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ORIGINAL ARTICLE

Pharmacological Management of Chronic Pain: How to Deal with the Catch-22 Situation

Trine Andresen[1] | Marieke Niesters[2] | Albert Dahan[2] | Bart J. Morlion[3] | Tony O'Brien[4] | Asbjørn M. Drewes[1*]

[1]Mech-Sense, Departments of Gastroenterology and Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark

[2]Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands

[3]Leuven Centre for Algology & Pain Management, University Hospital Leuven, Belgium

[4]Marymount University Hospital & Hospice, Curraheen, Cork; Cork University Hospital, Wilton, Cork and College of Medicine and Health, University College, Cork, Ireland

Abstract

Management of chronic pain is multidisciplinary, but pharmacotherapy is one of the mainstays of pain management. As applies in all medical therapies, clinicians must strive to achieve the best possible outcome for patients in terms of maximising benefit and minimizing risks, and ensure that this is conducted for each treatment and as an integral element in selecting appropriate therapies. If the balance between risk and benefits is not achieved and understood by the patient.

Chronic pain patients may already experience a degree of stigmatisation, which can be further exacerbated by evolving socio-political pressures in respect of analgesic availability and accessibility. Hence, we have a Catch-22 situation in which patients become ensnared; they may need supervised access to legitimate analgesic medication(s) but these are not easily accessible because of concerns of the analgesic side-effects and abuse/misuse potential influencing both the individual and wider society.

In this paper, we review the evidence in respect of analgesic use in chronic pain. We highlight the importance of: 1) better education and awareness of the problem, 2) evaluate the balance between effect and side effects rather than focusing on pain intensity alone, and include such composite measures in clinical trials, 3) identification of responders to treatment and systematic monitoring for misuse and 4) the use of big data to guide politicians away from inappropriate regulatory restrictions. Such a strategy will improve pain treatment and due to the major costs associated with chronic pain it will also be of benefit for society.

Keywords: Pain, Analgesics, Opioids, Management, Dependency, Health Policy

1 | INTRODUCTION

Chronic pain has per May 2019 been adopted by the World Health Organization (WHO) to the new international classification of diseases, ICD-11 [1]. It is defined as pain that lasts or recurs for more than three months. Chronic pain affects about 19% of the adult European population [2] and has tremendous impact on patients' personal life such as increased risk of depression and reduced quality of life [3]. Moreover, besides the comprehensive humanitarian and social burden, the economic impact of pain is greater than most other health conditions [4].

Management of chronic pain is challenging and the most affected patients often require a multidisciplinary approach including physiological, psychological, sociological and pharmacological interventions [5]. Although some pharmacological treatment regimens provide relief in pain intensity, that relief may only be significant for a minority of patients and improved management is an unmet need. Without evidence-based and validated strategies, treatment is often based on a "trial and error approach" causing the patient to feel "experimented upon"[6]–[8]. Several reasons for treatment failure have been identified and discussed e.g. incorrect diagnosis, failure to manage comorbid conditions, incorrect selection of therapy and inadequate measure [9].

To diminish the "trial and error approach", guidelines have led to the creation of flowcharts to guide clinicians into a more rational pain management approach [6], 10]–[12]. Pharmacological treatment is one of the cornerstones in such guidelines and pain management in general [13], and is the focus of this narrative review. A key element is to find the balance between effective treatment (reduction in pain combined with improvements in functioning and mental status) and acceptable side effects [5], [14]. Currently, numerous analgesic agents are available (from non-opioids/opioids to atypical analgesics), but unfortunately these are often associated with adverse effects, abuse/misuse potential [15]–[17], uncertain long-term effects [18], and insufficiently documented analgesia [19], [20]. Even if the recommended medication may improve pain, adverse effects often limit their use due to tissue damage or reduced compliance. This leaves the choice of pharmacological treatment in a conflicting "Catch-22"-like dilemma between efficacy, adverse effects, misuse/abuse or addiction potential.

Consequence of the above situation is that patients with chronic pain are treated with analgesics that are expensive, but are without documented long-term efficacy, cause serious adverse effects, and have a high risk of addiction and misuse/abuse as depicted in figure 1. Hence, physicians are left in an inevitable conflicting dilemma and patients may therefore not be offered reliable pain management. The aims of this review are therefore to: 1) briefly discuss the efficacy and side effects of analgesics in chronic pain; 2) review the catch-22 dilemma for pharmacological management of chronic pain and 3) provide new ideas to circumvent the dead end for pain management.

Analgesics and side effects

The cornerstone of pharmacological pain treatment has been based on the WHO ladder, which was developed for pain treatment in cancer patients. However, the ladder has also been adapted for use in patients with acute and non-cancer chronic pain [21]. Recently, this simple approach has been questioned and modification of the ladder may be essential to ensure its continued use in future pain management [22]–[26]. Furthermore, the ladder is mainly intensity based and side-effects are not in focus. Therefore, it may also contribute to and promote the uncritical prescribing of opioids. Unfortunately, documentation for efficacy of analgesics is poor when it comes to chronic pain Table 1. In this current review we will therefore use the frameworks: Non-opioids, opioids and atypical analgesics rather than the typical ladder nomenclature.

Supplementary information The online version of this article (https://doi.org/10.15520/jcmro.v4i02.382) contains supplementary material, which is available to authorized users.

Corresponding Author: *Asbjørn M. Drewes*
Mech-Sense, Departments of Gastroenterology and Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark

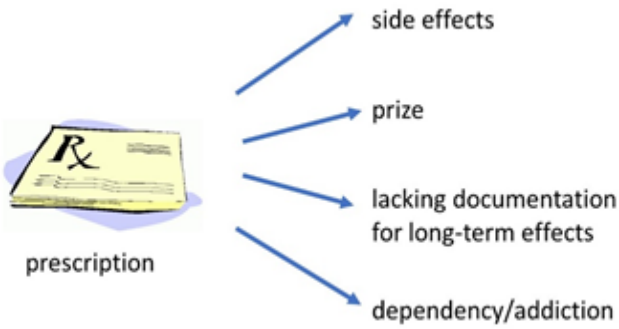

FIGURE 1: Analgesics are the backbone of pain medicine.Even though most medication can alleviate pain and associated symptoms,side-effects and prize often limit their use. Additionally, there is lack ofstudies showing long-term effects, and dependency/addiction is a substantialproblem with strong analgesics. This explains the so-called catch-22 situationthat limits optimal pain management.

Dilemmas with non-opioids

Non-opioids such as acetaminophen or NSAIDs are easy accessible and are recommended for the initial treatment of mild to moderate pain [27]. There is little evidence to support the efficacy of acetaminophen in patients with chronic pain [28], however, if misused acetaminophen is associated with an increased risk of chronic liver failure [29].

NSAIDs are widely used for their anti-inflammatory and analgesic effects [30]. NSAIDs are associated with a number of adverse effects such as heartburn, nausea, dyspepsia, abdominal pain as well as more serious gastrointestinal complications and cardiotoxic effects [30]–[32]. Additionally, NSAIDs have shown the same misuse potential (inability to stop its use, increasing dose without approval, use for purposes other than intended) as weak opioids such as tramadol [33].

Dilemmas with opioids

Weak opioids (tramadol/codeine) are used for treatment of mild to moderate pain. Codeine is a prodrug and is metabolized in the liver by CYP2D6 to morphine. Individuals who are "poor metabolizers" may experience inadequate pain relief, whereas individuals who are "ultra-rapid metabolizers" may experience symptoms of morphine overdose [34]. Due to this, codeine can be difficult to use.

Tramadol is also a prodrug that is metabolized particularly to O-desmethyltramadol, which is the main active metabolite. Effect and side effects are influenced by an individual's CYP genetics with poor metabolizers experiencing low O-desmethyltramadol and ultra-metabolizers experiencing high O-desmethyltramadol [35]. Tramadol is associated with similar side effects as observed for stronger opioids, but the abuse potential is lower as patients are less likely to escalate doses [36]. Nevertheless, careful prescribing of weak opioids is needed to prevent harm [35].

For both codeine and tramadol as well as other opioids, it is possible to use pharmacogenetic testing to optimize treatment [37].

Strong opioids can be used when necessary together with non-drug interventions, psychological support and rehabilitation [6]. However, their use is associated with risk of major side effects and abuse, diversion and addiction, and overdose is unfortunately common [38]. There is concern of the increase in opioid prescriptions in some countries, whereas patients in other (typically less developed) countries have no legal access to strong analgesics [39], [40] [41]. Increase in prescription of opioids with some more popular than others, may be due to solid marketing rather than scientific knowledge [42]. There is a concern related to the increase of opioid consumption in the Western World [43]. In some countries e.g. Australia, prescription of opioids seems to be the major source of misuse [44]. As a consequence, policymakers have responded with a national focus on reducing opioid prescribing through stringent guidelines [38]. Additionally, a variety of formulation strategies have been designed to minimize abuse potential of opioids [45]. On the other hand, strong opioids still play a role as therapeutic options in pharmacological management of chronic pain, but as with any other medical therapies treatment must be regularly reviewed and revised (efficacy/adverse effects) [6]. Few studies have shown long-term effects (i.e. > 3 months) and to our knowledge only for tapentadol (prolonged release) [46], [47] or for very specific patient groups e.g. low back pain [48].

Tapentadol is characterized by a dual mechanism of action (μ-opioid receptor agonism and noradrenaline reuptake inhibitor) [49], [50]. When compared with strong opioids it seems to have less side effects such as constipation, as well as a lower risk of abuse potential [47]. However, further research in relation to long-term treatment and misuse/abuse potential is needed.

It has been disputed how frequent opioid dependency is for prescription opioids. Estimates of misuse and abuse ranges from < 1% to 40% - a range related to difficulties with diagnosing and inconsistent definitions between studies [39]. For example, Noble et al. found in a review of 17 studies that signs of opioid addiction were only reported in 0.05% of patients and abuse in only 0.43% [51]. In a later study, Minozzi et al. (2013) estimated the prevalence range of opioid dependency from 0 to 31% in adult patients with pain [52]. Thus, although the opioid prescription is of concern and needs to be taken care of along ongoing follow-up, available evidence does not uniformly support that prescription opioids for chronic pain conditions – although of major concern - are associated with a major risk of developing dependence [52]. International guidelines also recommend short-term treatment with opioids for the relief of severe pain except in a few highly susceptible individuals (International Association for the Study of Pain (IASP)[1]) [6].

Dilemmas with atypical analgesics

Antidepressants (tricyclic and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (e.g. gabapentin and pregabalin) are drugs with the most convincing evidence in pain management, especially in neuropathic and functional pain disorders [53], [54]. It should be noted that for some types of pain, anti-neuropathic medication should be the first line, instead of running with the ladder [25].

Antidepressants reduce chronic pain in both depressed and non-depressed patients [53], but as chronic pain often goes hand in hand with comorbidities such as depression and anxiety [55], efficacy may be more pronounced in patients with such symptoms[18], [56]. Although there is evidence for the effect of antidepressants [53], side effects such as anticholinergic symptoms (dryness of the mouth), accommodation problems and weight gain often limit their use. Moreover, long-term effectiveness is still marginally documented [57].

The most used atypical analgesics are gabapentinoids, that are also recommended in guidelines for e.g. treatment of neuropathic pain [17]. However, it was recently proposed that gabapentin and pregabalin also possess a potential for misuse [58], [59]. The hypothetical background is that both gabapentin and pregabalin may have effects on the dopaminergic "reward" system [60]. However, the magnitude of the abuse potential and the mechanisms behind it are not fully understood [61]. Distinct pharmacokinetics of absolute bioavailability (gabapentin has a dose dependent bioavailability, whereas pregabalins bioavailability remains the same irrespective of dose) [62] may explain why pregabalin is perceived as more "powerful" by drug misusers [60]. Moreover, the gabapentinoids also have side effects that, although they diminish over time, may limit their use [14]. Other anti-epileptics such as carbamazepine, lamotrigine and topiramate have been used for chronic pain [63]. However, use is often limited by low efficacy or intolerable side effects [64] or inconclusive evidence for use [18].

Dilemmas with other drugs used in treatment of chronic pain

The use of cannabinoids has increased in a number of European countries advocated by legalization of cannabis for recreational and medical use, but reviews of safety and efficacy of cannabis-based medicine for chronic pain have come to inconsistent results [65]. Weak evidence of analgesia is mainly shown in neuropathic pain conditions, and it is recommended that cannabinoid-based treatment should only be considered in a multidisciplinary setting and by experienced clinicians, as they also carry a major risk of misuse [66]. As for other analgesics, cannabinoids carry a risk of side effects such as dizziness, dry mouth, nausea, fatigue, somnolence and euphoria [67].

Other treatment approaches are available and have shown efficacy in specific groups of patients – low dose naltrexone for fibromyalgia [68], ketamine for therapy-resistant severe neuropathic pain [69], [70], topical high concentration capsaicin patches

for postherpetic and diabetic neuropathy [71], and topical lidocaine patches for peripheral neuropathic pain [53]. However, again, efficacy has only been demonstrated in very specific and selected group of patients, which has limited their use and there is need for further research and long-term results with these substances. Other medication with analgesic properties e.g. the antipsychotics quetiapine and olanzapine exist and may be used as add-on therapy in treatment of painful conditions [63]. However, use is often limited by low efficacy or intolerable side effects [64] or inconclusive evidence for use [18]. Moreover, beside extrapyramidal and sedating side effects quetiapine and olanzapine also have misuse potential [44], [72].

The catch-22 dilemma for pharmacological pain management

Pain is prevalent in almost any medical field including surgery, internal medicine, general practice, oncology and palliative care. In this review we focus on management of *chronic* pain. Although a multidisciplinary approach with a variety of treatment possibilities is mandatory in chronic pain management, pharmacotherapy still plays an important role.

The efficacy of analgesics is often limited and the number needed to treat to achieve 50% pain reduction varies substantially between treatments. Therefore, as shown in Figure 1 , the clinician can be left in a difficult catch-22 dilemma for the pharmacological treatment as any possible benefit from increased dosing is outbalanced by harmful effects and risk of abuse/misuse. Patients may become desperate if pain is not relieved in a professional manner, and proper pain management can be caught in a dead end with major side effects and addiction.

Chronic pain is often associated with severe or extreme consequences for quality of life and social integrity [73]. If patients are restricted from suitable treatment options clinicians are left in a very difficult situation. If untreated chronic pain is underrecognized by politicians and health authorities this may lead to uncertainties and malpractice, and lead to serious chronic health problems [73]. In several countries strong analgesics are not available unless bought illegally, and even patients with severe acute and chronic pain are left to management with weak and insufficient analgesics [74]. Such policy may in fact be prone to criminal activity such as smuggling and drug dealing. Even in countries where analgesics are widely available, this patient related catch-22 situation may result in conflicts between patient and clinician and lead to mistrust and malpractice.

Consequences of the catch-22 dilemma

Stigmatism

Patients with chronic pain visit healthcare professionals much more frequently than the general population [75]. Additionally, it has been shown that communication between health professionals and patient can propagate stigma and lead patients preventing to seek help [76]. Health professionals may inadvertently and unfortunately contribute to stigmatization and there is a need to understand how patients cope with stigmatism [77], [78]. Patients with chronic pain may experience significant stigmatization that adds significantly to their burden of distress [79]. In the Institute of Medicine report [79] entitled *Relieving Pain in America*, a number of personal testimonies are reproduced that provide valuable insight into the impact of such negative attitudes on patients and carers:

1. It has been hell. First, you have to find someone who believes you. (testimony #135)
2. Doctors don’t recognize pain they cannot see or diagnose as a specific issue (testimony #314)
3. The stigma is one of the biggest barriers. I have been treated like a lowlife by medical people when I disclose that I have chronic pain and use opioids for it (testimony #383)

These themes of being believed, particularly in the context of a lack of a specific and demonstrable underlying pathology and/or indiscriminate negative attitudes toward the use of opioid medication are readily identifiable and credible.

As evidenced above, legitimate concerns regarding opioid abuse, misuse and diversion have the potential to compound the problem of stigmatization.

The thrust of commentary regarding opioid therapy, particularly in chronic non-cancer pain has become '*confusing, disjointed and sadly blameful'* for the majority of patients that benefit from such therapy, as well as the physicians who prescribe opioids [79]. There is an urgent need to create a paradigm shift in the way pain patients are viewed, portrayed, assessed and treated. Specifically, we must acknowledge that the vast majority of chronic pain patients are not drug seeking. Patients with severe strong pain that invalidate social life cannot be left without proper management and due to the considerations above this is very complex and difficult. Restrictive approaches to therapy may leave patients from adequate treatment options and/or seeking professional help, in the end influencing health status and quality of life.

Economic consequences

The consequence of the catch-22 dilemma is also economical. Chronic pain is considered as one of the most burdensome diseases in industrialized countries. However, seeking to calculate an accurate and reliable monetary figure of the total of cost of pain in a defined community is a most hazardous undertaking, characterized by almost insurmountable methodological challenges[80]. Hence, the cost of pain investigation and management is inextricably linked with the costs of investigating and treating a diverse array of underlying medical conditions. Besides high costs for disease management, it is also associated with major impacts on daily activities and quality of life, as well as high productivity losses due to work absences.

Several cost-of-illness studies have been conducted, but as referenced above, different methodologies, cost approaches and populations make them difficult to compare. Economic costs are estimated to be 2.0 billion USD per million citizens in the US [81] and in Europe up to 300 billion Euro per year (direct and indirect costs (lost productivity, social security and welfare payments)) [82]. This is acknowledged to be a conservative estimate and excludes significant groups such as institutionalized individuals (including nursing home residents), children under 18 years, military personnel and personal caregivers. It also makes no provision for lost productivity in respect of those aged under 24 years and those aged over 65 years [79]. This emphasizes the need for allocating resources to early prevention e.g., primary health care (more time for health professional-patient face-to-face time), access to multidisciplinary pain clinics, better education of health care professionals as possible ways of reducing costs. However, few resources and low priority compared to more "prestigious diseases" leaves the physician in a difficult situation.

Methodological aspects

There is a need for research that are based on individual patients or subgroups of patients rather than the disease i.e., identifying measurable phenotypic characteristics of patients who will respond to a specific treatment (87). Among the many problems in the field of pharmacological pain management are that most analgesics are relatively old and entered the marked before authorities requested proof of efficacy with acceptable toxicity. Therefore, documentation of efficacy for e.g., morphine is poor to non-existing. Among the randomized controlled clinical trials, many suffer from insufficient endpoints and poor methodology and data on long-term safety and efficacy are lacking. Furthermore, when it comes to registration of new analgesics, the demand from health authorities is often far beyond the experience in the clinical situation. Hence, multiple studies in several patient groups are required to document efficacy of medication. Additionally, the placebo (control) effect is appreciably large and this complicates study design [83]. The relevance of studies in many pain conditions (neuropathic, musculoskeletal, visceral etc.) can be questioned for chronic pain as the variability in presentation of pain is greater between patients than between the different pain syndromes [84]–[86]. Hence, successful treatment is likely to be based at the level of the individual rather than at the level of the disease [87]. This is not surprising as neuroplastic changes and hyperexcitability of neuronal circuits in the central nervous system play a major role in chronic pain, whereas the peripheral contribution is likely of minor importance [88], [89]. Interest in novel targeting strategies is being pursued [13], [90], [91], but promising preclinical candidates often fail during clinical trials as the translation between species and even strains is limited [13]. Furthermore, as pain is not considered a life-threatening disease

by the authorities, only very few adverse effects are tolerated when a new analgesic is considered for registration (despite the alternative may be strong opioids). Therefore, the pharmaceutical industry may be reluctant to investigate in the costly development of new analgesics.

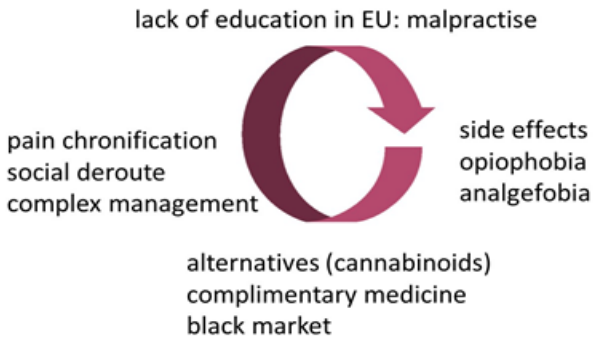

FIGURE 2: The vicious circle in current pain medicine.Although pain is a very prevalent condition, there is no formal education inpain medicine in most countries, and lack of understanding how to handlemedication leads to side effects and a bad reputation of analgesics amongpolitical stakeholders and health authorities. As a consequence, patients seekalternaveą treatments, undocumented complementary medicine and purchaseillegal drugs. This malpracceą can lead to chronification of pain withsubsequent social consequences. Pain patients are a fragile group with fewresources, and in comparison, with stronger patient organisations they are to ahigh degree neglected by society and prioritised low at medical schools amongcompetitive disciplines – and the vicious circle is established.

Can the dead end be circumvented?

Educational perspectives

In Europe only 2% of patients with chronic pain report that they have consulted a pain specialist [2] despite that specialist guided, multidisciplinary management of pain has shown to be clinically effective and cost-efficient alternative to single-clinician treatment or usual care [82]. When pain management is insufficient e.g. due to low priority, too few resources, patients may be left in a situation of inadequate access to professional pain management [76], [82]. As a consequence, patients may have a feeling that healthcare professionals lack relevant knowledge about chronic pain [82]. Outside pain clinics treatment with strong opioids (that are among the most difficult medications to administer) may be initiated inappropriately and as a consequence, patients seen in multidisciplinary pain centres may already be addicted or have initiated a social decline, Figure 2.

Education in pain medicine is in general poor in many countries. A survey found that only 48% of primary care professionals used pain assessment tools, and even when they were used, results were not documented. Additionally, 84% reported that training in chronic pain management was not comprehensive [92]. There seems to be a lack of general acceptance for education in pain management at most medical schools, even though there is a high international variability in the level of undergraduate education in pain. Indeed, pain teaching is inconsistent and limited and typically incorporated into other subjects. Even where pain teaching is dedicated and compulsory, only 0.2% of undergraduate medical teaching is allocated to pain [93].

Sub-specialization in pain medicine is available for physicians in Europe [3], [94]. Recently, the European Pain Federation EFIC® published detailed competency-based curricula for physicians, physiotherapists, nurses and clinical psychologists [95]. Nevertheless, there is a need for improving knowledge of chronic pain management e.g. through medical training (undergraduate and postgraduate level), by use of standardized assessment tools and improved physician/patient communication [82]. Education is essential and should not only be focused on analgesics, but needs to embrace the multimodal, multidisciplinary approach as pharmacological pain management is only one of many treatment possibilities in pain management. It shall also not only be directed towards clinicians, but must incorporate the patients, family members and carers, wider society, policy makers, regulators and legislators.

Predictors and risk assessment

Inter-patient variability in response to analgesic treatment can be of great frustration in clinical prac-

tice. Importantly, most patients with chronic pain present clinically with a substantial mix of nociceptive, neuropathic and nociplastic pain symptoms [96]. Factors such as stress, age, genetics, environment and immune responsivity may affect disease development, pain severity and chronicity, adding to the complexity of pain [97]. Moreover, development of effective analgesic alternatives to opioids, enabled by further understanding of the neurobiological bases of pain may offer better treatment options [98]. Hence, determination of optimal treatment for individual patients (precision medicine) to presumably improve clinical care is therefore warranted [87]. Several studies have been undertaken to determine if it is possible to explain interindividual variability in pain perception, response to drugs and risk of developing chronic pain syndromes. There is evidence that catechol-O-methyltransferase and opioid receptors exhibits polymorphism related to pain sensitivity and this has the potential to predict better outcomes [99].

Quantitative sensory testing is a promising tool and may aid to improve prediction of risk of developing chronic pain and be helpful in guiding clinical care to the principal of individualize-based medicine instead of the current "trial and error" approach" [11], [100]–[102]. Quantitative sensory testing is frequently used in experimental pain research and as part of a diagnostic tool in neuropathic pain, but there is need for further evidence [103]. It is also important to keep in mind that scoring of pain intensity is often difficult for chronic pain patients, especially when they are treated with opioids or other centrally acting drugs [104]. In fact, pain intensity should not necessarily be the primary endpoint, as many patients benefit from treatment on much more relevant parameters such as pain interference, improved sleep, better quality of life etc. [87]. Additionally, integration of pharmacogenomics could attribute and optimize individualized tailored treatment based on the genetic variation for each patient. It may also be a part of the solution to opioid overuse to identify potentially opioid-vulnerable patients [105], [106].

Increasing knowledge about chronic pain highlights the importance and necessity of stratifying (phenotyping) patients with chronic pain by use of various assessment tools e.g. functional magnetic resonance imaging, electrophysiology, genetic factors (e.g. pharmacogenomics), cornea confocal microscopy etc. [87], [105], [107]. Hence, the pain community may focus on investigations in new and existing analgesics in a few well defined and prevalent diseases in patients with specific phenotypes, and extrapolate such results across the different disease entities in patients with similar phenotypes rather than using a lot of energy to explore the effects in many different diseases.

Moreover, there is a need for risk-assessment tools to predict risk of abuse potential in patients with chronic pain. A patient´s potential risk of abuse should be assessed prior to start of treatment, and recommendation strategies should consist of registration of e.g., past long-term use of benzodiazepines/alcohol/cocaine, daily nicotine use, obesity, urine testing, interviews with spouses/family etc. A simpler instrument with the potential to identify and predict patients with abuse potential is still warranted [108]. Moreover, awareness and recognition of drug-seeking behaviour should be a part of initiating pharmacological treatment although display of such behaviour might not always be obvious [44]. Finally, the association between habitual overactivity behaviour and opioid use should also be taken into account as a study by Andrews et al. 2016 showed that individuals reporting higher levels of habitual overactivity were associated with more frequent "need" of opioid use over a 5-day period [109].

Politics

Treatment with e.g., opioids has been up for discussion for some time and it is a controversial and contested area of health care. Information about the currently political anxiety linked to opioids and the often ideologically-driven discussions do not seem to engage to a meaningful debate [110]. On the other hand, it has led to the attention to control the harmful use of opioids while addressing the needs of patients [74]. Whilst instituting all necessary steps to limit and prevent inappropriate opioid use, we must always be mindful that undertreated pain in all countries, both resource-rich and resource-poor, is a major public health crisis.

A balancing act will be needed to optimize the management of chronic pain patients. Indeed, while

opioid prescription and use for pain management is a major concern in some parts of the world, the context of opioid use clearly differs between countries. Several countries in Europe have in place significant barriers to optimal pain management due to inappropriate restrictions on supply and use. Opioids are an important part of a modern approach to pain management and palliative care, and misplaced barriers to access can lead to unnecessary suffering. However, opioids are definitely not a panacea for all types of pain, and must only be used in selected and supervised pain patients. Better monitoring systems are needed to enable the prescriber to detect early warning signs of misuse, abuse and addiction. Insight in the prescription and dispensing of medicines is a step which could easily be implemented by policy makers in this digital age. However, it is important to keep in mind that restricted access to opioid pharmacotherapy takes many forms. Although physicians have power in the role as prescribers of opioid pharmacotherapy, they may not have influence in the wider policy and practice systems that they are a part of [110]. A study by Houboug (2013) describes how limiting prescription of methadone to detoxification only indirectly leaves practitioners as central actors in the political work [111]. Personal and societal stigma towards drug users are other factors that physicians are facing. Moreover, although use of dosing guidelines can be poor, they may nonetheless exert significant pressure on providers to work in particular ways and influence opioid pharmacotherapy [110]. These issues demonstrate that the role of the treatment provider is never a neutral one.

The International Classification of Diseases 11th Revision (ICD-11) is the latest update of the global standard for diagnostic health information [112]. For the first time, the ICD-11 includes seven diagnostic categories of chronic pain. Importantly, one of these categories, termed chronic primary pain (MG30.0), acknowledges chronic pain as a health condition in its own right. In addition, six forms of chronic secondary pain (MG30.1-MG30.6), describe chronic pain that developed as a symptom in the context of an underlying disease such as cancer and rheumatoid arthritis among others. Chronic pain included into ICD-11 might be what is needed to deliver insight in the magnitude of the burden of pain and highlight the challenges in management of chronic pain for the public awareness, political support and action required at regional and national level. Additionally, it creates the opportunity to adopt a more patient-focused management strategy that minimizes unnecessary diagnostic interventions and embraces a multidisciplinary and multi-modal therapeutic strategy [113].

2 | CONCLUSION

The catch-22 situation that physicians face in pharmacological pain management where efficacy is counterbalanced by adverse effects, misuse potential, uncertain long-term effects and insufficiently documented analgesia is of major concern for nearly all analgesics. This balance between efficacy and adverse drug reaction applies to all medical therapies.

There is, however, light in the end of the tunnel of this conflicting dilemma. Better education and awareness of the problem is the first step. Better guidelines that include e.g., quantitative sensory testing, pharmacogenomics, monitoring for misuse etc. may replace the "trial and error approach" with more rational pharmacological pain management. Moreover, the recent international classification with different diagnostic categories of chronic pain may attribute to destigmatizing patients. A balance between effect and side effects and including parameters such as better quality of life, better sleep etc. shall be considered as endpoints in clinical trials, and such investigations should be designed to take the pain phenotype rather than disease entity into consideration. Tools for prediction of effect of the various analgesics together with databases for monitoring of misuse and effects should provide big data that can be used in future treatment and patient education Figure 3. Finally, better pain education is warranted. Al together, this will improve pain treatment and quality of life for the individual, and due to the major costs associated with chronic pain it will also be of major gain for society.

Abbreviations: NNT: Number Needed to Treat; NNH: Number Needed to Harm, HIV: Human Immunodeficiency Virus

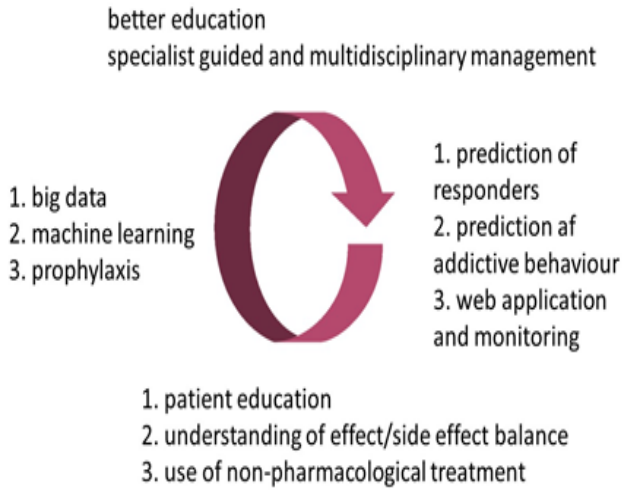

FIGURE 3: The dead end for pharmacological pain managementcan be circumvented with be. er pre-and postgraduate educaon in pain medicinesuch as the European Diploma for Pain Medicine established by EFIC. Complexpaen ts with chronic pain shall also be treated in a muldisciplinar y teamlead by pain specialists in close collaboraon with relevant speciales andsupport funcons. Addionally , there is emerging evidence that responders totreatment can be found if the pain system is explored with e.g., quant av esensory tesng and associated psychophysical covariates. Paen ts with a highlikelihood for addicon and side-effects can to a high degree be found withsimple quesonnair es and a thorough medical history, and electronic monitoringwith can be used to follow the pain, where some of the algorithms also allowtreatment advise. This leads to better paen t educaon where e.g., thebalance between effects and side effects can be used both as educaon andmonitoring tool. Regular monitoring carries the potenal for better follow upand paen t care across disciplines where non-pharmacological treatmentmodalies shall also be used. The data collected in this way can pave the roadfor machine learning and better understanding that may lead to prophylaxis ofchronic pain with fast-track management etc.

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Table 1. Pharmacological treatment of chronic non-cancer pain

	Therapeutic indication	Efficacy	Adverse effects	Attention/abuse and misuse potential
Non-opioids				
Paracetamol	Mild to moderate pain [114], [115]	No or little effect [28]	Overdose – increased risk of chronic liver failure [29]	Efficacy of continuous use is needed [28]
NSAIDS	Mild to moderate chronic pain [15]	Osteoarthritis; Rheumatoid arthritis; Low back pain [15]	Gastrointestinal complications: Cardiovascular effects [30], [32]	No long-term use due to serious adverse effects [31]. Abuse potential equal to tramadol [33]
Opioids				
Weak				
Codeine	Mild to moderate pain [116]	Controlled-release codeine effective in chronic non-malignant pain [117]	Constipation, nausea, vomiting etc. [119]	Potential for misuse [121]
Tramadol	Mild to moderate pain [116]	Modest effect in osteoarthritis-related pain [118]	Seizure, vomiting, nausea, constipation etc. [120]	Abuse potential/risk of serotonin syndrome [35]
Strong opioids	Moderate to severe chronic pain	Significant but small improvements in pain and physical functioning [19]. Effective in chronic non-malignant pain [6]	Constipation, cognitive impairment, tolerance and physical dependence, addiction [15]	Risk of addiction [15]. On the other hand, not associated with a major risk of developing dependence [52].

	Therapeutic indication	Efficacy	Adverse effects	Attention/abuse and misuse potential
				Iatrogenic opioid addiction is rare [122]. Not for long-term use [6]
Atypical analgesics				
Antidepressants	*Tricyclic antidepressants* – reduce chronic pain in both depressed and non-depressed patients [53]. Amitriptyline (25-150mg/day)[1]	Imipramine (NNT 1.7 – 3.2), amitriptyline[2] (NNT 2.5 – 4.2) [16], [53]	Anticholinergic effects, sedative effects, potential risk of falls [123]	Discontinuation rate due to side effects: 20% (NNH 6) [16]
	Selective noradrenaline serotonine reuptake inhibitors (SNRI) e.g. duloxetine/venlafaxine –	Relieve neuropathic pain, musculoskeletal pain, fibromyalgia. Neuropathic pain conditions (NNT 6.4) [17]	Duloxetine: nausea, dry mouth, dizziness, increased blood pressure, somnolence [18], [124]	Discontinuation rate due to side effects: 15-20% (NNH 11.8) [17]. Duloxetine: Increased risk of suicidal thoughts [18]
Anticonvulsive	*Gabapentin/pregabalin* – management of post-herpetic/diabetic neuropathic pain [16]–[18]	Gabapentin (NNT 6.3) [16]; Pregabalin (NNT 7.7) [17]	Sedation, dizziness, nausea, weight gain [18]	Potential for misuse/abuse [58], [60]
Other				
Cannabinoids	Considered for chronic neuropathic pain, otherwise individual therapeutic trial [65].	Effect of affective but not sensory perception of pain, only moderate analgesic effect [131]	Drowsiness, fatigue, nausea cognitive effects[3] [67]	Larger and longer trials are needed for long term safety [67]. Risk of abuse/misuse [65]

[1] >75mg/d is not recommended in adults <65 y due to anticholinergic and sedative effects (Gilron et al. 2015)
[2] Clinically the most studied tricyclic antidepressant in neuropathic pain conditions e.g. diabetic neuropathy, postherpetic neuralgia, central poststroke pain (Gilron et al. 2015)
[3] Danish Medicines Agency: Report of adverse events of treatment with cannabinoids 2018

	Therapeutic indication	Efficacy	Adverse effects	Attention/abuse and misuse potential
	Reduce pain to a modest degree [67]			
Tapentadol	Chronic pain [125]	Musculoskeletal pain, low back pain, neuropathic pain [125]. Osteoathritis [132], [133], low back pain [133], [134], diabetic peripheral neuropathy [135]	Nausea, vomiting, constipation etc. [125]	Lower risk of abuse potential than conventional opioids [125]. Further long-term safety is needed.
Low Dose Naltrexone	Chronic pain disorders [126]	Fibromyalgia, complex regional pain syndrome [126], [136]	Vivid dreams, headache, nausea, dry mouth, insomnia [136]	Further research needed
Ketamine	For therapy-resistant severe neuropathic pain[127]	Unknown	Hallucinations, memory defects, panic attacks, nausea, somnolence [127]	Abuse potential [127]
Neuromodulation	Pain relief in e.g. complex regional pain syndrome [128], [129]	Unknown	Unknown	Long term results are needed [128]
High concentration capsaicin	Treatment of postherpetic neuralgia, HIV-neuropathy, painful diabetic neuropathy [130]. Second line treatment of peripheral neuropathic pain [18]	Postherpetic neuralgia (NNT 8.8 at 8 weeks and NNT 7 at 12 weeks); Painful HIV-neuropathy (NNT 11); Painful diabetic neuropathy (NNT not calculated) [130]	Local skin reactions (erythema, papules, pruritus, pain, oedema); Systemic (diarrhoea, nausea, vomiting, hypertension, dizziness, headache) [130]	Unknown
Lidocaine patch		Post-herpetic neuralgia [137]; Post thoracotomy	Skin irritation [18]	Unknown

	Therapeutic indication	Efficacy	Adverse effects	Attention/abuse and misuse potential
	Treatment of peripheral neuropathic pain [18]	neuropathic pain [138]. Too few trials to estimate effect sizes [18]		

Abbreviations: NNT: Number Needed to Treat; NNH: Number Needed to Harm, HIV: Human Immunodeficiency Virus