Chapter 9
Pharmacological Pain Management: For Better or for Worse?

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Abstract Although taking advantage of the synergistic effect of non-pharmacological and pharmacological approaches for the treatment of pain is always recommended, drugs remain the first and sometimes the only line of available treatment. Analgesics as well as pain itself do have an impact on cognitive and emotional processes. The cognitive/affective central effect of analgesics prescribed for chronic pain treatment is well documented in the literature, but the causal relationship of pain to cognitive and emotional disorders remains to be explored. In order to provide satisfactory pain alleviation, analgesic treatment in frail patients and in patients with preexisting cognitive/affective impairment is particularly difficult. Considering the large array of adverse events of orally administered analgesics, topical analgesics may be an interesting option for pain treatment. Non-pharmacological therapies should always be included in a comprehensive pain management plan.

9.1 Introduction

Pain requires cognitive processing and is also an emotional experience. Neural systems involved in cognition, emotion, and pain overlap and may modulate each other reciprocally (Peyron et al. 2000; Lumley et al. 2011). Moreover, cognitive functioning and emotions are dysregulated by chronic pain (depression, anxiety, stress, fear) (Apkarian et al. 2004; Baliki et al. 2006), and a large literature has been published on consequences on health-related quality of life and on the burden of chronic pain

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in everyday life (Pickering and Leplege 2011). On the treatment side, positive emotional states (Lumley et al. 2011) and cognitive interventions (hypnosis, meditation, distraction, cognitive training (Kesler et al. 2013)) have given interesting results and may reduce pain. Non-pharmacological approaches are indeed recommended in synergy with pharmacological treatment, but the first line of treatment of chronic pain remains predominately pharmacological (Pickering 2012). In that context, analgesics used for chronic pain have a number of cognitive and emotional side effects, and the role played by analgesics on cognitive function and emotional status is difficult to dissociate from the impact of chronic pain itself, clinically but also fundamentally. "Symptom clusters" where pain, depression, fatigue and impaired cognition happen concomitantly may influence each other in a downward spiral.

Observational studies on large cohorts do not always consider the adverse effects of analgesics and their negative impact on neural systems. Indications on pain treatment are often not clearly or analytically reported in the literature. Several issues remain open: What is the cognitive/affective impact of analgesics that are commonly used and recommended for chronic pain treatment? What is the impact of analgesic treatment in patients with preexisting cognitive/affective impairment? Are nonsystemic routes of administration a viable option to prevent drug-induced cognitive-affective impairment?

9.2 What Is the Cognitive/Affective Impact of Chronic Pain Treatment?

Commonly prescribed drugs for chronic pain include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant drugs recommended for neuropathic pain treatment.

9.2.1 Paracetamol

Paracetamol has not been demonstrated to have any specific deleterious effects on cognitive processing. A recent functional magnetic resonance imaging study has shown that paracetamol reduced neural responses to social rejection in brain regions previously associated with distress caused by social pain and the affective component of physical pain (dorsal anterior cingulate cortex, anterior insula). Thus, paracetamol reduces behavioral and neural responses associated with the pain of social rejection, demonstrating a substantial overlap between social/emotional and physical pain (DeWall et al. 2010).

9.2.2 Aspirin and NSAIDs

Aspirin is widely used in stroke prevention, and atrial fibrillation is associated with a decline of cognitive function. A randomized controlled trial (Mavaddat et al. 2014) recently compared the effect of anticoagulation (warfarin) versus aspirin on cognitive function in elderly patients with atrial fibrillation and showed no superiority of aspirin over anticoagulation against cognitive decline. Several epidemiological studies (Imbimbo et al. 2010) have suggested that long-term use of NSAIDs may protect subjects carrying one or more ε4 allele of the apolipoprotein E against the onset of Alzheimer's disease (AD). However, a Cochrane study (Jaturapatporn et al. 2012) assessed the efficacy of aspirin, steroids, traditional NSAIDs, and COX-2 inhibitors in AD and concluded that their efficacy is not proven and that these drugs cannot be recommended to prevent cognitive decline of AD. It is interesting to note that inflammation is at the heart of a number of degenerative pathologies and pain states and has also been incriminated in depression, although inflammation as a cause or consequence of depression has been questioned for a number of years. A recent study showed no significant relationship between inflammatory markers and symptoms of depression and anxiety during aging in patients with NSAID use, suggesting no particular influence of this medication on depression (Baune et al. 2012).

9.2.3 Opioids

Over the last two decades, the clinical use of opioids for chronic pain treatment has become widespread with the development of immediate- and extended-release formulations for acute and chronic pain including cancer pain. Opioid analgesics do relieve pain and remain first-line drugs for severe, chronic pain. The continued increase in their medical use (Atluri et al. 2014) has led to concerns of misuse, abuse, and addiction in chronic pain patients (CDC 2011). Indeed the abuse liability during opioid therapy for pain treatment has been noted as a concern for a certain percentage of chronic pain patients (Fishbain et al. 2008). This point is important as opiate dependence contributes to cognitive impairment in the domains of attention and executive function, with comorbid depressive symptoms negatively affecting reaction times (Loeber et al. 2012). In general, the scientific literature devoted to the impact of opioids on cognition and emotion in chronic pain patients is poorly documented. Adverse events of opioids per se are well known, with mental dullness, somnolence, sedation, sleep disturbances, and even delirium due to opioid excess. Analgesic efficacy and side effects may however be quite heterogeneous among patients with variable pharmacological mu-opioid responses. It has also been shown that the kappa-opioid receptor modulates synaptic strength and controls neuroplasticity in different brain regions associated with cognition and emotion (Pasternak et al. 1999). The success of opioid therapy often depends on achieving a balance between analgesic effectiveness and acceptable side effects.

Current evidence for a lack of appreciable effect, benefit, or harm of a long-term stable opioid treatment on cognitive functioning in noncancer pain patients (Kendall et al. 2010) or in cancer pain patients (Kurita et al. 2009) is still limited (Ersek et al. 2004). It is interesting to note that the best-quality randomized clinical trials showed no deleterious effect on cognition and even some cognitive improvement with opioid treatment (Kendall et al. 2010). The discrepancy between studies may be linked to the different methodologies used to evaluate cognitive domains in the studies, as subjective cognitive complaints are not always associated with objective (neuropsychological tests) measures of cognitive function and may give different results. A large meta-analysis (Lindner et al. 2014) focused on cognitive impairment in cancer patients (but with no report on opioid consumption) and concluded that the likelihood to identify cognitive impairment rests on the type of design employed, as memory and attention impairments were only detected in cross-sectional studies. Repetition of cognitive neuropsychological testing (attentional capacity, psychomotor speed, information processing speed, short-term memory, semantic memory, decision-making) may bias the findings of longitudinal studies. There is a real need to establish a consensus concerning reliable assessment of cognition in patients, especially with those on opioid treatment. In the clinic, it is important to inform the patient that long-term treatment with opioids may not be harmless and may even marginally interfere with cognitive function; however, this potential side effect should not hinder clinicians from increasing opioid dosing and optimizing opioid therapy. Overmedication and undertreatment can both have detrimental consequences. Overmedication may lead to addiction, hyperalgesia and worsening of negative emotional state. Undertreatment may maintain emotional distress, depression, sleep, and anxiety disorders. A rational use of opioids for chronic pain will avoid allostatic emotional behavior and maintain or restore homeostatic regulation of emotional behavior (Shurman et al. 2010).

9.2.4 Antidepressants

Antidepressants are recommended as first-line treatment for neuropathic pain (Finnerup et al. 2005; Dworkin et al. 2010). However, the mechanism of action of antidepressants in pain alleviation is complex; the safety profile of tricyclic antidepressants (TCAs) must be carefully taken into account as they may impair cognition. Newer classes of antidepressants, duloxetine and venlafaxine (serotonin and norepinephrine reuptake inhibitors SRNIs), may be less analgesic but they have less adverse effects although fatigue is frequently reported. Depression and chronic pain share a number of common mechanisms (Nekovarova et al. 2014; Blackburn-Munro 2001; Chou 2007), and depression may precede or follow after chronic pain. Chronic pain and depression are both conceptualized as stress and all three modulate brain and synaptic plasticity. Pain and depression may influence the functions of the brain default mode network (Baliki et al. 2008; Marchetti et al. 2012), a network of interacting brain regions activated during "resting" states. Plastic changes induced by pain or/and depression at synaptic, cellular, and molecular levels modify

connectivity within the neuronal circuitry and contribute to structural and functional changes in the brain. Not surprisingly, an additive effect of depression and chronic pain has been shown in cancer patients in several domains of quality of life (Kroenke et al. 2010). Cognitive dysfunction accompanies depression (McIntyre et al. 2013) and pain, and this cognitive dysfunction often persists after remission of the depressive symptoms (Conradi et al. 2011). This suggests that currently used antidepressants, selective serotonin (5-HT) reuptake inhibitors (SSRI), and SNRIs may not be all that adequate to improve cognition in depressive patients (McClintock et al. 2011; Pehrson et al. 2014). We recently showed in patients with long-standing postzoster neuropathic pain (with mild depressive symptoms) that antidepressants (mainly TCAs) prescribed for pain impaired several cognitive domains (spatial memory and semantic memory) when compared to neuropathic pain patients without antidepressants (Pickering et al. 2014a) These findings confirmed reports of an association between memory disorders and TCAs/SSRIs antidepressants (Chavant et al. 2011), but antidepressants do not always induce cognitive impairment. They seem to display a dose-dependent and etiology-dependent pluripotent action. In depressed patients, SSRIs and SNRIs may improve executive functions and attention (Herrera-Guzman et al. 2010). In nondepressed patients with Alzheimer disease, TCAs and SSRIs diminish the severity of cognitive decline (Archer et al. 2007). Animal studies show that amitriptyline (a TCA) ameliorates neuropathic pain-induced deficits in abilities of spatial learning and memory (Hu et al. 2010) and cognitive function in Alzheimer rats (Chadwick et al. 2011). Considering the complexity and heterogeneity of these results, there is a need for larger clinical trials to study cognitive dysfunction in chronic pain with or without depressive symptoms. The cognitive deficits observed in chronic pain patients receiving antidepressants could be due to the chemical properties of the prescribed antidepressant or because of inappropriate dosing. They could also be linked to residual non-alleviated pain and to the combination of pain-induced and depression-induced cognitive loads. It is also plausible to suggest that the type of antidepressant, its mechanistic action on the opioidergic system (Wattiez et al. 2011), the etiology of the pain syndrome, the duration of pain, the comorbidities, the severity of the depressive symptoms, and the extent of the memory traces of depression and pain may all contribute to the complexity of cognitive homeostasis in chronic pain. Finally, as mentioned before, there are also methodological difficulties concerning the cognitive evaluation of patients using neuropsychological tests or via self-report (Amado-Boccara et al. 1995), and isolation of the specific effects of antidepressants on cognition in a patient suffering from chronic pain remains to be established.

9.2.5 Antiepileptics

Gabapentin and pregabalin are also recommended first-line neuropathic pain treatment. Adverse events of gabapentin related to cognition (somnolence (27.4 %) and falls, dizziness (23.9 %), and ataxia (7.1 %)) may lead to discontinuation of

treatment in 10 % of patients and are particularly important in older persons (Pickering 2014). In a recent study in the context of postherpetic neuropathic pain (Pickering et al. 2014a), antiepileptics induced less cognitive impairment than antidepressants, but the impact of antiepileptics on depression and cognition in the context of pain must be explored further.

9.2.6 Other Drugs

9.2.6.1 Hypnotics

Benzodiazepines are frequently prescribed in patients suffering from chronic pain, as anxiety and sleep disturbances are very common: a bidirectional association between sleep disturbances and chronic pain has been frequently discussed in the literature (Smith and Haythornthwaite 2004). There are common brain structures (periaqueductal gray matter, reticular nucleus of the thalamus, raphe magnus) involved in pain and in sleep (Demarco et al. 2003), and although benzodiazepines are widely used, their effects on cognition, mood, alertness, anxiety, or depression may or may not be independent of their analgesic properties. Benzodiazepines may have beneficial effects on pain-related anxiety, and cognitive disorders have been described with reports of memory disorders and increased reaction time (Pickering et al. 2014a; Chavant et al. 2011), confusion, and a potential risk of dependence and abuse with a long-term use.

9.2.6.2 *N*-Methyl-D-Aspartate Receptor as a Therapeutic Target

N-Methyl-D-aspartate receptors (NMDAR) are ubiquitous and are not only involved in the establishment of central sensitization (Dingledine et al. 1999) and in pain-related synaptic plasticity but also in many pathophysiological processes such as memory, learning, and neurological disorders (Begon et al. 2000; Niewoehner et al. 2007). NMDAR antagonists, such as ketamine, dextromethorphan, or memantine, are possible therapeutic options after failure with other recommended treatments for neuropathic pain and could prevent or treat painful symptoms (Zhou et al. 2011; Tawfic 2013). However, there is some heterogeneity among clinical trials with different efficacies according to the doses used, routes of administration, and type of pain pathology (postherpetic neuralgia, postamputation pain, phantom limb pain, diabetic neuropathy). The efficacy of ketamine in neuropathic pain has been reported (Eide et al. 1994; Jørum et al. 2003), although it may lessen with time, and ketamine is well known for its psychodysleptic and cognitive adverse events (Cvrcek 2008; Niesters et al. 2013). It prevents windup and improves pain and also depression. The parallel of ketamine effect in pain and in depression is striking as not all patients are responders to ketamine: ketamine improves pain in 65 % of patients (Rabben et al. 1999; Jackson et al. 2001) and improves depression in 64 % of patients within 1 day

of administration (Murrough et al. 2013). The duration of the analgesic effect of ketamine varies among studies and among patients, so does its antidepressant effect (Gálvez et al. 2014).

With a similar mechanism of action on NMDAR, dextromethorphan and memantine have less adverse events. They have been routinely prescribed for the antitussive properties and moderate to severe Alzheimer's disease, respectively. The influence of memantine and dextromethorphan on cognitive function in patients suffering from neuropathic pain is not currently known and is still under investigation (Pickering et al. 2014b). Activation of NMDAR is an essential step in pain central sensitization and "windup" (a temporal summation of C-fiber response in the spinal cord) and is also involved in memory formation and cognition processes. Such a windup phenomenon has also been demonstrated in depressive patients independently of pain (Klauenberg et al. 2008) underlining once more common aspects of chronic pain and depression.

Magnesium (Mg^{2+}) is a physiological blocker of the Na^{+}/Ca^{2+} channel of the NMDA receptor and is able to modulate NMDAR (Nowack et al. 1984). Mg homeostasis is proposed to be involved in biochemical dysregulations contributing to psychiatric disorders (Murck 2002). A significant association between Mg imbalance and cognitive impairment has been shown in hospitalized patients (Corsonello et al. 2001), and Mg therapy in animals is effective in facilitating cognitive recovery following brain injury in a task- and dose-dependent manner (Hoane 2007). A randomized, double-blind, controlled trial with patients suffering from neuropathic pain showed a diminution of the frequency of pain paroxysms and of the emotional impact of pain (Pickering et al. 2011). Despite experiencing background pain, patients were less bothered by it, suggesting a beneficial sensori-limbic dissociation that allowed an improvement of quality of life and of affect. More clinical studies are warranted on all NMDAR antagonists and on their anti-inflammatory effect that could also impact on their antidepressant potential, as demonstrated recently for ketamine (Hayley and Litteljohn 2013).

9.3 What Is the Impact of Pain Treatment in Patients with Preexisting Cognitive or Emotional Disturbance?

The challenges surrounding pain treatment are amplified in the presence of frailty and impaired cognition (McLachlan et al. 2011) and there are few data to support evidence-based decisions in such patients. Frailty (also associated with pain (Shega et al. 2012)), medications, and impaired cognition may impact on the pharmacokinetics and pharmacodynamics of analgesics in this population ranging from physiological age-related cognitive decline to severe psychiatric disease. The judicious clinical mantra of "start low and go slow approach" to analgesic dosing in frail older persons may lead to undertreatment of patients, but inappropriate dosing may conversely result in serious adverse events. In the absence of rigorously controlled trials in frail older people and those with cognitive impairment, a pharmacologically

guided approach can be used to optimize pain management which requires a systematic understanding of the pharmacokinetics and pharmacodynamics of analgesics in frail older people with or without changes in cognition. It is difficult from the existent literature to evaluate the positive or negative impact of analgesics on cognitive/affective domains in patients with preexisting cognitive/affective disorders and the biases of comorbidities and associated medications.

Patients suffering from dementia often present noncognitive symptoms (behavioral and psychological symptoms of dementia (BPSD)) that occur in 40–60 % of individuals living in care home settings (Ballard and Corbett 2013) and 60–98 % of patients with dementia (Sink et al. 2005). BPSD includes agitation, aggression, delusions, hallucinations, repetitive vocalizations, wandering, depression, apathy, anxiety, and disinhibition. However, most of these symptoms could also be due to pain or dehydration. Such a clinical presentation may be confusing as pain is frequent in patients with dementia who often cannot communicate their discomfort: pain should always be considered as a possible cause of agitation or aggression and should be adequately attended to and treated. Despite the poor evidence base and although non-pharmacological treatment is recommended in these patients, it has been a common practice for a number of years to use drugs acting on the central nervous system (Kamble et al. 2009). Antipsychotics, cholinesterase inhibitors, anticonvulsants, antidepressants, anxiolytics, and *N*-methyl-D-aspartate-receptor modulators (Schulze et al. 2013) are often prescribed without clear evidence-based efficacy. Administration of a non-opioid drug, paracetamol, 3 g per day, in a cluster randomized clinical trial showed in 352 patients a significant improvement in agitation accompanying parallel reductions in pain (Husebo et al. 2011).

9.4 Could Topical Administration of Drugs Be an Option to Prevent Drug-Induced Cognitive-Affective Impairment?

Topical analgesics often have a comparable efficacy to oral agents, with a good tolerability and safety profile. They may be an alternative or be added to oral treatments. They are particularly relevant for elderly patients who suffer from comorbidities and/or taking multiple medications. It allows the reduction of concomitant treatments and the risk of adverse events, as elderly patients are often prescribed oral combination therapies including drugs with central side effects (dizziness, sedation, impairment of cognition).

Topical NSAIDs seem to be the safest choice among all options for localized pain in superficial joints and have demonstrated efficacy similar to oral NSAIDs, with a low incidence of adverse events (Baraf et al. 2011). A randomized clinical trial with ibuprofen foam dressing has also shown a significant pain relief in five types of wound: arterial, venous, and mixed arterial-venous leg ulcers, vasculitis, and traumatic ulcers (Arapoglou et al. 2011). Transdermal fentanyl in non-naïve patients has been used for a number of years, with improved pharmaceutical forms

and dosages. Taken together, studies have shown no negative impact on cognitive function in patients with a stable opioid treatment for pain (Sabatowski et al. 2003; Menefee et al. 2004).

All patients with neuropathic pain are candidates for treatment with antidepressants and anticonvulsants, whereas localized neuropathic pain can benefit from topical treatment (Gloth 2011). Two drugs have been approved, 5 % lidocaine medicated plaster (Baron et al. 2009) and 8 % capsaicin patch (Haanpää and Treede 2012). In older patients suffering from postherpetic neuralgia, the 5 % lidocaine medicated plaster resulted in a reduced use of antidepressants and opioids (Clere et al. 2011). In another study, elderly patients with postherpetic neuralgia of several years duration had a significantly better cognitive performance with 5 % lidocaine patch than patients with orally administered drugs and their cognition was not altered when compared to healthy controls (Pickering et al. 2014a).

Although the number of available topical treatments is still limited, topical analgesics represent a very innovative pharmacological field with the potential of combining several mechanisms of action and therapeutic targets. With their oral analgesics sparing effects and their lesser deleterious impact on cognitive function, topical analgesics present advantages for optimization of pain treatment, especially in the elderly and in patients taking multiple medications acting on the central nervous system.

9.5 Non-pharmacological Therapies for Pain Management

Pain, especially when chronic and persistent, is better managed when a multidimensional and interdisciplinary approach is implemented. Although scientific evidence on the efficacy of non-pharmacological techniques is limited, these should also be part of a comprehensive pain management plan. They offer the advantage of being denied of any adverse effects on cognition, and some have been shown to improve cognition and emotion states. Non-pharmacological therapies are developed in Chaps. 10 and 11 and include psychological and physical/rehabilitative approaches.

9.5.1 Psychological Approaches

Psychological approaches have been categorized as cognitive-behavioral therapy, strategies based on emotional disclosure and mind-body interventions (e.g., yoga, mindfulness) (Keefe et al. 2013).

Cognitive-behavioral therapy (CBT) approach to pain management combines stress management, problem solving, goal setting, pacing of activities, and assertiveness. Its efficacy in reducing pain has been demonstrated numerous times, for various types of pain (Turk et al. 2008). A Cochrane review however failed to confirm positive effects of CBT on reducing pain, except for a small effect when

compared to "usual" treatment, and no difference with an "active control" (Williams et al. 2012). While the effect of CBT on mood in patients with chronic pain appears to be mild and of limited duration (Williams et al. 2012), it seems to be effective in reducing highly anxious thinking about pain and future pain (Eccleston et al. 2013). It therefore appears that, while its effect on general pain is limited, CBT is especially effective in improving problems arising from long-lasting disabling chronic pain.

Emotional disclosure interventions aim to reduce pain and pain-related mood impairment by working on negative thoughts and feelings triggered by pain. The response is highly variable between individuals, depending on personality and pain characteristics.

Mind-body interventions aim to cultivate awareness and acceptance of physical and emotional experiences. They include modalities such as mindfulness meditation and yoga. Evidence on their effectiveness on reducing pain, as well as pain-related disability and mood impairment, is mostly limited to open-label, nonrandomized studies. This limited evidence should however not discourage their inclusion as part of a multimodal and interdisciplinary pain management plan.

9.5.2 Physical Approaches

Evidence on response of pain to passive physical approaches such as TENS, ultrasounds, or massage is mostly limited to anecdotal experience and open-label, nonrandomized studies. No effect on pain-related mood impairment has been reported. Exercise however seems to be effective in relieving pain in a variety of pain conditions, sometimes with resultant mood improvement. Exercise can also prevent cognitive deterioration in older patients, whether they have or do not have premorbid cognitive impairment. The effect on cognition and emotions in patients with chronic pain needs to be explored.

9.6 Conclusion

Recommendations for chronic pain treatment support a more tailored approach based on the patient individualized risks, an optimization of the treatment strategy, and a multimodal therapeutic regimen. However, most analgesics, with their central mechanism of action, have cognitive and emotional adverse events that may be amplified in the presence of comorbidity, multiple medications use and aging. Evaluation, in the specific context of chronic pain, of the beneficial or deleterious effects on cognitive and emotional processes, and of drugs commonly used, needs to be explored further. While clinicians are aware of common side effects to be expected with recommended analgesics, the impact of these drugs in patients with long-standing chronic pain and emotional and cognitive dysfunction is not well

known. The impact of analgesics on the relationship between chronic pain and cognitive and affective impairment also remains to be elucidated. To avoid deleterious effects of analgesics on cognition in patients with chronic pain and to improve pain-related mood impairment, non-pharmacological therapies should always be included in a comprehensive pain management plan.

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