Medicines Management Programme

Appropriate prescribing of opioids in the management of chronic non-cancer pain

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Date approved:	20/09/2022
Version:	1.1

Contents

List of tables

List of figures

List of abbreviations

ADR	Adverse drug reaction
ATC	Anatomical therapeutic chemical
BNF	British National Formulary
BPS	British Pain Society
BZRA	Benzodiazepine receptor agonist (benzodiazepine and z-drug)
CDC	Centers for Disease Control and Prevention
CDS	Community drug schemes
CI	Confidence interval
CNCP	Chronic non-cancer pain
CNS	Central nervous system
DP	Drugs Payment (scheme)
EFIC	European Pain Federation
FPM	Faculty of Pain Medicine
GMS	General Medical Services
HPRA	Health Products Regulatory Authority

HSE	Health Service Executive
IASP	International Association for the Study of Pain
LTI	Long Term Illness
MAOI	Monoamine oxidase inhibitor
MHRA	Medicines and Healthcare products Regulatory Agency
MME	Morphine milligram equivalents
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
OIH	Opioid induced hyperalgesia
OR	Odds ratio
PCRS	Primary Care Reimbursement Service
RR	Relative risk
SIGN	Scottish Intercollegiate Guidance Networks
SNRI	Serotonin noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

Acknowledgements

The HSE-Medicines Management Programme (MMP) wishes to acknowledge the National Medicines Information Centre (NMIC) for their input and contributions to this document.

Definitions

For the purpose of this document:

- the term 'opioids' can refer to either naturally occurring compounds (opiates) or synthetic compounds,
- the term ‘opioids’ and ‘opioid analgesics’ may be used interchangeably,
- the term ‘chronic pain’ refers to a continuous pain that persists beyond the expected time of healing, or for longer than three months excluding cancer-related pain and pain experienced at the end-of-life or during palliative care,
- the term ‘long-term use’ of opioids is defined as treatment with opioids for a duration of more than three months, and
- the term ‘analysis’ refers to an analysis of dispensed pharmacy claims data.

1. Executive summary

The HSE-Medicines Management Programme (MMP) aims to promote safe, effective, and cost-effective prescribing. This document reviews the use of opioids in the management of chronic non-cancer pain (CNCP), harms associated with their use, and information to be considered prior to initiation. Trends in the utilisation of strong opioids on the Community Drug Schemes (CDS) between January 2011 and December 2020 are also reviewed.

Following consideration of the above, the MMP highlights the key findings regarding trends in utilisation of strong opioids, and a number of practice points in relation to the use of opioids in the management of CNCP.

Key findings from utilisation analysis of the GMS scheme:

- Utilisation of strong opioids has been consistently higher in **females** than in males over the years 2011-2020, with 62% of claims being dispensed to females in 2020.
- In 2020, the **median age** for utilisation of strong opioids was **67 years**.
- In 2020, **tramadol** was the **most commonly dispensed** strong opioid accounting for 26.4% of strong opioids dispensed, followed by **tramadol/paracetamol combination** (22.8% of strong opioids), **oxycodone** (12.8% of strong opioids) and **buprenorphine** (11.3% of strong opioids).
- There has been a 79% increase in the number of individuals dispensed **oxycodone** from the years 2011-2020, with approximately 24,000 individuals dispensed this strong opioid in 2020.
- Since the addition of **tapentadol** to the HSE-Primary Care Reimbursement Service (PCRS) reimbursement list in 2011, there has been an annual increase in utilisation, with approximately 20,000 individuals dispensed tapentadol in 2020 (10.9% of strong opioids).
- Approximately **82%** of individuals who initiated a strong opioid in January 2020 were dispensed the opioid for a **duration of one to three months**.
- An average of **32%** of individuals who initiated a strong opioid in January 2020 (ranging from 23% - 50% of individual strong opioids) were **co-prescribed a benzodiazepine or z-drug.**
- Approximately **33%** of individuals who were initiated on **tramadol alone**, a **tramadol combination product** or **tapentadol** in January 2020 **were co-prescribed an antidepressant or antipsychotic.**

Prior to initiation of opioids for CNCP, prescribers should ensure that individuals understand the expected benefit and risk of harms, and agree treatment goals, a review strategy and a plan for discontinuation.

Prescribers should consider the following in relation to HARMS associated with opioids:

- There is a dose dependent risk of serious harms.
- There is ↑ risk and severity of ADRs in older people and people with renal impairment.
- There is ↑ incidence of endocrine abnormalities, altered immune function, opioid induced hyperalgesia, cognitive decline, falls (and fractures), dependence and addiction with long-term use.
- Dependence and addiction is a significant risk with use of greater than three months duration.
- Co-prescribing with CNS depressants (e.g. a BZRA, gabapentin and pregabalin) can produce additive CNS depressant effects including respiratory depression.
- Co-prescribing with serotonergic drugs and antipsychotics can ↑ the risk of serotonin syndrome.
- Co-prescribing tramadol/tapentadol with serotonergic drugs, antipsychotics and other medicinal products that ↓ the seizure threshold, can also ↑ the risk of convulsions.

Prescribers should consider the following in relation to INITIATION of opioids:

- Opioids should only be considered for a trial in carefully selected individuals after optimising non-pharmacological treatments and non-opioid analgesics.
- When initiating treatment, prescribe immediate-release opioids instead of extended-release/long-acting opioids.
- Prescribe the lowest effective dose.

Prescribers should consider the following in relation to CONTINUATION of opioids:

- Continued treatment should only be considered after confirming clinically meaningful improvements in pain and function without significant risks or harms.
    - A 30% improvement in pain and/or a significant improvement in functional ability is considered a realistic treatment goal.
- Clinicians should evaluate the benefits and harms with newly initiated individuals within one to four weeks of starting an opioid for CNCP.
- This review should be repeated every three months or more frequently, thereafter.

Prescribers should consider the following in relation to DISCONTINUATION of opioids:

- If the benefits do not outweigh the harms of continued treatment, clinicians should optimise therapies and work with individuals to taper opioids to ↓ doses or to taper and discontinue.

Opioids should be discontinued if the person is still in pain despite using opioids, even if no other treatment is available.

Abbreviations: ADR: adverse drug reaction; BZRA: benzodiazepine and z-drug; CNCP: chronic non-cancer pain; CNS: central nervous system

2. Purpose

The purpose of this document is to support the appropriate and safe prescribing of strong opioids in the management of chronic non-cancer pain (CNCP). It highlights the potential harms associated with the use of opioids (Section 7) and summarises international recommendations on initiation and review of opioids in the management of CNCP (Section 8).

This document also reviews the utilisation of strong opioids on the Community Drug Schemes (CDS) over a ten-year period 2011-2020, through analysis of dispensed pharmacy claims data. The CDS includes the Drugs Payment (DP), Long Term Illness (LTI) and General Medical Services (GMS) schemes (Section 10).

Following consideration of clinical recommendations and current utilisation of strong opioids on the CDS, the HSE-Medicines Management Programme (MMP) highlights a number of practice points to support safe prescribing of opioids in the management of CNCP.

This review should be used in conjunction with clinical judgement and decision making appropriate to the individual. Prescribers should refer to resources such as the Summary of Product Characteristics (SmPC) to inform prescribing decisions concerning individual patients.

3. Scope

This document focuses on the use of strong opioids in the management of CNCP. The analysis will consider only licensed medicinal products containing strong opioids, which are reimbursed in Ireland.

The following strong opioids (and combination products), as classified in accordance with the British National Formulary (BNF), are included in the analysis: buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, oxycodone and naloxone combination products, tapentadol, tramadol, and tramadol combination products.[1] Oral preparations, transdermal patches and nasal sprays are included in the analysis. It is assumed that parenteral preparations are mainly prescribed in the acute and palliative care setting, therefore as the focus of this review is CNCP, they are excluded from the analysis.

There are some limitations to this analysis; the Health Service Executive-Primary Care Reimbursement Service's (HSE-PCRS) pharmacy claims data is limited by its inability to capture prescriptions that are solely funded by the individual, and therefore are not reimbursed under any of the state-funded CDS e.g., prescriptions that fall below the co-payment threshold on the DP scheme. In addition, the indication for prescribing is not captured and hence it is not possible to distinguish between opioid prescriptions for the management of CNCP, cancer pain, palliative care or acute pain.

The recommendations in this document do not apply to the use of strong opioids in the management of cancer pain, opioid agonist treatment, palliative and end-of-life care. The Department of Health, National Clinical Guideline, *Pharmacological Management of Cancer Pain in Adults* (2015) and other relevant clinical guidance should be referred to in these cases.

4. Background

Opioids are a class of drug that act at an opioid receptor and are usually used to relieve moderate-to-severe pain particularly of visceral origin. All of the clinically important opioids act as agonists at the mu-opioid receptor.[1]

The use of opioids to treat acute pain and pain at the end-of-life is well established, however, there is a lack of robust clinical evidence to support long-term use in the treatment of CNCP.[2,3] There is increased evidence of harms associated with long-term use of opioids including respiratory depression, increased incidence of falls, endocrine abnormalities, immunomodulation, opioid induced hyperalgesia, tolerance, dependence, misuse and mortality.[1-4]

A study by Norris et al. (2021) investigated the prescribing of strong opioids to individuals in Ireland on the GMS scheme over a ten-year period (2010-2019). The study found an overall increase in strong opioid prescribing in that period, particularly among older adults (aged ≥ 65 years); strong opioid prescribing prevalence increased from 14.43% in 2010 to 16.28% in 2019.[5]

Another study, by Lynn et al. (2021) investigated trends in drug poisoning death rates involving specific drug classes, including prescription opioids in Ireland from the years 2004-2017. The study showed that drug poisoning deaths involving prescription opioids, have increased over time.[6]

5. Pain

Pain can be defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[7] Physiologically, it can be described as neuropathic, nociceptive or nociplastic, and classified as either acute or chronic in nature.[7,8] Nociceptive pain is caused by tissue or potential tissue damage, neuropathic pain is caused by nerve injury, while nociplastic pain arises from the abnormal processing of pain signals without any clear evidence of tissue damage or discrete pathology involving the somatosensory system.[8,9]

5.1 Chronic pain

Chronic pain is a common, complex sensory, emotional, cognitive and behavioural long-term health condition, which occurs when pain cannot be resolved by available medical or other treatments. People with chronic pain commonly experience depression, sleep disturbance, fatigue, and decreased overall physical and mental functioning.[10] The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists beyond normal tissue healing time.[11] National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidance Networks (SIGN) and the British Pain Society (BPS) guidance defines chronic pain as pain that persists or recurs for more than three months.[10,12,13]

Chronic pain can be defined as primary or secondary. In chronic primary pain there is no clear underlying condition that adequately accounts for the pain or its impact; chronic secondary pain is pain linked to an underlying condition.[13]

Chronic primary pain is chronic pain in one or more anatomical regions that is characterised by significant emotional distress (anxiety, anger/frustration or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles).[14] It has no clear underlying condition or the pain (or its impact) appears to be out of proportion to any observable injury or disease.[13] Examples of chronic primary pain include fibromyalgia syndrome, chronic primary headache and orofacial pain.[14]

Chronic secondary pain is chronic pain that is secondary to an underlying condition e.g. osteoarthritis, rheumatoid arthritis, ulcerative colitis, endometriosis; the underlying condition adequately accounts for the pain or its impact.[13] Chronic primary pain and chronic secondary pain can co-exist.[13] Nociceptive pain is the most common form of chronic pain, encompassing arthritis and most forms of spinal pain.[8]

A study by Raftery et al. (2011), evaluating the prevalence, impact and cost of chronic pain in Ireland, reported a prevalence rate of chronic pain of 35.5% [95% confidence interval (CI): 32.8% - 38.2%]; no difference in the prevalence of chronic pain between genders was observed.[15] A 2016 systematic review by Fayaz et al., evaluating the prevalence of chronic pain in the UK reported a pooled estimate prevalence rate of 43.5% (95% CI: 38.4% - 48.6%).[16] A similar study in Denmark, by Eriksen et al. (2003), reported that the prevalence of chronic pain increased with age, affecting 29% of those greater than 67 years of age.[17] Both the UK and Danish studies reported a higher prevalence of chronic pain in women than men.[16,17]

5.1.1 Treatment of chronic pain

Chronic pain can be difficult to treat; it is rare for any analgesic to completely relieve chronic pain.[18] Analgesia, including opioids, is only effective in treating chronic pain in a small percentage of people.[18] However, it is difficult to identify those individuals in whom opioids will be effective at the start of treatment.[2] The aim of treatment is to reduce the impact of chronic pain on quality of life, mood and function.[7] Treatment should facilitate individuals to engage in pain management strategies or programmes.[19]

The following principles for the treatment of chronic pain are outlined in the *Quality prescribing strategy for chronic pain*, published by the Scottish Government and NHS Scotland (2018):

- Chronic pain is a condition which is individual to the patient and any therapeutic management plan needs to place the patient at the centre. The approach should be based on assisting the patient to achieve goals, which have been identified in partnership with the prescriber.
- Prescribers should help patients to develop their understanding of the value of self-management and non-pharmaceutical approaches, and support people to access the tools, resources and support available to put these approaches into practice.
- Prescribers should work with patients to develop their understanding of chronic pain, how it differs from acute pain and the impact this may have on goals of therapy. Difficult and honest conversations may be required to establish an understanding with the patient, that it is highly unlikely that the therapeutic management plan will result in full resolution of their pain symptoms (> 30%), but it may assist them with coping.
- Patients should be given information on the potential benefits of their medicine as well as risks and reported side-effects. This is particularly important regarding drugs which have the potential for misuse, including gabapentinoids and opioids.
- Patients should be aware that non-pharmaceutical options, or those offered along with prescribed medicines, may result in better achievement of goals and result in less harm than medicines alone. This may include referral to physiotherapy, mental health or occupational therapy services.
- Prescribers should particularly review patients who are co-prescribed analgesics and other potentially problematic drugs such as benzodiazepines, and those with a history of substance misuse.[20]

5.1.2 WHO pain relief ladder

In 1986, the World Health Organisation (WHO) developed a three-step ‘ladder’ approach for cancer-related pain relief in adults. The underlying principle is that analgesics should be used incrementally, starting with non-opioids

(step 1), progressing through mild opioids (step 2) and finally strong opioids (step 3), dosed in accordance with the individual's reported pain intensity. The use of adjunctive medicines (e.g. antidepressants, anti-epileptics) are encouraged at each step of the ladder.

The WHO analgesic ladder is widely used to guide the basic treatment of acute and chronic pain although it was developed and validated for cancer pain treatment, it can provide an analgesic strategy for non-specialists.[12] It has been suggested that the use of the WHO analgesic ladder to treat CNCP may contribute to inappropriate prescribing, as it doesn't consider the complexity of the person's individual needs, preferences for treatments, health priorities and lifestyle.[18,21]

CNCP may be caused by a number of different pathophysiologic mechanisms that may require different approaches to treatment. Reported intensity of pain relates poorly to the degree of tissue injury and is heavily influenced by several factors including thoughts, emotions, understanding of the meaning of pain, previous experience of pain and the individual's current distress. Furthermore, CNCP may continue for many years and a substantial reduction in pain intensity is rarely an achievable goal.[2]

Practice Points

- The aim of treatment of CNCP is to reduce the impact of pain on quality of life, mood and function.
- Opioids are only effective in treating CNCP in a small percentage of people.

6. Opioids

Opioids produce their effects by activating opioid receptors, located in the central nervous system (CNS), peripheral nervous system and peripheral tissues.[3] Opioids exert their analgesic effect predominately by binding to mu-opioid receptors.[1,22] Buprenorphine, fentanyl, methadone, morphine, oxycodone, tapentadol and tramadol are categorised as strong opioids in accordance with the BNF, while codeine, dihydrocodeine and meptazinol are classified as weak opioids.[1] Tapentadol and tramadol have additional mechanisms of analgesic action.[23, 24] Tapentadol has noradrenaline reuptake inhibition properties, while the inhibition of the reuptake of noradrenaline and the enhancement of serotonin release may contribute to tramadol's analgesic effect.[24]

Morphine remains the most valuable opioid analgesic for severe pain and is the standard against which other opioid analgesics are compared.[1] Reported equi-analgesic dose ratios vary widely among opioids and caution is advised when comparing doses and when switching between opioids (weak or strong), as there is limited evidence for the accuracy of dose equivalence tables. There is also significant individual variations in the metabolism of opioids which needs to be considered.[12]

The Faculty of Pain Medicine (FPM) of the Royal College of Anaesthetists in the UK has published the following approximate equi-analgesic potencies of oral opioids (Table 1).[2]

Table 1: Approximate equi-analgesic potencies of oral opioids[2]

Opioid	Potency (relative to morphine)	Equivalent dose to 10 mg oral morphine
Morphine	1	10 mg
Hydromorphone	5	2 mg
Oxycodone	1.5	6.6 mg
Tapentadol	0.4	25 mg
Tramadol	0.1	100 mg

7. Harms associated with opioids

7.1 Adverse drug reactions

The common (incidence of ≥ 1 in 100 to < 1 in 10) or very common (incidence of ≥ 1 in 10) adverse drug reactions (ADRs) reported for all opioids include arrhythmias, confusion, constipation, dizziness, drowsiness, dry mouth, euphoric mood, flushing, hallucination, headache, hyperhidrosis, hypotension (with high doses), miosis, nausea (more common on initiation), palpitations, respiratory depression (with high doses), skin reactions, urinary retention, vertigo, visual impairment, vomiting (more common on initiation) and withdrawal syndrome.[25] A full list of ADRs for each opioid can be found in the individual medicinal product SmPC. These are available at www.hpra.ie.[23,24,26-36]

There is a dose dependent risk of serious harms associated with opioid use.[37]

7.2 Long-term adverse effects

Long-term adverse effects are also associated with the use of opioids; these are mainly associated with the endocrine, immune and central nervous systems. There is an increased incidence of endocrine abnormalities, altered immune function, opioid induced hyperalgesia, cognitive decline, falls (and fractures), dependence and addiction.[2]

7.2.1 Endocrine abnormalities

Long-term use of opioids is associated with endocrine abnormalities, which can lead to amenorrhoea, erectile dysfunction, and infertility.[2]

7.2.2 Immunosuppression

Animal and human studies have demonstrated that opioids have an immunomodulating effect. These effects are mediated via opioid receptors both on immune effector cells and in the CNS. Individual opioids may differ in their propensity to cause immunosuppression.[2]

7.2.3 Opioid induced hyperalgesia

Prolonged use of opioids can lead to hyperalgesia, referred to as opioid induced hyperalgesia (OIH).[2] This can lead to inappropriate increases in opioid doses, which can further exacerbate rather than improve pain.[38] Hyperalgesia may be diagnosed if the individual on long-term opioids presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or breakthrough pain, as a result of tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain.[2] Management of OIH requires a dose reduction or changing to an alternative opioid preparation.[2]

7.2.4 Tolerance, dependence and addiction

Opioid tolerance can also develop with long-term use of opioids. Tolerance leads to a decrease in opioid potency with repeated administration; this requires an increase in dose to maintain equipotent analgesic effects.[22,39]

Opioid dependence is characterised by both tolerance and withdrawal symptoms.[40]

Dependence is different from addiction. Addiction also features tolerance and withdrawal but is accompanied by additional characteristics of cravings, lack of control, overuse and continued use despite harm. Addiction is also associated with problematic behaviours including unsanctioned dose escalations and seeking early prescriptions or prescriptions from multiple prescribers.[40]

Long-term use of opioids is associated with an increased risk of dependence and addiction, even at therapeutic doses. Dependence and addiction is a significant risk for opioid use of greater than three months duration.[4]

About 25% to 30% of people with chronic pain, who are treated with opioids, will demonstrate a medicine abuse behaviour.[41] There is an increased risk in individuals with current or history of substance use disorder or mental health disorder.[25]

7.2.5 Falls and fractures

There is an increased risk of bone fractures in individuals taking long-term opioids.[42] In a systematic review of observational studies, opioid use was associated with a significantly increased risk of fracture; the relative risk (RR) was 1.38 (95% CI: 1.15 - 1.66).[43] The causes are complex and include opioid induced hypogonadism and increased risk of falls. As older people are at increased risk of developing osteoporosis and pain, the opioids used to treat pain in this population may increase the risk of subsequent fractures.[2]

7.3 Safety concerns in older people

The risk and severity of ADRs is increased when opioids are used in older people as age-related changes in pharmacokinetics such as declines in hepatic and renal function, and pharmacodynamics make older people more susceptible to the adverse effects. Opioids increase the risk and incidence of falls and recent opioid use is associated with an increased risk of falls in older adults and an increased likelihood of death in those with fall-related injuries.[2,44]

7.4 Safety concerns in renal impairment

In individuals with renal impairment the elimination of opioids might be delayed and the risk and severity of ADRs is increased. Most manufacturers of opioids recommend a more conservative approach to dose initiation in individuals with renal impairment, according to the individual's requirements.[28,29,31-36] Guidance on the prescribing of each opioid in renal impairment can be found in the individual medicinal product SmPC.

7.5 Drug interactions

The manufacturers of medicinal products containing opioids warn against their concomitant use with other CNS depressants [e.g. benzodiazepines and z-drugs (BZRAs), other opioids, gabapentinoids, antipsychotics and muscle relaxants], as concomitant use can increase the risk of sedation, respiratory depression, coma and death because of the additive CNS depressant effect.[24,26-36]

The manufacturers of medicinal products containing opioids also warn that their concomitant use with serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) or a monoamine oxidase inhibitors (MAOIs), may increase the risk of serotonin syndrome, a potentially life-threatening condition.[24,26-36]

The manufacturers of medicinal products containing tapentadol or tramadol warn that the concomitant use of these opioids with SSRIs, SNRIs, tricyclic antidepressants, antipsychotics and other medicinal products that lower the seizure threshold can induce or increase the potential for convulsions.[24,32,33,35]

A Canadian study in 2020, with the objective to estimate the effect of concurrent use of opioids and BZRAs on the risk of hospitalisations and deaths among individuals who utilise opioids (n=1,056,773), showed that concurrent BZRA use occurred in 17% of individuals. Overall, concurrent use was associated with a higher risk of hospitalisation [odds ratio (OR): 1.13, p< 0.001] and all cause death (OR: 1.90; p< 0.001).[45]

A full list of drug interactions for each opioid can be found in the individual SmPC. These are available at www.hpra.ie.[23, 24, 26-36]

7.6 Safety alerts

7.6.1 HPRA drug safety newsletter (September 2021)

The Health Products Regulatory Authority (HPRA) issued a drug safety newsletter in 2021 warning that pregabalin use has been associated with reports of respiratory depression. The newsletter also highlighted that concomitant use of pregabalin with opioids has been associated with reports of respiratory failure, coma and/or death.[46]

7.6.2 MHRA drug safety update (September 2020)

In September 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) issued recommendations to healthcare professionals regarding the increased risk of dependence and addiction associated with long-term use of opioids in CNCP (longer duration than three months). The drug safety update warns that prior to initiation of opioids, prescribers should discuss the risks and features of tolerance, dependence, and addiction with individuals, and agree a treatment strategy and plan for discontinuation of treatment.[4]

Recommendations issued to healthcare professionals include:

- advise patients that prolonged use of opioids may lead to drug dependence and addiction, even at therapeutic doses;
- explain the risks of tolerance and potentially fatal unintentional overdose, and counsel patients and caregivers on signs and symptoms of opioid overdose;

- provide regular monitoring and support especially to individuals at increased risk, such as those with current or past history of substance use disorder (including alcohol misuse) or mental health disorder;
- at the end of treatment, taper dosage slowly to reduce the risk of withdrawal effects associated with sudden cessation of opioids; tapering from a high dose may take weeks or months; and
- consider the possibility of hyperalgesia if a patient on long-term opioid therapy presents with increased sensitivity to pain.[4]

7.6.3 MHRA drug safety update (March 2020)

In March 2020, the MHRA issued a reminder 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.[47]

Healthcare professionals are advised to only co-prescribe BZRAs and opioids if there is no alternative. If a decision is made to co-prescribe, the lowest possible doses should be given for the shortest duration and patients should be monitored for signs of respiratory depression.[47]

7.6.4 HPRA drug safety newsletter (August 2017)

The HPRA issued a drug safety newsletter in 2017 warning that gabapentin use has been associated with reports of respiratory depression. The newsletter also highlights that concomitant use of gabapentin with opioids has been associated with reports of respiratory failure, coma and/or death.[48]

7.6.5 HPRA third party publication (June 2013)

In June 2013, the HPRA issued a third party publication from the marketing authorisation holder of Durogesic Dtrans® transdermal patches, to advise caution to healthcare professionals regarding the increased risk of serotonin syndrome when fentanyl is co-administered with serotonergic drugs.[49]

The communication outlines that the development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as SSRIs, SNRIs and MAOIs. It states that serotonin syndrome may occur within the recommended dosage.[49]

7.7 Evidence of adverse events associated with opioid use in CNCP

A Cochrane Systematic Review (2017), *Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews,* investigated the occurrence and nature of adverse events associated with opioids used on a medium- or long-term basis for the treatment of CNCP in adults. The review investigated 14 different opioids (including morphine, oxycodone, tapentadol and tramadol) for a variety of CNCP, where opioids were administered for longer than a two-week duration.[50]

The review demonstrated a significantly increased risk of experiencing a serious adverse event with opioids compared to placebo (RR: 2.75, 95% CI: 2.06 - 3.67). The authors concluded that based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use of opioids in CNCP could be considered in clinical practice.[50]

Practice Points

Prescribers should consider the following in relation to harms associated with opioids:

- There is a dose dependent risk of serious harms.
- There is ↑ risk and severity of ADRs in older people and people with renal impairment.
- There is ↑ incidence of endocrine abnormalities, altered immune function, opioid induced hyperalgesia, cognitive decline, falls (and fractures), dependence and addiction with long-term use.
- Dependence and addiction is a significant risk with use of greater than three months duration.
- Co-prescribing with CNS depressants (e.g. a BZRA, gabapentin and pregabalin) can produce additive CNS depressant effects including respiratory depression.
- Co-prescribing with serotonergic drugs and antipsychotics can ↑ the risk of serotonin syndrome.
- Co-prescribing tramadol/tapentadol with serotonergic drugs, antipsychotics and other medicinal products that ↓ the seizure threshold, can also ↑ the risk of convulsions.

8. Clinical guidelines and guidance on opioids in the management of CNCP

Over the last number of years, there have been a number of published guidelines and guidance documents to promote the safe and appropriate use of opioids in the management of CNCP. In general, international recommendations state that opioids should only be considered for a trial in the treatment of CNCP in carefully selected individuals after optimising non-pharmacological treatments and non-opioid analgesics. International clinical guidelines and guidance on the use of opioids in the management of CNCP are summarised in table 2.

Table 2: Clinical guidelines and guidance on opioids in the management of CNCP

Review Body	Guideline/Guidance	Year	Excerpt/comment
Faculty of Pain Medicine (FPM) [UK][2]	*Opioids Aware (web-based resource)*	2022	The guidance recommends that: • there is little evidence that opioids are helpful for chronic pain, • patients who do not achieve useful pain relief from opioids within 2-4 weeks are unlikely to gain benefit in the long-term, • short-term efficacy does not guarantee long-term efficacy, • opioids should be discontinued if the person is still in pain despite using opioids, even if no other treatment is available.
National Institute for Health & Care Excellence (NICE) [UK][13]	*Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain*	2021	The guideline recommends that: • opioids are not initiated to manage chronic primary pain in people aged 16 years and over, • people with chronic primary pain taking opioids, should have their prescribing reviewed.
National Institute for Health & Care Excellence (NICE) [UK][51]	*Low back pain and sciatica in over 16s: assessment and management*	2016	The guideline recommends that opioids are not offered to manage chronic low back pain and chronic sciatica.
Scottish Intercollegiate Guidance Networks (SIGN) [UK][12]	*Management of chronic pain*	2019	The guideline recommends that opioids should be considered for short- to medium-term treatment of carefully selected patients with CNCP, for whom other therapies have been insufficient, and the benefits may outweigh the risks of serious harms, such as addiction, overdose and death.
European Pain Federation (EFIC)[52]	*European clinical practice recommendations on opioids for CNCP*	2021	The position paper recommends that: • opioids should not be considered for primary pain syndromes e.g. migraine headache, • opioids can be considered for certain chronic secondary pain syndromes e.g. chronic pain in rheumatoid arthritis and spinal cord injury, • opioid treatment lasting longer than three months should only be considered in treatment responders.

Review Body	Guideline/Guidance	Year	Excerpt/comment
International Association for the Study of Pain (IASP)[53]	Position statement on opioids	2018	The position statement recommends '*caution when prescribing opioids for chronic pain. Chronic pain treatment strategies that focus on improving the quality of life, especially those integrating behavioural and physical treatments are preferred'.*
NHS Scotland[20]	*Quality Prescribing for Chronic Pain* guidance	2018	The guidance recommends that: • prior to commencing treatment with opioids, patients should be made aware that opioids are not effective in every patient, • a 30% improvement in pain and/or a significant improvement in functional ability is considered a realistic aim and continued treatment with opioids should only be considered after confirming clinically meaningful improvements in pain and function without significant risks or harm.
Centers for Disease Control and Prevention (CDC) [US][54]	*Guideline for Prescribing Opioids for Chronic Pain*	2016	The guideline recommends when starting opioid therapy for chronic pain: • clinicians should prescribe immediate-release opioids instead of extended-release/long-acting opioids, • clinicians should prescribe the lowest effective dosage.
National Pain Centre [Canada][55]	*Canadian Guideline for Opioids for Chronic Non-Cancer Pain*	2017	The guideline recommends: • when considering therapy for patients with CNCP; optimise non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids, • for patients with CNCP who are beginning opioid therapy: restrict the prescribed dose to less than 90 MME daily rather than having no upper limit or a higher limit on dosing.

Abbreviations: CNCP: chronic non-cancer pain, MME: morphine milligram equivalents.

8.1 Faculty of Pain Medicine (UK)

The Faculty of Pain Medicine (FPM) of the Royal College of Anaesthetists in the UK developed a web-based resource, *Opioids Aware* for healthcare professionals to support prescribing of opioid medicines for pain (last updated January 2022).[2] The resource provides the following summary of the evidence relating to the effectiveness of opioids in chronic pain:

- There is little evidence that they are helpful for chronic pain.
- A small proportion of people may obtain good pain relief with opioids in the long-term if the dose can be kept low and use is intermittent, however it is difficult to identify these people at the start of treatment.
- The risk of harm increases substantially at doses above an oral morphine equivalent of 120 mg per day, but there is no increased benefit.
- Opioids should be discontinued if the person is still in pain despite using opioids, even if no other treatment is available.
- A detailed assessment of the emotional influences on the person's pain experience is essential for people with chronic pain who also have refractory and disabling symptoms, particularly if they are on high opioid doses.[2]

The FPM recommends a 'stepped approach' for chronic pain, which is not determined by pain intensity. Treatment should be commenced with non-opioid medicines, regardless of pain intensity. Trials of both weak and strong opioids may be considered for some patients with well-defined pain diagnoses who are symptomatic despite first-line interventions. The FPM states that all medicines prescribed for pain should be regularly reviewed to evaluate continued efficacy, and periodic dose tapering is required to evaluate this.[2]

The FPM issued the following practice points in relation to the effectiveness of opioids for chronic pain:

- Patients who do not achieve useful pain relief from opioids within 2-4 weeks are unlikely to gain benefit in the long-term.
- Patients who may benefit from opioids in the long-term will demonstrate a favourable response within 2-4 weeks.
- Short-term efficacy does not guarantee long-term efficacy.
- Data regarding improvement in quality of life with long-term opioid use are inconclusive.
- There is no good evidence of dose-response with opioids, beyond doses used in clinical trials, usually up to 120 morphine milligram equivalents (MME) per day. There is no evidence for efficacy of high dose opioids in long-term pain.[2]

8.2 National Institute of Health and Care Excellence

The NICE guidance *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain* published in April 2021 provides recommendations on the management of chronic primary pain.[13]

The guideline recommends that opioids are not initiated to manage chronic primary pain in people aged 16 years and over. If a person with chronic primary pain is already taking opioids, the prescribing of opioids should be reviewed with the patient as part of shared decision making as follows:

- explain the lack of evidence for these medicines for chronic primary pain, and
- agree a shared plan for continuing safely if they report benefit at a safe dose and few harms, or
- explain the risks of continuing if they report little benefit or significant harm, and encourage and support them to reduce and stop the medicine if possible.[13]

The guideline refers to other NICE guidelines on specific individual conditions for recommendations on the management of chronic secondary pain including low back pain and sciatica. NICE guidance *Low back pain and sciatica in over 16s: assessment and management* (2016) recommend that opioids are not offered to manage chronic low back pain and chronic sciatica.[51]

8.3 Scottish Intercollegiate Guidance Networks

SIGN published an updated clinical guideline on the *Management of chronic pain* in August 2019.[12] The guideline sets out the following recommendations and good practice points in relation to treatment of CNCP with opioids:

- Opioids should be considered for short- to medium-term treatment of carefully selected patients with CNCP, for whom other therapies have been insufficient, and the benefits may outweigh the risks of serious harms such as addiction, overdose and death. [*Level B recommendation*]
- Currently available screening tools should not be relied upon to obtain an accurate prediction of patients at risk of developing problem opioid use, but may have some utility as part of careful assessment either before or during treatment. [*Level B recommendation*]
- Signs of abuse, addiction and/or other harms should be sought at reassessment of patients using strong opioids. [*Level C recommendation*]

- All patients receiving opioid doses of greater than 50 MME per day should be reviewed regularly (at least annually) to detect emerging harms and consider ongoing effectiveness. Pain specialist advice or review should be sought at doses greater than 90 MME per day. [*Level D recommendation*]
- At initiation of treatment, ensure there is agreement between the prescriber and patient about expected outcomes. If these are not attained, then there should be a plan agreed in advance to reduce and stop opioids. [*Good practice point*]
- All patients on opioids should be assessed early after initiation, with planned reviews thereafter. These should be reviewed annually, at a minimum, and more frequently if required. The aim is to achieve the minimum effective dose and avoid harm. Treatment goals may include improvements in pain relief, function and quality of life. Consideration should be given to a gradual early reduction to the lowest effective dose or complete cessation. [*Good practice point*][12]

8.4 European Pain Federation

In 2021, the European Pain Federation (EFIC) published *European Clinical Practice Recommendations on opioids for CNCP*.[52] The recommendations relate to clinical evaluation, as well as opioid treatment assessment, monitoring, continuation and discontinuation.

The key clinical practice recommendations include:

- Firstly optimise non-pharmacological treatments and consider non-opioid analgesics. [*Weak recommendation*]
- Consider a trial of opioids if established non-pharmacological treatments and established non-opioid analgesics are not effective, and/or not tolerated, and/or contraindicated/not available. [*Weak recommendation*]
- Medication selection should consider the type of CNCP, the comorbidities of the patient, contraindications, patient preferences, benefits and harms of previous therapies and the benefit-risk ratio of available pharmacological alternative treatment options. [*Good clinical practice statement*]
- Opioids should not be considered for primary pain syndromes e.g., migraine headache [*Good clinical practice statement*]
- Opioids can be considered for certain chronic secondary pain syndromes e.g., chronic pain in rheumatoid arthritis and spinal cord injury. [*Good clinical practice statement*]

- Opioid treatment lasting longer than three months should only be considered in treatment responders. [*Good clinical practice statement*]
- During long-term opioid treatment, prescribers should consider reviewing the following at regular intervals (at least once every three months):
    - whether therapeutic goals continue to be met,
    - whether there are indications of adverse events, or
    - whether there is evidence of opioid use disorder or non-medical *use.* [*Good clinical practice statement*]
- After six months of opioid treatment with a good response, a dose reduction can be considered with the patient, to assess the indication for continued treatment and the response to the non-pharmacological treatments (e.g., multimodal therapy) that are being used in parallel. [*Good clinical practice statement*][52]

8.5 International Association for the Study of Pain

In February 2018, the International Association for the Study of Pain (IASP) issued a position statement on opioids recommending: '*caution when prescribing opioids for chronic pain. There may be a role for medium-term, low-dose opioid therapy in carefully selected patients with chronic pain who can be managed in a monitored setting. However, with continuous longer-term use, tolerance, dependence, and other neuroadaptations compromise both efficacy and safety. Chronic pain treatment strategies that focus on improving the quality of life, especially those integrating behavioural and physical treatments, are preferred. IASP also strongly advocates for continued research to identify ways to minimise opioid risk and find effective alternatives to opioids for the treatment of various pain problems'*.[53]

8.6 NHS Scotland

NHS Scotland *Quality Prescribing for Chronic Pain* guidance (2018) highlights that the potential benefits and risks of strong opioids should be discussed with patients. The guidance recommends that prior to commencing treatment with opioids, patients should be made aware that opioids are not effective in every patient. A one or two-week trial is recommended when prescribing opioids to observe efficacy, tolerability and suitability. A 30% improvement in pain and/or a significant improvement in functional ability is considered a realistic aim and continued treatment with opioids should only be considered after confirming clinically meaningful improvements in pain and function without significant risks or harm.[20]

8.7 Centers for Disease Control and Prevention (US)

The US Centers for Disease Control and Prevention (CDC) published a *Guideline for Prescribing Opioids for Chronic Pain - United States* (2016), making recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.[54] When considering the initiation or continuation of opioids for chronic pain, the following recommendations apply:

- Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. [*Recommendation category: A, evidence type: 3*]
- Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if the benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is a clinically meaningful improvement in pain and function that outweighs the risks to patient safety. [*Recommendation category: A, evidence type: 4*]
- Before starting and periodically during opioid therapy, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and the patient's and clinician's responsibilities for managing therapy. [*Recommendation category: A, evidence type: 3*]

The CDC guidance for prescribing opioids for chronic pain also provides recommendations on opioid selection, continuation, risk assessment and addressing harms of opioids use, and discontinuation including the following:

- When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting opioids. [*Recommendation category: A; evidence type: 4*]
- When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing the dosage to ≥ 50 MME per day, and should avoid increasing the dosage to ≥ 90 MME per day, and or should carefully justify a decision to titrate the dosage to ≥ 90 MME per day. [*Recommendation category: A; evidence type: 3*]
- Clinicians should evaluate the benefits and harms with patients within one to four weeks of starting an opioid for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every three months or more frequently. If benefits do not outweigh the harms of continued opioid therapy, clinicians should optimise other therapies and work with patients to taper

opioids to lower dosages or to taper and discontinue opioids. [*Recommendation category: A; evidence type: 4*][54]

8.8 National Pain Centre (Canada)

The *Canadian Guideline for Opioids for Chronic Non-Cancer Pain* (2017) published by the National Pain Centre provides guidance on the use of opioids to manage CNCP.[55] For initiation and dosing of opioids in patients with CNCP, the following recommendations apply:

- When considering therapy for patients with CNCP: *recommend* optimisation of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids. [*Strong recommendation*]
- For patients with CNCP, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimised non-opioid therapy: *suggest* adding a trial of opioids rather than continued therapy without opioids. [*Weak recommendation*]
- For patients with CNCP with an active substance use disorder: *recommend* against the use of opioids. [*Strong recommendation*]
- For patients with CNCP with an active psychiatric disorder whose non-opioid therapy has been optimised, and who have persistent problematic pain: *suggest* stabilising the psychiatric disorder before a trial of opioids is considered. [*Weak recommendation*]
- For patients with CNCP with a history of substance use disorder, whose non-opioid therapy has been optimised, and who have persistent problematic pain: *suggest* continuing non-opioid therapy rather than a trial of opioids. [*Weak recommendation*]
- For patients with CNCP who are beginning opioid therapy: *recommend* restricting the prescribed dose to less than 90 MME per day, rather than having no upper limit or a higher limit on dosing. [*Strong recommendation*]
- For patients with CNCP who are beginning opioid therapy: *suggest* restricting the prescribed dose to less than 50 MME per day. [*Weak recommendation*][55]

The Canadian guideline also provides recommendations in relation to rotation and tapering of opioids.

9. Considerations prior to initiation of opioids for CNCP

9.1 Managing an individual's expectations

Prior to initiation of opioids for the management of CNCP, clinicians should develop an individual's understanding of chronic pain, how it differs from acute pain and the impact this may have on goals of therapy, and ensure that the individual is aware of potential benefits of, harms of, and alternatives to opioids.[20, 54] Individuals should not expect complete pain relief with strong opioids; a reduction in pain of more than 30% is unlikely to be achieved with strong opioids when prescribed for chronic pain.[56]

The *Opioids Aware* web-based resource produced by the UK FPM provides the following checklist for prescribers to discuss with individuals when considering initiation of opioids:

- ✓ Explain that the evidence for the use of opioids as analgesics is most applicable to the management of acute pain.
- ✓ Explain that opioids are poorly effective for chronic pain. For a small proportion of individuals, opioids may be successfully used as part of a broader plan including non-medication treatments and self-management.
- ✓ Discuss the degree of pain relief that might be expected and that the patient understands that the aim is not complete pain relief but rather reducing pain sufficiently to engage in self-management.
- ✓ Agree specific functional goals that might be achieved.
- ✓ Discuss the potential harms of opioid treatment including sedation, nausea, constipation, effects on hormones, effects on the immune system, potential for the drugs to worsen pain, and potential for problematic drug use and addiction.
- ✓ Discuss opioids and impairment of driving skills.
- ✓ Discuss the opioid trial (see section 9.2).
- ✓ Discuss the circumstances in which opioid therapy will be stopped.
- ✓ Discuss arrangements for review.[2]

9.1.1 Resources

The *Opioids Aware* web-based resource provides patient information leaflets *About Pain* and *Thinking about opioid treatment for pain* which can support clinicians in ensuring individuals understand the expected benefit with opioids, potential harms associated with opioids, and agree goals of treatment, review and the plan for discontinuation. The leaflets are available at https://fpm.ac.uk/opioids-aware/information-patients.

The *My Live Well With Pain* website (https://my.livewellwithpain.co.uk) includes information leaflets and videos explaining chronic pain, empowering self-management of chronic pain, and highlighting the limited evidence and significant harms associated with opioids for the treatment of chronic pain.

The *Live Well With Pain* toolkit (https://livewellwithpain.co.uk) can help clinicians to support individuals towards better self-management of their chronic pain.

9.2 Opioid trial

The purpose of an opioid trial is to establish whether an individual achieves any reduction in pain with the use of opioids rather than achieving optimal doses and managing side-effects.[2] The *Opioids Aware* web-based resource includes the following recommendations in relation to the opioid trial:

- Discuss and agree the outcomes of an opioid trial. Goals usually include reduction in pain intensity and ability to achieve specific functional improvement.
- If the individual has constant pain, the opioid trial may be concluded in one or two weeks. If the individual has intermittent disabling flare ups of pain on a background of more manageable symptoms, the trial should be long enough to observe the effect of opioids on two or three episodes of increased pain.
- Where possible, the usefulness of opioids should be explored by prescribing a short (one to two week supply) of immediate-release morphine tablets (Sevredol®) or liquid (Oramorph Oral Solution®). The individual may be advised to explore different doses within a specified range e.g., morphine 5-10 mg. If reduction in pain is not achieved following a single dose of immediate-release morphine 20 mg, opioids are unlikely to be beneficial in the long-term.
- The individual should keep a diary during the opioid trial. This should include a twice-daily report of pain intensity, comment on sleep, note of activity levels and how any of these are changed following a dose of opioids.
- All doses of opioid should be recorded in the diary with a comment on side-effects.
- If the opioid trial is not successful, the medicine should be tapered and stopped within one week.[2]

Practice Point

Prior to initiation of opioids for CNCP, prescribers should ensure that individuals understand the expected benefit and risk of harms, and agree treatment goals, a review strategy and a plan for discontinuation.

10. Utilisation and expenditure on the community drug schemes

10.1 Data source

Data from the following CDS were analysed to examine trends in the prescribing of strong opioids from 2011 to 2020: GMS, DP and LTI schemes. These schemes are managed by the HSE-PCRS. The HSE-PCRS provides pharmacy dispensed claims data to the MMP for analysis.

GMS pharmacy claims data is submitted to the HSE-PCRS by community pharmacists who dispense medications under the GMS scheme. GMS data is expected to capture all incidences of a medicine being dispensed to an individual under this scheme, (except where a person receives a medicine relating to a specific condition which is covered under the LTI scheme, in which case dispensing of the medicine is captured through the LTI data).

In the case of the DP scheme, data is only available for individuals whose monthly prescription expenditure exceeded the threshold (€80 per month as of August 2022) above which the HSE-PCRS provides reimbursement. As such, the DP scheme is a less complete source of information than the GMS data for studies of individual dispensing patterns.

Utilisation is considered as the number of patients in receipt of an individual strong opioid.

10.2 Overall expenditure of strong opioids

Total expenditure of strong opioid prescriptions on the CDS was approximately €27.5 million in 2020. Approximately €24 million of this expenditure was on the GMS scheme.[57]

10.3 General Medical Services

10.3.1 Utilisation

The number of patients in receipt of strong opioids on the GMS scheme in Ireland has not changed significantly from years 2011 to 2020 (less than 3% decrease), however the patterns in prescribing have changed over the decade.[57] Figures 1 and 2 below illustrate the proportion of individual strong opioids reimbursed on the GMS scheme in 2011 and 2020 respectively.

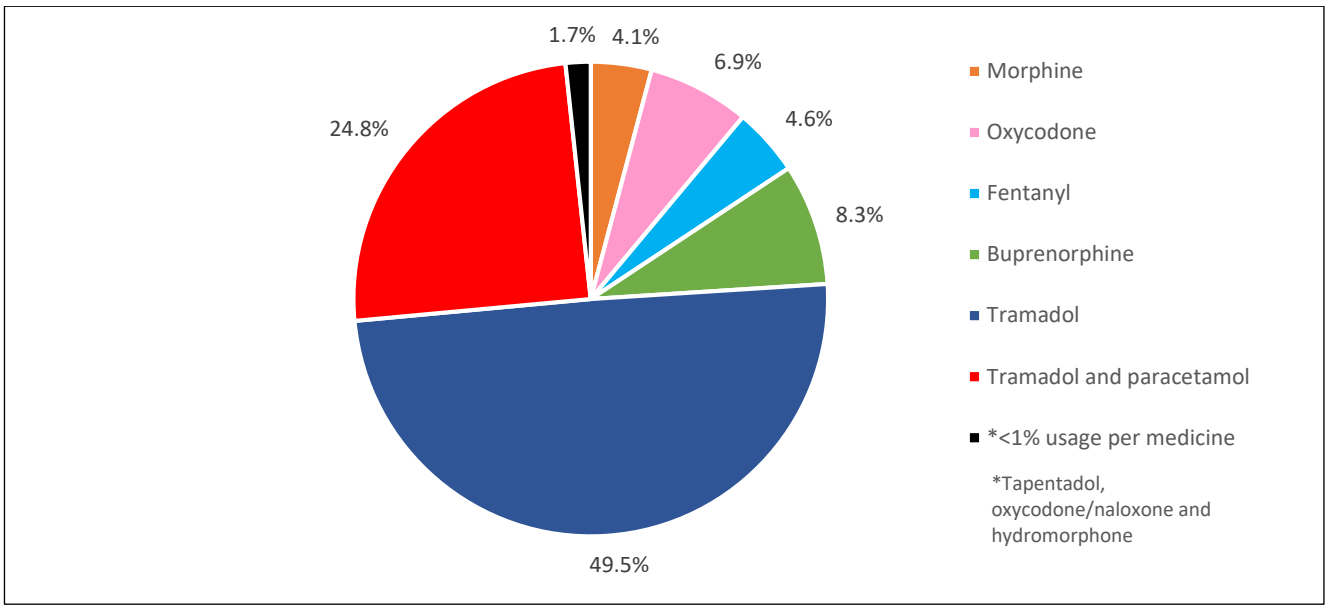

Figure 1: Proportion of individual strong opioids reimbursed on the GMS scheme in 2011

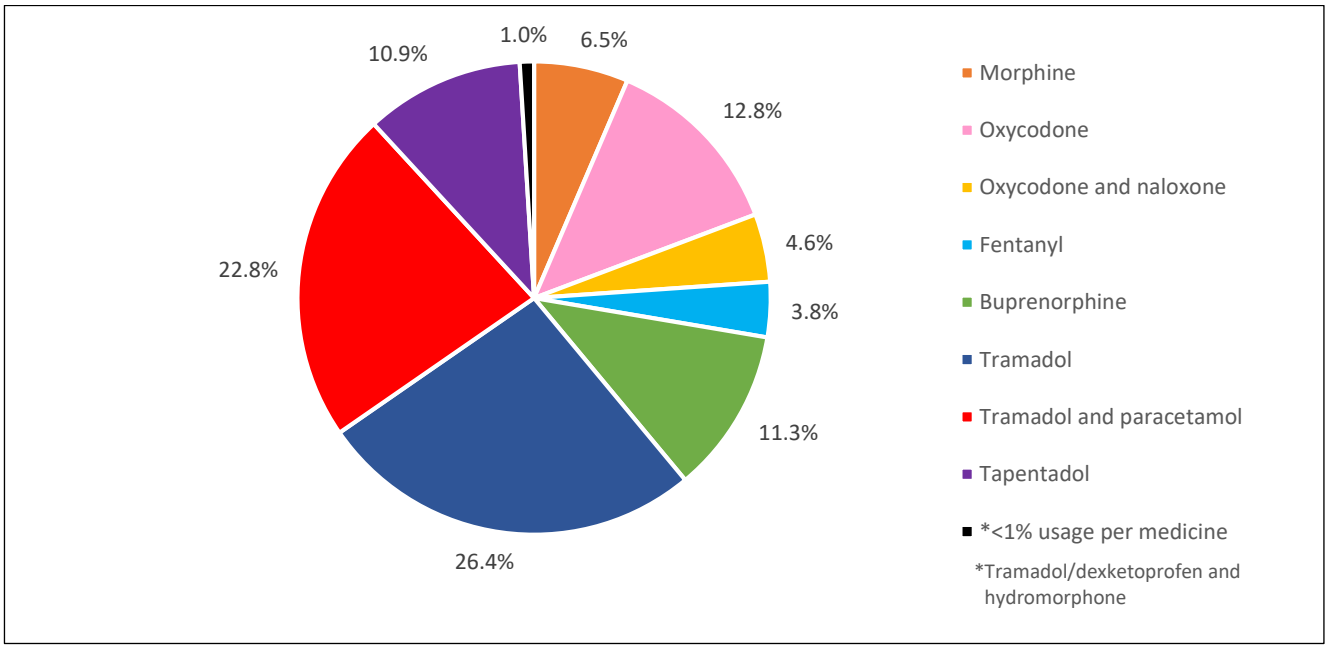

Figure 2: Proportion of individual strong opioids reimbursed on the GMS scheme in 2020

In 2011, tramadol was the most commonly prescribed strong opioid on the GMS scheme, accounting for 49.5% of the utilisation of opioids in that year and reflecting utilisation by approximately 95,000 individuals in Ireland. Tramadol/paracetamol combination products were the second most commonly prescribed strong opioids in 2011, accounting for 24.8% of the utilisation of strong opioids in that year and reflecting utilisation by approximately 48,000 individuals in Ireland.[57] Tramadol may behave as a strong or weak opioid depending on the dose used.[58]

Buprenorphine and oxycodone were the third and fourth most commonly prescribed strong opioids in 2011, accounting for 8.3% and 6.9% of the utilisation for strong opioids respectively and reflecting utilisation by approximately 16,000 and 13,000 individuals respectively. The remaining 10.5% of strong opioid utilisation consisted of fentanyl (4.6%), morphine (4.1%), and oxycodone/naloxone combination, tapentadol and hydromorphone each having less than 1% utilisation in 2011.[57]

In 2020, tramadol remained the most commonly prescribed strong opioid accounting for 26.4% of the utilisation of strong opioids in that year. This utilisation was reflected in approximately 49,000 people, a 48% reduction in the number of individuals utilising tramadol since 2011. Tramadol/paracetamol combination remained the second most commonly prescribed strong opioid in 2020, reflecting utilisation in 42,500 individuals, an 11% reduction in utilisation compared to 2011.[57] Oxycodone was the third most commonly prescribed strong opioid in 2020. There has been a 79% increase in the number of individuals dispensed oxycodone on the GMS scheme from the years 2011 to 2020, with approximately 24,000 individuals in receipt of this product in 2020, accounting for 12.8% of the total strong opioid utilisation.[57] Buprenorphine was the fourth most commonly prescribed strong opioid in 2020, accounting for 11.3% of the total strong opioid utilisation. This was a 33% increase on the utilisation from 2011, accounting for utilisation in approximately 21,000 people in 2020.

There has been an annual increase in the utilisation of tapentadol since its addition to the HSE-PCRS reimbursement list in 2011. Tapentadol, which was utilised in approximately 900 individuals in 2011, was utilised in approximately 20,000 individuals and accounted for 10.9% of the total strong opioid utilisation in 2020. Morphine utilisation increased by 52% from 2011 to 2020, reflecting utilisation in approximately 12,000 people in 2020. An oxycodone/naloxone combination product was added to the HSE-PCRS reimbursement list in 2010. This oxycodone/naloxone combination, which was utilised in 1,800 individuals in 2011, was utilised in approximately 8,700 individuals in 2020, and accounted for 4.6% of the total strong opioid utilisation in 2020.[57]

There was a 21% reduction in the utilisation of fentanyl over this ten-year period in the GMS population and it was dispensed to approximately 7,000 individuals in 2020. The utilisation of hydromorphone amongst the GMS population is low; less than 400 individuals in 2020.[57]

Figures 3 and 4 further illustrate the trends in the utilisation of individual strong opioid analgesics including, and excluding tramadol and tramadol combination products respectively on the GMS scheme from the years 2011 to 2020.[57] The number of people eligible for the GMS scheme in Ireland was approximately 1.7 million in 2011 and 1.6 million in 2020.[59]

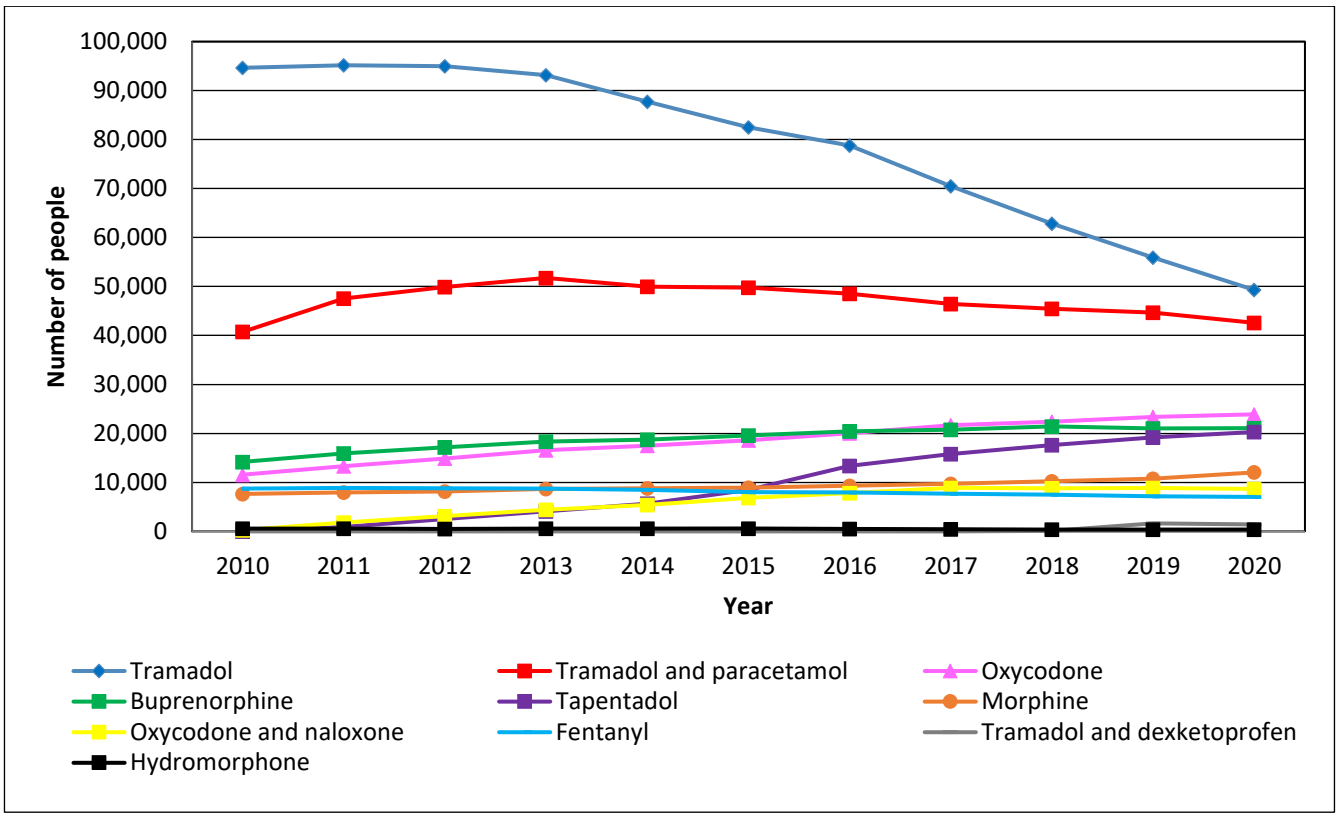

Figure 3: Trends in the utilisation of strong opioids on the GMS scheme from 2011-2020

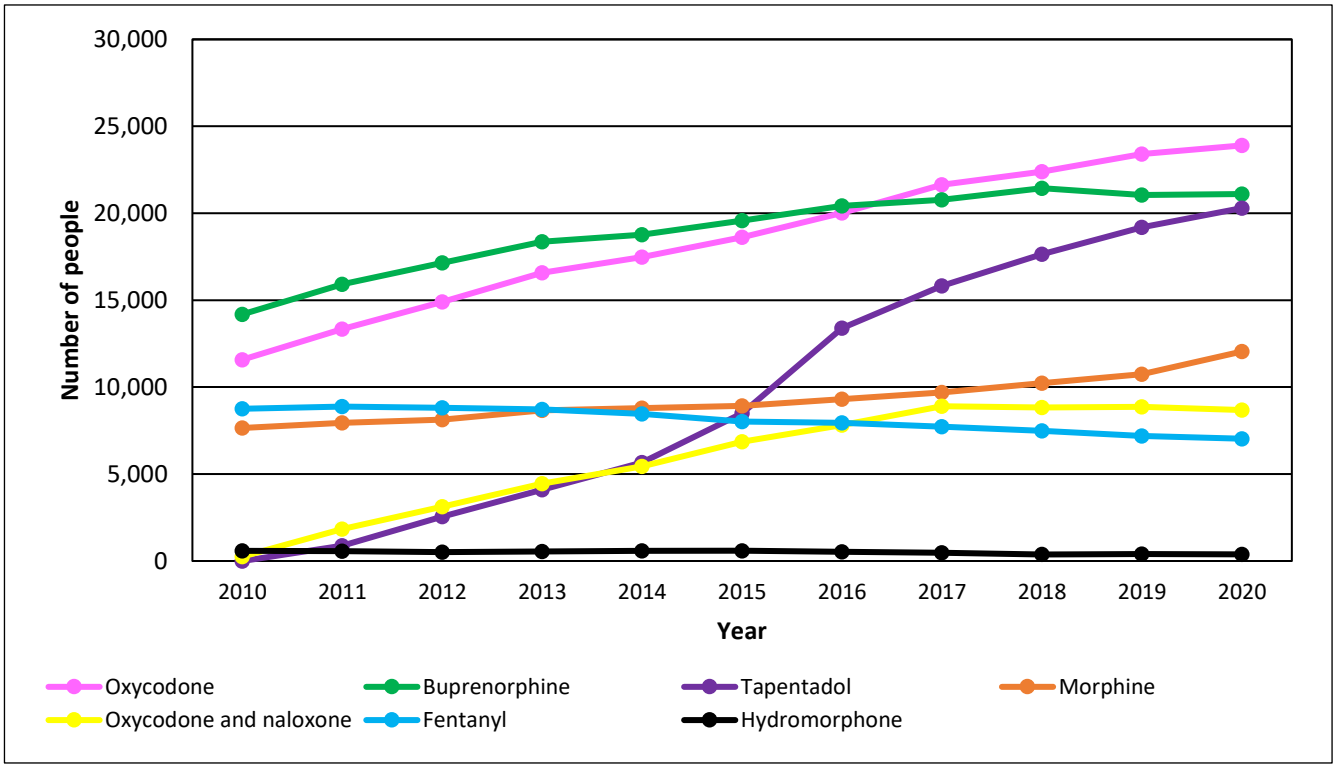

Figure 4: Trends in the utilisation of strong opioids excluding tramadol and tramadol combination products on the GMS scheme from 2011-2020

10.3.2 Demographic

Utilisation of strong opioids has been consistently higher in females than in males over the years 2011-2020, with 62.4% of claims on the GMS scheme being dispensed to females in 2020. In 2011 and 2022, the median age for utilisation of strong opioids was 67 years.[57]

10.4 Drugs Payment and Long Term Illness schemes

10.4.1 Utilisation

In 2011, tramadol was the most commonly prescribed strong opioid on the DP and LTI schemes combined, accounting for 53.2% of the utilisation of strong opioids in that year and reflecting utilisation by approximately 17,000 individuals in Ireland. Tramadol/paracetamol combination was the second most commonly prescribed strong opioid in 2011 on the DP and LTI schemes combined, accounting for 22.8% of the utilisation of strong opioids in that year and reflecting utilisation by approximately 7,000 individuals in Ireland. Oxycodone was the third most commonly prescribed strong opioid on the DP and LTI schemes combined in 2011, accounting for 10.1% of the utilisation for strong opioids and reflecting utilisation by 3,000 individuals. The remaining strong opioids had low utilisation on the DP and LTI schemes combined in 2011.[57]

Similar to the GMS scheme, a change in prescribing trends of strong opioids on the DP and LTI schemes combined was reflected in the 2020 HSE-PCRS reimbursement data. In 2020, tramadol remained the most commonly prescribed strong opioid on the DP and LTI schemes combined, accounting for 26.4% of the utilisation of strong opioids in that year. This utilisation was reflected in approximately 8,000 people, a 53% reduction in the number of individuals utilising tramadol since 2011.[57]

Oxycodone became the second most commonly prescribed strong opioid on the DP and LTI schemes combined, accounting for 18.8% of the total strong opioid utilisation in 2020. This was a 78% increase in its utilisation from 2011, reflecting utilisation in approximately 5,600 people in 2020. Tramadol/paracetamol was the third most common strong opioid utilised in 2020; utilisation decreased by 26% from 2011, reflecting utilisation in 5,000 individuals on the DP and LTI schemes combined in 2020.[57]

Tapentadol, similarly to trends on the GMS scheme, was increasingly utilised following its addition to the HSE-PCRS reimbursement list in 2011. It was utilised in less than 300 individuals in 2011, and by 2020 it was being utilised in approximately 4,000 people, and accounted for 13.1% of the total strong opioid utilisation on the DP and LTI schemes combined.

There was a 72% increase in the utilisation of morphine from years 2011-2020 on the DP and LTI schemes combined, with utilisation reflected in approximately 1,500 individuals in 2020. An oxycodone/naloxone combination, similarly to trends on the GMS scheme, showed an increase in utilisation, increasing from approximately 450 individuals in 2011 to approximately 2,000 patients in 2020. There has been a decrease in the utilisation of fentanyl (15%) and hydromorphone (40%) from years 2011 to 2020.[57]

Figures 5 and 6 illustrate the trends in the utilisation of strong opioids including, and excluding tramadol and tramadol combination products respectively on the DP and LTI schemes combined from the years 2011-2020.[57]

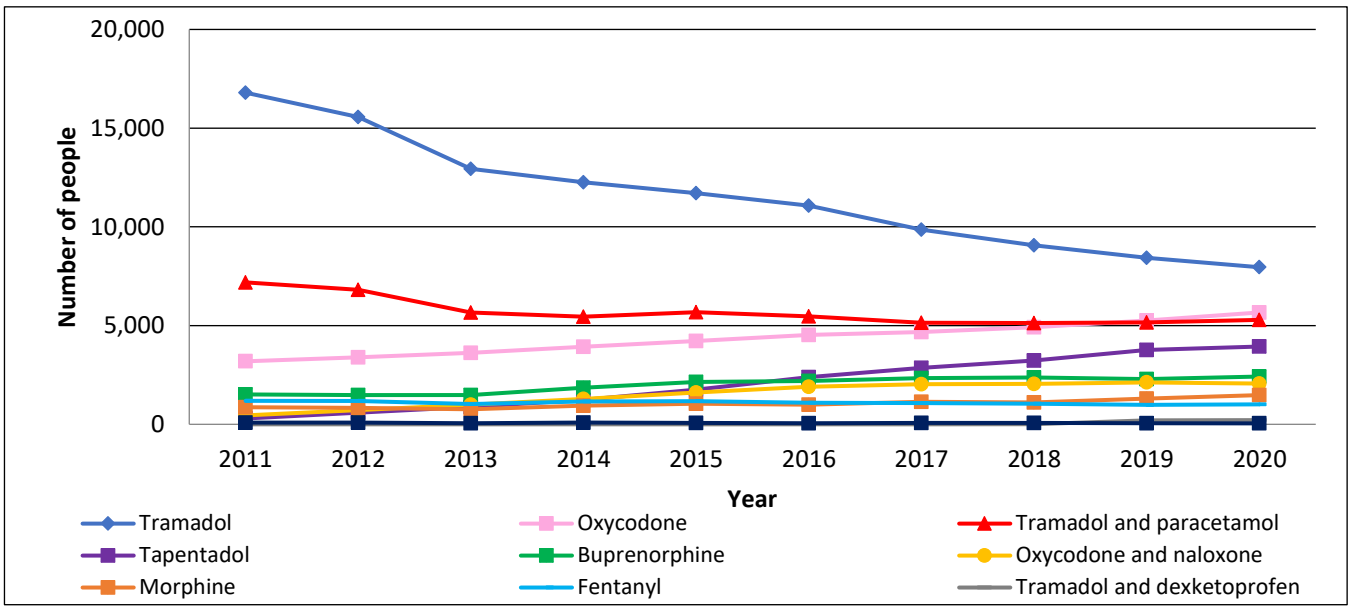

Figure 5: Trends in the utilisation of strong opioids on the DP and LTI schemes combined from 2011-2020

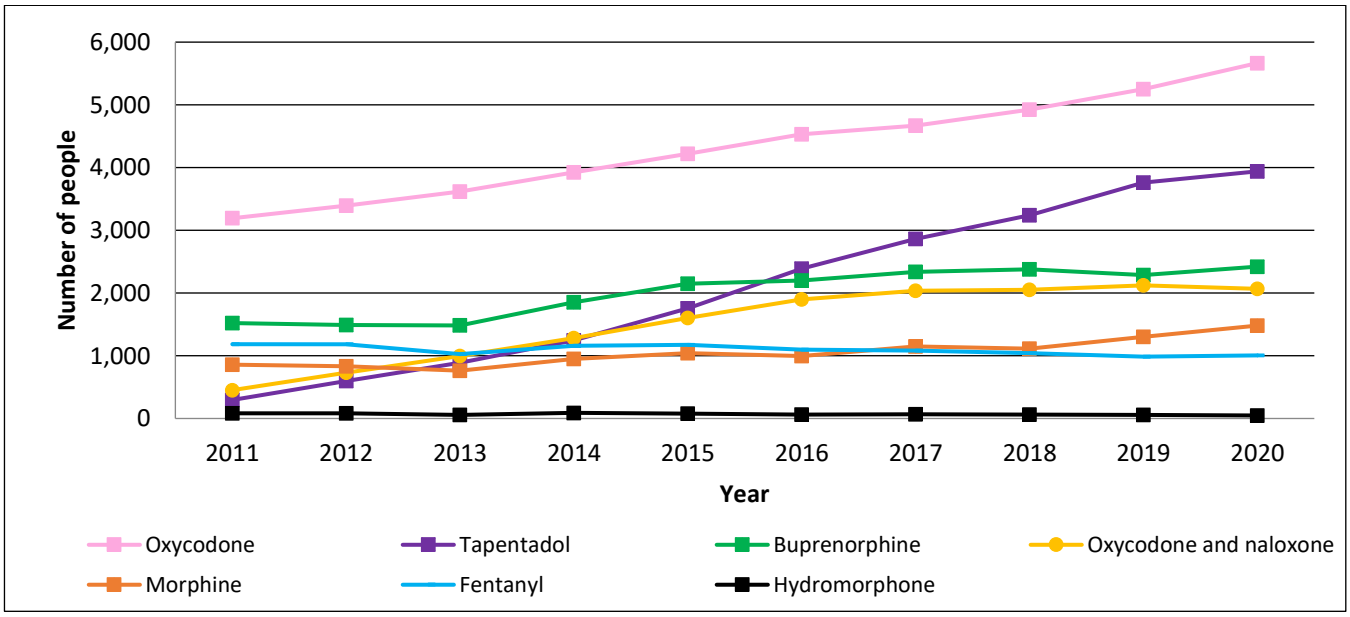

Figure 6: Trends in the utilisation of strong opioids excluding tramadol and tramadol combination products on the DP and LTI schemes combined from 2011-2020

10.4.2 Demographic

Utilisation of strong opioids has been consistently higher in females than in males on the DP and LTI schemes combined (2011-2020), with 61.2% of claims being dispensed to females in 2020. The median age for utilisation of strong opioids on the DP and LTI schemes combined was 65 years in 2020, which has increased from 58 years in 2011.[57]

10.5 Duration of use

A cross-sectional analysis of the HSE-PCRS pharmacy claims database was conducted by the MMP to investigate the duration of use of individual strong opioids on the GMS scheme. People who initiated a strong opioid in January 2020 on the GMS scheme were identified (n=10,461) and the number of months they were dispensed this opioid to December 2020 was investigated (this may not be consecutive months).[57]

The analysis showed that 81.86% of individuals who initiated a strong opioid under the GMS scheme in January 2020 were dispensed the opioid for a duration of one to three months. The analysis also showed that 7.64% and 10.51% of individuals who were initiated on a strong opioid under the GMS scheme in January 2020 were dispensed it for four to six months, or seven months or more, respectively.[57]

A higher proportion of individuals who were initiated buprenorphine (40%), hydromorphone (40%) or fentanyl (35.5%) under the GMS scheme, were dispensed it for more than 3 months during this period (Figure 7).[57]

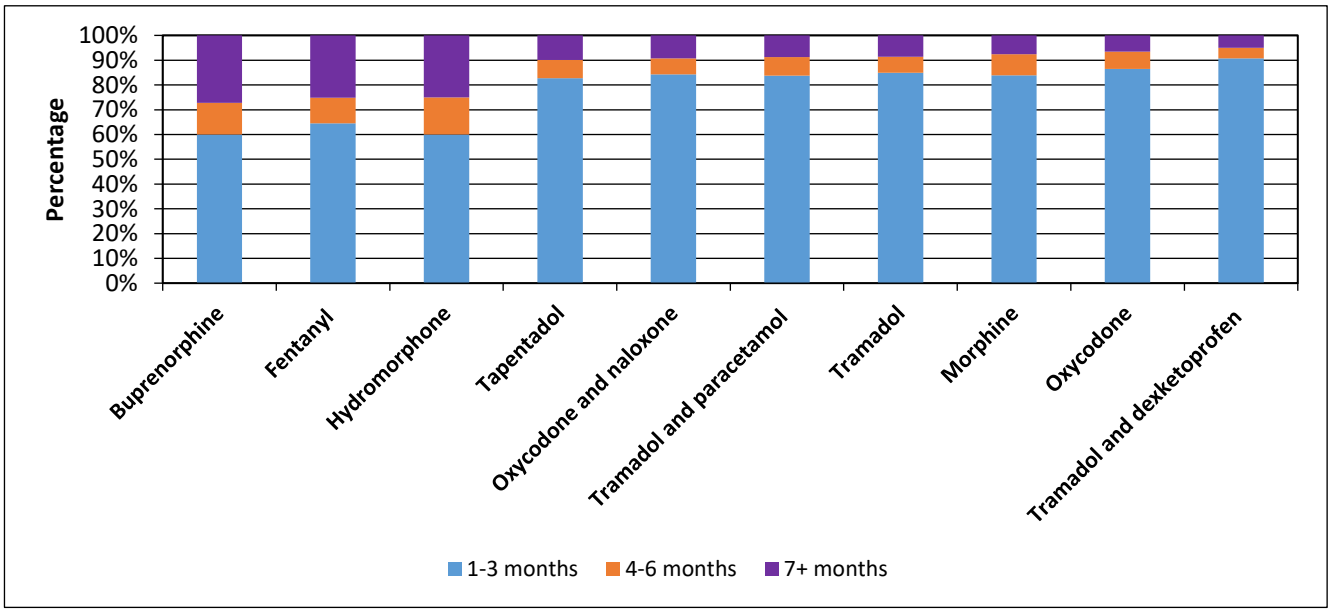

Figure 7: Duration of use of strong opioids initiated in January 2020 on the GMS scheme (January 2020 – December 2020)

10.6 Analysis of co-prescribing with drugs which interact with opioids

10.6.1 Opioids co-prescribed with a BZRA

A cross-sectional analysis of the HSE-PCRS pharmacy claims database was conducted by the MMP to investigate if BZRAs* are being co-prescribed to individuals with strong opioids. Individuals who initiated a strong opioid in January 2020 on the GMS scheme (n= 10,461) were identified and their use of a BZRA was investigated in the same one-month period.[57]

The analysis showed that an average of 32% individuals (ranging from 23% - 50% of individual strong opioids) were co-prescribed an opioid with a BZRA in January 2020 (Figure 8).[57]

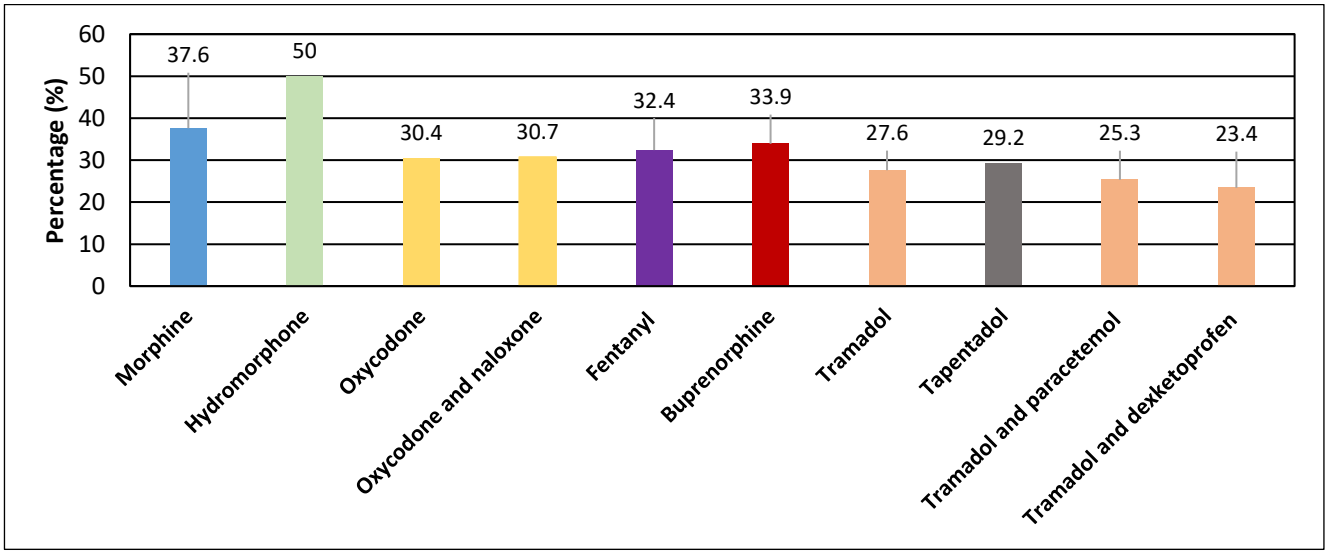

Figure 8: Percentage of people in receipt of individual strong opioids co-prescribed a BZRA in January 2020 on the GMS scheme

10.6.2 Opioids co-prescribed with an antidepressant or an antipsychotic

A cross-sectional analysis of the HSE-PCRS pharmacy claims database was conducted by the MMP to investigate if antidepressants and antipsychotics† are being co-prescribed to individuals with the strong opioids tramadol and tapentadol. Individuals who initiated tramadol or tapentadol in January 2020 on the GMS scheme were identified (n=6,412) and their use of an antidepressant or an antipsychotic was investigated in the same one-month period.[57]

*BZRAs that fall under anatomical therapeutic chemical (ATC) code: N05BA and N05CF were included in the analysis.

†Antidepressants and antipsychotics that fall under ATC code: N06AB, N06AX, N06AA or N05AH were included in the analysis.

The analysis showed that approximately 33% of individuals who were initiated on tramadol alone, a tramadol combination product or tapentadol in January 2020, were co-prescribed an antidepressant or antipsychotic.[57]

11. Summary

Opioids are of limited use in the management of CNCP; there is a lack of robust clinical evidence to support their long-term use in CNCP and there is strong evidence of harm associated with their use. Clinical guidelines on the use of opioids for the management of CNCP highlight the importance of individual evaluation and selection before initiation of opioids. These guidelines recommend, before initiation of opioids, that clinicians should discuss the harms and expected benefits of opioid analgesics (and of alternative treatments) with individuals and agree treatment goals including improvements in physical function and pain.

Clinically meaningful improvements in pain and function without significant risks or harms should be confirmed for continuation of treatment. The analgesic effect of opioids may diminish over time due to the development of tolerance, and therefore short-term efficacy does not guarantee long-term efficacy. Regular review of opioid prescribing is therefore required. Opioids should be discontinued if the agreed treatment goals are not being met. Discontinuation should occur if the individual is still in pain despite using opioids, even if no other treatment option is available.

The analysis in this review has highlighted that trends in opioid utilisation in Ireland have changed from years 2011-2020. There has been a 48% reduction in the number of individuals in receipt of tramadol alone on the GMS scheme from 2011 to 2020. There has been a 79% increase in the number of individuals dispensed oxycodone on the GMS scheme from years 2011-2020. There has been an annual increase in the utilisation of tapentadol since its addition to the HSE-PCRS reimbursement list in 2011. Approximately 20,000 individuals were in receipt of tapentadol on the GMS scheme in 2020.

In 2020, more females (62.4%) than males (37.6%) were in receipt of strong opioids on the GMS scheme and the median age for utilisation of strong opioids was 67 years. This highlights a safety concern as the risk and severity of ADRs increases in older people.

The analysis also highlights the high proportion of co-prescribing of strong opioids with BZRA in Ireland. The analysis showed that an average of 32% of individuals (ranging from 23%-50% of individual strong opioids) who were prescribed a strong opioid, were co-prescribed a BZRA in January 2020. This conflicts with clinical guidelines, the safety alert issued by the MHRA and information within the SmPC of individual opioids, which recommends against concomitant use of opioids with BZRA, as both cause CNS depression and can decrease respiratory drive.

There is also a high proportion of co-prescribing of tapentadol and tramadol with antidepressants and antipsychotics in Ireland. The analysis showed that approximately 33% of individuals who were initiated on tramadol alone, a tramadol combination product or tapentadol, were also dispensed an antidepressant or antipsychotic in January 2020 under the GMS scheme. This conflicts with information provided in the SmPC, which advises against the concomitant use of the relevant opioid and serotonergic drugs, due to the increased risk of serotonin syndrome and convulsions.

12. Conclusion

Opioids are of limited use in the management of CNCP; there is a lack of robust clinical evidence to support their long-term use in CNCP and there is strong evidence of harm associated with their use. There is evidence from the HSE-PCRS claims data that there is a higher utilisation of strong opioids among the older population and a large volume of individuals are co-prescribed opioids with drugs with significant drug interactions (e.g. BZRAs, antidepressants and antipsychotics), which are safety concerns.

Therefore the MMP highlights the following practice points in relation to the use of opioids in the management of CNCP:

Prior to initiation of opioids for CNCP, prescribers should ensure that individuals understand the expected benefit and risk of harms, and agree treatment goals, a review strategy and a plan for discontinuation.

Prescribers should consider the following in relation to HARMS associated with opioids:

- There is a dose dependent risk of serious harms.
- There is ↑ risk and severity of ADRs in older people and people with renal impairment.
- There is ↑ incidence of endocrine abnormalities, altered immune function, opioid induced hyperalgesia, cognitive decline, falls (and fractures), dependence and addiction with long-term use.
- Dependence and addiction is a significant risk with use of greater than three months duration.
- Co-prescribing with CNS depressants (e.g. a BZRA, gabapentin and pregabalin) can produce additive CNS depressant effects including respiratory depression.
- Co-prescribing with serotonergic drugs and antipsychotics can ↑ the risk of serotonin syndrome.
- Co-prescribing tramadol/tapentadol with serotonergic drugs, antipsychotics and other medicinal products that ↓ the seizure threshold, can also ↑ the risk of convulsions.

Prescribers should consider the following in relation to INITIATION of opioids:

- Opioids should only be considered for a trial in carefully selected individuals after optimising non-pharmacological treatments and non-opioid analgesics.
- When initiating treatment, prescribe immediate-release opioids instead of extended-release/long-acting opioids.
- Prescribe the lowest effective dose.

Prescribers should consider the following in relation to CONTINUATION of opioids:

- Continued treatment should only be considered after confirming clinically meaningful improvements in pain and function without significant risks or harms.
    - A 30% improvement in pain and/or a significant improvement in functional ability is considered a realistic treatment goal.
- Clinicians should evaluate the benefits and harms with newly initiated individuals within one to four weeks of starting an opioid for CNCP.
- This review should be repeated every three months or more frequently, thereafter.

Prescribers should consider the following in relation to DISCONTINUATION of opioids:

- If the benefits do not outweigh the harms of continued treatment, clinicians should optimise therapies and work with individuals to taper opioids to ↓ doses or to taper and discontinue.

Opioids should be discontinued if the person is still in pain despite using opioids, even if no other treatment is available.

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