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Clinical Pharmacy

for Pharmacy Students

Lesson 12:

Pain Management in Clinical Pharmacy

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12.1 Epidemiology and Impact of Pain

Epidemiological data consistently show that **pain is one of the most prevalent and disabling health problems worldwide**, with chronic pain affecting roughly one in five adults in many high-income countries and imposing a burden comparable to other major chronic conditions. Low back pain alone is now the leading single cause of years lived with disability (DALY) globally, with recent Global Burden of Disease analyses estimating more than half a billion prevalent cases and forecasting further increases as populations age.[1] Across clinical settings, this burden translates into substantial impairment of health-related quality of life, reduced participation in work and social roles, and high use of healthcare resources, particularly in primary care, musculoskeletal, oncological and perioperative services.

Acute pain is almost universal in the postoperative period and after trauma, and although it is by definition time-limited, inadequate early management is associated with a cascade of adverse physiological and psychological consequences and a higher risk of transition to persistent pain states. In surgical cohorts, more intense acute pain correlates with impaired physical function, reduced mobility and greater limitations in activities of daily living in the weeks following discharge. Postoperative pain that is not adequately controlled has also been linked with increased rates of cardiopulmonary complications, delayed rehabilitation, prolonged length of hospital stay and higher readmission rates, all of which contribute to the economic burden of surgical care.

Chronic pain spans a highly heterogeneous group of conditions, including chronic musculoskeletal pain, neuropathic syndromes, chronic post-surgical pain, cancer-related pain and chronic pain in survivorship after cancer therapy. Chronic pain prevalence varies depending on definition and case ascertainment, but most estimates cluster between 13 and 30% of adults, with a substantial proportion reporting moderate to severe interference with daily functioning and role performance. Certain subgroups such as older adults, women and people living with

[1] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123(2):e273-e283.

multimorbidity or lower socioeconomic status bear a disproportionate burden, which raises important equity considerations for service planning and resource allocation.

Cancer-related pain illustrates particularly starkly the gap between existing evidence and real-world practice, with an important proportion of patients continuing to report moderate or severe pain despite contact with specialist services and availability of effective pharmacological and non-pharmacological options. In low- and middle-income countries, regulatory, logistical and educational barriers to accessing strong analgesics contribute to widespread unrelieved cancer and end-of-life pain, raising ethical and human-rights concerns and prompting calls for global action to reduce these inequities. Even in high-income settings, heterogeneity in assessment practices, fragmentation of care and clinician concerns about long-term opioid therapy contribute to under-recognition and under-treatment of pain, especially among older adults and people with cognitive impairment or communication difficulties.[2]

At the same time, the last two decades have exposed the harms associated with liberal prescribing of opioids for chronic non-cancer pain, particularly in North America, where high-dose and long-term opioid regimens have been linked with increased risks of overdose, substance use disorders and opioid-related mortality. This has created a complex clinical and policy tension: effective relief of moderate to severe pain often requires timely access to potent opioid analgesics, yet indiscriminate or prolonged prescribing carries substantial risks for individuals and populations.

12.2 Pathophysiology and Classification of Pain

Pain is now conceptualized as a multidimensional experience grounded in distinct but often overlapping biological mechanisms, which has led to the adoption of mechanistic descriptors (**nociceptive, neuropathic and nociplastic**) alongside the traditional distinction between **acute and chronic pain**. Understanding these mechanisms is essential for rational prescribing, because different classes of analgesic and adjuvant drugs target specific components of peripheral and central nociceptive processing and therefore have variable efficacy across pain types.[3]

Following the 2020 revision by the International Association for the Study of Pain (IASP), pain is defined as **an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, emphasizing both its subjective nature and its frequent dissociation from demonstrable pathology**. This definition underpins the shift from viewing pain purely as a symptom to recognizing many persistent pain conditions as health problems in their own right, which in turn is reflected in the new chronic pain categories introduced into ICD-11[4].

[2] van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology - where do lifestyle factors fit in?. Br J Pain. 2013;7(4):209-217.
[3] Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982.
[4] ICD-11: International Classification of Diseases, 11th Revision (will be further explored in Pharmacoepidemiology and Pharmacovigilance course – 5th year).

The OxyContin overprescribing scandal in the 2000s

When Purdue Pharma launched controlled-release oxycodone (OxyContin) in 1996, it promoted the drug as a safe, long-acting analgesic for moderate to severe chronic pain, including non-cancer pain, with a purportedly low risk of addiction if used as directed. This messaging, reinforced by extensive detailing to clinicians, sponsored educational events and promotional materials, systematically downplayed the drug's abuse potential and encouraged liberal long-term prescribing at high doses. A widely cited claim that addiction occurred in "less than 1%" of appropriately treated patients, based on very limited and context-specific evidence, helped reassure prescribers and regulators and facilitated rapid uptake. Within a few years, OxyContin sales rose from tens of millions to over a billion dollars annually, accompanied by sharp increases in oxycodone prescribing, particularly in North America.

However, the combination of high oxycodone content per tablet, ease of tampering to defeat the controlled-release mechanism, and widespread availability created ideal conditions for diversion, misuse and dependence in both patients and the wider community. Epidemiological data from affected regions documented parallel rises in OxyContin prescribing, non-medical use, opioid use disorders and overdose deaths, especially in rural and socioeconomically disadvantaged areas. Van Zee's analysis in the American Journal of Public Health characterizes this trajectory as a "commercial triumph, public health tragedy," highlighting how the marketing of a potent controlled drug during a period of liberalized opioid use contributed to a large cohort of individuals exposed to long-term high-dose opioid therapy and to a subsequent wave of opioid-related harms that still shapes pain policy and opioid stewardship today.

- Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health. 2009;99(2):221-227. doi:10.2105/AJPH.2007.131714

From a temporal perspective, pain is usually described as **acute** when it arises in close temporal relation to tissue injury or a noxious stimulus and is expected to resolve with healing, typically over days to weeks. In contrast, **chronic** pain is generally defined as pain that persists or recurs for longer than three months, beyond normal tissue healing time, and is increasingly understood as a distinct disease process involving sustained changes in peripheral and central nociceptive pathways as well as psychological and social factors.

Nociceptive pain refers to pain arising from actual damage to non-neural tissues, due to activation of peripheral nociceptors by noxious mechanical, thermal or chemical stimuli, postoperative states and many inflammatory or degenerative musculoskeletal conditions. At the molecular level, tissue damage and inflammation release mediators such as prostaglandins, bradykinin, hydrogen ions, cytokines, and growth factors, which modulate ion channels and receptors on primary afferent terminals, lowering their activation thresholds and increasing firing rates. Clinically, nociceptive pain is often well localized, described as aching, throbbing or sharp, and shows a reasonably proportional relationship to the degree of tissue injury, although this proportionality may break down as central sensitization develops.

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system, which may involve peripheral nerves, dorsal root ganglia, plexuses, nerve roots or central pathways in the spinal cord and brain. Peripheral nerve injury can lead to ectopic impulse

generation, abnormal expression and trafficking of ion channels, and structural reorganization of synaptic connections, while central lesions may induce loss of inhibitory interneurons, alterations in descending modulatory pathways and maladaptive plasticity within cortical pain networks. Neuropathic pain is typically characterized by spontaneous burning, shooting or electric shock-like sensations, allodynia[5] to normally non-painful stimuli and hyperalgesia to noxious stimuli, with a distribution that is neuroanatomically plausible rather than confined to areas of primary tissue damage.

More recently, the IASP has introduced **nociplastic pain** as a third mechanistic descriptor, defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage that would activate peripheral nociceptors, or disease or lesion of the somatosensory system that would account for the pain. Nociplastic pain is thought to reflect disturbances in central pain processing and modulation, including augmented facilitation or deficient inhibition within spinal and supraspinal networks, and is particularly relevant to conditions such as fibromyalgia, some presentations of chronic low back pain, irritable bowel syndrome and temporomandibular disorders.[6] Although controversial and its pathophysiology remains less well defined than that of nociceptive and neuropathic pain, evidence points to widespread hyperalgesia, sensory hypersensitivity and often comorbid fatigue, sleep disturbance and cognitive symptoms, suggesting a system-wide disturbance in sensory regulation.[7]

In many patients, **pain has mixed or evolving mechanisms**, for example when a nociceptive component from osteoarthritis coexists with neuropathic features from nerve impingement or a superimposed nociplastic process. Recognition of these mixed presentations is important because targeting only the nociceptive component with peripheral anti-inflammatory drugs is unlikely to yield satisfactory relief if central sensitization or neuropathic mechanisms are prominent drivers of the clinical picture.

Pain mechanistic insights have direct implications for pharmacotherapy, because drugs exert their effects at specific points along the nociceptive pathway, from peripheral transduction to central modulation. For predominantly nociceptive pain driven by peripheral sensitization, agents such as paracetamol, non-steroidal anti-inflammatory drugs and selective cyclo-oxygenase-2 inhibitors are often effective first-line options, sometimes complemented by topical non-steroidal anti-inflammatory drugs or local anesthetics when the pain is superficial and localized. In contrast, neuropathic pain often responds poorly to simple analgesics alone and is more amenable to drugs that modulate voltage-gated calcium channels (gabapentinoids), enhance descending monoaminergic inhibition (tricyclic antidepressants and serotonin–noradrenaline reuptake inhibitors) or stabilize neuronal membranes via sodium channel blockade, although effect sizes remain modest and combination therapy is frequently required.

In nociplastic pain states, where central sensitization and dysregulated pain modulation are prominent, the relative benefits of opioids and non-steroidal anti-inflammatory drugs are generally limited, and greater emphasis is placed on centrally acting adjuvants, non-pharmacological strategies and interdisciplinary rehabilitation. Conditions characterized by

[5] **Allodynia** is pain evoked by a stimulus that does not normally provoke pain, such as light touch or gentle brushing of the skin.
[6] Roecker CB, Schut SM. Nociplastic pain: an introduction. J Can Chiropr Assoc. 2025;69(2):131-144.
[7] Macionis V. Nociplastic pain: controversy of the concept. Korean J Pain. 2025;38(1):4-13.

widespread pain, sleep disturbance and fatigue may respond better to low-dose tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors and certain anticonvulsants than to peripherally acting drugs, and careful titration and monitoring are essential given the chronicity of treatment and the risk of tolerability issues. Across all mechanistic categories, opioids retain an important role in acute severe nociceptive pain and cancer-related pain when used judiciously, but in chronic non-cancer contexts their use must be weighed against well-documented risks and is usually reserved for carefully selected patients after other mechanism-directed options have been optimized.

Mechanism-based classification also facilitates a more individualized approach to analgesic selection and sequencing, encouraging clinicians to re-evaluate the presumed pain mechanism when response to treatment is suboptimal and to adjust therapy accordingly. For example, poor response to structurally optimized non-steroidal anti-inflammatory drug therapy in longstanding low back pain should prompt consideration of neuropathic or nociplastic contributors and the introduction of centrally acting agents and non-pharmacological interventions rather than simple escalation of opioid doses. In this way, contemporary understanding of nociceptive, neuropathic and nociplastic mechanisms, and of peripheral and central sensitization, underpins rational prescribing and supports a shift from purely symptom-driven to mechanism-informed pain management.

12.2.1 Principles of clinical pain assessment

Clinical pain assessment aims to characterize a subjective experience in a reproducible way by systematically exploring intensity, functional impact, temporal profile and likely underlying mechanisms. A structured approach improves communication, guides mechanism-based treatment selection and provides a baseline for evaluating the effects of pharmacological and non-pharmacological interventions over time.

Self-report is the reference standard whenever possible, and unidimensional tools such as the 0–10 numerical rating scale, visual analogue scale and verbal descriptor scales are widely used in routine practice. Because a given intensity score can be associated with very different consequences for daily life, it should be interpreted together with measures or questions that capture interference with mobility, self-care, work, sleep and mood, especially in chronic pain.

Beyond intensity and impact, temporal pattern and mechanistic clues from history and examination are central to mechanism-informed prescribing. Clarifying whether pain is continuous or intermittent, activity-related or spontaneous, and exploring descriptors such as burning, electric shocks, or aching, together with simple sensory testing for allodynia or hyperalgesia, helps distinguish predominant nociceptive, neuropathic or nociplastic components.[8]

In patients who cannot reliably self-report, such as many cognitively impaired adults, critically ill patients and young children, **observational and proxy-based assessment tools** are required. Validated behavioral scales that rate facial expression, body movements, vocalizations, and changes in usual behavior, combined with input from family or primary caregivers and adapted to developmental stage in pediatrics, provide a structured way to infer pain and monitor response to treatment.

[8] Fink R. Pain assessment: the cornerstone to optimal pain management. Proc (Bayl Univ Med Cent). 2000;13(3):236-239.

Across all settings, reassessment after any significant treatment change is essential and should encompass pain intensity, functional capacity, adverse effects and progress towards patient-centered goals. **Using the same instruments over time** allows clinicians to judge whether a given intervention is beneficial, inadequate or harmful, and to adjust the management plan accordingly in an iterative, mechanism-guided manner.

12.3 Pharmacological management by pain mechanism

Rational pharmacotherapy in pain management should be explicitly grounded in the predominant underlying mechanism (i.e., nociceptive, neuropathic or nociplastic), being aware that many patients have mixed phenotypes and that drug therapy is only one component of multimodal care. For each mechanism, specific drug classes have the strongest evidence base and should form the stepwise treatment, with opioids reserved for defined indications and usually after optimization of non-opioid options.

12.3.1 Nociceptive pain

Nociceptive pain arising from tissue injury and inflammation (for example postoperative pain, acute musculoskeletal trauma, many forms of osteoarthritis) typically responds well to peripherally acting analgesics that target prostaglandin synthesis or other inflammatory mediators. First-line pharmacological options are paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclo-oxygenase-2 inhibitors, used on a regular, time-limited schedule when possible and tailored to gastrointestinal, renal and cardiovascular risk.

Topical formulations of NSAIDs or local anesthetics can be useful in localized nociceptive pain (such as superficial musculoskeletal injury or localized osteoarthritis) and may reduce systemic exposure in older or multimorbid patients. Short-term use of weak or strong opioids as part of a multimodal regimen can be appropriate for moderate to severe acute nociceptive pain or cancer-related nociceptive pain when non-opioid measures are insufficient, but long-term opioid therapy for chronic non-cancer nociceptive pain should be exceptional and guided by stewardship principles outlined later in this chapter.

12.3.2 Neuropathic pain

Neuropathic pain due to lesion or disease of the somatosensory system (for example painful diabetic polyneuropathy, post-herpetic neuralgia, radiculopathy) often responds poorly to simple analgesics alone and requires drugs that modulate neuronal excitability or descending inhibition. Contemporary guidelines converge on gabapentinoids (e.g., gabapentin, pregabalin), certain antidepressants (e.g., tricyclics such as amitriptyline, nortriptyline; serotonin–noradrenaline reuptake inhibitors such as duloxetine and venlafaxine), and topical lidocaine or capsaicin (for localized peripheral syndromes) as first-line or co-first-line pharmacological options, chosen and titrated according to comorbidities, age, and adverse effect profile.

Second-line options can include switching within or between these classes, combination therapy (for example SNRI plus gabapentinoid) and, in selected cases, tramadol or tapentadol when first-line agents are ineffective or poorly tolerated, always with careful monitoring for dependence, serotonin toxicity and other harms. Strong opioids generally have only modest efficacy in chronic neuropathic pain and are usually considered third-line, time-limited options in carefully selected patients who have failed multiple mechanism-appropriate trials and in whom functional benefit clearly outweighs risk.

12.3.3 Nociplastic pain

In nociplastic pain conditions such as fibromyalgia and some forms of chronic low back pain without clear structural pathology, peripherally acting analgesics and opioids have limited benefit and should not form the core of long-term pharmacotherapy. Instead, low-dose tricyclic antidepressants, SNRIs (e.g., duloxetine) and selected anticonvulsants (e.g., pregabalin or gabapentin) are often used as adjuvants to non-pharmacological strategies, with cautious titration, regular review of sleep, mood and cognition, and explicit discussion of realistic expectations (small to moderate symptom reductions rather than cure).

Many patients present with mixed-mechanism pain, in which nociceptive, neuropathic and nociplastic components coexist, for example osteoarthritis with radicular features and central sensitization. In such cases, treatment should prioritize the dominant mechanism while systematically addressing others: an NSAID or paracetamol for inflammatory nociceptive drivers, adjunctive gabapentinoids or antidepressants for neuropathic or nociplastic elements, and early integration of exercise therapy, psychological interventions and education to target central sensitization, with regular reassessment and de-escalation of ineffective drugs.

12.4 Opioid pharmacology and clinical use

Opioid analgesics remain central to the management of moderate to severe acute pain and cancer-related pain, and they have a more selective, cautiously defined role in chronic non-cancer pain, where benefits must be weighed against well-documented risks. Their clinical use demands a clear understanding of receptor pharmacology, pharmacokinetics and organ-specific considerations, together with careful definition of treatment goals, structured initiation and titration, judicious rotation when needed, and proactive management of predictable adverse effects.[9]

Most clinically used opioids exert their analgesic effects primarily through agonism at the μ-opioid receptor, with additional activity at κ- and δ-receptors or non-opioid targets for some agents. **Morphine** is the archetypal full μ-agonist, extensively glucuronidated to morphine-3- and morphine-6-glucuronide, the latter contributing to analgesia but accumulating in renal impairment, whereas **oxycodone** and **hydromorphone** are semi-synthetic μ-agonists with active metabolites and hepatic metabolism via cytochrome P450 pathways that can be affected by drug–drug interactions and liver dysfunction. **Fentanyl** is a highly lipophilic, potent μ-agonist with rapid onset and short redistribution-driven offset, making it suitable for transdermal and parenteral use in cancer and perioperative settings, while **buprenorphine** is a high-affinity partial μ-agonist and κ-antagonist with a ceiling effect on respiratory depression that may confer safety advantages but complicates subsequent switching to other opioids. **Tramadol** and **tapentadol** combine relatively low-efficacy μ-agonism with monoaminergic reuptake inhibition; tramadol has a CYP2D6-dependent active metabolite and a complex interaction profile, whereas tapentadol's dual mechanism and simpler metabolism may translate into comparable efficacy with somewhat fewer gastrointestinal adverse effects in some populations.

In **acute pain**, including postoperative and trauma-related pain, short-term opioid therapy is indicated when non-opioid and regional techniques alone do not provide adequate relief, with

[9] Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. Br J Clin Pharmacol. 2013;75(1):60-78.

the aims of reducing pain to a tolerable level, facilitating mobilization and rehabilitation, and preventing complications related to unrelieved pain. In **cancer pain**, strong opioids are first-line for moderate to severe nociceptive pain and many mixed-mechanism states, generally following adapted **WHO-style stepwise approaches** but increasingly embedded in multimodal regimens that also address neuropathic and nociplastic components and comorbid symptoms. For **chronic non-cancer pain**, reviews show that opioids confer only modest average improvements in pain and function over the short to medium term and are associated with increased adverse events, so guidelines recommend restricting their use to carefully selected patients with clearly defined functional goals when other mechanism-directed therapies have been optimized.[10]

Initiation of opioid therapy should start with the lowest effective dose of an immediate-release formulation, titrated cautiously according to regular assessments of pain intensity, functional gains and adverse effects. Immediate-release preparations are preferred when starting or adjusting treatment because they allow finer dose titration and clearer attribution of benefits and harms, with consideration of long-acting formulations only once a stable, effective dose has been established and ongoing need is evident, particularly in cancer and some persistent pain contexts. Breakthrough or incident pain requires provision for rescue doses administered at appropriate intervals and reviewed frequently to avoid inadvertent dose escalation driven by poorly controlled background pain or misclassified neuropathic flares. Lack of response should prompt a structured review of diagnosis, mechanism, adherence and comorbidities, rather than reflex dose escalation, and in chronic non-cancer pain, absent functional improvement despite adequate trials is a strong signal to taper and prioritize non-opioid strategies.

Opioid rotation is an important strategy when analgesia is inadequate or adverse effects are problematic despite appropriate titration and involves switching to an alternative opioid with the aim of improving the benefit–harm balance. Equianalgesic dose tables provide approximate potency ratios between agents but are derived from heterogeneous studies and do not account for incomplete cross-tolerance, interindividual pharmacokinetic variability, organ dysfunction or pharmacogenetic differences, so equianalgesic doses must be reduced when switching, with subsequent titration based on clinical response. Caution is needed when rotating from high-dose regimens, in frail older adults and in renal or hepatic impairment; in such settings, selecting opioids with inactive or non-renally cleared metabolites (for example fentanyl or carefully dosed buprenorphine) can reduce the risk of metabolite accumulation and neurotoxicity.

Opioid equianalgesic doses	
Opioid (oral)	**Approximate equianalgesic dose to 30 mg oral morphine**
Morphine	30 mg
Oxycodone	20 mg
Hydromorphone	7.5 mg
Codeine	200 mg
Tramadol	~300 mg (≈0.1 relative to morphine)
Tapentadol	~75 mg (≈0.4 relative to morphine)

Common opioid-related adverse effects are predictable consequences of receptor activation in the gut, central nervous system and endocrine systems, and they should be anticipated and managed proactively. Constipation is almost universal in long-term therapy because μ-receptor

[10] Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460.

activation in the gastrointestinal tract reduces motility and increases fluid absorption, and tolerance rarely develops. Prophylactic laxative regimens and, when necessary, peripherally acting μ-opioid receptor antagonists form the cornerstone of management. Nausea and vomiting are frequent in treatment due to delayed gastric emptying and stimulation of the chemoreceptor trigger zone, usually improving over days. Short-term antiemetics may be required if symptoms compromise nutrition or adherence. Sedation and cognitive impairment warrant dose review, timing adjustments and consideration of switching to a better-tolerated opioid, especially in older or multimorbid patients at risk of falls and delirium.

World Health Organization (WHO) stepwise approach to pain relief

The WHO–style stepwise approach to pain relief was originally developed for cancer pain but has strongly influenced analgesic prescribing more broadly. It proposes a simple, hierarchical framework in which **treatment is escalated according to pain intensity and response**, while encouraging regular dosing and attention to individual patient factors. Classically, the approach is depicted as a three-step ladder. **Step 1** recommends non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), with or without adjuvant agents (for example antidepressants or anticonvulsants for neuropathic components), for mild pain. **Step 2** adds a so-called "weak" opioid (such as codeine or low-dose tramadol) to the non-opioid backbone for moderate pain, still combined with adjuvants where indicated. **Step 3** replaces weak opioids with "strong" opioids (such as morphine, oxycodone, hydromorphone or fentanyl) for severe pain, again on a background of non-opioid and adjuvant therapies, with doses titrated according to individual response and tolerability.

Several conceptual features of this model remain clinically valuable. It emphasizes regular (around-the-clock) dosing rather than purely as-needed administration, integration of non-opioid and adjuvant drugs at every step, and the principle that pain management should be adapted to the person, not the disease alone. However, over time **important limitations have been recognized**. The distinction between "weak" and "strong" opioids is pharmacologically imprecise and may lead either to under-treatment when doses are capped or to unnecessary polypharmacy when fixed combinations are used without clear benefit. For chronic non-cancer pain, the ladder in its original form does not adequately incorporate concerns about long-term opioid harms, nor does it sufficiently emphasize mechanism-based prescribing or the central role of non-pharmacological therapies.

Consequently, various "modified" or "reverse" ladders have been proposed. These **adaptations often de-emphasize step-2 opioids**, recommend earlier use of adjuvant drugs for neuropathic and nociplastic pain, and place stronger emphasis on stepping down or discontinuing opioids when goals are not met. In contemporary practice, the WHO-style ladder is best viewed as a pragmatic historical framework: useful for structuring basic escalation of analgesic intensity, especially in cancer pain and resource-limited settings, but to be embedded within a broader, multimodal, mechanism-informed and time-limited strategy rather than followed rigidly.

- Miller E. The World Health Organization analgesic ladder. J Midwifery Womens Health. 2004;49(6):542-545.

12.4.1 Opioid Stewardship

Opioid stewardship describes a coordinated, system-level approach to opioid use that seeks to maximize analgesic benefit and functional gains while minimizing harms for individuals and populations. In contrast to traditional prescribing focused on individual encounters, stewardship programs explicitly balance three objectives: preserving access for patients with significant pain, limiting unnecessary or prolonged exposure, and reducing risks of misuse, overdose and other adverse outcomes, typically through multidisciplinary collaboration, standardized processes and continuous quality improvement.

Risk assessment is a core element before and throughout opioid therapy and should extend beyond generic contraindications to a structured appraisal of factors that increase the likelihood of serious harm. Key domains include prior or current substance use disorder, psychiatric comorbidities such as depression, anxiety and post-traumatic stress disorder, concurrent use of high-risk co-medications, medical comorbidities that heighten vulnerability to respiratory depression, and social factors such as unstable housing or limited support. Where available, risk prediction tools and validated screening instruments can complement clinical judgement, but stewardship reviews emphasize that they should not be used mechanistically; rather, they inform the intensity of monitoring, choice of formulation, dose ceilings and the need for early involvement of addiction or mental health services.

Monitoring strategies operationalize stewardship principles in everyday practice by embedding safeguards around **prescribing and review**. Common components include written treatment agreements that clarify expectations around goals, duration, safe use and refill policies; systematic use of prescription monitoring programs or electronic health record tools to identify duplicate prescribing or risky combinations; and scheduled reassessment of pain, function, adverse effects and aberrant behaviors at defined intervals, with particular attention to dose thresholds where risk escalates. **Audit-and-feedback interventions**, clinical decision-support prompts and pharmacist-led chart reviews have been associated with reductions in high-dose or prolonged opioid prescribing without deterioration in pain scores or increased emergency visits, suggesting that more conservative, guideline-concordant prescribing can be achieved without compromising symptom control when supported by multimodal alternatives.

Tapering and discontinuation are integral to stewardship and should be framed not as punitive measures but as part of planned care whenever risks outweigh benefits, treatment goals are not met, or the original indication has resolved. Current guidance converges on the principle that dose reductions must be gradual, collaborative and tailored to withdrawal symptoms, with many authors advocating proportional tapers in which reductions become progressively smaller as the total dose decreases, to smooth pharmacodynamic changes at the μ-opioid receptor and improve tolerability. Abrupt cessation is strongly discouraged except in situations of serious safety concerns such as suspected diversion or life-threatening toxicity, because rapid withdrawal is associated with severe distress, destabilization of co-existing mental health conditions and, in some reports, increased suicidality and overdose risk; effective stewardship therefore couples slow dose reduction with reinforcement of non-pharmacological pain strategies, psychological support and ready access to addiction treatment where needed.[11]

[11] Abie Horowitz M, Framer A, Strang J, Taylor D. Tapering and withdrawing opioids: guidance informed by fundamental principles to minimise withdrawal symptoms. Ther Adv Psychopharmacol. 2025;15:20451253251371504.

12.4.2 Practical Approach to Opioid Stewardship

A practical approach to opioid stewardship in routine care begins with a small set of recurring questions that clinicians can apply at every encounter, regardless of setting. At its core, each review should explicitly address whether an opioid remains indicated for this patient's pain mechanism, whether the current dose is the lowest that provides meaningful functional benefit, and what the specific plan is for dose reduction or discontinuation over time. Framing stewardship in this way helps to shift the focus from maintaining a static prescription to continuously testing the ongoing value of opioid therapy against clearly defined goals for function, participation and quality of life.

In practice, these questions can be organized into a simple bedside or ward-round checklist that structures the consultation without adding substantial time.

1. A first step is to **confirm indication and alignment with mechanism**: Is the pain predominantly nociceptive, neuropathic or nociplastic, and are non-opioid and adjuvant options optimized for that mechanism before or alongside opioid use.
2. The next step is **risk stratification**, incorporating brief screening for substance use disorder and psychiatric comorbidity, review of high-risk co-medications such as benzodiazepines and gabapentinoids, and identification of medical frailty or organ impairment, which will influence dose ceilings and monitoring intensity.
3. Once indication and risk are clear, clinicians can **interrogate benefit** by documenting not only current pain ratings but also specific functional benchmarks (for example walking distance, self-care, work, or sleep), and then judging whether observed gains justify ongoing exposure considering side-effects and risk profile.
4. The final part of a practical checklist concerns **forward planning and contingency**. For each patient on opioids, there should be a time-bound plan for review and potential dose adjustment, even when treatment is expected to continue, with explicit triggers for tapering such as lack of functional improvement, escalating dose without clear benefit, or emergence of problematic adverse effects or aberrant behaviors. When tapering is needed, clinicians can start from a default schedule (e.g., gradual 5–10% reductions of the total daily dose every few weeks, slowed or paused if withdrawal or pain flares arise) and adapt this according to patient preference, comorbidities and available supports, rather than resorting to abrupt cessation. In parallel, each visit should incorporate at least one concrete action to strengthen non-opioid components of the regimen, such as optimizing adjuvants, reinforcing physical and psychological therapies, or addressing sleep and mood, so that stewardship is experienced by patients not as "dose policing" but as an ongoing process of multimodal optimization.

12.4.3 The role of pharmacists in opioid stewardship

Across the body of evidence synthesized in a recent scoping review[12], pharmacists are consistently depicted as active, clinically engaged members of opioid stewardship efforts rather than passive dispensers, with several recurring categories of activities that appear across settings and jurisdictions. One might wonder if there is any difference between the role of clinical pharmacists in opioid and analgesia management and their role in managing other conditions.

[12] Gondora N, Versteeg SG, Carter C, et al. The role of pharmacists in opioid stewardship: A scoping review. Res Social Adm Pharm. 2022;18(5):2714-2747.

Education (patients, professionals, and community)

Educational activities are the most frequent pharmacist contribution to opioid stewardship, present in roughly three quarters of the studies summarized. Education is directed at patients, prescribers and other health professionals, students, first responders, and community stakeholders, often with measurable improvements in knowledge, attitudes, prescribing, and clinical outcomes.

For patients, pharmacists provide structured counselling on appropriate opioid use, expectations for pain relief, safe dose titration and tapering, recognition of adverse effects, and safe storage and disposal of leftover medicines. In cancer and chronic non-cancer pain settings, pharmacist-delivered teaching is embedded in broader pain management programs and is associated with reductions in opioid use, improved pain scores, and better understanding of treatment regimens.

For prescribers and other health professionals, pharmacists deliver targeted educational sessions (academic detailing, workshops, or case-based discussions) on guideline-concordant opioid prescribing, risk mitigation, use of prescription monitoring programs, and incorporation of risk assessment tools and treatment agreements. These interventions are often accompanied by improved use of prescription monitoring systems, more consistent application of risk mitigation strategies, and changes in prescribing patterns, such as reduced co-prescribing of opioids and benzodiazepines or reduced use of specific high-risk opioids.

In the public health sphere, pharmacists educate first responders and community stakeholders on overdose recognition, naloxone use, and practical aspects of programs such as “patch-for-patch” fentanyl initiatives, with demonstrated gains in knowledge, preparedness, and naloxone distribution. Educational activities thus operate at bedside, team, and community levels, and are portrayed as central to extending stewardship beyond traditional clinical encounters.

Medication therapy adjustments and structured medication review

Medication therapy adjustment is another dominant activity, appearing in more than half of the interventions described, often alongside systematic medication reviews. Pharmacists identify opportunities to optimize opioid and co-analgesic regimens by adjusting doses, switching agents, modifying formulations, aligning therapy with guidelines, or recommending de-escalation and tapering strategies.

These activities take multiple forms: developing and implementing individualized tapering plans for chronic non-cancer pain; optimizing cancer pain regimens (including management of side effects and rotation between opioids); designing and managing withdrawal or transition protocols (e.g. tapering from continuous infusions or from high-dose regimens); and adjusting peri-operative analgesic plans to reduce unnecessary opioid exposure at discharge. In many of these studies, pharmacists’ recommendations are highly accepted by prescribers, with acceptance rates often exceeding two-thirds and associated with clinically relevant outcomes such as reduced morphine milligram equivalents (MME), fewer patients discharged on opioids, or improved symptom control.

Structured medication review is frequently used as the entry point to these adjustments. Pharmacists conduct comprehensive assessments of current therapy, comorbidities, concomitant medications (notably benzodiazepines and other CNS depressants), and

adherence or misuse indicators, and then formulate recommendations or care plans. In team-based clinics and hospital services, these reviews are embedded in multidisciplinary care pathways; in community and primary care settings, they underpin pharmacist-led clinics or telephone-based interventions.

Opioid agonist therapy, naloxone, and other specific therapies

A substantial segment of the literature focuses on pharmacists' involvement with opioid agonist therapy and naloxone supply as components of stewardship. In these interventions, pharmacists prescribe or dispense methadone or buprenorphine/naloxone, support initiation and maintenance of opioid agonist treatment, and monitor adherence and response in collaboration with prescribers. These activities are particularly prominent in health systems treating patients with opioid use disorder, where pharmacists' expertise is leveraged to balance pain control, dependence treatment, and overdose risk.

Naloxone-related activities range from systematically identifying patients at high risk of overdose and proactively recommending or dispensing take-home naloxone, to developing and using electronic health-record order sets and standardized processes for co-prescribing naloxone with high-risk opioid regimens. Pharmacists also lead telephone-based naloxone education clinics and consult services, improving awareness and uptake of naloxone among patients and prescribers despite recurring barriers such as cost, time, and perceived need.

In addition, pharmacists participate in programs designed to reduce misuse of specific high-risk products, such as fentanyl patch initiatives that require returning used patches prior to refills. In these models, pharmacists verify appropriate use, identify tampering or diversion, and liaise with prescribers and, in some jurisdictions, law enforcement when concerns arise. Such targeted product-specific interventions are presented as practical applications of stewardship principles to concrete safety problems.

Risk assessment, screening tools, and monitoring

Risk assessment is another clear pillar of pharmacist activity in opioid stewardship. Pharmacists apply and sometimes help implement standardized screening instruments for overdose risk, misuse, or opioid-induced respiratory depression, integrating these tools into pharmacy or clinic workflows.

Examples include use of validated risk indices for serious opioid-related harms, as well as programs where community pharmacists screen every patient receiving an opioid prescription for misuse or overdose risk and tailor education and follow-up accordingly. These tools often sit alongside pharmacist review of prescription drug monitoring program data, urine drug screening protocols, pill counts, and treatment agreements, especially in primary care and veterans' health settings.

By operationalizing risk stratification at the point of prescribing or dispensing, pharmacists flag patients who may benefit from intensified monitoring, opioid tapering, naloxone co-prescribing, or referral to specialist services. In some interventions, pharmacists chair or participate in multidisciplinary controlled substance committees that oversee complex cases, update policies on monitoring (e.g. urine drug screening frequency), and ensure consistent application of risk mitigation strategies across a health system.

Policy development, protocols, and service design

Beyond direct patient care, pharmacists contribute to designing and implementing institutional policies, protocols, and care pathways that embody opioid stewardship principles. Activities include developing standardized order sets for patient-controlled analgesia or IV morphine infusions; creating withdrawal or tapering protocols; harmonizing chronic pain management approaches across clinics; and drafting opioid prescribing policies that specify monitoring requirements, acceptable dose ceilings, and indications for specialist referral.

Pharmacists also help design and run dedicated services such as opioid renewal clinics, team-based chronic pain management programs, perioperative pain management services, and pain pharmacist clinics that support complex surgical or high-risk patients. In these settings, their roles span protocol development, day-to-day clinical management, and coordination of follow-up, with demonstrated effects on utilization of health services (e.g. emergency department visits, unscheduled primary care visits) and on opioid cost and consumption.

At system level, pharmacists engage in data collection, audit, and feedback: they define and track indicators such as opioid consumption in MME, incidence of high-risk combinations, adherence to protocolized regimens, or documentation of pain and function measures. These data are used to refine protocols and to provide structured feedback to prescribers and services, reinforcing stewardship as an ongoing quality-improvement process rather than a one-off intervention.