Had appropriate actions been taken at a national level following the first known death from acetylfentanyl in February 2015, this death in August 2015 may have been prevented, and many potentially other unreported or unknown deaths from acetylfentanyl.

8.5.3 Ongoing research

8.5.3.1 Preventable Deaths Tracker

As of February 2021, the website is very basic, essentially hosting the web scrape's output. I applied for and successfully obtained an NIHR SPCR Engagement Award to develop further the website, which is ongoing. I shall use the findings from my wider analysis on coroners' conclusions and causes of death, response rates to PFDs, and geographical variation to develop the website. The aim of the tracker is to be an automated vigilance system for preventable deaths that will issue an alert and/or articles in *BMJ Evidence Based Medicine* that will highlight key

lessons and hold individuals or organisations accountable for their responses and actions to prevent future deaths.

8.5.3.2 Series in BMJ Evidence Based Medicine

On 1 December 2020, I launched the Coroners' Concerns to Prevent Harms series, publishing an editorial and the first article in the series (26,27). In that article, I discussed two deaths from ingestion of alcohol-based hand sanitisers (27). This was selected for press-release by the BMJ and was picked up by 14 news outlets, including the Daily Mail (42), the Telegraph (425), and the BBC; I interviewed with BBC Radio Oxford and BBC Radio 5 Live Saturday Breakfast. The second article was published on 10 February 2021 and discussed the diagnosis and treatment of gastrointestinal adverse drug reactions from diclofenac in adolescents (28), which I co-authored. The third article, discussing the overprescription of tramadol, written by Prof Ferner and Assoc Prof Cox, is in press (19 February 2021). The fourth article on deaths from burns owing to the accelerant properties of paraffin-based emollient creams when combined with flames (i.e. the light of a cigarette), which I co-wrote, has also been selected for press release by the BMJ and will be published following minor peer-review corrections. I am working up many other articles for the series and reaching out to experts to write and lead articles.

8.6 Discussion

8.6.1 Summary of findings

I co-created a computationally reproducible data-collection workflow to construct the Preventable Deaths Database, highlighted in a *Nature* publication (25). I included 176 opioid-related cases, nearly 6% of all PFDs. The rate of opioid PFDs increased by more than 3-fold over the seven-year study period. Most of the deaths involved males and were in those aged 30-49

years. I highlighted the stories behind the four deaths in those under 20 years of age and pertinent cases involving fentanyl patches and the purchasing of acetylfentanyl online. I constructed the Preventable Deaths Tracker (https://preventabledeathstracker.net/), obtained an NIHR SPCR Engagement Award, launched a monthly series in *BMJ Evidence Based Medicine* (26), and was interviewed on BBC Radio.

8.6.2 Strengths and limitations

The current format of PFDs on the Judiciary website limits their usefulness; https://www.judiciary.uk/subject/prevention-of-future-deaths/. I have created a searchable database and tool to make this important information available and usable, to ensure that pertinent lessons to prevent deaths are less easily forgotten. The automated, reproducible methods provided a 40-fold time saving, from 25 cases per hour using manual collection to approximately 1000 cases per hour using the web scraper (25). My scraper is also openly available on GitHub for others to use and build on. As of 19 February 2020, the repository that hosts the code had 17 "stars" and six "forks". A star saves or bookmarks my repository in someone else's GitHub account, indicating that they "like" my project or allowing them to visit my repository and see updates easily. A fork means that someone has created a personal copy of my code, allowing them to use and edit my code without affecting my master copy. Web scraping is commonly used in other fields, being described as "[one of] the most powerful tools journalists have to hold companies and governments accountable." (426) However, its use in medical research is less common. The purposes of the *Nature* article were to give others the knowledge of such a tool and to encourage others to apply it to their research. As our article was put into production, the editor at *Nature* emailed saying, "*your article inspired me to write my own web scraper (in R)*"; an exciting feat! It was also picked up by "Hacker News", receiving

151 comments (427), which I am told is impressive in the world of programming. But for medical research, this open way of working contributes to the ethos of open science, reduces biases and research waste, and improves the transparency of research (33,40).

Doctors issue death certificates detailing the causes of deaths, but there is no statutory duty to report a death to the coroner. The legal duty to hold an inquest and write PFDs when a coroner believes that action should be taken to prevent future deaths, resides with coroners, but such actions are not mandatory or enforced (411,428). Coroners receive no training or guidance about when a PFD is warranted or how to write a PFD. Thus, the number of PFDs in the database and tracker, and the types of data in PFDs, are constrained by the working practices of coroners, who may vary in their thresholds for writing a PFD, their level of vigilance to opioid-related deaths, and the types of information considered important and thus included in PFDs. Therefore, the 176 cases do not represent all preventable opioid-related deaths between 2013 and 2019 in England and Wales. I controlled for coroners' working practices by calculating the rate of opioid-related PFDs per all PFDs each year. I defined the year as the date of report because of missing death dates and the variation in time from death to the date of report. I found 38% of coroners did not report the age or date of birth of the deceased.

The small number of reports in 2013 may be attributed to the slow application of regulations 28 and 29 of the Coroners (Investigations) Regulations 2013 (412,413), as the first PFD on the Judiciary website was dated 30 July 2013. The Judiciary states, "The Chief Coroner's Office is currently working to upload all Reports made since 25 July 2013. Please ensure you check back with this page on a regular basis." (429) I found various omissions, errors, and inconsistencies on

the Judiciary website while running the scrape. This added several rows of code to the scraper, caused inconsistencies in the database (e.g. different date formats), and meant that I had to spend hours filtering the database to identify duplicates.

8.6.3 Implications

8.6.3.1 Implications for policy

Understanding the causes of deaths and how they can be prevented is critical for improving healthcare outcomes globally. At a population level, over-reporting or under-reporting of deaths can have a profound impact on policy decisions, which in turn can affect global economies and the day-to-day lives of citizens, as we have witnessed during the covid-19 pandemic. At the individual level, understanding how and why deaths occur may prevent similar deaths or serious harms from occurring in the future. In this chapter, I analysed individual case reports where an opioid caused or contributed to deaths in England and Wales. Each case report is unique and puts a much-needed personal story to the population ONS statistics on drug-related deaths. The cases illustrate that there is no single policy that will drastically prevent such deaths. Instead, my findings support the need for improving how primary information is collected, used, and shared, and the need for using population-level statistics together with case reports to understand the problems and develop policies.

While the UK does not have the same volume of opioid deaths as North America, groups in the UK call for the government to recognise the increase in opioid deaths as a public health crisis (430). The two PFDs involving acetylfentanyl were addressed to the ACMD and the Secretary of State for Health, but neither case had a response on the Judiciary website (423,424). However, in July 2017, the Home Secretary commissioned the ACMD to consider deaths from fentanyl and

fentanyl analogues; their report was published on 3 January 2020 (431). They found that rates of registered deaths involving fentanyl and fentanyl derivatives increased from 8 in 2008 to 135 in 2017, which are probably under-estimates, as toxicology analyses are not always carried out and may not identify novel fentanyl analogues. They concluded, "fentanyl and fentanyl-analogues present a significant ongoing risk to UK public health." (431) There are eight recommendations in the report, including the need for further research, training, and clear reporting of whether fentanyl and/or its analogues were tested, and the outcome of the test, for all drug poisoning deaths (431). In July 2019, the UK's National Crime Agency also issued an "amber alert" for fentanyl analogues (432), including acetylfentanyl.

There is currently no agreed threshold for the number or rate of opioid-related deaths in a specific population that determines when officials should announce a public health crisis and call for further action (430). However, the government should not wait until the rates of opioid and fentanyl deaths in the UK reach US levels before taking action. My findings and the 2020 and 2016 ACMD reports (409,431), illustrate an increase in opioid- and fentanyl-related deaths in the UK, which is of great concern. A more comprehensive surveillance system that identifies problematic opioid use, prescribing, harms, and preventable overdoses and deaths, should be established to avert a US-style opioid crisis in the UK.

Individuals or organisations who receive a PFD are required under statute to respond to the coroner within 56 days of the date of report. However, this is not enforced, and there appears to be no leadership, accountability, or quality assurance of the concerns raised by coroners and the subsequent responses and actions taken (433). In the study by Ferner et al. of 100 deaths

involving a medicine or part of the medication process or both (415), 91 public organisations and 22 private organisations were sent one or more PFDs. At the start of their study, 21% of PFDs had responses on the Judiciary website. After sending 63 Freedom of Information (FOI) requests to obtain responses from public organisations, 28% of PFDs responded on the website by study completion (415). However, it is difficult to establish the reasons for the lack of responses, whether because the addressee did not receive the PFD, or received it but did not write or send a response, or whether the Chief Coroner's Office did not receive the response, or whether the response was received but not added to the website.

I had a fruitful experience submitting an FOI for a response to a PFD included in my first article for the *BMJ Evidence Based Medicine* series on deaths from ingesting alcohol-based hand sanitiser (27). The PFD was sent to the Department of Health and an NHS Trust, but no response was available from the Trust on the Judiciary website. I first sent an email to the Trust and the Judicial Office independently to ask them whether a response had been written and received. Two weeks after receiving no responses to my emails, I submitted an FOI to the Trust, which was successful (434), and the response was later added to the Judiciary website. However, following my email to the Judicial Office, all PFDs before September 2017 were removed from the website. I was shocked and outraged that such important and rich data had vanished. While I cannot ascertain causality between my email to the Judicial Office and the removal of cases, the timing was salient. I submitted an FOI to Her Majesty's Courts and Tribunals Service to explain the removal and make all PFDs available as per regulations 28 and 29 of the Coroners (Investigations) Regulations 2013 (435). This FOI was successful (435), and all cases were

restored to the website. The reason for removal was that it had been "a technical error" (Appendix 8.2).

Following our Nature publication on web scraping, coroner Dr Richard Brittain, made contact with me to learn more about my research. We spoke via Teams and have exchanged several emails about PFDs. Dr Brittain has shared his personal experiences of writing PFDs in the middle of a very busy schedule as a practising doctor and coroner, the culture of PFDs, and how he uses his personal calendar to send reminders regarding responses to his PFDs. These discussions have highlighted the administration, time, and cost burden of the current system for both coroners, addressees, and the Chief Coroner's Office. Technology should be harnessed to streamline the process and flow of information. Coroners could use a secure form, similar to a Google Form, where they are prompted to enter important information about the case, including age, the date of death, and substances involved (e.g. opioids). Once complete, it would be automatically sent to addressees, who would be required to respond via a secure structured form that would also be automatically sent back with date and time stamps, and automatically added to the searchable database online. If responses were not received, reminders could be automatically issued. If important public health issues were identified (e.g. deaths from acetylfentanyl), alerts could be issued and disseminated as necessary. In the meantime, my web scraper and the Preventable Deaths Tracker shares the database, which can be searched and downloaded. If grant funding can be obtained, the Tracker can be developed to continue surveillance and dissemination of this essential information, and nudge those overdue in their responses. Once the Tracker is functioning in this capacity, future research should assess the Tracker's effectiveness in increasing response rates.

8.6.3.2 Implications for patients, the public, and clinical practice

The primary aims of this research are to reduce harm, improve patient safety, and prevent premature deaths from opioids. After spending more than two years reading these reports and working on this research, I feel a sense of duty to the deceased and their families, as "every opioid-related death represents a missed opportunity for prevention" (396). The families left behind following the Shipman and Gosport tragedies provide critical lessons, including the importance of believing the voices of patients, families, and whistleblowers (436,437). In the Gosport independent inquiry, they found that the coroner had not issued a PFD, at that time called Rule 43 of the Coroners Rules 1984, which preceded regulation 28 of the Coroners (Investigations) Regulations 2013. While it is difficult to know whether PFDs and the coronial system prevent future deaths, they highlight important lessons and should be used to promote patient safety in medicine, which is gaining global recognition following the WHO's Global Patient Safety Action Plan 2021-2030 published in January 2021 (438). Ensuring safety in the NHS depends on a culture "*...in which human error is not punished, but individuals are held accountable for their actions (or failure to act); in which the expectation is that errors and near misses will be reported; and in which such reports will be reviewed and acted upon to prevent recurrence of harmful situations*." (439) In addition, these deaths should not encourage opioids to be withheld from patients, as such reactions have had devastating consequences in the USA and can lead to unnecessary suffering, as discussed in Chapter 3.

The National Safety Council (NSC) in the USA created a memorial to the victims of the opioid crisis, called Prescribed to Death, which travels between States to raise awareness of the gravity of the problem (440). The instalment engraves 22,000 faces on individual white tablets to symbolise those lost to prescription opioids in 2015 (Figure 8.5). The mission of the NSC is to

eliminate preventable opioid deaths, a mission I share. Examining individual case reports on deaths provides a different perspective to that of population-level mortality data. Putting a face and story to each death is a powerful reminder of the harms that opioids can cause, and the actions required to prevent premature deaths from opioids increasing in England and Wales.

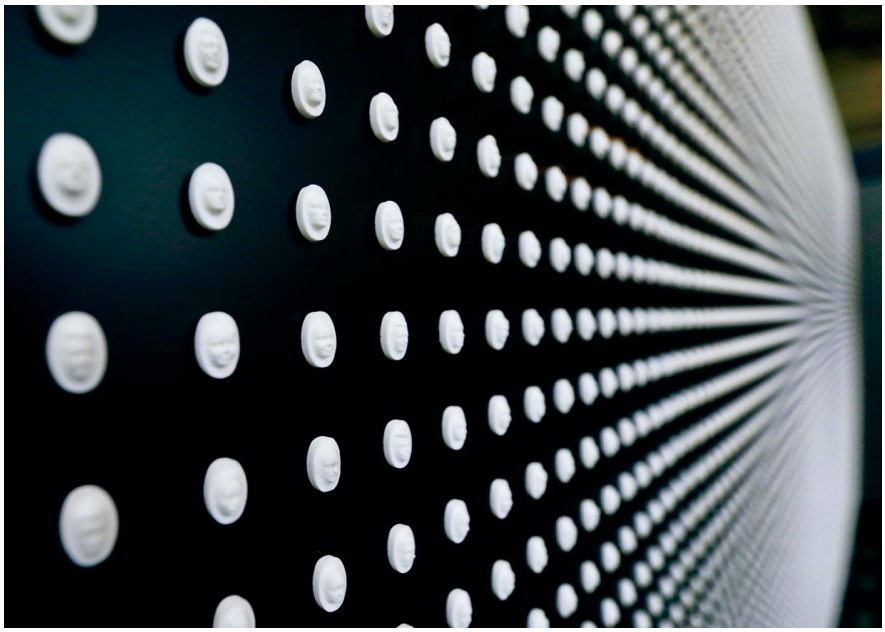


Figure 8.5: Prescribed to Death, commissioned by the US's National Safety Council, (64)

My continuing research will provide a list of priorities for preventing opioid-related deaths, which will assist healthcare professionals prescribing for people taking opioids for chronic conditions or managing those conditions. The two deaths I have outlined involving fentanyl patches, a 10-year-old with pain associated with cerebral palsy and a 74-year-old with terminal cancer, provide key lessons for clinical practice, which should be disseminated. In Chapter 7, section 7.6.3.2, I mentioned a patient on 990 mg OME/day in fentanyl patches. This patient told Dr Quinlan and I about two occasions when he experienced two serious overdoses from fentanyl while on holidays and in the sun. The information in the Preventable Deaths Database can also be used to contribute to guideline development. For example, a colleague contacted me about a

statement from nephrologists that wanted to update the British Renal Society's guidelines to recommend oxycodone and fentanyl over morphine following a patient's death with end-stage kidney disease in whom morphine was over-prescribed on two occasions. I filtered the database and could not find evidence of this case. There may also be a need to educate medical practitioners about the types of deaths that should be brought to coroners' attention (441). Such deaths and the articles published in the Coroners' Concerns to Prevent Harms series can be used by medical schools as cases to teach medical students and promote best practice.

The sex and age group differences I found are supported by previous research (400,442). I also showed (Chapter 7) that being male was associated with receiving high doses of opioids (21). The deaths of females are less likely to be reported to coroners and to proceed to an inquest than the deaths of males (443). This sex difference in coroners' reports should be explored further to ensure that systematic biases and a highly male-dominated profession do not give male deaths a higher status than females (444).

The Preventable Deaths Database and Tracker also has practical applications for coroners. In September 2020, an email was sent to members of the Coroners' Society of England and Wales to ask that child-related PFDs should be emailed to a member of the Medico-Legal Committee so that a gathering system could be established. My database provides such a system, and I welcome coroners, lawyers, and policymakers to use it. I reached out to that coroner, and we had a productive discussion and exchanged several emails about PFDs, my research, and its implications. In January 2021, the coroner presented my research to the Medico-Legal Committee and following the meeting emailed me, stating: "*I am pleased to say that the Medico*

Legal Committee gave your research wholehearted support. Apparently, the last Senior Coroner was keen to ratify PFD Reports and had tentatively started looking into this, but he has just moved on. However, the work is ongoing and what you are doing ties in precisely and will assist the Chief Coroner's Office… I think what you are doing is brilliant and will help inform Public Health messaging, improve access to and compliance with PFD's."

My database and knowledge from reading all PFD reports dated between 2013 and 2019 on the Judiciary website could be used to develop training and provide a gold standard for coroners who write PFDs, a gap highlighted in my discussions with coroners and the literature (433). Framing PFDs constructively, reducing legal jargon, and directing reports to relevant addressees may be more likely to contribute to patient safety. But future research is needed to assess the relevance of the recipients of PFDs, as I outlined in section 8.4.4. The database can be used to assess the number of PFDs written by all 98 coroners in England and Wales to audit trends and variations, which have been previously reported (443,445,446). There is a perception that writing a PFD denotes a failure of the coroner's ability to resolve concerns during an inquest. A long-serving coroner has also boasted that he never once wrote a PFD claiming this to merit success. A survey or focus group with coroners in England and Wales would help identify cultural norms, attitudes towards PFDs, working practices of coroners, and the current system's strengths and weaknesses.

8.6.4 Implications for future research

I outlined ongoing research (sections 8.4.4) that warrants a larger programme of research, which will require grant funding. The 2016 ACMD report encourages the UK Government to fund such research investigating the causes and prevention of opioid-related deaths (409). The Preventable

Deaths Database's ability to automatically update using my scraper means that surveillance of preventable deaths can continue. But manual screening of PFDs for opioids and extraction for variables outside of the scraper (e.g. age, sex, and causes of death) is required, which is time-consuming and liable to errors. Funding could be sought to trial more sophisticated methods that combine my web scraper with an algorithm that uses natural language processing to screen PDFs for opioid nomenclature, as described in Chapter 5, and extract other key information that could feed into the Preventable Deaths Tracker. My web scraper can also be used by others and applied in other areas of research to simplify and automate data collection. I have identified several research questions while screening the thousands of PFDs, including preventable deaths in care homes and prisons, particularly deaths involving falls in the elderly, preventable deaths in children and adolescents, and deaths involving licit and illicit drugs purchased online. I have a growing list of articles to write for the Coroners' Concerns to Prevent Harms series to disseminate information and lessons to healthcare professionals, medical students, policymakers, and the public. Missing data from PFDs, such as ethnicity and other demographic and medical and treatment histories, would be valuable variables to add to future PFDs and explore.

8.7 Conclusion

The use of opioids contributes to premature mortality, which I found to increase in England and Wales, which can be prevented. The current culture, systems, and processes of writing, receiving, responding, and disseminating PFDs, limits the value of coroners' reports. I co-created a computer program to efficiently and reproducibly collect all PDFs to build the Preventable Deaths Database and Tracker (https://preventabledeathstracker.net/). My findings provide lessons for healthcare professionals prescribing or managing people taking opioids and coroners when writing PFDs. Deaths are the hallmark of the opioid crisis in the USA. If I can obtain grant

funding, my future research can enhance surveillance, improve patient safety, and potentially prevent a similar public health crisis in the UK.

8.8 Chapter summary

- I created the Preventable Deaths Database by scraping the website of the Courts and Tribunal Judiciary.
- There were 176 opioid-related PFDs between 2013 and 2019, representing 5.8% of all PFDs. The rate of opioid-related PFDs increased by 262% over the study period.
- Most (66%) deaths were in males and those aged 30-49 years.
- I constructed the Preventable Deaths Tracker (https://preventabledeathstracker.net/), and I am disseminating key lessons from PFDs in the Coroners' Concerns to Prevent Harms series in *BMJ Evidence Based Medicine*.

Chapter 9

"If I had an hour to solve a problem,
I'd spend 55 minutes thinking about the problem,
and five minutes thinking about solutions."
~Albert Einstein

9 Discussion and conclusions

Undertaking this thesis on the use of opioids was motivated by my personal experiences and the gaps in the evidence-base and the quality of the evidence. Working in an Australian pharmacy, seeing customers repeatedly return for their weekly boxes of codeine, and conducting my Honours research in private pain clinics (31), gave me first-hand experience of the disparity between prescribing opioids and managing patients taking them in clinical practice and the lack of high-quality evidence to support the use of opioids in these patients. This sparked my interest in evidence-based medicine (EBM) and has resulted in the work contained in this thesis.

There has been much opioid-related research in the past decade. Most of it has been conducted in high-income countries and has shown increased prescribing and subsequent harm. Efforts have focused disproportionately on large observational studies that omit clinically relevant outcomes and resource-intensive initiatives to reduce prescribing of opioids, which are not having widespread impact, before the problem has been adequately defined. In the USA, nearly half a million people died from an opioid overdose between 1999 and 2019 (447). US policies that restricted the prescription of opioids were associated with an increase in overdose deaths attributed to non-prescribed opioids, such as heroin and synthetic opioids (448). This public health crisis in the USA provides lessons for the UK and illustrates the importance of EBM.

Therefore, the overarching aims of my thesis were to assess global and national use of opioids and drivers of suboptimal use, and to consider preventive strategies to avert opioid-related harms and deaths.

9.1 Summary of findings

I conducted six studies to address the overarching aim of my thesis and four research gaps (Figure 9.1). Chapter 1 provides an overview of my thesis, structure, and rationale for pursuing this doctorate and my accomplishments. In chapter 2, I provide a summary of opioid pharmacology and the contemporary history of opioids. I reviewed the literature and key reports, highlighting research gaps and the preliminary research to which I have contributed on opioid prescribing trends and geographical variation in England between 1998 and 2018 published in the *Lancet Psychiatry* (3). I presented my observations from the opioid deprescribing clinics in Oxford and the PPI I used for my thesis.

In chapter 3, I described how I conducted a cross-sectional study to determine the amount of controlled opioids consumed globally, regionally, and nationally in 2015-2017. I found that 90% of the world's population consumed one-tenth of the world's opioids, highlighting the "unrelieved pain crisis" (449). The UK was ranked 11th of 214 countries and territories and consumed 3.5% of the world's opioids. Oxycodone, morphine, methadone, tilidine, and hydrocodone were the most commonly controlled opioids consumed globally.

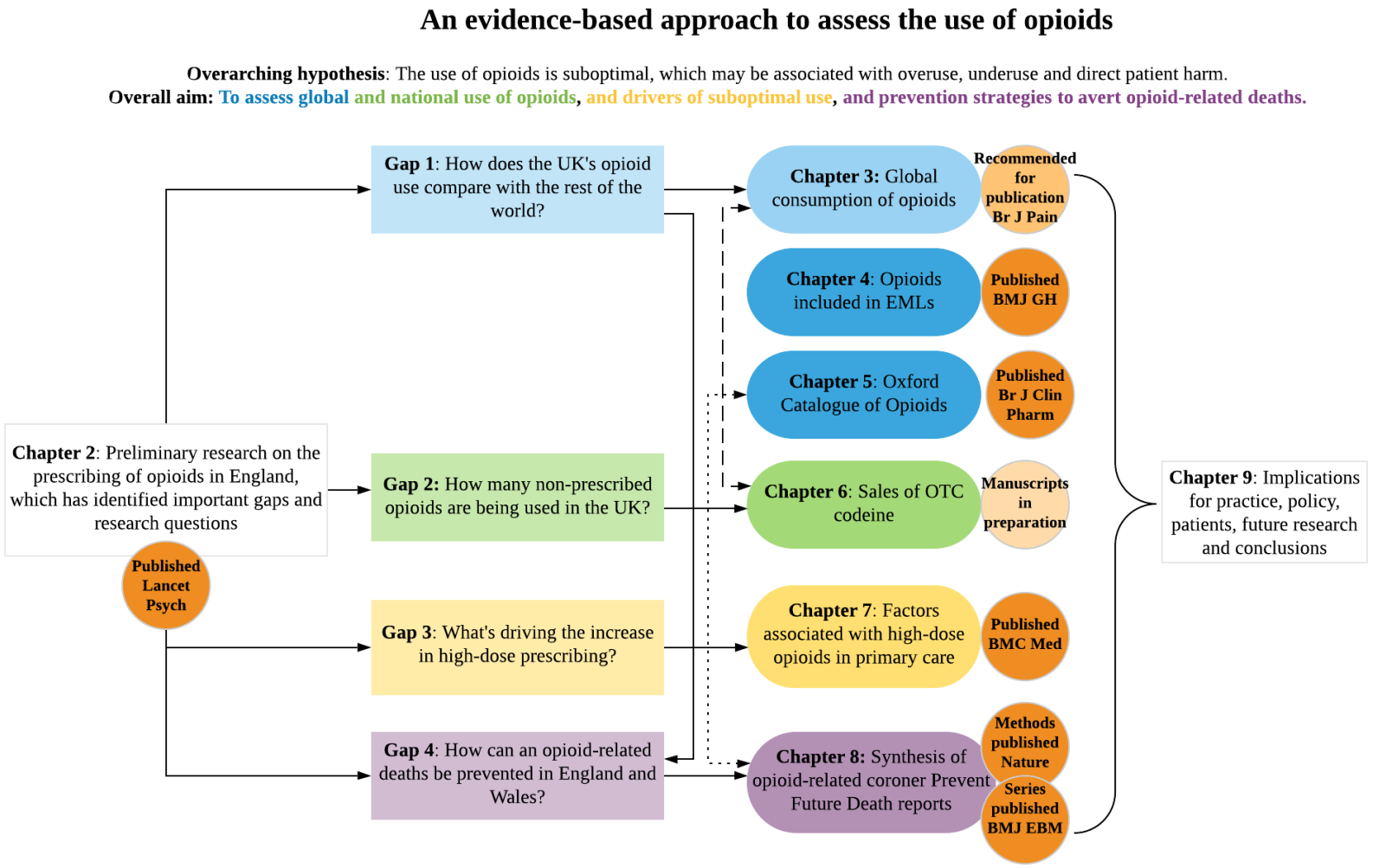


Figure 9.1: Flow chart of the four key gaps (rectangles) I address in six results chapters (rectangular ovals), which form the basis of my DPhil thesis. Orange circles indicate the publication status of each chapter.

In chapter 4, I described how I examined 137 national essential medicines lists (EMLs) for opioids, as a marker of access, and compared national lists with the WHO's Model List of Essential Medicines. I found wide variation in the numbers and types of opioids included in lists, with countries including significantly more than the WHO Model List. Morphine, fentanyl, codeine, pethidine, and tramadol were the most commonly included opioids in national EMLs.

In chapter 5, I reported the development of the Oxford Catalogue of Opioids, which used a systematic search of seven pharmacological resources, and presented the findings from phase one on opioid nomenclature. I identified 233 unique opioid medicaments, and just over a quarter were either drugs with an International Nonproprietary Name (INN) using the stem "-fentanil" or were structural analogue of fentanyl. The resource, https://www.catalogueofopioids.net/, will be developed for scientists, prescribers, and patients, to promote the safe use of opioids by improving access to better quality information and standardising the naming of opioids.

In chapter 6, I assessed sales of OTC codeine products in the UK and 30 other countries over six years between April 2013 and March 2019 to examine the use of non-prescribed opioids. The total units of codeine-containing products sold OTC and total public expenditure increased by 3% and 54%, respectively. In the UK, sales of OTC codeine-containing products fell by 8%, while public expenditure increased by 12%. However, the variation in types of products available and the sheer volume of these products being sold OTC in the UK may be a cause for concern. In the most recent year of data (April 2018 to March 2019), people in the UK purchased 11.5 dosage units per resident, costing £1.64 per person.

In chapter 7, I described how I conducted a systematic review and meta-analysis of observational studies to examine drivers of the use of high-dose opioids in primary care. I included six studies conducted in Australia, the UK, and the USA, which contained over 4.2 million participants taking opioids. There were 154,749 people (3.6%) taking high doses and the rest were taking low doses. I identified five factors associated with high-dose opioids, including co-prescription of benzodiazepines, depression, Emergency Department visits, unemployment, and being male.

In chapter 8, I aimed to understand the types of opioid-related deaths in England and Wales, to provide context to population-level ONS data on drug poisonings. I used a novel methods called web scraping to collect coroners' Prevent Future Death (PFD) reports. I created the Preventable Deaths Database, developed the Preventable Deaths Tracker (https://preventabledeathstracker.net/), launched the *BMJ Evidence Based Medicine* Coroners' Concerns to Prevent Harms series, and reported preliminary findings. I found 176 cases in which an opioid caused or contributed to death, representing nearly 6% of all PFDs between 2013 and 2019. Opioid-related deaths increased by more than 3-fold in six years. Most of the deaths occurred in males and people aged 30-49 years.

9.2 Strengths and limitations of my thesis

9.2.1 Strengths and limitations in relation to previous research

Research has previously assessed the use of opioids, as I outlined in chapter 2. In my thesis, I address some key gaps in this previous research. Previous reports and studies that have examined the global consumption of opioids contained out-of-date data that focused on analgesics or a

subset of opioids (1,150,151,160–162). In chapter 3, I described how I conducted an analysis to update previous research and include all types of opioids.

Previous studies have assessed the inclusion of drugs in national EMLs for neuropathic pain (186) or morphine (187), and restricted their evaluations to low- and middle-income countries. As the affordability of essential medicines and the issue of suboptimal prescribing increases, the benefits of adopting EMLs are being recognised in high-income countries (188,189). Therefore, for chapter 4, I included 137 countries with national EMLs and examined all types of opioids listed, except for opioid receptor antagonists.

To my knowledge, there was no central repository of opioid drugs. For chapter 5, I systematically searched commonly used pharmacological resources to create this repository. As described by one of the peer reviewers, *A major strength of this study is that the catalogue of opioids developed would be of significant value to various fields, including clinical practice, research and drug development, and public health*.

Investigating the use of non-prescribed opioids is a challenge. Opioids may be purchased online, through the black-market, obtained illicitly, from a family or friend, or in some countries purchased OTC in the form of codeine combined most commonly with a non-opioid analgesic or NSAID. Therefore, previous research on the use of codeine has relied on case reports (266–268), self-reported questionnaires (269–276), qualitative studies (277–280), and data from poisons centres, hospital admissions, or coronial systems (281–285). Before my research, one study had investigated the consumption of OTC cough syrup containing codeine in Taiwan using data from

IQVIA (322). In chapter 6 I have provided the first study, to my knowledge, of the sales of OTC codeine products in the UK and 30 other countries over six years.

Observational studies have used population-level prescribing data to examine the use of opioids (3,368–370). But patient-level data are needed to determine the number of people taking opioids and to calculate dosages for each patient. A systematic review, published one month before my review, examined the proportion of people with chronic non-cancer pain for whom an opioid had been prescribed, the types of opioids prescribed, and factors associated with prescribing (450). But this review included all observational studies and did not assess high-dose opioids. My systematic review in chapter 7 is the first study to synthesise observational studies that use patient-level data to assess factors associated with high-dose opioids.

A previous study by Ferner and colleagues examined 500 coroner PFD reports, and found 17 deaths that involved an opioid (414). For chapter 8, I expanded on these methods to create a computationally reproducible data-collection method to establish the Preventable Deaths Database that identified 176 preventable opioid-related deaths.

I have discussed the limitations of my individual studies in each results chapter (chapters 3 to 8). But overall, my thesis has a quantitative focus, as these methods best addressed the research gaps I identified when reviewing the literature (chapter 2). Therefore, my research does not explore *why* increases, decreases, and variations in opioid use and harms have occurred, as I did not use qualitative research methods. Several qualitative studies have been conducted to understand the experiences of people using prescribed (147,451–455) and non-prescribed opioids (278,280), the

experiences of managing these patients (270,456–462), including a systematic review of this evidence (388). However, there are also other stakeholders and viewpoints that have not been investigated, including coroners, regulators, policymakers, and pharmaceutical companies, which may provide different insights into the problems of opioid use and potential solutions. Future research will therefore require mixed methods to address these gaps.

It is important to mention the inherent limitations of observational research, including biases, confounding, and the inability to demonstrate causality. The most common and consistent bias in my research was reporting bias. Reporting bias is an umbrella term that is defined as "*a distortion of presented information from research due to the selective disclosure or withholding of information by parties involved with regards to the topic selected for study and the design, conduct, analysis, or dissemination of study methods, findings or both*." (44) However, this definition is most applicable to trials and systematic reviews. In my observational research, there were omissions, heterogeneity, and potential under-reporting in the datasets that limit the generalisability and interpretation of results. For example, the data obtained from IQVIA (chapter 6) represents a sample of pharmaceutical markets. While coverage was high, it cannot represent all sales of OTC codeine in the UK and abroad. Since drug development is a long, complex, expensive, and risky process, other opioids may have been developed but not trialled or reported, and hence did not make it into the Catalogue of Opioids (chapter 5). In chapter 8, there were various omissions, errors, and inconsistencies in PFD reports, responses to PFDs, and the Judiciary website. I am also certain that there have been other preventable opioid-related deaths that have not resulted in a PFD. While observational studies have their limitations, the methods I have used were the most appropriate and practical for answering the research questions.

Owing to the nature of available data used in my thesis, it was not possible to estimate the prevalence of opioid use or associated harms. I calculated consumption or sales rates per person using population statistics. However, these measures assumed that all ages of the population, including children, consumed or purchased opioids, which is a limitation. In chapter 8, my denominator was the number of PFD reports dated each year to allow for trends in opioid-related deaths to be examined. It is also not possible to triangulate the datasets to their primary sources (e.g. by counting the number of OTC codeine products sold in pharmacies in Oxford). There are also likely confounding variables that may be influencing the use of opioids, which I did not measure or account for in my analyses.

The difficulties in measuring opioid usage in research can limit the translation of outcomes into clinical practice. Previous studies have measured opioid consumption using defined daily doses (DDD) (1,138,463) or oral morphine equivalents (OME) (149,150,152,160,161). For chapter 3, I could not convert the volume of consumption into DDD or OME, because conversion factors are not available for all types of opioids included in my analysis. This limits the comparability of my findings with previous research. For chapters 6 and 7, I was able to control this by using dosage units and only including studies that measured high doses with OME, which are most clinically relevant.

As with most published research, the timeliness of data can limit its relevance and impact. When I began chapter 3, I used the most up to date (2015-2017) data on global opioid consumption; it now appears that data from 2019 has been published (464). For chapter 4, data for the GEM

database were extracted from the WHO's web portal in June 2017, and it is likely that some countries have updated their EMLs since. In chapters 5 and 7, manual searches used to identify opioid drugs and observational studies would need to be manually updated to stay relevant. In chapter 6, additional data would need to be purchased from IQVIA to evaluate new trends, such as the impact of Brexit or the covid-19 pandemic on sales of OTC codeine; the shift in opioid use during the covid-19 pandemic has already been highlighted (465). However, chapter 8 provides some hope. Using programming, data can be collected efficiently and reproducibly.

9.2.2 Overall strengths and limitations

The main strength of my thesis is the use of systematic methods and their variety. I performed two cross-sectional studies (chapter 3 and 4) and a retrospective observational study (chapter 6) using three novel datasets; the United Nations International Narcotics Control Board (INCB) consumption statistics, the Global Essential Medicines (GEM) database, and electronic point-of-sale (EPoS) data on OTC codeine products. For chapters 5 and 7, I used my evidence synthesis skills to systematically search pharmacological resources to create a catalogue of opioids and conduct a systematic review of observational studies. For chapter 8, I used mixed methods: programming to collect coroner reports (i.e. the web scraper and Preventable Deaths Database) and develop the Preventable Deaths Tracker, evidence synthesis to screen eligible coroner reports, and descriptive statistics and thematic analysis to categorise opioid-related deaths. Most of these studies have been peer-reviewed and published in high-impact academic journals, including *BMJ Global Health* (17), *British Journal of Clinical Pharmacology* (18), *BMC Medicine* (21), *Nature* (25), *British Journal of Pain* (16), and *BMJ Evidence Based Medicine* (26–28).

My thesis has a global and national focus. It uses diverse datasets that represent 214 countries and non-metropolitan territories (chapter 3); essential medicines lists used by 137 countries (chapter 4); 233 opioids (chapter 5); the sales of OTC codeine products in 31 countries (chapter 6); data from observational studies conducted in high-income countries (chapter 7); and coroners' reports in England and Wales (chapter 8). Therefore, this increases the external validity and applicability of the findings in my thesis.

My application of open science practices to my research is a strength of my thesis. I created an "Open Science Checklist" that I used for each results chapter (chapters 3-8). I developed the theoretical and technical skills necessary for this by attending the Oxford-Berlin Summer School for Open Research in September 2019. However, this training was two years after I began my DPhil. It would have been beneficial to have received training on tools for open science towards the start of my DPhil, as having these skills transformed my research ideas (e.g. chapter 8), and this way of working improves the transparency of research, reduces biases and research waste, accelerates knowledge generation, and can be used to train and educate others in research methods and ethics (33,40,466). This was my motivation to establish the Oxford Primary Care ReproducibiliTea Journal Club, and I often run tutorials for fellow DPhil students to show others how to use the OSF to pre-register their protocols and GitHub to share their data and code. The benefits and applications of working openly are endless. However, many barriers and challenges remain (466), preventing open research from being the norm, which will require cultural changes, recognition, and incentives from all levels of the research ecosystem.

My use of PPI and observations at the opioid deprescribing clinic is a strength of my research. Incorporating PPI in quantitative research can be challenging. I assumed that when a gap in the evidence was identified, and the appropriate data were sourced to fill that gap, PPI would be unnecessary. However, I have learnt that this assumption is incorrect, and that PPI can be incorporated in all stages of the research cycle. I directly used PPI for chapters 3, 6, and 7. It may therefore be seen as a limitation that I did not seek to include patients in all aspects of my research. But it taught me what results were important for patients and improved how I presented and disseminated my research for all chapters. One patient, Sean Jennings, has been a tremendous asset to my research, co-authoring an article in *The Conversation* to convey the findings from the systematic review in chapter 7 (22), and we have stayed in contact. Time spent with patients has expanded my clinical and practical knowledge of opioids and enriched my DPhil experience. Overall, working with patients reinforces my motivation to continue my research to prevent harms and be a voice for those silenced by pain or prematurely deceased because of opioids.

The order in which I present the chapters is not the order in which I began or completed the work described, which skewed my ability to incorporate useful developments into my research. For example, if the list of opioid drug names had been developed first (chapter 5), the search for opioids in the Global Essential Medicines database (chapter 4) and my opioid-related search terms for my systematic review (chapter 7) could have been streamlined. Chapter 7 was the first study I began after the preliminary research findings that showed a 6.7-fold increase in the prescribing of high-dose opioids in England between 1998 and 2016 (3). The aim of the work described in chapter 7 was to understand what was driving this increase in high-dose opioids.

The ideal study design to answer this question would be a prospective study using patient-level clinical data from electronic health records (e.g. CPRD). But access to such data for doctoral students has several challenges, including obtaining funding to purchase the data, the potential delay in obtaining ethical approval, data management, and sufficient training in how to use such data. The next most feasible study design was a systematic review of observational studies that used patient-level data. Of the six studies included in my systematic review, two were cross-sectional, and four had cohort designs. Thus, future research should consider a prospective study to address this gap.

There were also time and cost restrictions. It took nearly two years to obtain data on sales of OTC codeine products, owing to several barriers. However, my use of FOI requests helped identify IQVIA as the best data source, and the data were then provided swiftly. I sourced two novel datasets using FOI requests during my DPhil, which I have not presented in this thesis owing to the volume of research I undertook and time restraints. These datasets were on controlled opioids dispensed privately and patient-level counts for each opioid formulation to quantify the number of people for whom opioids were dispensed in England. I escalated the latter FOI to the Information Commissioner's Office (ICO), which resulted in a significant outcome. I hope to use these datasets in the future. Finally, my PPI discussion group was limited to three people owing to location issues, travel and health implications, and in-person PPI costs.

9.3 Implications of my thesis

First, and most importantly, there are implications for clinical practice. When I set out to do this doctorate, I thought I would be focusing on identifying ways of reducing inappropriate prescribing of opioids in primary care. I soon realised the challenges of defining

"appropriateness". I started with the concept of opioid dosage. I questioned whether arbitrary thresholds for low- and high-dose opioids, which have substantial variation between countries and practice (92,93,128,129), could be used as a marker of "appropriateness". Anecdotally, it is easy to invent case studies where an opioid prescription may seem "appropriate", for example, in a patient with terminal cancer, or where a prescription may seem "inappropriate", for example, in a patient with a history of addiction. But equally, there are real-life counterexamples. A fentanyl patch was prescribed for a patient with terminal cancer and carcinomatosis, which seems appropriate. However, she accidentally overdosed in a hot bath (chapter 8, section 8.5.2.1). A patient who was using high doses of opioids and had a history of alcoholism was being deprescribed in the opioid clinic, which seems appropriate. However, he reverted to using alcohol and became homeless. Would maintaining this patient on a stable high-dose of opioids have been more appropriate?

In chapter 3 I highlighted the disparities in opioid use globally and discussed the importance of ensuring access to opioids for acute pain, palliative care, cancer pain, and opioid dependence. In chapters 4 and 5 I reported variations in opioids included in national EMLs and the wide variety of opioids that have been developed. In chapter 6, I reported the finding that large amounts of codeine-containing products are being purchased by the public and I questioned whether this form of access to opioids is safeguarding society from harms. In chapter 7, I identified factors that may be used to categorise patients at risk of harm and areas on which to focus clinical care, such as increasing provisions for managing depression and reducing the use of benzodiazepines in people taking high-dose opioids. And finally, in chapter 8, I uncovered 176 preventable opioid-related deaths that have key lessons for prescribing and managing patients taking opioids.

So, after appraising the evidence, conducting this research, spending time with patients, and talking with experts, I began to appreciate the complexities of this problem and to realise that it is not clinically practical or ethical to provide GPs with a blanket definition of what constitutes an "appropriate" or "inappropriate" opioid prescription. Rather, my conclusions for clinical practice are that opioids are essential medicines that can be prescribed to the right patient, at the right dosage and intervals, and for the right duration and reasons.

The one-size-fits-all ban on opioids in the draft NICE guidelines for "chronic pain in over 16's" (104) will not meet the needs of all patients with chronic pain associated with various etiologies. The evidence clearly shows that for opioid naïve individuals with chronic pain, opioids are not the answer. More resources for physical therapies, psychology, and other social services, would need to be available and accessible before such a guideline could be used. To capture this problem's complexity, I urge policymakers to consider the 176 premature opioid deaths I identified in chapter 8. A pertinent comment from a GP highlights the conundrum posed in clinical practice: "*At the moment it feels like everyone is doing different things. If NICE says we can't prescribe opiates and the MHRA says they can't be bought over the counter, then are we banning them? What's the strategy?*" (245) There is therefore an urgent need to understand who may benefit from opioids. In the meantime, resources should be optimised to effectively manage patients already taking opioids and to expand provisions to prevent unnecessary use of opioids, avoidable harms, and premature deaths.

Governments around the world are reclassifying codeine to prescription-only, including jurisdictions in Minnesota (July 2013), Manitoba (February 2016), France (July 2017), and

Australia (February 2018). Research from Australia and Manitoba consistently suggests that reclassifying OTC codeine reduces unsafe use (321,348,349). In the UK, the Government has been slow to act. The MHRA's Opioid Expert Working Group (EWG) is reviewing the evidence to advise the Government on the next steps. The MHRA's previous attempts to use data to examine the effectiveness of policy changes were not successful, because "*The MHRA did not perform a formal review of sales data and ADR reports at 6 and 12 months after amendment of the Marketing Authorisations (MAs) as planned. This was because it took longer than anticipated for the updated product information to reach pharmacies, due to the number of products affected*." (102) I therefore hope my research findings from chapter 6 can be used by the Opioid EWG, the MHRA, and the Government to design, implement, and measure the effectiveness of potential new policies. If codeine is reclassified to prescription-only in the UK, targeted public health campaigns will be required to educate the public and prescribers. If no changes are made to the status of codeine in the UK, my findings still support the need for tailored public health measures that educate the public, particularly young adults, who may be influenced by pop culture, on the appropriate use of codeine and real-time monitoring systems to prevent "pharmacy shopping".

In UK medical schools, the content and time allocated to teaching clinical pharmacology, drug nomenclature, prescribing, and pain management varies (202,467–472). The resource I created in chapter 5, the Oxford Catalogue of Opioids, could be developed and tailored to reduce such variation in medical schools. This catalogue will also be designed to assist scientists, prescribers, and educate the public, as peer reviewers have signposted that it has "*...significant value to various fields, including clinical practice, research and drug development, and public health*",

and that "*This catalogue can indeed be of importance for both scientists and prescribers.*" To coincide with my findings from chapter 6, the first opioid vignette I shall publish on the catalogue will deal with codeine.

The Preventable Deaths Database and Preventable Deaths Tracker (chapter 8) have the potential to become a vigilance system for all preventable deaths in England and Wales. It can provide training for coroners and educate the public, clinicians, and policymakers through the *BMJ Evidence Based Medicine* Coroners' Concerns to Prevent Harms series.

The methods I used for chapters 4, 5, 6, and 8 have significant implications for future research. The search strategy I used to examine the GEM data and create the Catalogue of Opioids could be applied to other drug classes, such as cardiovascular medicines, to assess their inclusions in national EMLs or to create, for example, Catalogues of Statins, Beta-blockers, or ACE inhibitors. Chapter 6 reveals that it is possible to obtain data on OTC products, which could be used to investigate non-opioid and topical analgesics, ingestion remedies, hay fever medicines, sleeping aids, eye care, and smoking cessation products, to name a few. While web scrapers are commonly used in other fields, their application to medical research is novel and should be expanded to streamline data collection and increase efficiency and reproducibility. For example, a first-year DPhil student, Dr Elizabeth Thomas, has designed a web scraper to collect guidelines from the NICE website for her first DPhil study (473), following our chat about web scraping.

9.4 Future research

Many solutions will be needed to improve the state of this complex problem. From focusing my time on the problems, two themes have emerged from my research as critical areas for future research. The first theme is the need for better data to improve monitoring and vigilance of prescribed and non-prescribed opioids, ensuring evidence-based decision-making in clinical practice and policy. The second theme is the need for training and education to serve patient safety and ensure that lessons from past mistakes are learnt. There are two primary outputs generated from my thesis that address these themes: The Oxford Catalogue of Opioids and the Preventable Deaths Database and Tracker. In this section, I focus on the future research needed to expand these outputs.

9.4.1 The Oxford Catalogue of Opioids

In chapter 5, I presented the findings from phase 1 of the Catalogue. Phases 1 and 2 of the Catalogue were published in the *British Journal of Clinical Pharmacology* (BJCP) in February 2021 (18). A funded research programme is now required to develop phase 3 of the Oxford Catalogue of Opioids (https://www.catalogueofopioids.net/). The aim of phase 3 is to create a visual platform that will aid prescribers and researchers and inform patients, carers, and the public about the properties of opioids to improve their safety and reduce avoidable harms. Two work streams (WS) of research are required to develop and disseminate the catalogue:

- WS1: Opioid vignettes
- WS2: Evidence synthesis

Following completion of WS1-2, there may also be scope to examine the effectiveness of the Oxford Catalogue of Opioids to raise awareness and improve knowledge of opioids. I have

outlined potential expenses to include in a grant application (Table 9.1) and propose five years of support (£100,000 in non-staff costs) to carry out and sustain this research.

First, I shall work with key stakeholders to develop a PPI network, including prescribers and medical students, opioid researchers, and patients and carers, to establish key gaps in knowledge that the catalogue could fill, and design the resource for these target groups. There are a few individuals in my network with whom I can connect, to gauge their interest in this stage of the research, including Dr Jim Huddy (a GP and the NHS Kernow CCG clinical lead for chronic pain), Dr Jane Quinlan (Pain Consultant in Oxford), the Department of Pharmacology in Oxford, the Oxford Medical School, Seema Gadhia (a pharmacist interested in opioids from the Oxford Academic Health Science Network) and the PPI group I created during my DPhil. I shall also reach out to the British Pain Society and the British Pharmacology Society. I shall engage with this network throughout WS1-2, for design, content development, and dissemination.

WS1 will involve the writing of opioid vignettes for the website. In chapter 5, I identified 233 opioids. It is unlikely to be feasible to write an individual vignette for each drug. I shall first focus on the 32 opioids included in the BNF, which are most relevant to patients and prescribers. There may also be some opioids on the list for which there is insufficient evidence for which individual vignettes are necessary. For example, for fentanyl derivatives and analogues, one vignette may be sufficient. I shall engage with the editorial team at the Drug and Therapeutics Bulletin (DTB) to gauge their interest in publishing some key vignettes, such as the five opioids included in the WHO's Model List of Essential Medicines: codeine, fentanyl, loperamide, methadone, and morphine. To engage with students and facilitate education and training, I

propose hosting the "Oxford Catalogue of Opioids Away-day", to be held twice each year and open to 15 medical and pharmacology students in the UK. The first session would be held in person at a college in Oxford, and the second would be facilitated online for those who may not be able to attend in person. The benefits of this approach would be three-fold; 1) the students would receive a tailored tutorial from eminent clinical pharmacologists; 2) the students would have an output on the website and a possible opportunity to publish their vignette in DTB or another journal of interest; and 3) selection to attend the event in Oxford will expand their networks and potentially be an asset to their CVs.

WS2 will involve systematic reviews of opioids, starting with the five opioids included in the WHO's Model List, to evaluate dose-response relationships and numbers needed to treat for both benefits and harms (NNT_B and NNT_H). In section 9.2.4 and chapter 3 I outlined the lack of opioid conversion factors that limit conversion of opioids to OME and the ability to combine and compare different types and formulations of opioids. The outcomes of the reviews will be used to create the "Oxford league table of opioids" as previously developed for analgesics in acute pain by Bandolier (241), and the dose-response curves will be used to improve the calculation and conversion of OMEs, enhancing safety in clinical practice and the translation of opioid research. As endorsed by one of the BJCP's peer reviewers, "*I do hope, in the interest of prescribers, that it shall be expanded with the strength of different opioids in phase 3*."

As with the PPI network, I shall integrate engagement, training, and education opportunities throughout the research programme. At the most basic level, the blog on the website will share updates about the catalogue, publications, and when new opioid vignettes are added. The blog

will be shared on social media with relevant societies and my PPI network. In each WS, there will be dedicated ways to involve students and provide education and training, including clinical pharmacology, drug nomenclature, and research methods.

Table 9.1: Proposed expenditure to develop the Oxford Catalogue of Opioids

Items	Annual cost (£)
Non-staff costs	
Annual fee to maintain website via Wix.com	122.44
Website development	10000.00
PPI activities – patients, prescribers, students, and scientists	2000.00
Opioid pharmacology away-day in person (1st half of year)	3000.00
Opioid pharmacology away-day online (2nd half of year)	500.00
1x publication article processing charges per year	3000.00
Engagement activities	2000.00
Total for one year	**£20,622.44**
Total for five years	**£103,112.20**
Staff costs	
Lead post-doctoral researcher (GCR) – 20% x 5 years	
Research assistant – 100% x 5 years	
Systematic reviewer – 100% x 3 years	

9.4.2 The Preventable Deaths Database and Tracker

In chapter 8, I presented preliminary findings that identified 176 premature opioid-related deaths and outlined future research that requires support. The overarching aim of this programme of research is to reduce avoidable harms, serve patient safety, and educate the public, clinicians, and policymakers. It will create a comprehensive system that enhances surveillance and vigilance to premature deaths in England and Wales. There are four WS of research:

- WS1: Opioid-related deaths
- WS2: Preventable Deaths Database
- WS3: Preventable Deaths Tracker - https://preventabledeathstracker.net/

- WS4: Priority research areas – community safety initiatives

Following completion of WS1-4, there may also be scope to examine the effectiveness of the Preventable Deaths Tracker to increase compliance with regulations 28 and 29 of the Coroners (Investigations) Regulations 2013. I have outlined potential expenses to include in a grant application (Table 9.2) and propose five years of support (£156,000 in non-staff costs) to carry out and sustain this research. I shall create a PPI network with key stakeholders, including bereaved families, coroners, and pathologists, with whom to engage during WS1-4.

WS1 will involve three stages: 1) assessment of the 176 opioid-related PFD reports to identify coroners' concerns; 2) evaluation of responses to the coroners' concerns and the actions taken or proposed to prevent future opioid deaths; and 3) establishment of a panel of stakeholders to examine the relevance and usefulness of coroners' concerns, the quality of responses and their actions, and the suitability of addressees to identify gaps to prevent opioid deaths.

WS2 will maintain the Preventable Deaths Database. It will require technical support to run the web scraper each month, screen and extract data from new cases, and categorise the types of deaths. Initially, there will be a backlog of data to process from 2020 and 2021. Once the data are updated, an analysis will be conducted on the whole Preventable Deaths Database to determine and rank the most common premature deaths. This analysis will be seminal to prioritise future research (WS4).

WS3 will develop the Preventable Deaths Tracker (https://preventabledeathstracker.net/). First, it will require software engineers to use sophisticated methods that integrate my web scraper with

an algorithm that uses natural language processing to automatically screen and extract information from PFDs and feed this to the Preventable Deaths Tracker website. This may take some trial and error and may not be entirely achievable. An analysis on the whole Preventable Deaths Database will be conducted to assess response rates and compliance with regulations 28 and 29 of the Coroners (Investigations) Regulations 2013 for all individuals and organisations who have received PFD reports. Their response rate will rank each individual and organisation. Using feedback from my PPI network, a system to call out and nudge addressees who are overdue will be considered.

WS4 will focus on priority research areas that the findings from WS2 will inform. But in the meantime, I have highlighted four priority areas from reading >3000 PFD reports, including preventable deaths in care homes, premature deaths in children and adolescents, and deaths attributed to falls in the elderly and to illicit and licit drugs purchased online. Together, WS2 and WS3 will provide a formidable resource for research that governments, public organisations, regulators, guideline developers, medical societies, coroners, lawyers, and think-tanks can commission my research team to conduct tailored analyses.

As with the PPI network, I shall integrate public engagement, training, and education opportunities throughout this research programme. I shall add a blog to the Tracker website to share updates, publications, and cases that need immediate dissemination (e.g. Amber Alerts!). Social media will be used to share all outputs and connect with relevant stakeholders. I shall continue submitting articles to the *BMJ Evidence Based Medicine* series on Coroners' Concerns and shall embed ways to involve students and coroners to provide training.

Table 9.2: Proposed expenditure to develop the Preventable Deaths Database and Tracker

Items	Annual cost (£)
Non-staff costs	
Annual fee to maintain website	122.44
Website development	20000.00
PPI activities	4000.00
W1 & W4 stakeholder panels	2000.00
1x publication article processing charges per year	3000.00
Engagement activities	2000.00
Total for one year	**£31,122.44**
Total for five years	**£155,612.20**
Staff costs	
Lead post-doctoral researcher (GCR) – 60% x 5 years	
2 x Research assistants – 100% x 5 years	
Software engineer – 60% x 2 years	

9.4.3 Interventions to improve the safe use of opioids in primary care

Across England, GPs, Clinical Commissioning Groups (CCGs), and specialist centres are working on ways to reduce opioid prescribing and improve the management of people with chronic pain (391,392,474–478). However, this is not standard practice across the country, and patients in low resource areas who are taking opioids may fall through the cracks. There may also be variation in how services are run and there is minimal data on the benefits, harms, and cost-effectiveness of such services. There are also two leading trials funded by the National Institute for Health Research (NIHR), the I-WOTCH study and PROMPPT study, which are evaluating the effectiveness of tapering and reviewing opioids prescribed to people with chronic non-cancer pain in primary care (479,480). Following the outcomes of these trials, I hope to combine their results with the findings from my thesis to design a feasibility study to test a data-driven intervention in primary care that uses education (e.g. dashboards through the RCGP Research and Surveillance Centre database) to inform prescribers on the number of patients

being prescribed opioids in their practice, the OME dosage of each patient, the number of patients on high doses (i.e. >120 mg OME per day), the duration of their opioid use, rates of concurrent benzodiazepines prescribing, and markers of harm (e.g. number of adverse events and patient deaths from opioids). If the feasibility study is effective in improving the education and safety of opioids, I hope the findings can be rolled out across England to ensure no areas or patient groups are left behind.

9.5 My reflections

9.5.1 My research reflections

I arrived in Oxford with some research experience and not one publication. In three and a half years, I have 21 publications, including ten first author and three last author publications (Appendix 1.1). While I am a strong advocate for quality over quantity, this is a huge research achievement. My most exciting publications are the co-authored article in *Nature*, my first-author editorial in *The BMJ* to "foster future leaders" in EBM, and the Coroners' Concerns to Prevent Harms series in *BMJ Evidence Based Medicine* that led to interviews on BBC Radio. But these outputs, and the research in this thesis, was only possible because Prof Carl Heneghan responded to an email from a publicationless Aussie who was enthusiastically passionate about improving the evidence-base and reducing the harms from opioids. For me, this highlights two important lessons about academic research and training of the next generation; the number of publications should not be a marker of one's abilities, and the importance of self-motivation in one's research. I have reflected on this while supervising Final Honours Scheme (FHS) students for the Oxford Medical School. Two students are undertaking research in areas they want to pursue their medical speciality, cardiology and psychiatry. They are using the Preventable

Deaths Database to assess deaths from cardiovascular disease and suicides. They are both self-motivated by their research, which translated into high-quality Honours theses and manuscripts for publication.

During supervision meetings, Carl often recommended I think about my employable skills following the DPhil, focusing on research methods. This has been extremely useful, and while I have significantly more methodological approaches and research skills to develop, I feel more confident in identifying my strengths and knowledge gaps. Throughout the DPhil, I learnt to craft research questions, design studies, source the appropriate data, analyse the data using Stata and Python, visually present the data, use tools to openly share all aspects of my research, write my findings for publication, and turn my results into resources that generate new research questions. I learnt the importance of PPIE and how to implement this in quantitative research. I also wrote and obtained research grants, started a journal club, created a scholarship for early-career researchers to attend EBMLive, and represented my cohort as the DPhil representative, providing fellow students with support and establishing the annual departmental DPhil training programme to benefit future DPhil students. Overall, I have developed skills in quantitative observational research, evidence synthesis, and critical appraisal that can be applied across disciplines.

When I arrived in Oxford, I had no research network in the UK. Since, I have formed a variety of collaborations, networks, and mentors across the globe, including with:

- Oxford's EBM DataLab;
- members of ReproducibiliTea and Reproducible Research Oxford (RROx), involving all four divisions of the university and the wider UK Reproducibility Network;

- members of *The BMJ*;
- Prof Robin Ferner and Assoc Prof Anthony Cox (University of Birmingham);
- attendees of the Clinical Pharmacology Colloquium;
- coroners in England, Dr Richard Brittain and Rosamund Rhodes-Kemp;
- Dr Nav Persaud, Dr Tara Gomes, and Dr Peter Gill (University of Toronto);
- Uppsala Monitoring Centre, Sweden;
- WHO's Expert Committee on the Selection and Use of Essential Medicines;
- Open Pain Research Advocacy and Appraisal (OPeRA) group in Australia, Ireland, and the UK; and
- eight Doug Altman Scholars and six Building Capacity Bursary awardees;
- Rotarians in Australia and the UK, the Rotary Foundation's executive staff in the USA, and partner organisations, including Action Through Enterprise (ATE) in Ghana and the Home for Rescue of the Afflicted Children (HORAC) in Nepal.

From these collaborations, I had the opportunity to attend a meeting at BMA House with senior members of *The BMJ*, represent Rotary Scholars at the Rotary Foundation Major Gifts Initiative where I met Prof Louise Richardson, the Vice-Chancellor of Oxford who was also once a Rotary Scholar, and the General Secretary and Chief Executive Officer of the Rotary Foundation. For my research, I travelled to Bangor University, the University of Toronto, and Erice, Sicily. These experiences have not only expanded my networks but encouraged me to think globally and reflect on the impact of my research and career aspirations.

I have learnt a tremendous amount and feel confident that I can transition to a "fully-fledged" researcher. But I appreciate this is just the beginning of my academic career and research

journey, and my skills are a work in progress. I hope to develop methods in rapid evidence synthesis, advance my programming and web development skills, learn how to analyse electronic health records, and progress in teaching and supervision of research. My doctorate training and the research in this thesis have been my most significant academic, professional, and personal milestone.

9.5.2 My personal reflections

I moved to Oxford in September 2017 from Brisbane, Australia, having no family, relatives, or support networks in this country. So I must reflect on the challenges of completing this doctorate while my support network is on the other side of the world, which the global pandemic exacerbated. But these challenges have strengthened my resilience and allowed me to reflect on my purpose and role in the world. I recognise that I have immense privilege as a white person studying at Oxford. I have learnt to self-check my biases, and I am educating myself on systemic injustices, intersectional feminism, and structural racism. I have also taken time to learn about the history of women in Oxford, and I am tremendously grateful to the generations of women who have gone before me. While I recognise the reality and challenges, I have experienced and will face as I attempt to progress in academia as a woman, this also fills me with a sense of determination and duty to be a role model and ally for the next generation of young women pursing STEM and research.

Personally, my acceptance to Oxford was a huge achievement. I will be the first member of my family to attain a PhD and study overseas and at Oxford. But I am most proud of the three scholarships I received to fund my studies as an international student, as I was rejected from countless (>20) scholarships in the UK and Australia. Following an unsuccessful and

unwelcomed research proposal I submitted while working as a research assistant, a colleague and now great friend, encouraged me to apply for an award she found advertised in the Australian Women's Weekly magazine. I later won the 2016 Australian Women of the Future Award, Judges Choice Winner, for my dedication to pain research and helping others. This award provided me with a travel grant to attend my first international conference and interview face-to-face in Oxford. But most importantly, this award gave me a platform that ultimately resulted in scholarships that fully funded my DPhil. This experience taught me the importance of encouraging others and being an enabler, as my Honours and DPhil supervisors have been for me.

9.6 Concluding remarks

In this thesis, I have used principles of evidence-based medicine to assess national and global use of opioids. My research highlights that opioids can be overused or underused and can cause fatal and non-fatal harms at all levels of the healthcare system. But opioids must still have a place in modern medicine by being used in the right patient, at the right dosage and intervals, and for the right duration and reasons. I focused on identifying major problems and generated two resources, the Oxford Catalogue of Opioids and the Preventable Deaths Database and Tracker. I outlined future research to develop these resources to create a data-driven system, embedded with training and education, to improve evidence-based decision-making in clinical practice and policy, serve patient safety, and reduce avoidable harm.

Appendices

10 Chapter 1 Appendix

Appendix 1.1: List of publications during my DPhil

DPhil-related publications

1. Curtis, HJ. Crocker, R. Walker, AJ. **Richards, GC**. Quinlan, J. Goldacre, B. 2019, "*Opioid prescribing trends and geographical variation in England 1998-2017: a retrospective database study.*" Lancet Psychiatry, 6:2; pg140-150, https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(18)30471-1/fulltext
2. **Richards GC**, Aronson JK, Mahtani KR, Heneghan C. "*Global, regional, and national consumption of controlled opioids: a cross-sectional study of 214 countries, states, and territories*". British Journal of Pain, https://doi.org/10.1177/20494637211013052
3. **Richards, GC.** Aronson, JK. Heneghan, C. Mahtani, KR. Koshiaris, C. Persaud, N. 2020. "*Relation between opioid consumption and inclusion of opioids in 137 national essential medicines lists.*" BMJ Global Health. https://gh.bmj.com/content/5/11/e003563
4. **Richards, GC.** Sitkowski, K. Heneghan, C. Aronson, JK. 2021. "*The Oxford Catalogue of Opioids: a systematic synthesis of opioid drug names and their pharmacology.*" British Journal of Clinical Pharmacology. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.14786
5. **Richards, G.C.** Mahtani, K.R. Muthee, T.B. DeVito, N.J. Koshiaris, C. Aronson, J.K. Goldacre, B. Heneghan, C. 2020 "*Factors associated with the prescribing of high-dose opioids in primary care: a systematic review and meta-analysis.*" BMC Medicine. 18:68, https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01528-7
6. DeVito, N. J., **Richards, G.** & Inglesby, P. *"How we learnt to stop worrying and love web scraping.*" Nature, 585, 621–622. *https://www.nature.com/articles/d41586-020-02558-0*
7. **Richards, GC.** Aronson, JK. Heneghan, C. 2020. "*Coroners' concerns to prevent harms: a series of coroners' case reports to serve patient safety and educate the public, clinicians, and policy-makers.*" BMJ Evidence Based Medicine. https://ebm.bmj.com/content/early/2020/11/24/bmjebm-2020-111567
8. Thomas, E. **Richards GC**. 2021. "*Diclofenac in adolescents: diagnosing and treating gastrointestinal adverse drug reactions can prevent future deaths*." BMJ Evidence Based Medicine. http://dx.doi.org/10.1136/bmjebm-2020-111640
9. **Richards, GC**. 2020. "*Alcohol-based hand sanitizers: a warning to mitigate future poisonings and deaths.*" BMJ Evidence Based Medicine. https://ebm.bmj.com/content/early/2020/12/02/bmjebm-2020-111568
10. Bilip, MK. **Richards GC**. 2021. "*Emollients and smoking: a fire hazard that could be prevented to reduce future deaths*." BMJ Evidence Based Medicine. In Press.

Non-DPhil publications

11. Bell S, **Richards GC**. 2021. "*Off-label medicine use: ethics, practice and future directions."* Aust J Gen Prac. https://www1.racgp.org.au/ajgp/2021/may/off-label-medicine-use
12. Bradley, SH, DeVito, NJ, Lloyd, KE, **Richards GC**, et al. 2020. "*Reducing bias and improving transparency in medical research: A critical overview of the problems, progress so far and suggested next step*s." J Roy Soc Med. https://journals.sagepub.com/doi/full/10.1177/0141076820956799
13. Muthee, T. B. M. Kimathi, D. **Richards, G. C.** Etyang, G. Nunan, D. Williams, V. Heneghan, C. 2020. "*Factors influencing the implementation of cardiovascular risk scoring in primary care: a mixed-method systematic review.*" Implementation Science. https://implementationscience.biomedcentral.com/articles/10.1186/s13012-020-01022-x
14. Cashin, A.G. Bagg, M. K. **Richards, G.C**. Toomey, E. McAuley, J.H. Lee, H. 2020 "*Limited engagement with transparent and open science standards in the policies of pain journals: a cross-sectional evaluation*" BMJ Evidence Based Medicine. http://dx.doi.org/10.1136/bmjebm-2019-111296
15. Gill, P.J. Ali, S.M. Elsobky, Y. Okechukwu, R.C. Ribeiro, T.B. Junior, A.C.S.S. Umpierre, D. **Richards, G.C.** 2019 "*Building Capacity in evidence-based medicine in low-income and middle-income countries: problems and potential solutions.*" BMJ Evidence Based Medicine, https://ebm.bmj.com/content/early/2019/11/21/bmjebm-2019-111272
16. **Richards, G.C.** Bradley, S. et al. 2019 "*Challenges facing early-career and mid-career researchers: potential solutions to safeguard the future of evidence-based medicine.*" BMJ Evidence-Based Medicine, https://ebm.bmj.com/content/early/2019/10/25/bmjebm-2019-111273
17. Gbinigie, OA. Onakpoya, IJ. **Richards, GC.** Spencer, EA. Koshiaris, C. Bobrovitz, N. Heneghan, CJ. 2019, "*Biomakers for diagnosing serious bacterial infections in older outpatients: a systematic review*." BMC Geriatrics, 19:190, https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-019-1205-0
18. **Richards, GC**. 2019. "*Treating post-operative pain? Avoid tramadol, long-acting opioid analgesics and long-term use.*" BMJ Evidence-Based Medicine, 25:5, https://ebm.bmj.com/content/25/3/110
19. **Richards, GC**. Macdonald, H. Gill, PJ. 2019, "*A scholarship to foster future leaders in evidence based medicine.*" The BMJ, 364: l775 https://www.bmj.com/content/364/bmj.l775.long
20. Street, TD. Somoray, K. **Richards, GC.** Lacey, SJ. 2019 "*Continuity of care for patients with chronic conditions from rural or remote Australia: a systematic review*", Aust J Rural Health, 1-7. doi.org/10.1111/ajr.12511
21. **Richards, GC,** Lluka, LJ, Smith, MT, et al. 2018 "*Effects of long-term opioid analgesics on cognitive performance and plasma cytokine concentrations in patients with chronic low back pain: a cross-sectional pilot study*", Pain Reports, 3:4 pe669, doi:10.1097/PR9.0000000000000669

Published letters to the editor

22. Price, J. Albury, A. Frie, K. **Richards G.** O'Sullivan, J. 2018 "*Response: Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in health men and women*" BMJ Open: https://bmjopen.bmj.com/content/8/3/e020167.responses#response-randomised-trial-of-coconut-oil-olive-oil-or-butter-on-blood-lipids-and-other-cardiovascular-risk-factors-in-healthy-men-and-women

Published conference abstracts

23. Richards GC, Curtis HJ, MacKenna, Walker, A, Goldacre B. 2020. "*Controlled drug prescribing of opioids by private prescribers in England, 2014-2018*." Pharmacoepidemiology and Drug Safety. https://onlinelibrary.wiley.com/doi/10.1002/pds.5114
24. **Richards GC**, Aronson JA, Muthee TB, et al. 2019. "*Factors associated with the prescribing of high-dose opioids in primary care: A systematic review and meta-analysis*." British Journal of Clinical Pharmacology, 86(6), 1199. https://doi.org/10.1111/bcp.14266
25. Muthee TB, Kimathi D, **Richards GC***, et al. "6 Factors affecting the implementation of cardiovascular risk scoring in primary care; a mixed-method systematic review*." BMJ Evidence-Based Medicine, 2019;**24:**A45. https://ebm.bmj.com/content/24/Suppl_1/A45.1
26. **Richards GC**, Mahtani KR, Goldacre B*, et al. "135 Trends and variation in the sales of over-the-counter analgesics: a protocol for a retrospective database study and policy review*." BMJ Evidence Based Medicine, 2018;**23:**A63-A64. https://ebm.bmj.com/content/23/Suppl_2/A63.2
27. **Richards G**, Mahtani K, Goldacre B*, et al. "65 Factors and variation driving inappropriate opioid analgesic prescribing in the community: a systematic review protocol."* BMJ Evidence Based Medicine, 2018;**23:**A32-A33. https://ebm.bmj.com/content/23/Suppl_1/A32.2

Publications under peer review

28. **Richards, GC.** Aronson, JK. MacKenna, B. Goldacre, B. Hobbs, FDR. Heneghan, C. 2021. "*Sales of over-the-counter products containing codeine in 31 countries, 2013-2019: a retrospective observational study.*" Addiction (ADD-21-0446; https://www.medrxiv.org/content/10.1101/2021.04.21.21255888v1)
29. Ains, A. Heneghan, C. Aronson, JK. DeVito, NJ. **Richards, GC.** 2021. "*Deaths from cardiovascular disease involving anticoagulants: a systematic synthesis of coroners' case reports to prevent future deaths.*" BJGP (BJGP-2021-0290; https://www.medrxiv.org/content/10.1101/2021.04.28.21256272v1)
30. Aronson, JK. Ferner, R. **Richards, GC.** 2021. "*Deaths from using medications purchased online.*" BMJ Evidence Based Medicine (bmjebm-2021-111759)
31. McFadden, E. Lay-Flurrie, S. **Richards, G.C.** Heneghan, C. "*The long-term impact of vaginal surgical mesh devices in UK primary care: a cohort study in the CPRD*". JAMA (JAMA21-5593)
32. Bandyopadhyay, S. Kawka, M. Marks, K. **Richards, GC.** Taylor, EH. Sravanam, S. Thango, N. Figaji, A. Peter, N. Lakhoo, K. "*Traumatic brain injury related paediatric*

mortality and morbidity in low- and middle-income countries: a systematic review" World Neurosurgery (WNS-21-2055)

33. Boone, CG. Antoniou, T. Juurlink, DN. von den Baumen, TR. Kitchen, SA. **Richards GC.** Tadrous, M. Gomes, T. "*The impact of regulatory discussion on low-dose codeine purchasing in Canada: time series analysis*" CMAJ Open.
34. Albasri, A. **Richards, G.C**. Lee, J. Roberts, N. McManus, R. Fletcher, B. R. "*What is the effectiveness of interventions delivered by general practice-based pharmacists: systematic review and meta-analysis*", PLOS One (PONE-D-20-19616).
35. Haroon, I.A. **Richards, G.C.** Persaud, N. "*Association between opioid approvals and opioid-related deaths in four high-income countries: cross-sectional comparison*" JAMA Network Open.
36. **Richards, G. C.** Anwar, S. Quinlan, J. "*Averting a UK opioid crisis: getting the public health messages 'right'*" J Royal Soc of Med (JRSM-20-0026).

Publications in process

37. Anthony, GL. Aronson, J.K. Heneghan, C. Britain, R. Goldacre, B. **Richards, G.C.** "*Preventable suicides involving medicaments: a systematic analysis of coroners*" case reports in England and Wales" Lancet Psychiatry.
38. **Richards, G.C.** Aronson, J.K. MacKenna, B. Curtis, H.J. Goldacre, B. Hobbs, FDR. Heneghan, C. "*Sales of over-the-counter codeine-containing products in the United Kingdom 2013-2019*"
39. Gardener, AD. Dunan, D. Hicks, E. Jacklin, C. Tan, G. Lee, H. **Richards, G.C.** "*Engagement with transparent and open science standards in policies of selected medical and health sciences journals: an audit and evaluation*"
40. **Richards, G.C.** DeVito, N. Bilip, M. Thomas, E. Ferner, R. E. Cox, A. R., Heneghan, C. Goldacre, B. Aronson, J.K. "*Preventable deaths from opioids: a systematic analysis of coroners' prevent future death reports in England and Wales*"
41. **Richards, G.C.** Curtis, H.J. MacKenna, B. Walker, A. Aronson, J.K. Heneghan, C. Goldacre, B. "*Controlled drug prescribing of opioids by private prescribers in England, 2014-2019*"

Appendix 1.2 Posters, presentations and keynote speaking during my DPhil

CONFERENCE POSTERS

1. Reward EQUATOR Conference 2020, Berlin 20-22 Feb 2020: Rombey, T. Gill, P. **Richards, G.C**. Bradley, S. "The Declaration to Improve Health Research"
2. Pharmacology 2019, the British Pharmacology Society, Edinburgh UK, 15-17 Dec 2019: **Richards, G**, Mahtani, K, Muthee, TB, DeVito, NJ, Koshiaris, C, Aronson, JK, Goldacre, B, Heneghan, C, "Factors associated with the prescribing of high-dose opioids in primary care: a systematic review and meta-analysis"
3. EBMLive Conference 2019, 15-18 July 2019: Muthee, T. B. M. Kimathi, D. **Richards, G. C.** Roberts, Williams, V. Nunan, D. Heneghan, C. "*Factors affecting the implementation of cardiovascular risk scoring in primary care: a mixed-method systematic review*"
4. Rotary District 1090 Conference, Portsmouth UK, 9 Mar 2019: **Richards, G**, Mahtani, K, Goldacre, B, Heneghan, C, "Factors and variation driving inappropriate opioid analgesics prescribing in the community: preliminary findings"
5. 6th Preventing Overdiagnosis Conference, Copenhagen, 20-22 Aug 2018: **Richards, GC**, Mahtani, KR, Goldacre, B, Heneghan, C, "Trends and variation in the sales of over-the-counter analgesics: a protocol for a retrospective database study and policy review".
6. 6th Evidence Live, Oxford, 18—20 Jun 2018: **Richards, G**, Mahtani, K, Goldacre, B, Heneghan, C, "Factors and variation driving inappropriate opioid analgesics prescribing in the community: a systematic review protocol"

CONFERENCE PRESENTATIONS

1. Clinical Pharmacology Colloquium, online, "The Preventable Deaths Tracker: a systematic analysis of coroners' Prevent Future Deaths reports" [**08 Dec 2020**]
2. Inaugural Global Essential Medicines Meeting, Toronto Canada, Title of talk: "Overuse and underuse of opioids: an analysis of global opioid consumption and the listing of opioids on national essential medicines lists" **[20–21 Nov 2019]**
3. 4E's Forum - Improving the Detection, Analysis and Reporting of Harms in Healthcare Erice Sicily, Title of talk: "Communication to prevent future opioid-related deaths" **[9 Oct 2019]**
4. Royal College of General Practitioners (RCGP) Conference, Glasgow Scotland, Title of seminar: "OpenPrescribing: Making NHS data useful for GPs" **[4 Oct 2018]**
5. Clinical Pharmacology Colloquium, Bangor Wales, Title of talk: "Factors associated with the prescribing of high dose opioids in primary care: preliminary findings from a systematic review and meta-analysis" **[12 May 2018]**

INVITED SPEAKER

1. Breakfast meeting at the Rotary Club of Misbourne Matins, District 1090, UK [**10 February 2021** – via Zoom]
2. Rotary District 1090 Foundation Showcase on Health [**19 November 2020** – via Zoom]
3. Dinner meeting at the Rotary Club of Balmoral, District 9630, Australia [**22 June 2020** – via Zoom]
4. Breakfast meeting at the Rotary Club of Woden Daybreak, District 9710, Australia [**18 June 2020** – via Zoom]

5. Dinner meeting at the Rotary Club of Belconnen, District 9710, Australia [**20 May 2020** – via Zoom]
6. The Royal Society of Medicine Spotlight on Opioids Event: Is there a prescription opioid crisis in the UK? Title of talk: "Geographical variation in prescribing [of opioids]" [**23 Apr 2020** – postponed due to covid-19]
7. Preventing Overdiagnosis through the Shared Understanding of Medicine (POSSUM) Conference 2020, title of talk: "Rethinking Opioids: Evidence and Practice" [**2 April 2020** – cancelled due to covid-19]
8. Rotary International Paul Harris Fellow Awards for District 1090, UK [**23 Feb 2020**]
9. Reproducibility Oxford (RROx) launch event, Oxford UK, title of talk: "Open science initiatives run by early-career researchers in Oxford" [**13 Jan 2020]**
10. Panellist at the Pint of Science 'Clinical trial transparency – let's talk' event for Open Access Week at St Aldates Tavern, Oxford UK [**23 Oct 2019**]
11. School Assembly at Lourdes Hill College, Australia [**29 May 2019**]
12. Clinical Scientific Meeting at the Pain Management Centre, University College London Hospital (UCLH), title of talk: "Optimising the prescribing of opioid analgesics in primary care" [**4 Apr 2019**]
13. Seminar with junior researchers from the University of Erlangen, Germany, at Green Templeton College, Oxford, title of talk: "Can we explain variation in the prescribing of opioids in primary care?" [**12 March 2019**]
14. Breakfast meeting at the Rotary Club of Reading Matins, District 1090, UK [**6 Feb 2019**]
15. Dinner meeting at the Rotary Club of Farringdon, District 1090, UK [**13 Jun 2019**]
16. Dinner meeting at the Rotary Club of Ascot, District 1090, UK [**2 Apr 2018**]
17. Dinner meeting at the Rotary Club of Farringdon, District 1090, UK [**9 Oct 2017**]

Appendix 1.3 Blogs

1. **Richards, G.C.** 2021. Welcome to the Oxford Catalogue of Opioids! https://www.catalogueofopioids.net/post/welcome-to-the-oxford-catalogue-of-opioids
2. **Richards, G. C.** 2020. High-dose opioids – five factors that increase the risk of harm. The Conversation: https://theconversation.com/high-dose-opioids-five-factors-that-increase-the-risk-of-harm-133546
3. **Richards, G.C**. et al., 2020. Shining a spotlight on the policies of pain journals. BMJ EBM Spotlight Blog: https://blogs.bmj.com/bmjebmspotlight/2020/02/11/shining-a-spotlight-on-the-policies-of-pain-journals/
4. **Richards, G.C**. Onakpoya, I.J. 2019. Reporting biases. Catalog of Bias: https://catalogofbias.org/biases/reporting-biases/
5. **Richards, G.C.** Gill, P.J. 2019. EBMLive and Early Career Researchers. EBMLive Blog: https://ebmlive.org/early-career-researchers/
6. **Richards, G.C.** Gill, P.J. 2019. The inaugural 2019 Doug Altman Scholarships. EBMLive Blog: https://ebmlive.org/announcement-the-inaugural-2019-doug-altman-scholarships/
7. **Richards, G.C**. DeVito, N. Goldacre, B. 2018 "Unreported clinical trial of the week: Study of indomethacin capsules to treat pain following surgery in children (NCT02633969)" BMJ opinion: https://blogs.bmj.com/bmj/2018/10/26/unreported-clinical-trial-of-the-week-study-of-indomethacin-capsules-to-treat-pain-following-surgery-in-children-aged-6-to-less-than-17-years-of-age-nct02633969/
8. **Richards, G**. 2018 "Making NHS data useful for GPs: OpenPrescribing at the RCGP Annual Conference 2018" NIHR SPCR blog: https://www.spcr.nihr.ac.uk/news/blog/making-nhs-data-useful-for-gps-openprescribing-at-the-rcgp-annual-conference-2018
9. **Richards, G**. 2018 "Opioids for pain: what's the problem?" the Centre for Evidence-Based Medicine blog: https://www.cebm.net/2018/09/opioids-for-pain-whats-the-problem/
10. **Richards, G.C**. DeVito, N. Goldacre, B. 2018 "Unreported clinical trial of the week: Liposomal Bupivacaine (Exparel) for postoperative pain control for open and laparoscopic abdominal hernia repair (NCT02128646)" BMJ opinion: https://blogs.bmj.com/bmj/2018/08/09/unreported-clinical-trial-of-the-week-liposomal-bupivacaine-exparel-for-postoperative-pain-control/

Appendix 1.4: Certificate from the Staff and Educational Development Association (SEDA) for the completion of the Developing Learning and Teaching course

This is to certify that

Georgia Catherine Richards

has successfully completed

Developing Learning and Teaching

at

University of Oxford

This programme was accredited by the

STAFF AND EDUCATIONAL DEVELOPMENT ASSOCIATION

under the Professional Development Named Award

Supporting Learning

(Aligned with Descriptor 1 of the UK Professional Standards Framework)

Signed:

Carole Davis
Co-Chair, SEDA

Roisin Curran
Co-Chair, Professional Development Framework Committee

Date: August 2019

SEDA

STAFF AND EDUCATIONAL DEVELOPMENT ASSOCIATION

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Appendix 1.5: Open Science Checklist for my DPhil results chapters

		Chapters						
Principles		**3**	**4**	**5**	**6**	**7**	**8**	**%**
Open methods	Protocol	●	●	●	●	●	●	100
	Preregistration			●	●	●	●	67
	Materials	●	●	●	●	●	●	100
	Statistical code	●	●	●	●	●	●	100
Open data	Data	●	●	●		●	●	83
Open access	Pre-print	●			●			33
	Publication	●	●	●		●		67
	Blogs			●		●		33
	Tools			●			●	33

11 Chapter 3 Appendix

Appendix 3.1: Substances included and excluded from the International Narcotic Control Board data on narcotic consumption, in alphabetical order. Opioids **included** in our opioid consumption dataset:

1. (+)-cis-3-methylfental
2. 3-Acetylmorphine
3. 3-Methylfentanyl
4. 3-Methylthiofentanyl
5. 3-Monoacetylmorphine
6. 4-Fluoroisobutyrfentanyl
7. 6-Acetylmorphine
8. 6-Monoacetylmorphine
9. Acetorphine
10. Acetyl-alpha-methylfentanyl
11. Acetyldihydrocodeine
12. Acetylfentanyl
13. Acetylmethadol
14. Acetylmorphine
15. Acrylfentanyl
16. AH-7921
17. Alfentanil
18. Allylprodine
19. Alphacetylmethadol
20. Alphameprodine
21. Alphamethadol
22. alpha-Methylfentanyl
23. alpha-Methylthiofentanyl
24. Alphaprodine
25. Anileridine
26. Benzethidine
27. Benzoylmorphine
28. Benzylmorphine
29. Betacetylmethadol
30. beta-Hydroxy-3-methyl fentanyl
31. beta-Hydroxyfentanyl
32. Betameprodine
33. Betamethadol

34. Betaprodine
35. Bezitramide
36. Butyrfentanyl
37. Carfentanil
38. Carfentanyl
39. Clonitazene
40. Codeine
41. Codeine-6GLUC
42. Codeine-6-glucuronide
43. Codeine-Methyl
44. Codeine-N-oxide
45. Codoxime
46. Conc. of poppy straw (C) ACA
47. Conc. of poppy straw (C) AMA
48. Conc. of poppy straw (C) AOA
49. Conc. of poppy straw (C) ATA
50. Conc. of poppy straw (C) GW
51. Conc. of poppy straw (M) ACA
52. Conc. of poppy straw (M) AMA
53. Conc. of poppy straw (M) AOA
54. Conc. of poppy straw (M) ATA
55. Conc. of poppy straw (M) GW
56. Conc. of poppy straw (N) GW
57. Conc. of poppy straw (O)
58. Conc. of poppy straw (O) ACA
59. Conc. of poppy straw (O) AMA
60. Conc. of poppy straw (O) AOA
61. Conc. of poppy straw (O) ATA
62. Conc. of poppy straw (O) GW
63. Conc. of poppy straw (O)-AOA
64. Conc. of poppy straw (T)
65. Conc. of poppy straw (T) ACA
66. Conc. of poppy straw (T) AMA
67. Conc. of poppy straw (T) AOA
68. Conc. of poppy straw (T) ATA
69. Conc. of poppy straw (T) GW
70. Conc. of poppy straw (T)-ATA
71. Conc. of poppy straw (total) anhydrous codeine alkaloid
72. Conc. of poppy straw (total) anhydrous morphine alkaloid
73. Conc. of poppy straw (total) anhydrous oripavine alkaloid

74. Conc. of poppy straw (total) anhydrous thebaine alkaloid
75. Concentrate of poppy straw (M)
76. Concentrate of poppy straw (M)AMA
77. Concentrate of poppy straw (M)-ATA
78. Desomorphine
79. Dextromoramide
80. Dextropropoxyphene
81. Diampromide
82. Diethylthiambutene
83. Difenoxin
84. Dihydrocodeine
85. Dihydroetorphine
86. Dihydroisomorphin-6GLUC
87. Dihydromorphine
88. Dihydromorphine-6GLUC
89. Dihydrothebaine
90. Dimenoxadol
91. Dimepheptanol
92. Dimethylmorphine
93. Dimethylthiambutene
94. Dioxaphetyl butyrate
95. Diphenoxylate
96. Dipipanone
97. D-Isomethadone
98. Drotebanol
99. Ethylmethylthiambutene
100. Ethylmorphine
101. Etonitazene
102. Etorphine
103. Etorphine-3metheth
104. Etoxeridine
105. Fentanyl
106. Furanylfentanyl
107. Furethidine
108. Heroin
109. Hydrocodone
110. Hydromorphinol
111. Hydromorphone
112. Hydromorphone-3GLUC
113. Hydromorphone-N-oxide

114. Hydroxypethidine
115. Isomethadone
116. Ketobemidone
117. L-Alphacetylmethadol
118. Levo-A-acetylmethadol
119. Levomethorphan
120. Levomoramide
121. Levophenacylmorphan
122. Levopropoxyphene
123. Levorphanol
124. L-Isomethadone
125. L-Methadol
126. L-methadone
127. Metazocine
128. Methadone
129. Methadone intermediate
130. Methyldesorphine
131. Methyldihydromorphine
132. Metopon
133. Monoacetylmorphine
134. Moramide intermediate
135. Morpheridine
136. Morphine
137. Morphine-3,6DGLUC
138. Morphine-3BD,GLUC
139. Morphine-3-B-D-glucuronide
140. Morphine-3GLUC
141. Morphine-3-PROP
142. Morphine-6BD,GLUC
143. Morphine-6-B-D-glucuronide
144. Morphine-6GLUC
145. Morphine-DIMETETH
146. Morphine-METHYBRO
147. Morphine-METHYIOD
148. Morphine-N-oxide
149. MPPP
150. MT-45
151. Myrophine
152. Nicocodine
153. Nicodicodine

154. Nicomorphine
155. Noracymethadol
156. Norcodeine
157. Norlevorphanol
158. Normethadone
159. Normethadone intermediate
160. Normorphine
161. Normorphine-3GLUC
162. Norpipanone
163. Ocfentanyl
164. OLD Morphine-6GLUC
165. Opium
166. Opium - non medical use
167. Opium marc
168. Opium, prepared
169. Oripavine
170. Oxycodone
171. Oxycodone-N-oxide
172. Oxymorphone
173. Papaver bracteatum
174. para-Fluorofentanyl
175. PEPAP
176. Pethidine
177. Pethidine intermediate A
178. Pethidine intermediate B
179. Pethidine intermediate C
180. Phenadoxone
181. Phenampromide
182. Phenazocine
183. Phenomorphan
184. Phenoperidine
185. Pholcodine
186. Piminodine
187. Piritramide
188. Poppy straw (C) GW
189. Poppy straw (M)
190. Poppy straw (M) GW
191. Poppy straw (M) GW-ACA
192. Poppy straw (M) GW-AMA
193. Poppy straw (M) GW-AOA

194. Poppy straw (M) GW-ATA
195. Poppy straw (M)-ACA
196. Poppy straw (M)-AMA
197. Poppy straw (M)-AOA
198. Poppy straw (M)-ATA
199. Poppy straw (N) GW
200. Poppy straw (T)
201. Poppy straw (T) GW
202. Poppy straw (T) GW-ACA
203. Poppy straw (T) GW-AMA
204. Poppy straw (T) GW-AOA
205. Poppy straw (T)-ACA
206. Poppy straw (T)-AOA
207. Poppy straw (T)-ATA
208. Poppy straw (total) anhydrous codeine alkaloid
209. Poppy straw (total) anhydrous morphine alkaloid
210. Poppy straw (total) anhydrous thebaine alkaloid
211. Proheptazine
212. Properidine
213. Propiram
214. Racemethorphan
215. Racemoramide
216. Racemorphan
217. Remifentanil
218. Sufentanil
219. Tetrahydrofuranylfentanyl
220. Thebacon
221. Thebaine
222. Thiofentanyl
223. Tilidine
224. Trimeperidine
225. U-47700

Opioids **excluded** from our opioid consumption dataset:

1. ???
2. Cannabis
3. Cannabis (non-medical use)
4. Cannabis oil
5. Cannabis resin
6. Cannabis resin-non medical use
7. Coca leaf

8. Coca leaf - non medical use
9. Coca paste
10. Cocaine
11. DUMMY
12. Ecgonine
13. Ecgonine-Benetest
14. Ecgonine-Bezest,4
15. Ecgonine-Bezprest
16. Ecgonine-Cinmeest
17. Ecgonine-Diflbene
18. Ecgonine-Ethylest
19. Ecgonine-Methyest
20. Ecgonine-M-Hydrox
21. Not covered substances
22. Other
23. Schedule III preparations
24. Special C.P.S
25. Unknown (ND019---)
26. Unspecified sources
27. Blank

Appendix 3.2: Calculations for global, regional and national consumption of opioids

INCB recommends using a three-year mean to display the data, and previous studies have used this to account for annual variation in reporting, providing more stable data (Bosetti et al., 2018). To calculate global consumption, we summed data for each year (2015-17) and converted it to tonnes:

246085.6 kg (2015) + 258950.6 kg (2016) + 205006.5 kg (2017) = **710042.6 kg**

710042.6/1000 = **710 tonnes**

To calculate mean consumption per person globally, we used the total above in kgs, divided it by three to calculate the average, converted it to milligrams (mg) and divided it by the global population using population estimates from the United Nations World Population Prospects 2019 database (United Nations, 2019):

((710042.6/3)*1000000)/7464021934 = **31.71 mg per person globally**

For each region (i.e. Africa, Americas, Asia, Europe and Oceania), we summed the total consumption for 2015, 2016 and 2017 and the population data. We converted the consumption data from kg to mg, divided it by three to calculate the average and determined the annual consumption rate per person for each region. Here we provide an example using data for Africa:

1828.348 kg (2015) + 1499.103 kg (2016) + 1897.066 kg (2017) = **5224.52 kg**

((5224.517/3)*1000000)/1223428193 = **1.42 mg per person in Africa**

To calculate the annual mean consumption of opioids, we summed data for each year (2015-17) in kgs for each country, divided by three to determine the average, converted to mg and divided by 2016 population data from the WHO Global Health Observatory for each country (WHO, 2019). Here we provide an example using Germany's data:

36462.86 kg (2015) + 45260.479 kg (2016) + 36302.21 kg (2017) = **118025.34 kg**

((118025.34/3)*1000000)/81915000 = **480.28 mg per person in Germany**

Appendix 3.3: Annual mean consumption of opioids in milligrams per person for countries, territories, states, and islands (n=214) in descending order of consumption.

Country	Mean opioid consumption (mg/person)
Germany	480.277
Iceland	428.442
USA	397.854
Canada	332.671
Austria	251.011
Belgium	222.879
Switzerland	201.847
Denmark	196.648
Australia	187.829
New Zealand	149.341
UK	124.246
Ireland	119.976
Luxembourg	115.436
Norway	110.801
Sweden	97.926
Israel	91.502
Falkland Islands	83.760
Netherlands	82.392
France	70.816
Slovenia	64.451
Finland	61.837
Mauritius	55.534

Italy	55.174
Spain	50.881
Wallis & Futuna Islands	45.309
Malta	42.147
Gibraltar	39.890
Norfolk Island	37.226
Sint Maarten	32.128
Barbados	31.185
North Macedonia	26.076
Estonia	26.066
Bulgaria	25.534
Cyprus	25.440
Christmas Island	24.961
Hong Kong	24.165
Czechia	21.582
Seychelles	20.909
Montserrat	19.798
Republic of Korea	19.636
Oman	19.292
Portugal	17.931
French Polynesia	17.713
Poland	17.594
Viet Nam	17.481
Andorra	17.454
New Caledonia	16.531
Malaysia	16.407

South Africa	16.377
Bahamas	15.673
Palau	15.530
Myanmar	14.821
Georgia	14.790
Croatia	14.785
Argentina	14.329
Slovakia	14.229
Chile	12.537
Bahrain	12.055
Latvia	11.521
Anguilla	11.402
Trinidad & Tobago	11.087
Japan	10.817
Romania	10.459
Ukraine	10.253
Guyana	10.216
Lithuania	10.013
Hungary	9.951
Serbia	9.930
Greece	8.267
Colombia	7.658
Uruguay	7.419
Jamaica	7.241
Costa Rica	6.788
Dominica	6.788

China, Macao SAR	6.617
Saudi Arabia	6.359
Turks & Caicos Islands	6.342
Sri Lanka	6.003
Niue	6.001
Kyrgyzstan	5.936
Saint Vincent & the Grenadines	5.834
Saint Helena	5.727
Brazil	5.663
Montenegro	5.659
Cook Islands	5.608
Moldova (the Republic of)	5.537
Albania	5.057
Belarus	4.852
Timor-Leste	4.746
El Salvador	4.481
British Virgin Islands	4.479
Democratic People's Republic of Korea	4.475
Eswatini	4.343
Belize	4.331
Lebanon	4.123
Tonga	4.003
Jordan	3.980
Bosnia & Herzegovina	3.921
Côte d'Ivoire	3.898
China	3.853

Namibia	3.660
Brunei Darussalam	3.639
Armenia	3.636
Curaçao	3.478
Kuwait	3.430
Islamic Republic of Iran	3.325
Turkey	3.323
Fiji	3.277
Thailand	3.221
Panama	3.180
Botswana	3.165
Singapore	3.145
Mongolia	3.134
Tunisia	2.739
Ghana	2.672
Zimbabwe	2.407
Federated States of Micronesia	2.311
Peru	2.271
Cuba	2.214
Uganda	2.034
Tuvalu	2.030
Kenya	1.927
Guatemala	1.856
Russian Federation	1.812
Papua New Guinea	1.782
Ascension Island	1.654

Syrian Arab Republic	1.642
Qatar	1.613
Zambia	1.550
United Arab Emirates	1.534
Malawi	1.485
Kazakhstan	1.309
Morocco	1.289
Senegal	1.241
Tanzania (United Republic of)	1.159
Dominican Republic	1.022
Solomon Islands	0.910
Ecuador	0.859
Bangladesh	0.826
Maldives	0.763
Azerbaijan	0.735
Honduras	0.734
Mexico	0.709
Indonesia	0.708
Nicaragua	0.677
Cabo Verde	0.600
Rwanda	0.597
Afghanistan	0.555
Ethiopia	0.539
India	0.527
Nepal	0.521
Lao People's Democratic Republic	0.457

Egypt	0.377
Philippines	0.360
Uzbekistan	0.325
Turkmenistan	0.310
Bolivia (Plurinational State of)	0.303
Suriname	0.293
Kiribati	0.288
Bhutan	0.247
Sudan	0.242
Benin	0.237
Mozambique	0.223
Algeria	0.164
Libya	0.151
Bolivarian Republic of Venezuela	0.129
Tajikistan	0.113
Togo	0.111
Comoros	0.063
Burkina Faso	0.054
Burundi	0.049
Madagascar	0.037
Pakistan	0.033
Haiti	0.028
Democratic Republic of the Congo	0.026
Nigeria	0.012
Chad	0.006
Sierra Leone	0.005

Angola	0.002
Antigua & Barbuda	0
Aruba	0
Bermuda	0
Cambodia	0
Cameroon	0
Cayman Islands	0
Central African Republic	0
Cocos (Keeling) Islands	0
Congo	0
Djibouti	0
Equatorial Guinea	0
Eritrea	0
Gabon	0
Gambia	0
Grenada	0
Guinea	0
Guinea-Bissau	0
Iraq	0
Lesotho	0
Liberia	0
Mali	0
Marshall Islands	0
Mauritania	0
Nauru	0
Niger	0

Paraguay	0
Saint Kitts & Nevis	0
Saint Lucia	0
Samoa	0
Sao Tome & Principe	0
Somalia	0
South Sudan	0
Tristan da Cunha	0
Vanuatu	0
Yemen	0

Appendix 3.4: Total volume of consumption for 2015-17 by type of opioid and Anatomical Therapeutic Classification subgroup

Medicine	Total volume of consumption (kgs)
Analgesics (n=12)	**492,810.4**
Oxycodone	225645.8
Morphine	112674.0
Tilidine	98928.7
Pethidine	15459.4
Hydromorphone	12602.5
Codeine	11317.6
Dihydrocodeine	6339.8
Fentanyl	4483.6
Opium	3505.3
Trimeperidine	676.7
Piritramide	608.661
Dextropropoxyphene	568.3
Opioid substitution therapies (n=2)	**113,850.2**
Methadone	112224.7
Diamorphine	1625.5
Cough suppressants (n=2)	**95,486.1**
Hydrocodone	94387.1
Pholcodine	1099
Anaesthetics (n=3)	**300.1**
Remifentanil	229.8
Alfentanil	57.8
Sufentanil	12.6
Antidiarrheal (n=2)	**68.1**
Diphenoxylate	64.8
Difenoxin	3.3

No consumption data were available for buprenorphine, butorphanol, dextromethorphan, eluxadoline, loperamide, nalbuphine, noscapine, papaveretum, pargeverine, pentazocine, tapentadol and tramadol.

12 Chapter 4 Appendix

Appendix 4.1: Master list of Anatomical Therapeutic Classification (ATC) chemical substance codes for opioids

Drug name	ATC code
Acetyldihydrocodeine	R05DA12
Alfentanil	N01AH02
Anileridine	N01AH05
Bezitramide	N02AC05
Buprenorphine	N02AE01, N07BC01, N07BC51
Butorphanol	N02AF01
Codeine	R05DA04, N02AJ07, N02AJ08, N02AJ09, N02AJ06, N02AA59, N02AA79
Dextromethorphan	R05DA09
Dextromoramide	N02AC01
Dextropropoxyphene	N02AC04, N02AC54, N02AC74
Dezocine	N02AX03
Diamorphine	N07BC06
Difenoxin	A07DA04
Dihydrocodeine	N02AA08, N02AJ02, N02AJ03, N02AJ01, N02AA58
Dimemorfan	R05DA11
Diphenoxylate	A07DA01
Eluxadoline	A07DA06
Ethylmorphine	R05DA01, S01XA06
Fentanyl	N01AH01, N02AB03, N01AH51, QN02AB03
Hydrocodone	R05DA03
Hydromorphone	N02AA03, N02AA53, N02AG04
Ketobemidone	N02AB01, N02AG02
Levacetylmethadol	N07BC03
Levomethadone	N07BC05
Lofexidine	N07BC04
Loperamide	A07DA03, A07DA05, A07DA53
Meptazinol	N02AX05

Methadone	N07BC02, N02AC52
Morphine	N02AA01, N02AG01, A07DA52, N02AA51
Nalbuphine	N02AF02
Nicomorphine	N02AA04
Normethadone	R05DA06
Noscapine	R05DA07
Opium	A07DA02, N02AA02, R05DA05, R05DA20, R05FA02, R05FA01
Oxycodone	N02AA05, N02AA55, N02AA56, N02AJ018, N02AJ019, N02AJ017
Papaveretum	N02AA10
Pentazocine	N02AD01
Pethidine	N02AB02, N02AG03,N02AB52, N02AB72
Phenazocine	N02AD02
Phenoperidine	N01AH04
Pholcodine	R05DA08
Piritramide	N02AC03
Remifentanil	N01AH06
Sufentanil	N01AH03
Tapentadol	N02AX06
Thebacon	R05DA10
Tilidine	N02AX01
Tramadol	N02AX02, N02AJ013, N02AJ014, N02AJ015

Appendix 4.2: Countries without national EMLs

1. Andorra
2. Australia
3. Austria
4. Azerbaijan
5. Bahamas
6. Belgium
7. Benin
8. Brunei Darussalam
9. Canada
10. Comoros
11. Cyprus
12. Denmark
13. Equatorial Guinea
14. Eswatini
15. Finland
16. France
17. Gabon
18. Germany
19. Greece
20. Guatemala
21. Guinea-Bissau
22. Hungary
23. Iceland
24. Ireland
25. Israel
26. Italy
27. Japan
28. Kazakhstan
29. Kuwait
30. Lao People's Democratic Republic
31. Libya
32. Liechtenstein
33. Luxembourg
34. Mauritius
35. Micronesia (Federated States of)
36. Monaco
37. Netherlands
38. New Zealand
39. Niger
40. Norway
41. Panama
42. Qatar
43. Republic of Korea
44. Samoa
45. San Marino
46. Sao Tome & Principe
47. Saudi Arabia
48. Sierra Leone

49. Singapore
50. South Sudan
51. Spain
52. Switzerland
53. Turkey
54. Turkmenistan
55. UK
56. United Arab Emirates
57. USA
58. Uzbekistan

Appendix 4.3: Numbers and types of opioids included in national EMLs group by quantiles in descending order

Country	Year of list	Number of opioids in EMLs (% of all drugs)	Type of opioids in EMLs	% similarity with WHO	No. differences from WHO
Top quantile (9)					
Slovakia	2012	19 (1.92)	**codeine, fentanyl, loperamide, morphine,** buprenorphine, dextromethorphan, difenoxin, dihydrocodeine, diphenoxylate, eluxadoline, hydromorphone, opium, oxycodone, pentazocine, pethidine, sufentanil, tapentadol, tramadol & trimeperidine	80	15
Islamic Republic of Iran	2014	16 (1.79)	**codeine, fentanyl, loperamide, methadone, morphine,** alfentanil, buprenorphine, dextromethorphan, diphenoxylate, hydromorphone, oxycodone, pentazocine, pethidine, remifentanil, sufentanil & tramadol	100	11
Czechia	2012	15 (1.86)	**codeine, fentanyl, morphine**, alfentanil, buprenorphine, dihydrocodeine, hydromorphone, nalbuphine, oxycodone, pentazocine, pethidine, piritramide, remifentanil, sufentanil & tramadol	60	12
Slovenia	2017	15 (1.88)	**codeine, fentanyl, loperamide, methadone,**	100	10

			morphine, alfentanil, buprenorphine, hydromorphone, oxycodone, pethidine, pholcodine, piritramide, remifentanil, tapentadol, tramadol & trimeperidine		
Syrian Arab Republic	2008	15 (1.54)	**codeine, fentanyl, morphine,** buprenorphine, dextromethorphan, dextropropoxyphene, diphenoxylate, hydrocodone, noscapine, oxycodone, pentazocine, pethidine, remifentanil, sufentanil & tramadol	60	12
Tunisia	2012	14 (1.93)	**codeine, fentanyl, loperamide, morphine,** alfentanil, buprenorphine, dextromethorphan, dextropropoxyphene, opium, pethidine & pholcodine	80	10
Malta	2008	13 (2.12)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, dextromethorphan, dextropropoxyphene, dihydrocodeine, pethidine, pholcodine, remifentanil & tramadol	100	8
Barbados	2011	12 (1.89)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan, dextropropoxyphene, dihydrocodeine, diphenoxylate, papaveretum, pentazocine, pethidine & tramadol	80	8

Iraq	2010	12 (2.08)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan, dextropropoxyphene, dihydrocodeine, diphenoxylate, oxycodone, pentazocine, pethidine & tramadol	80	8
Jamaica	2012	12 (2.61)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, diphenoxylate, oxycodone, pethidine, pholcodine, remifentanil & tramadol	100	7
Croatia	2010	12 (1.99)	**codeine, fentanyl, loperamide, methadone, morphine,** alfentanil, buprenorphine, hydrocodone, oxycodone, pentazocine, pethidine, sufentanil & tramadol	80	8
Mexico	2011	12 (1.69)	**codeine, fentanyl, loperamide, morphine,** buprenorphine, dextromethorphan, dextropropoxyphene, hydromorphone, nalbuphine, oxycodone, remifentanil & tramadol	80	8
8th quantile					
Portugal	2011	11 (1.21)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, dextromethorphan, dextropropoxyphene, hydromorphone,	100	6

			pargeverine & tramadol		
Romania	2012	11 (1.73)	**codeine, fentanyl, methadone, morphine,** buprenorphine, dextromethorphan, dihydrocodeine, oxycodone, pentazocine, pethidine & tramadol	80	7
Thailand	2013	11 (2.00)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, dextromethorphan, nalbuphine, opium, pethidine & tramadol	100	6
Ethiopia	2014	11 (1.55)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, diphenoxylate, pentazocine, pethidine, pholcodine & tramadol	100	6
Oman	2009	10 (1.73)	**codeine, fentanyl, loperamide, methadone, morphine**, hydromorphone, nalbuphine, pethidine, remifentanil & tramadol	100	5
Ecuador	2013	10 (2.71)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, hydromorphone, oxycodone, remifentanil & tramadol	100	5
Philippines	2008	10 (1.93)	**codeine, fentanyl, loperamide, morphine,** butorphanol, dextromethorphan,	80	6

			nalbuphine, oxycodone, pethidine & tramadol		
Cameroon	2010	10 (2.83)	**codeine, fentanyl, loperamide, morphine**, buprenorphine, dextromethorphan, pethidine, sufentanil & tramadol	80	6
Morocco	2012	10 (2.91)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, dextromethorphan, pholcodine, sufentanil & tramadol	100	5
Serbia	2010	10 (2.11)	**fentanyl, loperamide, methadone, morphine,** alfentanil, hydromorphone, pethidine, remifentanil, sufentanil & tramadol	80	6
Côte d'Ivoire	2014	10 (1.98)	**codeine, fentanyl, methadone, morphine,** buprenorphine, oxycodone, pethidine, remifentanil, sufentanil & tramadol	80	6
Jordan	2011	10 (1.69)	**codeine, fentanyl, loperamide, methadone, morphine,** alfentanil, dihydrocodeine, pethidine, remifentanil & tramadol	100	5
Nigeria	2010	10 (3.27)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, dihydrocodeine, diphenoxylate, pentazocine & pethidine	100	5
7th quantile					

Viet Nam	2008	9 (1.14)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan, dextropropoxyphene, pethidine, sufentanil & tramadol	80	5
Poland	2017	9 (2.03)	**fentanyl, loperamide, methadone, morphine,** buprenorphine, dihydrocodeine, oxycodone, tapentadol & tramadol	80	5
Democratic Republic of the Congo	2010	9 (2.87)	**codeine, fentanyl, loperamide, morphine,** buprenorphine, dextromethorphan, remifentanil, sufentanil & tramadol	80	5
Belize	2008	9 (2.40)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, hydromorphone, oxycodone & pethidine	100	4
Maldives	2011	9 (1.67)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan, pentazocine, pethidine, pholcodine & tramadol	80	5
Trinidad & Tobago	2010	9 (1.82)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, pethidine, pholcodine & tramadol	100	4
Togo	2012	9 (3.03)	**codeine, fentanyl, loperamide, morphine,** alfentanil, buprenorphine, dihydrocodeine, sufentanil & tramadol	80	5

Congo	2013	9 (2.97)	**codeine, fentanyl, loperamide, morphine,** buprenorphine, dextromethorphan, remifentanil, sufentanil & tramadol	80	5
Namibia	2016	9 (2.34)	**codeine, fentanyl, loperamide, methadone, morphine,** alfentanil, pethidine, tilidine & tramadol	100	4
Senegal	2013	9 (2.65)	**codeine, fentanyl, methadone, morphine,** alfentanil, buprenorphine, nalbuphine, sufentanil & tramadol	80	5
Belarus	2012	9 (2.42)	**fentanyl, loperamide, morphine,** buprenorphine, butorphanol, hydromorphone, opium, tramadol & trimeperidine	60	6
Burkina Faso	2014	9 (3.28)	**codeine, fentanyl, loperamide, methadone, morphine,** buprenorphine, nalbuphine, remifentanil & sufentanil	100	4
North Macedonia	2008	9 (2.30)	**codeine, fentanyl, methadone, morphine,** alfentanil, pentazocine, remifentanil, sufentanil & tramadol	80	5
6th quantile					
Montenegro	2011	8 (1.77)	**fentanyl, loperamide, methadone, morphine,** alfentanil, pethidine, remifentanil & tramadol	80	4
The Republic of Moldova	2011	8 (1.68)	**codeine, fentanyl, loperamide, methadone, morphine,**	100	3

			dextromethorphan, tramadol & trimeperidine		
Honduras	2009	8 (2.17)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan, oxycodone, pethidine & tramadol	80	4
Plurinational State of Bolivia	2011	8 (2.25)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, pethidine & remifentanil	100	3
Colombia	2011	8 (2.14)	**fentanyl, loperamide, methadone, morphine,** dihydrocodeine, hydromorphone, oxycodone & pethidine	80	4
Chile	2005	8 (2.29)	**codeine, fentanyl, loperamide, methadone, morphine,** pargeverine, pethidine & tramadol	100	3
Uruguay	2011	8 (1.52)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan, pethidine & tramadol	100	3
Cabo Verde	2009	8 (1.41)	**codeine, fentanyl, loperamide, methadone, morphine,** alfentanil, pethidine & tramadol	100	3
Estonia	2012	8 (1.98)	**codeine, fentanyl, loperamide, methadone, morphine,** diphenoxylate, oxycodone & tramadol	100	3
Argentina	2011	8 (1.69)	**codeine, fentanyl, loperamide, morphine,** dextromethorphan,	80	4

			dextropropoxyphene, remifentanil & tramadol		
5th quantile					
Sweden	2016	7 (2.42)	**codeine, fentanyl, loperamide, morphine,** buprenorphine, hydromorphone & oxycodone	80	3
Uganda	2012	7 (1.92)	**codeine, fentanyl, loperamide, morphine,** papaveretum, pethidine & remifentanil	80	3
Nauru	2010	7 (3.03)	**codeine, fentanyl, loperamide, morphine,** diphenoxylate, pethidine & pholcodine	80	3
Botswana	2012	7 (2.06)	**codeine, fentanyl, loperamide, morphine,** dihydrocodeine, pethidine & tramadol	80	3
Cuba	2012	7 (1.37)	**codeine, fentanyl, morphine,** diphenoxylate, nalbuphine, pethidine & tramadol	60	4
Tonga	2007	7 (3.06)	**codeine, fentanyl, loperamide, morphine,** alfentanil, pethidine & pholcodine	80	3
Madagascar	2008	7 (2.77)	**fentanyl, loperamide, morphine,** dextromethorphan, dextropropoxyphene, noscapine & pethidine	60	4
Central African Republic	2009	7 (2.37)	**codeine, loperamide, morphine,** noscapine, opium, pentazocine & pethidine	60	4
Peru	2012	7 (1.64)	**codeine, fentanyl, morphine,** dextromethorphan,	60	4

			oxycodone, pethidine & tramadol		
Bolivarian Republic of Venezuela	2011	7 (2.26)	**codeine, fentanyl, morphine,** dextromethorphan, oxycodone, pethidine & tramadol	60	4
Malawi	2015	7 (2.16)	**codeine, fentanyl, loperamide, morphine,** dihydrocodeine, pethidine & tramadol	80	3
Indonesia	2011	7 (2.51)	**codeine, fentanyl, methadone, morphine,** dextromethorphan, pethidine & sufentanil	80	3
Marshall Islands	2007	7 (3.26)	**codeine, fentanyl, loperamide, morphine,** nalbuphine, pethidine & tramadol	80	3
Costa Rica	2014	7 (1.80)	**codeine, fentanyl, loperamide, methadone, morphine,** dextromethorphan & tramadol	100	2
Zimbabwe	2011	7 (2.02)	**codeine, fentanyl, loperamide, morphine,** alfentanil, pethidine & tramadol	80	3
Palau	2006	7 (2.59)	**codeine, fentanyl, loperamide, morphine,** hydrocodone, pethidine & tramadol	80	3
Algeria	2016	7 (1.56)	**codeine, loperamide**, buprenorphine, dextromethorphan, dextropropoxyphene, pholcodine & tramadol	40	5
4th quantile					
Antigua & Barbuda	2007	6 (2.04)	**codeine, fentanyl, methadone, morphine,** pethidine & tramadol	80	2
Rwanda	2010	6 (2.08)	**codeine, fentanyl, morphine,**	60	3

			pentazocine, pethidine & tramadol		
United Republic of Tanzania	2013	6 (1.66)	**codeine, loperamide, methadone, morphine,** pethidine & tramadol	80	2
Cook Islands	2007	6 (2.50)	**loperamide, morphine,** dextromethorphan, diphenoxylate, pethidine & tramadol	40	4
Bosnia & Herzegovina	2009	6 (3.30)	**codeine, loperamide, methadone,** buprenorphine, pholcodine & tramadol	60	3
El Salvador	2009	6 (1.66)	**fentanyl, loperamide, morphine,** nalbuphine, pethidine & tramadol	60	3
Democratic People's Republic of Korea	2012	6 (2.71)	**codeine, methadone, morphine,** opium, papaveretum & pethidine	60	3
Eritrea	2010	6 (1.78)	**codeine, loperamide, morphine,** dextromethorphan, pethidine & tramadol	60	3
Mali	2012	6 (2.11)	**codeine, fentanyl, loperamide, morphine** & tramadol	80	2
Bahrain	2015	6 (1.09)	**fentanyl, loperamide, methadone, morphine,** pethidine & remifentanil	80	2
Guyana	2010	6 (2.14)	**codeine, fentanyl, loperamide, methadone, morphine** & pethidine	100	1
Afghanistan	2014	6 (2.31)	**methadone, morphine**, buprenorphine, opium, pethidine & tramadol	40	4
Kenya	2016	6 (1.44)	**codeine, fentanyl, loperamide, methadone, morphine** & buprenorphine	100	1
Tajikistan	2009	6 (2.20)	**codeine, fentanyl, loperamide,**	80	2

			morphine, tramadol & trimeperidine		
Myanmar	2010	6 (1.90)	**codeine, fentanyl, methadone, morphine,** pethidine & tramadol	80	2
Paraguay	2009	6 (1.95)	**codeine, fentanyl, morphine,** alfentanil, dextromethorphan & pethidine	60	3
Lebanon	2014	6 (2.11)	**fentanyl, loperamide, morphine,** dextromethorphan, pethidine & tramadol	60	3
Dominican Republic	2015	6 (1.68)	**codeine, fentanyl, loperamide, morphine,** nalbuphine & tramadol	80	2
Fiji	2015	6 (2.02)	**codeine, fentanyl, methadone, morphine,** diphenoxylate & pethidine	80	2
Latvia	2012	6 (1.95)	**fentanyl, morphine,** dihydrocodeine, tilidine, tramadol & trimeperidine	40	4
Malaysia	2014	6 (1.94)	**loperamide, methadone, morphine,** dihydrocodeine & diphenoxylate	60	3
Egypt	2012	6 (1.85)	**fentanyl, methadone, morphine,** dextromethorphan, pethidine & tramadol	60	3
3rd quantile					
Saint Vincent & the Grenadines	2010	5 (1.87)	**codeine, fentanyl, methadone, morphine** & pethidine	80	1
Kiribati	2009	5 (2.29)	**codeine, fentanyl, loperamide, morphine** & pethidine	80	1
Grenada	2007	5 (1.76)	**fentanyl, methadone, morphine,** pethidine & tramadol	60	2
Suriname	2014	5 (1.75)	**codeine, fentanyl, loperamide,**	80	1

			morphine & sufentanil		
Sudan	2014	5 (1.66)	**loperamide, morphine,** dextromethorphan, diphenoxylate & pethidine	40	3
Gambia	2001	5 (3.03)	**codeine, loperamide, morphine,** dihydrocodeine & pethidine	60	2
China	2012	5 (1.71)	**codeine, fentanyl, morphine,** diphenoxylate & pethidine	60	2
Mozambique	2016	5 (1.93)	**codeine, fentanyl, loperamide, morphine** & tramadol	80	1
Zambia	2013	5 (1.74)	**codeine, loperamide, morphine,** dihydrocodeine & pethidine	60	2
Solomon Islands	2017	5 (1.92)	**codeine, fentanyl, morphine,** oxycodone & pethidine	60	2
Ghana	2010	5 (1.65)	**codeine, fentanyl, morphine,** pethidine & tramadol	60	2
Saint Kitts & Nevis	2007	5 (1.72)	**fentanyl, methadone, morphine,** pethidine & tramadol	60	2
Saint Lucia	2007	5 (1.72)	**fentanyl, methadone, morphine,** pethidine & tramadol	60	2
Seychelles	2010	5 (1.68)	**codeine, fentanyl, morphine**, pethidine & tramadol	60	2
Russian Federation	2014	5 (0.96)	**fentanyl, loperamide, morphine,** tramadol & trimeperidine	60	2
Guinea	2012	5 (2.09)	**codeine, loperamide, morphine,** pentazocine & pethidine	60	2
Bhutan	2016	5 (1.70)	**codeine, fentanyl, morphine,** pethidine & tramadol	60	2
Kyrgyzstan	2009	5 (1.58)	**fentanyl, methadone, morphine,**	60	2

			buprenorphine & trimeperidine		
Dominica	2007	5 (1.75)	**fentanyl, methadone, morphine,** pethidine & tramadol	60	2
2nd quantile					
Timor-Leste	2015	4 (1.67)	**codeine, fentanyl, morphine** & tramadol	60	1
Burundi	2012	4 (1.36)	**codeine, fentanyl, morphine** & tramadol	60	1
Georgia	2007	4 (1.61)	**fentanyl, loperamide, morphine** & dextromethorphan	60	1
Nepal	2011	4 (1.33)	**methadone, morphine,** buprenorphine & pethidine	40	2
Liberia	2011	4 (1.86)	**loperamide, morphine,** buprenorphine & pethidine	40	2
Sri Lanka	2013	4 (1.26)	**fentanyl, loperamide, methadone** & tramadol	60	1
Papua New Guinea	2012	4 (1.48)	**codeine, fentanyl, morphine** & pethidine	60	1
Tuvalu	2010	4 (2.23)	**codeine, fentanyl, morphine** & pethidine	60	1
Niue	2006	4 (1.86)	**fentanyl, loperamide, morphine** & pethidine	60	1
Djibouti	2007	4 (1.99)	**fentanyl, loperamide, morphine** & pethidine	60	1
Armenia	2010	4 (1.48)	**fentanyl, loperamide, morphine** & trimeperidine	60	1
Mongolia	2009	4 (1.55)	**codeine, fentanyl, morphine** & tramadol	60	1
India	2015	4 (1.09)	**fentanyl, morphine,** pentazocine & tramadol	40	2
South Africa	2014	4 (2.08)	**loperamide, morphine,** pethidine & tramadol	40	2
1st quantile					
Lesotho	2005	3 (1.54)	**morphine**, pethidine & diamorphine	20	2
Brazil	2014	3 (0.74)	**codeine, methadone & morphine**	60	0

Mauritania	2008	3 (1.40)	**loperamide, morphine** & buprenorphine	40	1
Albania	2011	3 (1.40)	**codeine, morphine** & pethidine	40	1
Vanuatu	2006	3 (1.69)	**codeine, fentanyl & morphine**	60	0
Chad	2007	3 (1.24)	**codeine, fentanyl & morphine**	60	0
Lithuania	2012	3 (0.88)	**fentanyl, morphine** & tramadol	40	1
Pakistan	2016	3 (0.80)	**loperamide, methadone & morphine**	60	0
Ukraine	2009	3 (1.07)	**methadone, morphine** & buprenorphine	40	1
Yemen	2009	3 (1.20)	**fentanyl, morphine** & pethidine	40	1
Haiti	2012	2 (1.02)	**fentanyl & morphine**	40	0
Bangladesh	2008	2 (1.07)	**morphine** & pethidine	20	1
Nicaragua	2011	2 (0.73)	**fentanyl & morphine**	40	0
Bulgaria	2011	1 (0.28)	**fentanyl**	20	0
Angola	2008	1 (1.56)	**fentanyl**	20	0
Somalia	2006	1 (1.20)	pethidine	0	1
Cambodia	2003	0 (0)	-	-	-

13 Chapter 5 Appendix

Appendix 5.1: The 233 drugs of the Oxford Catalogue of Opioids in alphabetical order with their chemical (IUPAC) names.

Index name*	IUPAC
3-methylfentanyl	n-[3-methyl-1-(2-phenylethyl) piperidin-4-yl]-n-phenylpropanamide
3-methylthiofentanyl	n-[3-methyl-1-(2-thiophen-2-ylethyl) piperidin-4-yl]-n-phenylpropanamide
4-chloroisobutyrfentanyl	2-methyl-n-(4-chlorophenyl)-n-[1-(1-phenylpropan-2-yl)piperidin-4-yl] propenamide
4-fluoro isobutyrfentanyl	n-(4-fluorophenyl)-2-methyl-n-[1-(2-phenylethyl) piperidin-4-yl] propenamide
4-phenylfentanyl	n-phenyl-n-[4-phenyl-1-(2-phenylethyl)piperidin-4-yl] propenamide
6'-guanidinonal trindole	2-[(1s,2s,13r,21r)-22-(cyclopropylmethyl)-2,16-dihydroxy-14-oxa-11,22-diazaheptacyclo [13.9.1.01,13.02,21.04,12.05,10.019,25] pentacosa-4(12),5(10),6,8,15,17,19(25)-heptaen-8-yl] guanidine
7-benzylidenenaltrexone	(4R,4aS,6E,7aR,12bS)-6-benzylidene-3-(cyclopropylmethyl)-4a,9-dihydroxy-1,2,4,5,7a,13-hexahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one
acetorphine*	[(1r,2s,6r,14r,15r,19r)-19-[(2r)-2-hydroxypentan-2-yl]-15-methoxy-5-methyl-13-oxa-5-azahexacyclo[13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11,16-tetraen-11-yl] acetate
acetyldihydrocodeine	[(4r,4ar,7s,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] acetate
acetylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] acetamide
acetylmethadol*	[6-(dimethylamino)-4,4-diphenylheptan-3-yl] acetate
acrylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] prop-2-enamide
ah-7921	3,4-dichloro-n-[[1-(dimethylamino) cyclohexyl] methyl]benzamide
alfentanil*	n-[1-[2-(4-ethyl-5-oxotetrazol-1-yl)ethyl]-4-(methoxymethyl)piperidin-4-yl]-n-phenylpropanamide
alimadol*	3-methoxy-3,3-diphenyl-n-prop-2-enylpropan-1-amine
alletorphine*	(1r,2s,6r,14r,15r,19r)-19-[(2r)-2-hydroxypentan-2-yl]-15-methoxy-5-prop-2-enyl-13-oxa-5-azahexacyclo[13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11,16-tetraen-11-ol
allylprodine*	(1-methyl-4-phenyl-3-prop-2-enylpiperidin-4-yl) propanoate
alphacetylmethadol*	[(3r,6r)-6-(dimethylamino)-4,4-diphenylheptan-3-yl] acetate
alphameprodine*	[(3s,4r)-3-ethyl-1-methyl-4-phenylpiperidin-4-yl] propanoate

alphamethadol*	(3r,6r)-6-(dimethylamino)-4,4-diphenylheptan-3-ol
alphamethylacetylfentanyl	n-phenyl-n-[1-(1-phenylpropan-2-yl)piperidin-4-yl] acetamide
alphamethylfentanyl	n-phenyl-n-[1-(1-phenylpropan-2-yl)-4-piperidyl] propenamide
alphamethylthiofentanyl	n-phenyl-n-[1-(1-thiophen-2-ylpropan-2-yl) piperidin-4-yl] propanamide
alphamethylthiofentanyl	n-phenyl-n-[1-(1-thiophen-2-ylpropan-2-yl)-4-piperidyl] propenamide
alphaprodine	[(3s,4r)-1,3-dimethyl-4-phenylpiperidin-4-yl] propanoate; hydrochloride
alvimopan*	2-[[(2s)-2-benzyl-3-[(3r,4r)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]propanoyl]amino] acetic acid
anazocine*	9-methoxy-3-methyl-9-phenyl-3-azabicyclo [3.3.1] nonane
anileridine*	ethyl 1-[2-(4-aminophenyl)ethyl]-4-phenylpiperidine-4-carboxylate
apadoline*	n-propyl-10-[(2r)-1-pyrrolidin-1-ylpropan-2-yl]phenothiazine-2-carboxamide
asalhydromorphone*	[(4r,4ar,7ar,12bs)-9-(2-acetyloxybenzoyl)oxy-3-methyl-2,4,4a,5,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] 2-acetyloxybenzoate
asimadoline*	n-[(1s)-2-[(3s)-3-hydroxypyrrolidin-1-yl]-1-phenylethyl]-n-methyl-2,2-diphenylacetamide
axomadol*	(1r,3r,6r)-6-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexane-1,3-diol
benzethidine*	ethyl 4-phenyl-1-(2-phenylmethoxyethyl)piperidine-4-carboxylate
benzhydrocodone	[(4r,4ar,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,5,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] benzoate
benzodioxolefentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl]-2h-1,3-benzodioxole-5-carboxamide
benzoylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] benzamide
benzylfentanyl	n-(1-benzylpiperidin-4-yl)-n-phenylpropanamide
benzylmorphine	(4r,4ar,7s,7ar,12bs)-3-methyl-9-phenylmethoxy-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
betacetylmethadol*	[(3s,6r)-6-(dimethylamino)-4,4-diphenylheptan-3-yl] acetate
betahydroxyfentanyl	n-[1-(2-hydroxy-2-phenylethyl)piperidin-4-yl]-n-phenylpropanamide
betahydroxythiofentanyl	n-{1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl}-n-phenylpropanamide
betameprodine*	(3-ethyl-1-methyl-4-phenylpiperidin-4-yl) propanoate
betamethadol*	(3s,6r)-6-(dimethylamino)-4,4-diphenylheptan-3-ol
betamethylfentanyl	n-phenyl-n-[1-(2-phenylpropyl)piperidin-4-yl] propenamide

betaprodine*	[(3r,4r)-1,3-dimethyl-4-phenylpiperidin-4-yl] propanoate
bezitramide*	4-[4-(2-oxo-3-propanoylbenzimidazol-1-yl)piperidin-1-yl]-2,2-diphenylbutanenitrile
bremazocine*	(1s,9r)-1-ethyl-10-[(1-hydroxycyclopropyl)methyl]-13,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
brifentanil*	n-[(3r,4s)-1-[2-(4-ethyl-5-oxotetrazol-1-yl)ethyl]-3-methylpiperidin-4-yl]-n-(2-fluorophenyl)-2-methoxyacetamide
bromadoline*	4-bromo-n-[(1s,2s)-2-(dimethylamino) cyclohexyl]benzamide
brorphine	1-{1-[1-(4-bromophenyl)ethyl]piperidin-4-yl}-1,3-dihydro-2h-benzimidazol-2-one
bu-08028	(1s,2s,6r,14r,15r,16r)-5-(cyclopropylmethyl)-16-[(2s)-2-hydroxy-3,3-dimethylpentan-2-yl]-15-methoxy-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20]icosa-8(20),9,11-trien-11-ol
buprenorphine*	(1s,2s,6r,14r,15r,16r)-5-(cyclopropylmethyl)-16-[(2s)-2-hydroxy-3,3-dimethylbutan-2-yl]-15-methoxy-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20]icosa-8(20),9,11-trien-11-ol
butinazocine*	10-but-3-ynyl-13,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-1,4-diol
butorphanol*	(1s,9r,10s)-17-(cyclobutylmethyl)-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-triene-4,10-diol
butyrfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl]butanamide
carbazocine	20-(cyclopropylmethyl)-3,20-diazapentacyclo [10.5.3.01,13.02,10.04,9]icosa-2(10),4,6,8-tetraene
carfentanil*	methyl 1-(2-phenylethyl)-4-(n-propanoylanilino) piperidine-4-carboxylate
carperidine*	ethyl 1-(3-amino-3-oxopropyl)-4-phenylpiperidine-4-carboxylate
ciramadol*	3-[(r)-dimethylamino-[(1r,2r)-2-hydroxycyclohexyl]methyl]phenol
clonitazene*	2-[2-[(4-chlorophenyl)methyl]-5-nitrobenzimidazol-1-yl]-n,n-diethylethanamine
codeine	(4r,4ar,7s,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
codoxime*	2-[(z)-[(4r,4ar,7ar,12bs)-9-methoxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro [3,2-e] isoquinolin-7-ylidene] amino] oxyacetic acid
cogazocine	10-(cyclobutylmethyl)-1-ethyl-13,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
crotonylfentanyl	(2e)-n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl]but-2-enamide.
cyclazocine*	10-(cyclopropylmethyl)-1,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
cyclopentylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] cyclopentanecarboxamide
cyclopropylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide
cyprenorphine*	(1r,2s,6r,14r,15r,19r)-5-(cyclopropylmethyl)-19-(2-hydroxypropan-2-yl)-15-methoxy-13-oxa-5-

	azahexacyclo[13.2.2.12,8.01,6.02,14.012,20]icosa-8(20),9,11,16-tetraen-11-ol
desmethylmoramide*	4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-ylbutan-1-one
desmethylprodine	(1-methyl-4-phenylpiperidin-4-yl) propanoate
desmetramadol*	3-[(1r,2r)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol
desomorphine*	(4r,4ar,7as,12bs)-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-9-ol
dextromethorphan*	(1s,9s,10s)-4-methoxy-17-methyl-17-azatetracyclo [7.5.3.01,10.02,7] heptadeca-2(7),3,5-triene
dextromoramide*	(3s)-3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-ylbutan-1-one
dextropropoxyphene*	[(2s,3r)-4-(dimethylamino)-3-methyl-1,2-diphenylbutan-2-yl] propanoate
dezocine*	(1r,9s,15s)-15-amino-1-methyltricyclo [7.5.1.02,7]pentadeca-2(7),3,5-trien-4-ol
diamorphine	[(4r,4ar,7s,7ar,12bs)-9-acetyloxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] acetate
diampromide*	n-[2-[methyl(2-phenylethyl)amino]propyl]-n-phenylpropanamide
dibenzoylmorphine	(9-benzoyloxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl) benzoate
diethylthiambutene*	n,n-diethyl-4,4-dithiophen-2-ylbut-3-en-2-amine
difenoxin*	1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid
dihydrocodeine*	(4r,4ar,7s,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
dihydroetorphine	(1s,2s,6r,14r,15r,16r)-16-[(2r)-2-hydroxypentan-2-yl]-15-methoxy-5-methyl-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11-trien-11-ol
dihydromorphine	(4r,4ar,7s,7ar,12bs)-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol
dimemorfan*	(1s,9s,10s)-4,17-dimethyl-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-triene
dimenoxadol*	2-(dimethylamino)ethyl 2-ethoxy-2,2-diphenylacetate
dimepheptanol*	6-(dimethylamino)-4,4-diphenylheptan-3-ol
dimethylthiambutene*	n,n-dimethyl-4,4-dithiophen-2-yl but-3-en-2-amine
dinalbuphine sebacate*	bis[(4r,4as,7s,7ar,12bs)-3-(cyclobutylmethyl)-4a,7-dihydroxy-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-9-yl] decanedioate
dioxaphetyl butyrate*	ethyl 4-morpholin-4-yl-2,2-diphenylbutanoate
diphenoxylate*	ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate

dipipanone*	4,4-diphenyl-6-piperidin-1-ylheptan-3-one
diprenorphine*	(1s,2s,6r,14r,15r,16r)-5-(cyclopropylmethyl)-16-(2-hydroxypropan-2-yl)-15-methoxy-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20]icosa-8(20),9,11-trien-11-ol
drotebanol*	(1r,9r,10s,13r)-3,4-dimethoxy-17-methyl-17-azatetracyclo [7.5.3.01,10.02,7]heptadeca-2(7),3,5-triene-10,13-diol
eluxadoline*	5-[[[(2s)-2-amino-3-(4-carbamoyl-2,6-dimethylphenyl)propanoyl]-[(1s)-1-(5-phenyl-1h-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid
embutramide*	n-[2-ethyl-2-(3-methoxyphenyl)butyl]-4-hydroxybutanamide
enadoline*	2-(1-benzofuran-4-yl)-n-methyl-n-[(5r,7s,8s)-7-pyrrolidin-1-yl-1-oxaspiro[4.5]decan-8-yl]acetamide
eptazocine*	(1s,9s)-1,11-dimethyl-11-azatricyclo[7.4.1.02,7]tetradeca-2(7),3,5-trien-4-ol
ethoheptazine	ethyl 1-methyl-4-phenylazepane-4-carboxylate
ethylmethylthiambutene*	n-ethyl-n-methyl-4,4-dithiophen-2-ylbut-3-en-2-amine
ethylmorphine	(4r,4ar,7s,7ar,12bs)-9-ethoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
etonitazene*	2-[2-[(4-ethoxyphenyl)methyl]-5-nitrobenzimidazol-1-yl]-n,n-diethylethanamine
etorphine*	(1r,2s,6r)-19-(2-hydroxypentan-2-yl)-15-methoxy-5-methyl-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11,16-tetraen-11-ol
etoxeridine*	ethyl 1-[2-(2-hydroxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate
fedotozine	(2r)-n,n-dimethyl-2-phenyl-1-[(3,4,5-trimethoxyphenyl) methoxy]butan-2-amine
fentanyl*	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] propanamide
fluradoline*	2-(3-fluorobenzo[b][1]benzoxepin-5-yl)sulfanyl-n-methylethanamine
furanylfentanyl	n-phenyl-n-[1-(2-phenylethyl) piperidin-4-yl]furan-2-carboxamide
furethidine*	ethyl 1-[2-(oxolan-2-ylmethoxy)ethyl]-4-phenylpiperidine-4-carboxylate
gemazocine*	10-(cyclopropylmethyl)-1-ethyl-13,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
gsk1521498	N-[[2,6-difluoro-4-[3-(1H-1,2,4-triazol-5-yl)phenyl]phenyl]methyl]-2,3-dihydro-1H-inden-2-amine
homprenorphine*	2-[5-(cyclopropylmethyl)-11,15-dimethoxy-13-oxa-5-azahexacyclo [13.2.2.12,8.01,6.02,14.012,20] icosa-8(20),9,11,18-tetraen-16-yl] butan-2-ol
hydrocodone*	(4r,4ar,7ar,12bs)-9-methoxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one
hydromorphinol*	(4r,4as,7s,7ar,12bs)-3-methyl-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro [3,2-e] isoquinoline-4a,7,9-triol

hydromorphone*	(4r,4ar,7ar,12bs)-9-hydroxy-3-methyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro [3,2-e]isoquinolin-7-one
hydroxypethidine*	ethyl 4-(3-hydroxyphenyl)-1-methylpiperidine-4-carboxylate
ibazocine*	1,13,13-trimethyl-10-(3-methylbut-2-enyl)-10-azatricyclo [7.3.1.02,7] trideca-2(7),3,5-trien-4-ol
ici-174864	(2S)-2-[[(2S)-2-[[2-[[(2S)-2-[bis(prop-2-enyl)amino]-3-(4-hydroxyphenyl)propanoyl]amino]-2-methylpropanoyl]amino]-3-phenylpropanoyl]amino]-4-methylpentanoic acid
iqmf-4	n-[1-phenylpyrazol-3-yl]-n-[1-(2-phenethyl)-4-piperidyl] propenamide
isobutyrylfentanyl	2-methyl-n-phenyl-n-[1-(1-phenylpropan-2-yl)piperidin-4-yl] propenamide
isofentanyl	n-(1-benzyl-3-methylpiperidin-4-yl)-n-phenylpropanamide
isomethadone*	6-(dimethylamino)-5-methyl-4,4-diphenylhexan-3-one
ketazocine*	(1r,9s,13r)-10-(cyclopropylmethyl)-4-hydroxy-1,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-8-one
ketobemidone*	1-[4-(3-hydroxyphenyl)-1-methylpiperidin-4-yl]propan-1-one
ketorfanol*	(1s,9r,10r)-17-(cyclopropylmethyl)-3-hydroxy-17-azatetracyclo [7.5.3.01,10.02,7]heptadeca-2(7),3,5-trien-13-one
lefetamine*	(1R)-N,N-dimethyl-1,2-diphenylethanamine
levacetylmethadol*	[(3s,6s)-6-(dimethylamino)-4,4-diphenylheptan-3-yl] acetate
levallorphan*	(1r,9r,10r)-17-prop-2-enyl-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-trien-4-ol
levomethadone*	(6r)-6-(dimethylamino)-4,4-diphenylheptan-3-one
levomethorphan*	(1r,9r,10r)-4-methoxy-17-methyl-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-triene
levomoramide*	(3r)-3-methyl-4-morpholin-4-yl-2,2-diphenyl-1-pyrrolidin-1-ylbutan-1-one
levophenacylmorphan*	2-[(1r,9r,10r)-4-hydroxy-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-trien-17-yl]-1-phenylethanone
levorphanol*	(1r,9r,10r)-17-methyl-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-trien-4-ol
lofentanil*	methyl (3r,4s)-3-methyl-1-(2-phenylethyl)-4-(n-propanoylanilino)piperidine-4-carboxylate
loperamide*	4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-n,n-dimethyl-2,2-diphenylbutanamide
meptazinol*	3-(3-ethyl-1-methylazepan-3-yl)phenol
metazocine*	1,10,13-trimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
metethoheptazine*	ethyl 1,3-dimethyl-4-phenylazepane-4-carboxylate
methadone*	6-(dimethylamino)-4,4-diphenylheptan-3-one

metheptazine*	methyl 1,2-dimethyl-4-phenylazepane-4-carboxylate
methoxyacetylfentanyl	2-methoxy-n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl]acetamide
methyldesorphine*	(4r,4ar,7as,12bs)-3,7-dimethyl-2,4,4a,5,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-9-ol
methyldihydromorphine*	(4r,4ar,7s,7ar,12bs)-3,7-dimethyl-1,2,4,4a,5,6,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol
methylnaltrexone*	(4r,4as,7ar,12bs)-3-(cyclopropylmethyl)-4a,9-dihydroxy-3-methyl-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-3-ium-7-one
metopon*	(4r,4ar,7ar,12bs)-9-hydroxy-3,7a-dimethyl-2,4,4a,5,6,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one
mirfentanil*	n-[1-(2-phenylethyl)piperidin-4-yl]-n-pyrazin-2-ylfuran-2-carboxamide
morpheridine*	ethyl 1-(2-morpholin-4-ylethyl)-4-phenylpiperidine-4-carboxylate
morphine*	(4r,4ar,7s,7ar,12bs)-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinoline-7,9-diol
moxazocine*	(1s,9r,13r)-10-(cyclopropylmethyl) -13-methoxy-1-methyl-10-azatricyclo[7.3.1.02,7] trideca-2(7),3,5-trien-4-ol
mt-45	1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
myrophine*	[(4r,4ar,7s,7ar,12bs)-3-methyl-9-phenylmethoxy-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] tetradecanoate
n-methylnorcarfentanil	methyl 1-methyl-4-(n-phenylpropanamido)piperidine-4-carboxylate
nalbuphine*	(4r,4as,7s,7ar,12bs)-3-(cyclobutylmethyl)-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e] isoquinoline-4a,7,9-triol
naldemedine*	(4r,4as,7ar,12bs)-3-(cyclopropylmethyl)-4a,7,9-trihydroxy-n-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]-1,2,4,5,7a,13-hexahydro-4,12-methanobenzofuro[3,2-e] isoquinoline-6-carboxamide
nalfurafine*	(e)-n-[(4r,4as,7r,7ar,12bs)-3-(cyclopropylmethyl)-4a,9-dihydroxy-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl]-3-(furan-3-yl)-n-methylprop-2-enamide
nalmefene*	(4r,4as,7as,12bs)-3-(cyclopropylmethyl)-7-methylidene-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinoline-4a,9-diol
nalmexone*	(4r,4as,7ar,12bs)-4a,9-dihydroxy-3-(3-methylbut-2-enyl)-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one
nalorphine*	(4r,4ar,7s,7ar,12bs)-3-prop-2-enyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinoline-7,9-diol
naloxegol*	(4r,4as,7s,7ar,12bs)-7-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy] ethoxy]ethoxy]ethoxy]ethoxy]-3-prop-2-enyl-1,2,4,5,6,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e] isoquinoline-4a,9-diol
naloxone*	(4r,4as,7ar,12bs)-4a,9-dihydroxy-3-prop-2-enyl-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one

naltrexone*	(4r,4as,7ar,12bs)-3-(cyclopropylmethyl)-4a,9-dihydroxy-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one
naltriben	(1S,2S,13R,21R)-22-(cyclopropylmethyl)-11,14-dioxa-22-azaheptacyclo[13.9.1.01,13.02,21.04,12.05,10.019,25]pentacosa-4(12),5,7,9,15,17,19(25)-heptaene-2,16-diol
naltrindole	(1S,2S,13R,21R)-22-(cyclopropylmethyl)-14-oxa-11,22-diazaheptacyclo[13.9.1.01,13.02,21.04,12.05,10.019,25]pentacosa-4(12),5,7,9,15,17,19(25)-heptaene-2,16-diol
narceine	6-[2-[6-[2-(dimethylamino)ethyl]-4-methoxy-1,3-benzodioxol-5-yl]acetyl]-2,3-dimethoxybenzoic acid
nexeridine*	[1-[1-(dimethylamino)propan-2-yl]-2-phenylcyclohexyl] acetate
nicocodine*	[(4r,4ar,7s,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-yl] pyridine-3-carboxylate
nicodicodine*	[(4r,4ar,7s,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,5,6,7,7a,13-octahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-yl] pyridine-3-carboxylate
nicomorphine*	[(4r,4ar,7s,7ar,12bs)-3-methyl-9-(pyridine-3-carbonyloxy)-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] pyridine-3-carboxylate
noracymethadol*	[6-(methylamino)-4,4-diphenylheptan-3-yl] acetate
norcodeine*	(4r,4ar,7s,7ar,12bs)-9-methoxy-1,2,3,4,4a,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol
norlevorphanol*	17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-trien-4-ol
normethadone*	6-(dimethylamino)-4,4-diphenylhexan-3-one
normorphine*	(4r,4ar,7s,7ar,12bs)-1,2,3,4,4a,7,7a,13-octahydro-4,12-methanobenzofuro[3,2-e] isoquinoline-7,9-diol
norpipanone*	4,4-diphenyl-6-piperidin-1-ylhexan-3-one
noscapine*	(3s)-6,7-dimethoxy-3-[(5r)-4-methoxy-6-methyl-7,8-dihydro-5h-[1,3]dioxolo[4,5-g]isoquinolin-5-yl]-3h-2-benzofuran-1-one
ocfentanil*	n-(2-fluorophenyl)-2-methoxy-n-[1-(2-phenylethyl)piperidin-4-yl] acetamide
ohmefentanyl	n-[1-(2-hydroxy-2-phenylethyl)-3-methylpiperidin-4-yl]-n-phenylpropanamide
oliceridine*	n-[(3-methoxythiophen-2-yl)methyl]-2-[(9r)-9-pyridin-2-yl-6-oxaspiro[4.5]decan-9-yl] ethanamine
oripavine	(4r,7ar,12bs)-7-methoxy-3-methyl-2,4,7a,13-tetrahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-9-ol
orthofluorofentanyl	n-(2-fluorophenyl)-n-[1-(2-phenylethyl)piperidin-4-yl] propanamide
oxilorphan*	(1s,9r,10s)-17-(cyclopropylmethyl)-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-triene-4,10-diol
oxpheneridine*	ethyl 1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine-4-carboxylate
oxycodone*	(4r,4as,7ar,12bs)-4a-hydroxy-9-methoxy-3-methyl-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one

oxymorphone*	(4r,4as,7ar,12bs)-4a,9-dihydroxy-3-methyl-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one
papaveretum	(4r,4ar,7s,12bs)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol;(4r,4ar,7s,12bs)-3-methyl-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinoline-7,9-diol;1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline; hydrochloride
parafluorobutyrylfentanyl	N-(4-Fluorophenyl)-N-[1-(2-phenylethyl)piperidin-4-yl]butanamide
parafluorofentanyl	n-(4-fluorophenyl)-n-[1-(2-phenylethyl)piperidin-4-yl] propanamide
pentamorphone*	(4r,4as,7ar,12br)-9-hydroxy-3-methyl-4a-(pentylamino)-2,4,7a,13-tetrahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-one
pentazocine*	(1r,9r,13r)-1,13-dimethyl-10-(3-methylbut-2-enyl)-10-azatricyclo[7.3.1.02,7] trideca-2(7),3,5-trien-4-ol
pepap	[4-phenyl-1-(2-phenylethyl)piperidin-4-yl] acetate
pethidine*	ethyl 1-methyl-4-phenylpiperidine-4-carboxylate
phenadoxone*	6-morpholin-4-yl-4,4-diphenylheptan-3-one
phenampromide*	n-phenyl-n-(1-piperidin-1-ylpropan-2-yl) propenamide
phenazocine*	1,13-dimethyl-10-(2-phenylethyl)-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-4-ol
pheneridine*	ethyl 4-phenyl-1-(2-phenylethyl)piperidine-4-carboxylate
phenomorphan*	(1r,9r,10r)-17-(2-phenylethyl)-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-trien-4-ol
phenoperidine*	ethyl 1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylate
pholcodine*	(4r,4ar,7s,7ar,12bs)-3-methyl-9-(2-morpholin-4-ylethoxy)-2,4,4a,7,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinolin-7-ol
picenadol*	3-[(3r,4s)-1,3-dimethyl-4-propylpiperidin-4-yl]phenol
piminodine*	ethyl 1-(3-anilinopropyl)-4-phenylpiperidine-4-carboxylate
pinadoline*	3-chloro-n'-(5-chloropentanoyl)-6h-benzo[b][1,4]benzoxazepine-5-carbohydrazide
piritramide*	1-(3-cyano-3,3-diphenylpropyl)-4-piperidin-1-ylpiperidine-4-carboxamide
prodine	(1,3-dimethyl-4-phenylpiperidin-4-yl) propanoate
proheptazine*	(1,3-dimethyl-4-phenylazepan-4-yl) propanoate
properidine*	propan-2-yl 1-methyl-4-phenylpiperidine-4-carboxylate
propiram*	n-(1-piperidin-1-ylpropan-2-yl)-n-pyridin-2-ylpropanamide

proxorphan*	(1s,9r,10r)-17-(cyclopropylmethyl)-13-oxa-17-azatetracyclo[7.5.3.01,10.02,7] heptadeca-2(7),3,5-trien-4-ol
quadazocine*	1-cyclopentyl-5-[(1s,9r)-4-hydroxy-1,10,13-trimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-13-yl]pentan-3-one
r-30490	n-[4-(methoxymethyl)-1-(2-phenylethyl)piperidin-4-yl]-n-phenylpropanamide
remifentanil*	methyl 1-(3-methoxy-3-oxopropyl)-4-(n-propanoylanilino)piperidine-4-carboxylate
sameridine*	n-ethyl-1-hexyl-n-methyl-4-phenylpiperidine-4-carboxamide
semorphone*	(4r,4as,7ar,12bs)-4a,9-dihydroxy-3-(2-methoxyethyl)-2,4,5,6,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one
spiradoline*	2-(3,4-dichlorophenyl)-n-methyl-n-[(5r,7s,8s)-7-pyrrolidin-1-yl-1-oxaspiro[4.5]decan-8-yl]acetamide
sufentanil*	n-[4-(methoxymethyl)-1-(2-thiophen-2-ylethyl)piperidin-4-yl]-n-phenylpropanamide
tapentadol*	3-[(2r,3r)-1-(dimethylamino)-2-methylpentan-3-yl]phenol
tetrahydrofuranylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl]oxolane-2-carboxamide
tetramethylcyclopropylfentanyl	2,2,3,3-tetramethyl-n-(1-phenethylpiperidin-4-yl)-n-phenylcyclopropane-1-carboxamide
thebacon*	[(4r,4ar,7ar,12bs)-9-methoxy-3-methyl-2,4,4a,5,7a,13-hexahydro-1h-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl] acetate
thebaine	(4r,7ar,12bs)-7,9-dimethoxy-3-methyl-2,4,7a,13-tetrahydro-1h-4,12-methanobenzofuro[3,2-e] isoquinoline
thiafentanil	methyl 4-(n-(2-methoxyacetyl)anilino)-1-(2-thiophen-2-ylethyl)piperidine-4-carboxylate
thiofentanyl	n-phenyl-n-[1-(2-thiophen-2-ylethyl)piperidin-4-yl] propanamide
tianeptine*	7-[(3-chloro-6-methyl-5,5-dioxo-11h-benzo[c][2,1]benzothiazepin-11-yl)amino]heptanoic acid
tilidine*	ethyl (1s,2r)-2-(dimethylamino)-1-phenylcyclohex-3-ene-1-carboxylate
tipp-psi	(2S)-2-[[(2S)-2-[[(3S)-2-[(2S)-2-amino-3-(4-hydroxyphenyl)propanoyl]-3,4-dihydro-1H-isoquinolin-3-yl]methylamino]-3-phenylpropanoyl]amino]-3-phenylpropanoic acid
tonazocine*	1-[(1r,9s,13s)-4-hydroxy-1,10,13-trimethyl-10-azatricyclo[7.3.1.02,7]trideca-2(7),3,5-trien-13-yl]octan-3-one
tramadol*	(1r,2r)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol
trefentanil*	n-[1-[2-(4-ethyl-5-oxotetrazol-1-yl)ethyl]-4-phenylpiperidin-4-yl]-n-(2-fluorophenyl)propanamide
trimebutine*	[2-(dimethylamino)-2-phenylbutyl] 3,4,5-trimethoxybenzoate
trimeperidine*	(1,2,5-trimethyl-4-phenylpiperidin-4-yl) propanoate
u-47700	3,4-dichloro-n-[2-(dimethylamino)cyclohexyl]-n-methylbenzamide

valerylfentanyl	n-phenyl-n-[1-(2-phenylethyl)piperidin-4-yl] pentanamide
veradoline*	4-[2-(6,7-dimethoxy-1-methyl-3,4-dihydro-1h-isoquinolin-2-yl) ethyl]aniline
volazocine*	10-(cyclopropylmethyl)-1,13-dimethyl-10-azatricyclo[7.3.1.02,7]trideca-2,4,6-triene
xorphanol*	(1r,9r,10r,11s)-17-(cyclobutylmethyl)-11-methyl-13-methylidene-17-azatetracyclo [7.5.3.01,10.02,7]heptadeca-2(7),3,5-trien-4-ol

*Names identified in the INN search (n=170); if there was no INN name, the BAN or the name reported in the BNF was selected, otherwise the next most common drug name was selected. INN: International Non-proprietary Names; IUPAC: International Union of Pure and Applied Chemistry.

14 Chapter 6 Appendix

Appendix 6.1: Report provided by the MHRA following my FOI request on May 02, 2019

RESTRICTED COMMERCIAL

NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

NON-PRESCRIPTION ANALGESICS WORKING GROUP

Title: Risk Management of codeine and dihydrocodeine containing OTC analgesics
Type of paper: For information

PRODUCT	**ACTIVE(S) rINN:**
Numerous	Codeine Dihydrocodeine
COMPANIES Numerous	**THERAPEUTIC CLASSIFICATION:** C[redacted]
LEGAL STATUS: P	**DATE OF MEETING**: 14 **MARCH** 2014
CONSIDERATION BY OTHER COMMITTEES: CSM/2005/12th CHM/09/7th	**ASSESSOR(S)**: [redacted]

TABLE OF CONTENTS

INTRODUCTION

The purpose of this paper is to provide background information on risk minimisation measures that have been taken by MHRA in relation to OTC analgesics containing codeine or dihydrocodeine (DHC). The paper does not present a detailed analysis and review of the literature and evidence or a risk analysis of these products. Rather it provides an update on risk management of OTC analgesics containing codeine or dihydrocodeine and how these products are positioned overall in the self-management of pain in the OTC setting.

LICENSING BACKGROUND

Under the Misuse of Drugs Act and the Prescription Only Medicines (Human Use) Order 1997, there are provisions for small quantities of the controlled drugs, codeine and DHC, to be available in non-prescription medicines and sold through pharmacies only. They may include doses of up to 25.6mg of codeine phosphate (i.e. 12.8mg per tablet for a 2 tablet dose) and up to 14.92mg of DHC tartrate (i.e. 7.46mg per tablet for a 2 tablet dose).

There are 47 authorised P products containing codeine and 2 containing DHC; these are in combination with other active ingredients, for use as painkillers. Examples of a range of commonly used codeine and DHC containing products are included in the table at **Annex 1.**

Of the codeine containing products, 40 are combined with paracetamol, 4 with ibuprofen and 3 with aspirin. The DHC containing products are all combined with paracetamol. Some codeine containing products also include other active ingredients, such as caffeine.

RISK MINIMISATION MEASURES TAKEN FOR OTC MEDICINESCONTAINING CODEINE OR DIHYDROCODEINE

Past reviews of the risk management of OTC medicines containing codeine or dihydrocodeine have specifically addressed risks of abuse and misuse. Any measures introduced to manage the risks of other painkillers such as paracetamol, aspirin and ibuprofen would apply to the codeine or dihydrocodeine OTC products that they are combined with.

In February 2005 the CSM considered the abuse and misuse of OTC medicines containing codeine or DHC and issued the following advice:

- Strengthen the warnings on the SPC, PIL and label to reflect the importance of not taking the medicines for more than three days continuously without medical review, and to warn about the risks of addiction and headache from overuse
- Limit the pack size to 32 tablets by voluntary agreements with companies, with any pack sizes available above 32 tablets labelled as “dispensing only”
- Agree with companies, a responsible approach to promotional activities

In June 2005 the CSM received an update on proposals to implement the above advice and agreed the final wording for warnings. Details are attached at **Annex 2.**

In July 2009, the CHM considered a further review of risk minimisation measures in relation to codeine and dihydrocodeine containing analgesics following the publication of the report of an inquiry undertaken by the All-Party Parliamentary Drug Misuse Group (APPDMG) into the physical dependence and addiction to prescription and OTC medicines. In the report of the inquiry, published in January 2009, a number of recommendations were made to reduce the risk of misuse of medicines, in particular, OTC medicines containing codeine or DHC. The CHM Paper is at **Annex 3.** The CHM Minute is at **Annex 4.** The Commission issued the following advice:

- Strengthen further the warnings on patient information leaflets, labels and advertising about the risk of addiction, the importance of not taking the medicine for more than three days consecutively and the need to seek advice from a doctor if painkillers are needed for longer than three days

- Limit the indications for non-prescription use to the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone

- Reduce the pack size of all codeine and dihydrocodeine containing non-prescription medicines, including effervescent forms to 32.

- Provide more information in the patient leaflet about the signs and symptoms of addiction.

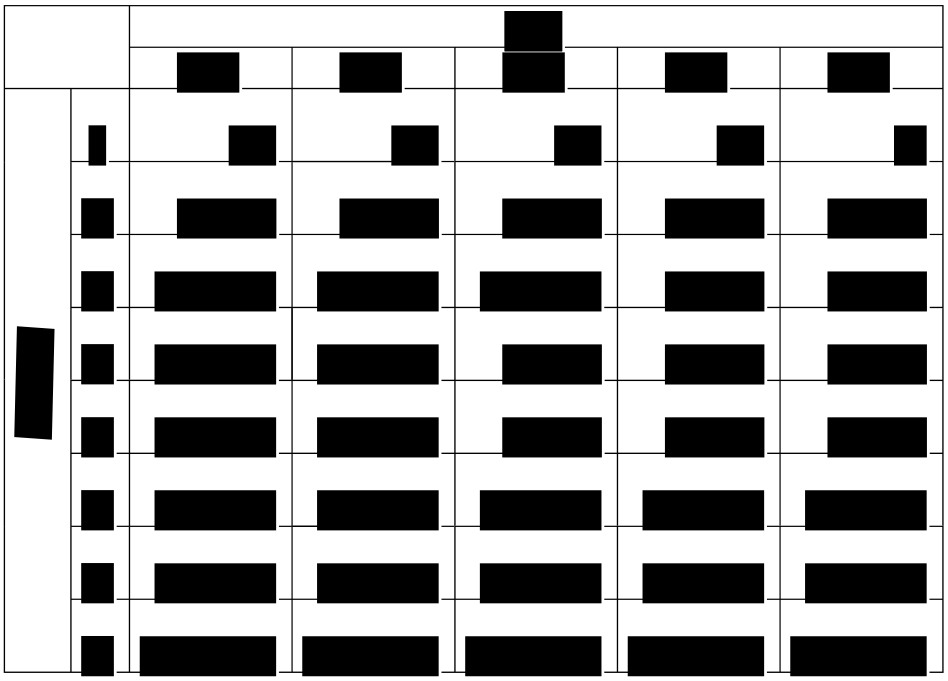
- Review the patient support leaflet drafted by PAGB in consultation with the British Pain Society

Examples of patient information complying with the new risk minimisation measures are at **Annex 5**.

The final British Pain Society leaflet that was published on the websites of the Pain Society and the PAGB is at **Annex 6.**

[redacted]

[redacted]



[redacted]

[redacted]

The data suggests that since 2008, sales have been declining each year for all pack sizes except the 30 pack size. The 30 pack size is unusual for the OTC setting and it is possible that these packs are supplied on prescription, although this cannot be confirmed. In any case, the combined sales figures for the 30 and 32 pack sizes show a decrease in overall sales from 2008 ([redacted] to 2012 [redacted]).

YELLOW CARD REPORTS

A review of the yellow card data was undertaken looking at line listings for codeineand dihydrocodeine with ADRs of abuse/misuse. ADRs included:

Intentional
overdose
Overdose
Dependene
Drug abuse
Drug dependence,
postpartum
Substance abuse
Withdrawal syndrome

The data for DHC containing analgesics was negligible – 5 cases since 1981, of whichone case was reported in each of the following years: 1981, 1984, 2009, 2011, and 2013.

The data for codeine containing analgesics revealed 92 line listings over a periodbetween 1975 and 2013. Details are set out in table 2.

Table 2: Line listings of Yellow Card reports for OTC Codeine containing analgesics between 1984and 2013 for addiction and abuse related ADRs

Year	1984	1991	1993	1996	1997	1999	2000	2001	2002	2002	
Number of line listings	1	2	1	1	2	1	4	8	4	2	
Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	
Number of line listings	3	2	4	2	3	2	3	6	12	26	

The limitations of using ADR data to establish an increased incidence of addiction ormisuse to these medicines is recognised but it is helpful to consider trends. The data shows that in the last two years there was a significant increase in the number of reports. However, on further examination it can be seen that the majority of these reports originated from literature articles, in particular, one in 2012 and one in 2013. The 2013 article was about addiction to OTC medicines. It was a qualitative analysis of experiences and views of people self-reporting over-the-counter-medicine abuse, and associated treatment and support sought. [Cooper RJ. 'I can't be an addict. I am.' Over-the-counter medicine abuse: A qualitative study. BMJOpen 2013;3:e002913. Available from: http://dx.doi.org/10.1136/bmjopen-2013-002913].

DISCUSSION

OTC analgesics containing codeine or DHC are available in combination with paracetamol, ibuprofen and aspirin. All risk minimisation measures that are implemented for NSAIDs and paracetamol will also apply to these combination products. The additional risk associated with OTC analgesics containing codeine orDHC is addiction resulting from abuse and misuse.

A number of risk minimisation measures have been taken, including limiting the indications to the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone (i.e. second line treatment); restriction to short term use; front of pack warnings about the risk of addiction; further informationin the patient leaflet about the risk of addiction and details of the signs and symptomsof addiction; and the availability of additional patient information to support the responsible use of these painkillers and encourage their use as second line treatment in the short term management of pain.

Sales figures show that the number of packs sold is decreasing year on year. It can beassumed that in real terms the total amount of OTC codeine and DHC containing analgesics purchased OTC has been reduced by a greater extent. This is because at the end of 2009 the pack size of the effervescent forms was limited to 32 in line with the solid forms. Before that they were available in packs of up to 100. Therefore the true decrease in use of codeine and DHC containing analgesics will be larger than these figures show because the figures for the larger packs sold before 2009 have not been included.

Review of yellow card reports of abuse and misuse shows a significant increase in thenumber of line reports in the last two years. But further analysis reveals that most of these were attributed to two specific articles about dependence on OTC medicines andthe individuals discussed in the articles were not new cases.

Other contributing factors to the increase in yellow card reports over the last few years could be an increased awareness of the risk and signs of addiction and overuseof these products, which was one of the intended aims of the regulatory action taken in 2009, and the new definition of the term ‘adverse reaction’ that was introduced with the new pharmacovigilance legislation in 2012 to include uses outside the termsof the marketing authorisation, including the misuse and abuse of the medicinal product.

It is recognised that yellow card reports might not reveal an accurate picture of trendsin addiction to and abuse of OTC medicines. While there are no concrete figures on the prevalence of addiction to these medicines, anecdotal evidence suggests that thereis a problem. An on line article in the Chemist and Druggist on 27th February 2014 reported that a poll of 283 readers (community pharmacists) found that 33 per cent suspected addiction to OTC

medicines on a daily basis, while 30 per cent were suspicious about OTC medicines sales two or three times a week. (The question posed in the poll did not specify which OTC medicines but it can be assumed that codeine and DHC containing analgesics would be included.) As sales of these medicines are decreasing year on year, it could be assumed that high awareness by community pharmacists of possible addition has led to more active supervision of their sales and more caution in supply.

Another indicator of trends in addiction and abuse of OTC medicines would be increased proactive representation from patient support groups to the media and parliament. Since the publication of the report of the All-Party Parliamentary Drug Misuse Group (APPDMG) into the physical dependence and addiction to prescriptionand OTC medicines, and following implementation of the new risk minimisation

measures by MHRA, there have been no significant approaches from parliament orpatient groups to indicate that the problem is on the increase.

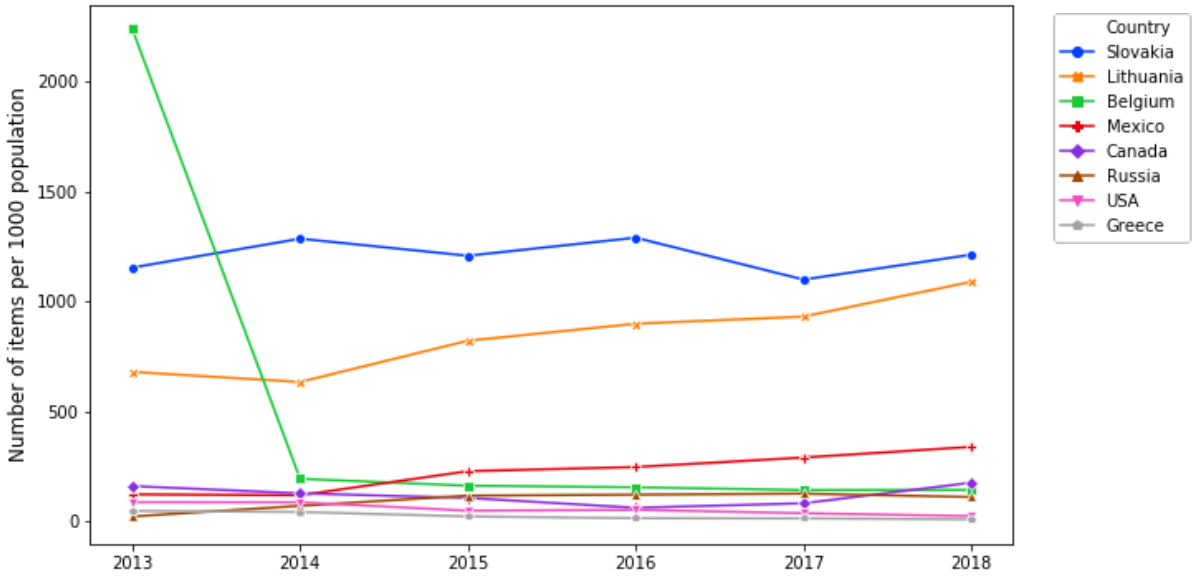
CONCLUSION

The main focus of the Ad Hoc Working Group's review of non-prescription analgesics is in relation to the current evidence of cardiovascular and GI risk, which isassociated with the NSAIDs and paracetamol. Any new risk minimisation measures identified or actions taken to optimise use of these medicines will also apply to codeine and DHC containing OTC analgesics, as they will also contain one or more ofthese actives. In relation to the management of risk of addiction and overuse of these medicines, no action is currently envisaged but further action will be taken if new evidence of an increase in addiction and overuse emerges.

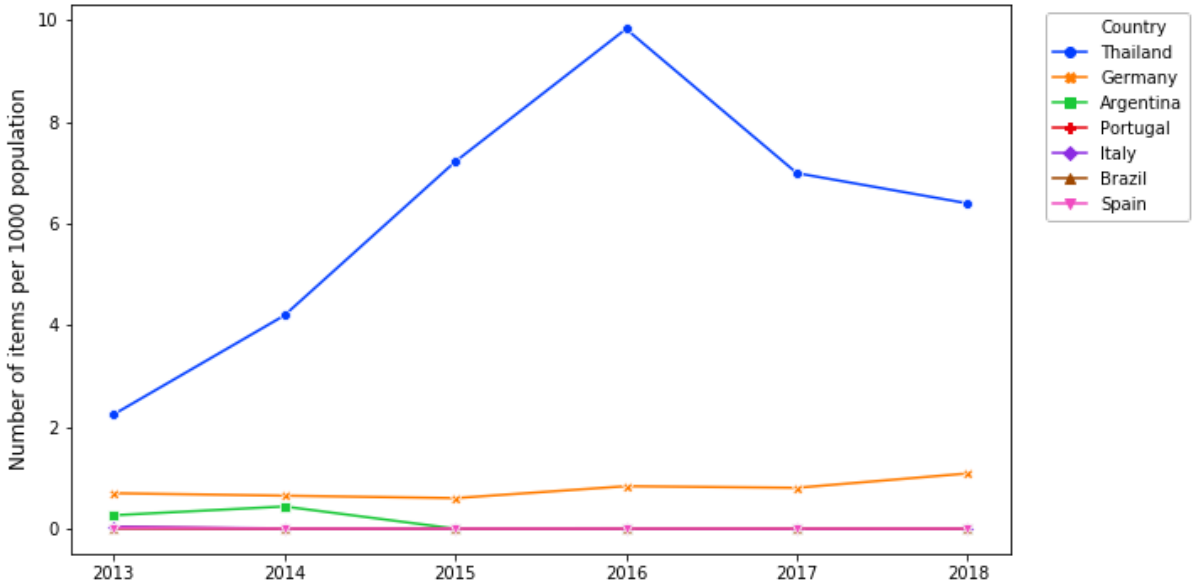
In view of the actions already taken on the risk management of OTC analgesics containing codeine and dihydrocodeine specifically in relation to addiction or misuse, and in the absence of new evidence of an increase in addiction to these medicines, it isconsidered that no further action is needed as part of this review.

It is significant to note the enhanced patient information that has been introduced for these products, not only regarding the warnings about addiction but also regarding thedetails in the patient leaflet about the signs and symptoms of addiction and the BritishPain Society patient leaflet about managing pain effectively using OTC medicines.

It is also significant to note that these products are indicated for second line treatmentin the OTC setting.



Appendix 6.2: Over-the-counter products containing codeine sold per 1000 population starting in April 2013-March 2014, and ending in April 2018-March 2019, for countries in the third quartile of sales, based on their mean units sold per person.



Appendix 6.3: Over-the-counter products containing codeine sold per 1000 population starting in April 2013-March 2014, and ending in April 2018-March 2019, for countries in the last quartile of sales, based on their mean units sold per person.

15 Chapter 7 Appendix

Appendix 7.1: MEDLINE strategy and results.

Search #	Search terms	# of results
1	exp Analgesics, Opioid/	109489
2	exp Narcotics/	117473
3	1 or 2	117473
4	opioid*.ti,ab.	79690
5	narcotic*.ti,ab.	14579
6	"opioid analgesic*".ti,ab.	4475
7	opiate*.ti,ab.	24064
8	opium.ti,ab.	2439
9	4 or 5 or 6 or 7 or 8	112098
10	codeine*.ti,ab.	4774
11	morphine*.ti,ab.	48019
12	("MS Contin" or "MST Continus" or Oramorph or Sevredol).ti,ab.	118
13	Papaveretum.ti,ab.	138
14	Ketobemidone.ti,ab.	134
15	Dextromoramide.ti,ab.	177
16	Hydromorphone.ti,ab.	1466
17	(Himop or Jurnista or Palladon*).ti,ab.	14
18	Piritramide.ti,ab.	353
19	Dextropropoxyphene*.ti,ab.	530
20	Oxycodone.ti,ab.	2989
21	(Oxycontin or Oxynorm).ti,ab.	240
22	Dihydrocodeine.ti,ab.	433
23	(Meperidine or Pethidine*).ti,ab.	4850

24	Nicomorphine.ti,ab.	43
25	Dolosal.ti,ab.	20
26	Fentanyl.ti,ab.	17437
27	Abstral.ti,ab.	7
28	Actiq.ti,ab.	26
29	Durogesic.ti,ab.	44
30	(Instanyl or Ionsys or Sublimaze).ti,ab.	43
31	Methadone.ti,ab.	12800
32	Amidone.ti,ab.	44
33	Pentazocine.ti,ab.	2333
34	(Fortral or Fortwin or Sosegon).ti,ab.	52
35	Bezitramide.ti,ab.	20
36	Phenazocine.ti,ab.	70
37	Buprenorphine.ti,ab.	6016
38	Norspan*.ti,ab.	4
39	Subutex.ti,ab.	94
40	(Temgesic or Transtec).ti,ab.	70
41	Butorphanol.ti,ab.	1434
42	Nalbuphine.ti,ab.	885
43	Nubain.ti,ab.	44
44	Tramadol.ti,ab.	4608
45	Adamon.ti,ab.	9
46	(Tramal or Tramazac).ti,ab.	98
47	Tilidine.ti,ab.	133
48	Tapentadol.ti,ab.	418
49	Palexia*.ti,ab.	10
50	Dezocine.ti,ab.	142

51	meptazinol.ti,ab.	219
52	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	92514
53	3 or 9 or 52	196757
54	exp INAPPROPRIATE PRESCRIBING/ or exp Drug Prescriptions/ or exp Drug Utilization/ or exp Practice Patterns, Physicians'/	98731
55	exp Potentially Inappropriate Medication List/	279
56	exp Prescription Drugs/	5235
57	exp Prescription Drug Misuse/	11706
58	exp Medical Overuse/ or exp Deprescriptions/ or exp Prescriptions/	39044
59	exp Prescription Drug Overuse/ or exp Drug Misuse/ or exp Self Medication/	16227
60	exp Behind-the-Counter Drugs/ or exp Nonprescription Drugs/	5885
61	prescri*.ti,ab.	195505
62	Utiliz*.ti,ab.	514119
63	utilis*.ti,ab.	44114
64	dispens*.ti,ab.	35225
65	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64	852797
66	53 and 65	19678
67	exp Primary Health Care/	145132
68	exp Ambulatory Care Facilities/	52697
69	exp Physicians, Primary Care/	2888
70	exp Outpatient Clinics, Hospital/	16767
71	exp Ambulatory Care/	51044
72	exp Emergency Service, Hospital/ or exp Family Practice/ or exp General Practice/	142600
73	exp General Practice, Dental/	4727

74	exp Office Visits/	6681
75	exp Physicians, Family/ or exp General Practitioners/	22706
76	exp Emergency Medical Services/	128929
77	exp Pharmacies/ or exp Community Pharmacy Services/	11288
78	exp Community Health Services/ or exp Community Medicine/ or exp Community Health Nursing/ or exp Community Health Centers/	299456
79	exp Community Dentistry/	1213
80	exp Home Nursing/ or exp Residential Facilities/	58938
81	(ambulatory adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab.	17870
82	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	112376
83	((primary* adj3 (care or health*)) or community or communities or population).ti,ab.	1775651
84	(clinic? or office or visit? or "health centre" or "health center" or "medical centre" or "medical center").ti,ab.	560228
85	("out of hours" or ooh or "after hours").ti,ab.	4235
86	(emergency adj5 (department? or dept* or ward? or room? or unit? or service? or care or setting? or facilit*)).ti,ab.	127109
87	exp Housing for the Elderly/ or exp Assisted Living Facilities/ or exp Home Care Services/ or exp Homes for the Aged/	60450
88	exp INSTITUTIONALIZATION/ or exp Long-Term Care/	32735
89	((nursing or residential or longterm or long-term or institutional) adj2 home).ti,ab.	23609
90	(((residential or longterm or long-term) adj2 care) or facilit*).ti,ab.	624294
91	exp Home Care Services/	45434
92	((home or domiciliary) adj (visit* or call*)).ti,ab.	8212
93	((refill or repeat) adj prescri*).ti,ab.	461
94	67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93	3285822

95	66 and 94	7761
96	predict*.ti,ab.	1419106
97	characteristic*.ti,ab.	1259013
98	varian*.ti,ab.	480043
99	variat*.ti,ab.	649635
100	factor*.ti,ab.	3073031
101	96 or 97 or 98 or 99 or 100	5779446
102	95 and 101	2612

Appendix 7.2: International brand names for opioids collated using the UpToDate database

Drug name	Brand names	Countries	# of countries	Included or excluded
Codeine	N/A	N/A	N/A	Included
Morphine	MS Contin	AU, BE, CN, IT, LU, NL, VE, KR	8	Included
	MST Continus	AE, AR, BF, BG, BH, BJ, CI, CY, CZ, EE, EG, ES, ET, GB, GH, GM, GN, HK, HR, ID, IE, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MT, MU, MW, MY, NE, NG, OM, PH, PK, PL, QA, RO, SA, SC, SD, SG, SK, SL, SN, SY, TH, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW	61	Included
	Oramorph	BE, ES, FR, GB, IE, LU, PT, SE	8	Included
	Sevredol	AU, CH, CZ, HR, IE, NZ, RO, SI, SK, TR	10	Included
Hydro-morphone	Himop	CR, DO, GT, HN, NI, PA, SV	7	Included
	Jurnista	AT, AU, CR, CZ, DE, DK, DO, EE, ES, GT, HN, HU, ID, IT, MX, NI, NZ, PA, PH, PT, SA, SG, SI, SV, ZW	25	Included
	Palladon*	CH, DK, FI, IS, NL, NO, SE, SI, SE, BE, CZ, EE, ES, GB, GR, HN, IE, IL, LU, PT	20	Included
	Liberaxim	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
Nicomorphine	N/A	N/A	N/A	Included

Oxycodone	Oxycontin	AR, AT, BR, CH, CL, CN, CO, CR, CY, CZ, DK, DO, EC, EE, ES, FI, GB, GT, HK, HN, IE, IL, IT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, SE, SG, SV, VE, HR, HU, IS, LU, RO, SI, SK, TR, VN	45	Included
	Oxynorm	AT, AU, BE, CH, CY, DK, ES, FI, FR, GB, HK, IE, IS, MY, NO, NZ, PH, SE, SG, TR, JP, SG,	22	Included
Dihydro-codeine	N/A	N/A	N/A	Included
Papaveretum	N/A	N/A	N/A	Included
Ketobemidone	N/A	N/A	N/A	Included
Pethidine	Meperidine	N/A	N/A	Included
	Dolosal	BR, CR, DO, GT, HN, NI, PA, SV	8	Included
Fentanyl	Abstral	BM, ES, GB, HR, IE, PH, QA, TR	8	Included
	Actiq	AU, CH, DE, DK, ES, FI, FR, GB, IE, IL, KR, PT, SE	13	Included
	Durogesic	AE, AU, BH, CN, CO, CY, EG, ES, ID, IN, JO, KW, LB, LK, MX, NZ, PH, PK, PY, QA, SA, SG, TH, VN	24	Included
	Instanyl	AT, BE, CZ, DE, DK, EE, ES, FR, HR, IS, LT, LU, MT, NL, PL, SE, SI, SK	18	Included
	Ionsys	AT, BE, BG, CH, CZ, DE, DK, EE, FI, FR, GB, GR, HN, IE, IT, MT, NL, NO, PT, RU, SE, SK, TR	23	Included
	Sublimaze	AR, AU, GB, IE, NZ, PH, ZA	7	Included
Dextro-moramide	N/A	N/A	N/A	Included

Piritramide	N/A	N/A	N/A	Included
Dextro-propoxyphene	N/A	N/A	N/A	Included
Bezitramide	N/A	N/A	N/A	Included
Pentazocine	Fortral	AT, AU, BG, DE, DK, GB, HR, IE, NZ, PL	10	Included
	Fortwin	BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW	29	Included
	Sosegon	AE, BF, BH, BJ, CI, CY, EC, EG, ET, GH, GM, GN, IL, IQ, IR, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PK, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW	42	Included
Phenazocine	N/A	N/A	N/A	Included
Bupren-orphine	Norspan patch	AU, DE, DK, EE, FI, HK, KR, NO, NZ, PH	10	Included
	Subutex	AE, AT, AU, BE, BG, CH, CZ, DE, DK, FR, GR, HR, ID, IE, IL, IS, LU, LV, MT, NO, PT, QA, SE, TW	23	Included
	Temgesic	AE, AT, BE, BF, BH, BJ, BR, CH, CI, CY, DE, DK, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, HK, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PK, QA, RU, SA, SC, SD, SE, SG, SK, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW	66	Included
	Transtec	BE, CH, CL, CO, DE, DK, EC, ES, GB, HN, HR, HU, IE, IT, MX, NL, NO, PE, PL, PT, SK	21	Included

Butorphanol	N/A	N/A	N/A	Included
Nalbuphine	Bufigen	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
	Nalcryn	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
	Nubain	AE, AT, BF, BH, BJ, BR, CI, CY, CZ, DE, EE, EG, ET, GB, GH, GM, GN, GR, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PL, QA, SA, SC, SD, SI, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW	57	Included
Methadone	Amidone	CR, DO, GT, HN, NI, PA, SV	7	Included
	Rubidexol	CR, DO, GT, HN, MX, NI, PA, SV	8	Excluded
Tramadol	Adamon	AR, CR, DO, GT, HN, NI, PA, PY, SV	9	Included
	Bongesic	CR, DO, GT, HN, NI, PA, SV	7	Excluded
	Mabron	AE, BH, CY, EG, ET, IQ, IR, JO, KW, LB, LV, LY, MY, OM, QA, SA, SG, SY, YE	20	Excluded
	Trabilin	BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, NI, PA, SR, SV, TT	15	Excluded
	Tradolan	AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE	16	Excluded

	Tramal	AE, AT, AU, BF, BH, BJ, CH, CI, CN, CO, CR, CU, CY, CZ, DE, DO, EC, EE, EG, ET, FI, GH, GM, GN, GR, GT, HN, HR, IQ, IR, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MT, MU, MW, NE, NG, NI, NL, NZ, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SK, SL, SN, SV, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW	72	Included

Appendix 7.3: All factors reported by included studies

1. Sociodemographic characteristics

1.1 Age					
Study ID	**High-dose**		**Low-dose**		**Mean difference, years (95% CI)**
	Mean age (years)	**SD**	**Mean age (years)**	**SD**	
Morasco, 2019	54.2	9.7	53.0	10.0	1.20 (-4.6, 6.9)
Chang, 2018a	53.8	12.7	55.4	15.8	-1.6 (-1.7, -1.5)
Chang, 2018b	47.22	10.6	-	-	-
Campbell, 2015	55.4	13.2	61.3	13.6	-5.9 (-7.5, -4.3)
Kobus, 2012	54.7	15.0	54.7	15.5	0 (-1.5, 1.5)
Chapman, 2013	Age was reported for all participants on opioids, split by women and men. Women had a mean age of 67 years (SD: 17, range: 24 to 104 years) and men were 62 years (SD: 16, range: 19 to 97 years).				
1.2 Gender (male)					
	High-dose		**Low-dose**		**RR (95% CI)**
	Count (%)		**Count (%)**		
Morasco, 2019	14 (82%)		25 (74%)		1.12 (0.83, 1.51)
Chang, 2018a	72,692 (48%)		1,464,693 (38%)		1.28 (1.28, 1.29)
Chang, 2018b	1,468 (53%)		83,150 (44%)		1.18 (1.14, 1.22)
Campbell, 2015	205 (48%)		260 (39%)		1.22 (1.07, 1.40)
Chapman, 2013	103 (39%)		1,422 (38%)		1.04 (0.89, 1.22)
Kobus, 2012	201 (44%)		1,767 (37%)		1.21 (1.08, 1.35)
1.3 Ethnicity					
	Variable		**High-dose**	**Low-dose**	**RR (95% CI)**
			Count (%)	**Count (%)**	
Morasco, 2019	Caucasian		15 (88%)	24 (71%)	1.25 (0.95, 1.65)

Kobus, 2012	Caucasian	362 (80%)	3,614 (75%)	1.06 (1.01, 1.12)
Kobus, 2012	Black	7 (2%)	134 (3%)	0.56 (0.26, 1.18)
	Native American/ Alaskan	9 (2%)	49 (1%)	1.95 (0.97, 3.95)
	Asian Pacific Islander	4 (1%)	40 (1%)	1.06 (0.38, 2.96)
	Other	7 (2%)	99 (2%)	0.75 (0.35, 1.61)
	Unknown/declined to answer	64 (14%)	879 (18%)	0.77 (0.61, 0.98)
	Hispanic	5 (2%)	93 (3%)	0.57 (0.23, 1.40)
1.4 Employment status				
Morasco, 2019	Unemployed	3 (18%)	7 (21%)	0.86 (0.25, 2.91)
Campbell, 2015	Unemployed	245 (58%)	263 (40%)	1.45 (1.28, 1.64)
Morasco, 2019	Employed	1 (6%)	3 (9%)	0.67 (0.07, 5.94)
	Other	1 (6%)	4 (12%)	0.50 (0.06, 4.13)
	Receiving disability	12 (71%)	20 (60%)	1.20 (0.79, 1.82)
1.5 Education				
		High-dose	**Low-dose**	**Mean difference, years**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Years of education	15.2 (2.6)	13.5 (2.0)	1.7
1.6 Marriage status				
Morasco, 2019	Married	7 (41%)	11 (32%)	1.27 (0.60, 2.69)
	Separated/ divorced	8 (41%)	16 (47%)	1.00 (0.54, 1.85)
	Single	2 (12%)	5 (15%)	0.80 (0.17, 3.71)
	Widowed	0 (0%)	2 (6%)	0.39 (0.02, 7.68)
1.7 State of residence				

Chang, 2018a	California	47,446 (31%)	1,416,000 (36%)	0.87 (0.86, 0.87)
	Florida	54,338 (36%)	1,207,982 (31%)	1.16 (1.15, 1.17)
	Georgia	20,692 (14%)	689,886 (18%)	0.77 (0.76, 0.78)
	Maryland	12,487 (8%)	250,868 (6%)	1.29 (1.26, 1.31)
	Washington	15,866 (11%)	330,335 (8%)	1.24 (1.22, 1.26)
1.8 Insurance coverage				
Kobus, 2012	Medicare	154 (34%)	1,352 (28%)	1.21 (1.06, 1.39)
	Medicaid	1 (0.2%)	3 (0.06%)	3.54 (0.37, 33.99)

2. Treatment-related characteristics

2.1 Coprescription				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Chang, 2018a	Benzodiazepines	61,623 (41%)	314,364 (8%)	5.06 (5.03, 5.10)
Chang, 2018b	Benzodiazepines	1,226 (44%)	8,488 (5%)	9.36 (9.96, 10.28)
Campbell, 2015	Benzodiazepines	172 (40%)	169 (26%)	1.58 (1.33, 1.88)
Kobus, 2012	Sedative-hypnotic prescription 6-months before/ after index visit	276 (61%)	2,022 (42%)	1.45 (1.34, 1.57)
Campbell, 2015	Antidepressants	246 (58%)	323 (49%)	1.18 (1.06, 1.32)
2.2 Opioid schedule				
Campbell, 2015	Australian Schedule 4	146 (34%)	197 (30%)	1.15 (0.97, 1.37)
	OTC analgesic use	259 (61%)	424 (64%)	0.95 (0.86, 1.04)
Kobus, 2012	Long-acting	400 (88%)	1,637 (34%)	2.60 (2.47, 2.74)
2.3 Type of opioid drug				

Campbell, 2015	Past week oxycodone	251 (59%)	400 (61%)	0.91 (0.82, 1.01)
	Past week morphine	86 (20%)	75 (11%)	1.78 (1.34, 2.37)
	Past week buprenorphine	36 (8%)	209 (32%)	0.25 (0.18, 0.35)
2.4 Adverse events and adverse drug reactions				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Number of adverse events	91-199: 5 (2-9.5) ≥200: 6 (3-11)	21-90: 4 (1-7) 1-20: 2 (0-6)	Not possible
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	ICD-10 lifetime pharmaceutical opioid dependence	49 (12%)	28 (4%)	2.72 (1.7, 4.25)
	ICD-10 12-month pharmaceutical opioid dependence	26 (6%)	13 (2%)	3.11 (1.61, 5.98)
2.5 Duration of opioid use				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Years prescribed opioids	91-199: 6 (2-13) ≥200: 7.8 (3-15)	21-90: 3 (1.1-8) 1-20: 2.5 (0.6-5)	Not possible
2.6 Opioid treatment problems and risks				
		High-dose	**Low-dose**	**Mean difference**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Risk for prescription opioid misuse from the Pain Medication	26.6 (6.4)	25.3 (9.2)	1.3

	Questionnaire			
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	Prescribed opioid difficulty scale (PODS) intermediate- high (≥8)	297 (70%)	367 (56%)	1.26 (1.15, 1.38)
2.7 Treatment-related behaviours				
		High-dose	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	
Campbell, 2015	Past 3-month tampering	38 (9%)	29 (4%)	2.03 (1.27, 3.25)
	Past 3-month doctor shopping	6 (1%)	5 (1%)	1.86 (0.57, 6.07)
	Past 3-month different drug route	7 (2%)	1 (0.2%)	10.87 (1.34, 88.04)
	Used other person's opioid medication past 3-months	12 (3%)	12 (2%)	1.55 (0.70, 3.42)
2.8 Number of opioid drugs				
		High-dose	**Low-dose**	**Statistical analysis**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Number of opioid drugs	91-199: 1 (1-1) ≥200: 1 (1-2)	21-90: 1 (1-1) 1-20: 1 (1-1)	Not possible

Clinical Characteristics

3. Substance use

3.1 Illicit drug use				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Count (%)	**Count (%)**	

Campbell, 2015	Illicit drug use past 12 months	71 (17%)	67 (10%)	11.03 (5.75, 21.14)
3.2 Non-illicit substance use				
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Days of alcohol use in past 30 days	0.6 (1.3)	2.1 (5.1)	-1.5
3.3 Substance use problems/disorders				
		Count (%)	**Count (%)**	**RR (95% CI)**
Chang, 2018b	Opioid disorders	530 (19%)	1,243 (1%)	28.95 (26.34, 31.82)
Campbell, 2015	Lifetime overdose on any substance	79 (19%)	103 (16%)	1.19 (0.91, 1.55)
Kobus, 2012	Substance use disorder	141 (31%)	1,151 (24%)	1.30 (1.13, 1.51)
		Mean (days)	Mean (days)	
Chang, 2018b	Magnitude of high-risk use in 2012	115.7	-	-
3.4 Potential substance use problems				
		Count (%)	**Count (%)**	**RR (95% CI)**
Campbell, 2015	Past 12 months risky drinking (>5 standard drinks)	96 (23%)	165 (25%)	0.90 (0.73, 1.13)

4. Physical health and patient behaviours

4.1 Morbidity measures						
Study ID	**Variable**	**High-dose**		**Low-dose**		**Mean difference**
		Mean score	**SD**	**Mean score**	**SD**	
Chang, 2018a	Chronic disease score	27.3	21.8	13.3	13.9	14
Chang, 2018b	Aggregated	8.4	4.3	-	-	-

	diagnostic cluster morbidity group (ADG) 2012					
	Aggregated diagnostic cluster morbidity group (ADG) 2013	8.3	4.5	-	-	-
	Rx-defined morbidity groups (Rx-MGs) 2012	8.9	4.5	-	-	-
	Rx-defined morbidity groups (Rx-MGs) 2013	8.8	10.0	-	-	-
	Count of chronic conditions 2012	4.0	3.1	-	-	-
	Count of chronic conditions 2013	4.0	3.3	-	-	-
	Active ingredients 2012	13.1	8.2	-	-	-
	Active ingredients 2013	12.8	8.3	-	-	-
	Concurrent risk score 2012	4.7	6.8	-	-	-
	Concurrent risk score 2013	4.8	47.4	-	-	-

		Median	IQR	Median	IQR	Mean difference
Kobus, 2012	Comorbidity (RxRisk) score	895.9	653–2,115	895.9	653–1,432	0
4.2 Smoking						
Study ID		**High-dose**		**Low-dose**		**RR (95% CI)**
		Count (%)		**Count (%)**		
Morasco, 2019		30.7% of the sample endorsed smoking cigarettes				Not possible
Kobus, 2012		256 (57%)		2,489 (52%)		1.09 (1.00, 1.19)
4.3 Body Mass Index (BMI)						
Kobus, 2012	BMI ≥ 30	235 (52%)		2,388 (50%)		1.05 (0.95, 1.15
4.4 Physical health score						
		High-dose		**Low-dose**		**Statistical analysis**
		Median (IQR)		**Median (IQR)**		
Campbell, 2015	SF-12	91-199: 25.9 ≥200: 25.8		21-90: 26.6 1-20: 28.1		Not possible

5. Pain measures

5.1 Duration of pain				
Study ID	**Variable**	**High-dose**	**Low-dose**	**RR (95% CI)**
		Median (IQR)	**Median (IQR)**	
Campbell, 2015	Years living with pain	91-199: 11 (5-22) ≥200: 15 (5-12)	21-90: 10 (2-21) 1-20: 11 (3-23)	Not possible
	12 month chronic pain conditions	91-199: 2 (2-3) ≥200: 2 (2-3)	21-90: 2 (1-3) 1-20: 2 (1-3)	Not possible
5.2 Pain measures				
		High-dose	**Low-dose**	**Linear**

		Slope of function, k	Slope of function, k	regression model
Morasco, 2019	Delay discounting	-5.8 (2.3)	-4.8 (2.0)	DD was significantly associated with dose (p-value: 0.003)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Pain severity from the Multi-dimensional Pain Inventory	4.5 (1.0)	4.1 (0.9)	0.40
	Pain interference from the Multi-dimensional Pain Inventory	4.7 (1.0)	4.6 (1.0)	0.10
		Mean (SD)	**Mean (SD)**	**RR (95% CI)**
Campbell, 2015	Pain severity from the Brief Pain Inventory	91-199: 5.4 (1.6) ≥200: 5.4 (1.8)	21-90: 4.8 (1.8) 1-20: 4.4 (1.8)	1.21 (1.11, 1.31) 1.21 (1.1, 1.35)
	Pain interference score from the Brief Pain Inventory	91-199: 6.1 (2.1) ≥200: 6.2 (2)	21-90: 5.3 (2.3) 1-20: 4.7 (2.3)	1.18 (1.09, 1.26) 1.23 (1.13, 1.34)
	Pain self-efficacy (PSEQ)	91-199: 27.4 (12.7) ≥200: 24.7 (12.5)	21-90: 31.8 (12.) 1-20: 35.8 (13.8)	0.97 (0.96, 0.99) 0.96 (0.94, 0.97)
5.3 Type of pain conditions				
		High-dose	**Low-dose**	**RR (95% CI)**
		Count, %	**Count, %**	
Campbell, 2015	Arthritis or rheumatism	256 (60%)	424 (64%)	0.94 (0.85, 1.03)

	Back or neck problems	344 (81%)	484 (73%)	1.10 (1.03, 1.18)
	Frequent/severe headaches	134 (32%)	170 (26%)	1.22 (1.01, 1.48)
	Visceral pain	96 (23%)	141 (21%)	1.06 (0.84, 1.33)

6. Healthcare utilisation

6.1 Clinic visits				
Study ID	**Variable**	**High-dose**	**Low-dose**	**Median difference**
		Median	**Median**	
Kobus, 2012	Clinic visits of any type 6 months before/after index date	22	17	5
		Count (%)	**Count (%)**	**RR (95% CI)**
Kobus, 2012	Any pain clinic visit 6 months before/after index date	104 (23%)	530 (11%)	2.09 (1.73, 2.51)
6.2 Secondary & tertiary care use				
		High-dose	**Low-dose**	**RR (95%)**
		Count (%)	**Count (%)**	
Chang, 2018b	>1 emergency visit in 2012	829 (30%)	51,534 (27%)	1.09 (1.03, 1.16)
	>1 emergency visit in 2013	765 (28%)	34,338 (18%)	1.51 (1.42, 1.61)
Kobus, 2012	ER visit 6 months before/ after index visit	277 (50%)	1,878 (39%)	1.57 (1.45, 1.70)

Chang, 2018b	>1 hospitalisation in 2012	443 (16%)	17,061 (9%)	1.76 (1.62, 1.92)
	>1 hospitalisation in 2013	396 (14%)	11,110 (6%)	2.42 (2.21, 2.66)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Kobus, 2012	Hospitalisation 6 months before/ after index date	1.9 (1.3)	1.5 (1.1)	0.4
		Count (%)	**Count (%)**	**RR (95%)**
	ED visit with back pain diagnosis	131 (29%)	1,348 (28%)	1.03 (0.89, 1.20)
	Filled opioid prescription 5 days after ED visit	285 (63%)	2,696 (56%)	1.12 (1.04, 1.21)
6.3 Multiple prescribers				
Chang, 2018a	Obtain opioids from ≥ 4 unique prescribers & pharmacies over a 90 day period	1,176 (0.78%)	1,948 (0.05%)	15.6 (14.51, 16.76)
		Median	**Median**	**Median difference**
Kobus, 2012	Median opioid prescribers	4	3	1 (p=<0.001)
6.4 Healthcare costs				
		$ (USD)	**$ (USD)**	
Chang, 2018b	Total concurrent cost (2012)	30,486	-	-
	Total prospective cost (2013)	31,045	-	-

	Medical cost 2012	19,275	-	-
	Medical cost 2013	19,663	-	-
	Pharmacy cost 2012	11,211	-	-
	Pharmacy cost 2013	11,382	-	-
	Opioid medication cost 2012	6,169	-	-
	Opioid medication cost 2012	6,079	-	-

7. Mental health

7.1 Depression				
Study ID	**Variable & measure/metric**	**High-dose**	**Low-dose**	**RR (95%)**
		Count (%)	**Count (%)**	
Campbell, 2015	Moderate-severe depression [score of 10 on the PHQ-9]	221 (52%)	256 (39%)	1.34 (1.17, 1.53)
Kobus, 2012	ICD-9 diagnostic codes for depression: 296.2, 296.3, 300.4, 309.0, 309.1, 311	190 (42%)	1,425 (30%)	1.42 (1.26, 1.59)
		Mean (SD)	**Mean (SD)**	**Mean difference**
Morasco, 2019	Severity of depressive symptoms using the Beck	21.5 (12.1)	20.0 (13.7)	1.5

	Depression Inventory-2			
7.2 Anxiety				
		High-dose	**Low-dose**	**Mean difference**
		Mean (SD)	**Mean (SD)**	
Morasco, 2019	Severity of anxiety symptoms using the Generalized Anxiety Disorder-7	9.9 (5.6)	9.9 (6.0)	0
		Count (%)	**Count (%)**	**RR (95%)**
Campbell, 2015	Moderate-severe anxiety	98 (23%)	137 (21%)	1.14 (0.85, 1.53)
Kobus, 2012	ICD-9 diagnostic codes for anxiety: 300.0 – 300.09	89 (20%)	510 (11%)	2.06 (1.61, 2.65)
7.3 Post-traumatic stress disorder (PTSD)				
		High-dose	**Low-dose**	
		Count (%)	**Count (%)**	**RR (95%)**
Kobus, 2012	Posttraumatic stress disorder diagnostic code 309.81	20 (4%)	96 (2%)	2.21 (1.38, 3.55)
7.4 Any of depression, anxiety, PTSD or substance use				
Kobus, 2012	Report of depression, anxiety, PTSD and/or substance use disorder	280 (62%)	2,263 (47%)	1.32 (1.22, 1.42)

8. Patient beliefs

8.1 Relief from current medicines			
Study ID	**High-dose**	**Low-dose**	**Statistical analysis**
	Median (IQR)	**Median (IQR)**	
Campbell, 2015	91-199: 6 (5-8) ≥200: 6 (5-8)	21-90: 7 (5-8) 1-20: 7 (5-8)	Not possible

9. Prescriber behaviours

9.1 High-risk prescribers						
Study ID	**Variable**	**High-dose**		**Low-dose**		**RR (95% CI)**
		Mean %	**SD**	**Mean %**	**SD**	
Chang, 2018a	Proportion of prescriptions from high-risk prescribers	122,159 (81%)	31.8	973,865 (25%)	39.4	3.24 (3.23, 3.25)
Percentile group		**Count (%)**		**Count (%)**		**RR (95% CI)**
Chang, 2018a	100% (all opioid prescriptions from high-risk prescribers)	77,217 (51%)		572,633 (15%)		3.48 (3.46, 3.50)
	50-99% of prescriptions from high-risk prescribers	51,277 (34%)		471,351 (12%)		2.81 (2.79, 2.83)
	1-49% of prescriptions from high-risk prescribers	8,747 (6%)		222,041 (6%)		0.10 (0.10, 0.10)
	0% (no prescriptions from high-risk prescribers)	13,573 (9%)		2,629,436 (68%)		0.13 (0.13, 0.15)
9.2 High-volume prescribers						
Study ID	**Variable**	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**
Chang, 2018a	Daily opioid dose per transaction	120	70.8	48	42.7	72
	Days supplied per	27	6.8	25	8.3	2

	transaction					
	Opioid volume per person	56	36.4	3	7.0	53
	Opioid prescription per person	18	11.0	2	5.0	16
		Count (%)		**Count (%)**		**RR (95% CI)**
Chang, 2018a	Proportion of total opioid volume	50,975 (34%)		1,488,066 (38%)		0.88 (0.88, 0.89)
	Proportion of total opioid prescriptions	16,590 (11%)		1,406,261 (36%)		0.31 (0.30, 0.31)
9.3 Low-volume prescribers						
		High-dose		**Low-dose**		**Mean difference**
		Mean	**SD**	**Mean**	**SD**	
Chang, 2018a	Daily opioid dose per transaction	102	70.2	35	27.9	67
	Days supplied per transaction	23	10.2	15	11.2	8
	Opioid volume per person	10	21.4	1	3.6	9
	Opioid prescription per person	4	7.5	3	4.0	1
		Count (%)		**Count (%)**		**RR (95% CI)**
Chang, 2018a	Proportion of total opioid volume	8,747 (6%)		864,792 (22%)		0.26 (0.26, 0.27)
	Proportion of total opioid prescriptions	3,620 (2%)		1,967,208 (51%)		0.05 (0.05, 0.05)

16 Chapter 8 Appendix

Appendix 8.1: PFD case reports involving an opioid, ordered by date of report

ref ID	Date of report	URL
2013-0248	3-Oct-13	https://www.judiciary.uk/publications/kubilay-2013-0248/
2013-0239A	14-Oct-13	https://www.judiciary.uk/publications/shokri-gharab-2013-0239/
2013-0289	1-Nov-13	https://www.judiciary.uk/publications/manning-2013-0289/
2013-0307	11-Dec-13	https://www.judiciary.uk/publications/damion-stanley-joseph-henson/
2014-0011	10-Jan-14	https://www.judiciary.uk/publications/pauline-meredith/
2014-0028	21-Jan-14	https://www.judiciary.uk/publications/kyle-ashley-smith/
2014-0039	27-Jan-14	https://www.judiciary.uk/publications/judith-marshall/
2014-0110	11-Mar-14	https://www.judiciary.uk/publications/teresa-lonergan/
2014-0115	14-Mar-14	https://www.judiciary.uk/publications/michael-tarratt/
2014-0139	28-Mar-14	https://www.judiciary.uk/publications/sebastian-davies/
2014-0141	31-Mar-14	https://www.judiciary.uk/publications/deanne-smith/
2014-0177	16-Apr-14	https://www.judiciary.uk/publications/kathryn-sawyer/
2014-0247	19-May-14	https://www.judiciary.uk/publications/denise-parramore/
2014-0266	11-Jun-14	https://www.judiciary.uk/publications/bridget-cahill/
2014-0267	11-Jun-14	https://www.judiciary.uk/publications/june-rose/
2014-0272	17-Jun-14	https://www.judiciary.uk/publications/sol-hadhasseh/
2014-0332A	8-Jul-14	https://www.judiciary.uk/publications/anthony-ponting/
2014-0319	9-Jul-14	https://www.judiciary.uk/publications/andrew-hooper/
2014-0333	18-Jul-14	https://www.judiciary.uk/publications/kathleen-cornthwaite/
2014-0335	22-Jul-14	https://www.judiciary.uk/publications/edward-devlin/
2014-0369	31-Jul-14	https://www.judiciary.uk/publications/toni-skillington/
2014-0359	5-Aug-14	https://www.judiciary.uk/publications/clare-bain/
2014-0378	14-Aug-14	https://www.judiciary.uk/publications/thomas-warren/
2014-0383	22-Aug-14	https://www.judiciary.uk/publications/tessa-summers/
2014-0396	8-Sep-14	https://www.judiciary.uk/publications/anthony-offord/
2014-0404	12-Sep-14	https://www.judiciary.uk/publications/clive-turner/
2014-0456	20-Oct-14	https://www.judiciary.uk/publications/samuel-duckworth/
2014-0495	11-Nov-14	https://www.judiciary.uk/publications/amar-majid/
2014-0517	26-Nov-14	https://www.judiciary.uk/publications/anthony-huggan/
2014-0518	27-Nov-14	https://www.judiciary.uk/publications/david-greenfield/
2014-0538	17-Dec-14	https://www.judiciary.uk/publications/darren-hayes/
2015-0069	19-Feb-15	https://www.judiciary.uk/publications/george-ball/
2015-0068	20-Feb-15	https://www.judiciary.uk/publications/richard-jones/
2015-0088	9-Mar-15	https://www.judiciary.uk/publications/leonardus-vries/

2015-0089	9-Mar-15	https://www.judiciary.uk/publications/darren-linfoot/
2015-0127	30-Mar-15	https://www.judiciary.uk/publications/jason-houghton/
2015-0138	15-Apr-15	https://www.judiciary.uk/publications/nicholas-rowley/
2015-0147	20-Apr-15	https://www.judiciary.uk/publications/andrew-farrow/
2015-0156	22-Apr-15	https://www.judiciary.uk/publications/laurence-boyens/
2015-0192	8-May-15	https://www.judiciary.uk/publications/thaker-hafid/
2015-0184	11-May-15	https://www.judiciary.uk/publications/keith-gallimore/
2015-0229	15-Jun-15	https://www.judiciary.uk/publications/isaac-bahar/
2015-0231	17-Jun-15	https://www.judiciary.uk/publications/andre-mickley/
Tommy Faisali	6-Jul-15	https://www.judiciary.uk/publications/tommy-faisali/
2015-0260	7-Jul-15	https://www.judiciary.uk/publications/michael-thorley/
2015-0282	16-Jul-15	https://www.judiciary.uk/publications/john-lloyd/
2015-0298	24-Jul-15	https://www.judiciary.uk/publications/carl-smith/
2015-0382	18-Sep-15	https://www.judiciary.uk/publications/liam-smith/
2015-0394	29-Sep-15	https://www.judiciary.uk/publications/lee-boden/
2015-0410	22-Oct-15	https://www.judiciary.uk/publications/glenda-day/
2015-0432	12-Nov-15	https://www.judiciary.uk/publications/guy-robinson/
2015-0463	16-Nov-15	https://www.judiciary.uk/publications/nadine-brookes-walker/
2015-0486	25-Nov-15	https://www.judiciary.uk/publications/dean-boland/
2015-0117	22-Dec-15	https://www.judiciary.uk/publications/shalini-ganesh-ram/
2016-0014	19-Jan-16	https://www.judiciary.uk/publications/irene-pearson/
2016-0042	21-Jan-16	https://www.judiciary.uk/publications/elvis-snelson/
2016-0058	16-Feb-16	https://www.judiciary.uk/publications/philip-denning/
2016-0075	26-Feb-16	https://www.judiciary.uk/publications/devindar-seth/
2016-0131	9-Mar-16	https://www.judiciary.uk/publications/william-higgleton/
2016-0123	10-Mar-16	https://www.judiciary.uk/publications/christine-stevenson/
2016-0239	29-Jun-16	https://www.judiciary.uk/publications/lee-davies/
2016-0353	1-Jul-16	https://www.judiciary.uk/publications/daniel-paylor/
2016-0249	14-Jul-16	https://www.judiciary.uk/publications/fred-whittaker/
2016-0260	19-Jul-16	https://www.judiciary.uk/publications/patricia-mercieca/
2016 – 0270	25-Jul-16	https://www.judiciary.uk/publications/patricia-cleghorn/
2016-0330	15-Sep-16	https://www.judiciary.uk/publications/richard-breatnach/
2016-0371	20-Oct-16	https://www.judiciary.uk/publications/sian-jones/
2016-0412	8-Nov-16	https://www.judiciary.uk/publications/michelle-lawrence/
2016-0401	8-Dec-16	https://www.judiciary.uk/publications/rachal-murphy/
2016-0453	16-Dec-16	https://www.judiciary.uk/publications/mark-lilliott/
2017-0002	13-Jan-17	https://www.judiciary.uk/publications/sarah-tyler/
2017-0031	8-Feb-17	https://www.judiciary.uk/publications/david-read/
2017-0049	21-Feb-17	https://www.judiciary.uk/publications/jack-portland/
2017-0048	23-Feb-17	https://www.judiciary.uk/publications/grant-burns/
2017-0072	20-Mar-17	https://www.judiciary.uk/publications/james-spencer/

2017-0101	27-Mar-17	https://www.judiciary.uk/publications/steven-fone/
2017-0096	29-Mar-17	https://www.judiciary.uk/publications/lyndsey-holt/
2017-0105	4-Apr-17	https://www.judiciary.uk/publications/kymberley-holden/
2017-0117	6-Apr-17	https://www.judiciary.uk/publications/steven-amos/
2017-0121	13-Apr-17	https://www.judiciary.uk/publications/luke-moulding/
2017-0129	20-Apr-17	https://www.judiciary.uk/publications/sian-hollands/
2017-0197	13-Jun-17	https://www.judiciary.uk/publications/craig-hamilton/
2017-0195	16-Jun-17	https://www.judiciary.uk/publications/aaron-mccaffrey/
2017-0232	11-Jul-17	https://www.judiciary.uk/publications/mark-berry/
2017-0318	27-Jul-17	https://www.judiciary.uk/publications/maureen-colclough/
2017-0324	1-Aug-17	https://www.judiciary.uk/publications/hayley-sheehan/
2017-0244	24-Aug-17	https://www.judiciary.uk/publications/jonathan-meaney/
2017-0210	8-Sep-17	https://www.judiciary.uk/publications/anne-marie-james/; https://www.judiciary.uk/publications/melvin-james/
2017-0221	12-Sep-17	https://www.judiciary.uk/publications/frances-greenhalgh/
2017-0283	5-Oct-17	https://www.judiciary.uk/publications/christopher-roberts/
2017-0295	13-Oct-17	https://www.judiciary.uk/publications/christina-fletcher/
2017-0306	19-Oct-17	https://www.judiciary.uk/publications/ronald-brewer/
2017-0308	24-Oct-17	https://www.judiciary.uk/publications/david-jackson/
2017-0307	27-Oct-17	https://www.judiciary.uk/publications/stephen-coulson/
2017-0391	13-Nov-17	https://www.judiciary.uk/publications/john-scallan/
2017-0403	17-Nov-17	https://www.judiciary.uk/publications/paul-mullen/
2017-0424	27-Nov-17	https://www.judiciary.uk/publications/shaun-berryman/
2017-0349	30-Nov-17	https://www.judiciary.uk/publications/penelope-benton/
2017-0358	8-Dec-17	https://www.judiciary.uk/publications/stuart-walls/
2017-0373	18-Dec-17	https://www.judiciary.uk/publications/pamela-hands/
2018-0005	5-Jan-18	https://www.judiciary.uk/publications/marcus-hamilton/
2018-0012	10-Jan-18	https://www.judiciary.uk/publications/john-omeara/
2018-0042	13-Feb-18	https://www.judiciary.uk/publications/angela-byrne/
2018-0047	15-Feb-18	https://www.judiciary.uk/publications/timothy-shaw/
2018-0056	22-Feb-18	https://www.judiciary.uk/publications/james-quinton/
2018-0067	6-Mar-18	https://www.judiciary.uk/publications/rastislav-petrisko/
2018-0076	14-Mar-18	https://www.judiciary.uk/publications/thomas-curtin/
2018-0093	29-Mar-18	https://www.judiciary.uk/publications/ross-reeves/
2018-0109	19-Apr-18	https://www.judiciary.uk/publications/amanda-spark/
2018-0133	28-Apr-18	https://www.judiciary.uk/publications/sara-moran/
2018-0135	8-May-18	https://www.judiciary.uk/publications/jonathan-earp/
2018-0165	21-May-18	https://www.judiciary.uk/publications/michalla-sweeting/
2018-0173	7-Jun-18	https://www.judiciary.uk/publications/marcus-hance/
2018-0178	13-Jun-18	https://www.judiciary.uk/publications/keiron-bould/
2018-0181	15-Jun-18	https://www.judiciary.uk/publications/darren-carrington/

2018-0203	18-Jun-18	https://www.judiciary.uk/publications/colin-johns/
2018-0188	22-Jun-18	https://www.judiciary.uk/publications/david-travers/
2018-0194	25-Jun-18	https://www.judiciary.uk/publications/andrew-craig/
2018-0247	20-Jul-18	https://www.judiciary.uk/publications/kathleen-bamforth/
2018-0269	8-Aug-18	https://www.judiciary.uk/publications/donald-clegg/
2018-0272	8-Aug-18	https://www.judiciary.uk/publications/ian-wolstenholme/
2018-0256	24-Aug-18	https://www.judiciary.uk/publications/karl-willis/
2018-0287	7-Sep-18	https://www.judiciary.uk/publications/scott-carton/
2018-0416	4-Oct-18	https://www.judiciary.uk/publications/stephen-jackson/
2018-0318	23-Oct-18	https://www.judiciary.uk/publications/nicola-lawrence/
2018-0315	24-Oct-18	https://www.judiciary.uk/publications/jennifer-lacey/
2018-0309	29-Oct-18	https://www.judiciary.uk/publications/thomas-mcauley/
2018-0310	29-Oct-18	https://www.judiciary.uk/publications/karl-brunner/
2018-0354	16-Nov-18	https://www.judiciary.uk/publications/dawn-gill/
2018-0336	22-Nov-18	https://www.judiciary.uk/publications/karen-moran/
2018-0365	22-Nov-18	https://www.judiciary.uk/publications/matthew-craven/
2018-0402	21-Dec-18	https://www.judiciary.uk/publications/cady-stewart/
2018-0409	31-Dec-18	https://www.judiciary.uk/publications/janice-davies/
2019-0012	11-Jan-19	https://www.judiciary.uk/publications/ricardo-holgate/
2019-0016	11-Jan-19	https://www.judiciary.uk/publications/jacqueline-elliott/
2019-0487	24-Jan-19	https://www.judiciary.uk/publications/arun-viswambaran/
2019-0077	1-Feb-19	https://www.judiciary.uk/publications/stephen-harte/
2019-0045	11-Feb-19	https://www.judiciary.uk/publications/paul-gillam/
2019-0050	14-Feb-19	https://www.judiciary.uk/publications/matthew-hamilton/
2019-0070	27-Feb-19	https://www.judiciary.uk/publications/theresa-feehan/
2019-0474	27-Feb-19	https://www.judiciary.uk/publications/janie-mcfadyen/
2019-0092	19-Mar-19	https://www.judiciary.uk/publications/graham-tailby/
2019-0125	17-Apr-19	https://www.judiciary.uk/publications/nathan-cooke/
2019-0223	28-Jun-19	https://www.judiciary.uk/publications/heather-birchall/
2019-0228	1-Jul-19	https://www.judiciary.uk/publications/andrew-mccall/
2019-0232	5-Jul-19	https://www.judiciary.uk/publications/alexander-boamah/
2019-0233	9-Jul-19	https://www.judiciary.uk/publications/leroy-medford/
2019-0291	9-Jul-19	https://www.judiciary.uk/publications/allan-davies/
2019-0241	17-Jul-19	https://www.judiciary.uk/publications/allan-joslin/
2019-0259	29-Jul-19	https://www.judiciary.uk/publications/alex-blake/
2019-0280	1-Aug-19	https://www.judiciary.uk/publications/deborah-chapman/
2019-0269	16-Aug-19	https://www.judiciary.uk/publications/george-rimmer/
2019-0263	22-Aug-19	https://www.judiciary.uk/publications/christopher-summerhayes/
2019-0302	28-Aug-19	https://www.judiciary.uk/publications/amir-siman-tov/
2019-0355	4-Sep-19	https://www.judiciary.uk/publications/imran-mahmood/

2019-0301	18-Sep-19	https://www.judiciary.uk/publications/graham-saffery/
2019-0462	21-Sep-19	https://www.judiciary.uk/publications/ricky-barcock/
2019-0328	1-Oct-19	https://www.judiciary.uk/publications/oliver-sharp/
2019-0331	2-Oct-19	https://www.judiciary.uk/publications/richard-ridout/
2019-0489	4-Oct-19	https://www.judiciary.uk/publications/michael-lobban/
2019-0337	10-Oct-19	https://www.judiciary.uk/publications/abdeslam-benelghazi/
2019-0340	10-Oct-19	https://www.judiciary.uk/publications/ian-bean/
2019-0481	17-Oct-19	https://www.judiciary.uk/publications/elisa-fuller/
2019-0351	21-Oct-19	https://www.judiciary.uk/publications/harold-uzomechina/
2019-0348	23-Oct-19	https://www.judiciary.uk/publications/kenneth-daly/
2019-0380	5-Nov-19	https://www.judiciary.uk/publications/neville-mcnair/
2019-0369	14-Nov-19	https://www.judiciary.uk/publications/joanna-flynn/
2019-0387	18-Nov-19	https://www.judiciary.uk/publications/deborah-headspeath/
2019-0395	20-Nov-19	https://www.judiciary.uk/publications/gary-leyland/
2019-0417	5-Dec-19	https://www.judiciary.uk/publications/gemma-macdonald/
2019-0420	6-Dec-19	https://www.judiciary.uk/publications/maureen-wharton/
2019-0421	10-Dec-19	https://www.judiciary.uk/publications/brenda-drew/
2019-0424	13-Dec-19	https://www.judiciary.uk/publications/catherine-mcnamara/
2019-0432	16-Dec-19	https://www.judiciary.uk/publications/clive-miles/
2019-0444	19-Dec-19	https://www.judiciary.uk/publications/doris-clark/
2019-0448	20-Dec-19	https://www.judiciary.uk/publications/matthews-rogers/

Appendix 8.2: Response to my FOI to Her Majesty's Courts and Tribunals Service

Disclosure Team
Ministry of Justice
102 Petty France
London
SW1H 9AJ
data.access@justice.gov.uk
18th September 2020

Georgia Richards
request-687917-39f68bd8@whatdotheyknow.com

Dear Ms Richards

Freedom of Information Act (FOIA) Request – 200827011

Thank you for your request dated 27th August 2020 in which you asked for the following information from the Ministry of Justice (MoJ):

1. **an explanation as to why all Prevention of Future Deaths cases dated before 12/09/2017 have been recently (mid-August 2020) removed from the Courts andTribunal Judiciary website, https://www.judiciary.uk/subject/prevention-of- future-deaths/, when previously there were over 3,200 cases dated back until 01/08/2013?**
2. **that all Prevention of Future Death cases be made open and available to all members of the public on the Courts and Tribunal Judiciary website as per regulations 28 and 29 of the Coroners (Investigations) Regulations 2013.**

Your request has been handled under the FOIA. Your request has been dealt with by theJudicial Office, which is an office of the Ministry of Justice, and which provides official andlegal support to the Lord Chief Justice, the Chief Coroner and other senior judges.

Your request has been dealt with by the Judicial Office, which is an office of the Ministry ofJustice, and which provides official and legal support to the Lord Chief Justice, the Chief Coroner and other senior judges.

I can confirm that the MoJ holds the information that you have requested. The reports priorto September 2017 were removed due to a technical error and have now been restored to the site. Thank you for bringing this to our attention.

Appeal Rights

If you are not satisfied with this response you have the right to request an internal review byresponding in writing to one of the addresses below within two months of the date of this response.

data.access@justice.gov.uk

Disclosure Team, Ministry of Justice

You do have the right to ask the Information Commissioner's Office (ICO) to investigate anyaspect of your complaint. However, please note that the ICO is likely to expect internal complaints procedures to have been exhausted before beginning their investigation.

Yours sincerely

Judicial Office

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