

## VIEWPOINT

The opioid epidemic: helping  
rheumatologists prevent a crisisAnne-Priscille Trouvin,<sup>1,2</sup> Francis Berenbaum,<sup>3,4</sup> Serge Perrot<sup>2,5</sup>

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**ABSTRACT**

An endemic increase in the number of deaths attributable to prescribed opioids is found in all developed countries. In 2016 in the USA, more than 46 people died each day from overdoses involving prescription opioids. European data show that the number of patients receiving strong opioids is increasing. In addition, there is an upsurge in hospitalisations for opioid intoxication, opioid abuse and deaths in some European countries. This class of analgesic is increasingly used in many rheumatological pathologies. Cohort studies, in various chronic non-cancer pain (CNCP) (osteoarthritis, chronic low back pain, rheumatoid arthritis, etc), show that between 2% and 8% of patients are treated with strong opioids. In order to help rheumatologists prescribe strong opioids under optimal conditions and to prevent the risk of death, abuse and misuse, recommendations have recently been published (in France in 2016, the recommendations of the French Society of Study and Treatment of Pain, in 2017, the European recommendations of the European Federation of IASP Chapters and the American Society of International Pain Physicians). They agree on the same general principles: opioids may be of interest in situations of CNCP, but their prescription must follow essential rules. It is necessary to make an accurate assessment of the pain and its origin, to formulate therapeutic objectives (pain, function and/or quality of life), to evaluate beforehand the risk of abuse and to get a specialised opinion beyond a certain dose or duration of prescription.

**INTRODUCTION**

Since the 1990s, strong and weak opioids have been prescribed in a field that is increasingly extensive, including acute pain and also chronic cancer and non-cancer pain. Since 1985, and the WHO classification of analgesics for cancer pain, strong opioids were prescribed beyond the initial scope of the WHO recommendations to treat non-cancer pain, including chronic pain, which, if we rely on the judicial claims in the USA, was helped by deceptive companies business practices' made false representations the opioid addictiveness, its efficacy, in order to delude authorities, prescribers and patients.<sup>1</sup> Twenty years ago, the first US recommendations were published to reinforce proper opioid prescription practices in chronic non-cancer

pain (CNCP).<sup>2</sup> Despite this, the problem has only become more pronounced.

**CURRENT ISSUE****Clear increase in sales**

In the USA, between 2002 and 2012, the number of opioid prescriptions has doubled.<sup>3</sup> In Europe, there is the same trend with a slight time lag compared with the North American continent. In the UK and in France, opioid prescriptions grow regularly and in particular, strong opioid users doubled between 2004 and 2017.<sup>4,5</sup>

**'Epidemic' of deaths from prescription opioids**

Despite numerous recommendations, guidelines and preventative measures, many studies over the last 20 years show a significant increase in mortality related to prescribed opioids. The latest figures show an increase of 345% of all deaths attributable to opioids from 2001 to 2016 and an estimate of 1.68 million person-years of life lost in 2016.<sup>6</sup> In Europe, data on opioid mortality follow the same trend as for the North American continent, especially for Northern Europe. In England and Wales, the number of opioid deaths increases of 425% in 20 years.<sup>7,8</sup> In France, opioid-related deaths increased by 146% between 2000 and 2015 (table 1).<sup>4</sup>

**Abuse and misuse**

Beyond the increase in deaths, studies note a strong trend towards the emergence of drug abuse with prescription opioids. Thus, in a cohort of 32 499 patients who initiated a strong opioid treatment for CNCP, 11.4% progressed to a chronic intake of more than 3 months.<sup>9</sup> Vowles *et al*, in a meta-analysis, found that in long-term opioid-treated patients for CNCP, rates of misuse averaged between 21% and 29%.<sup>10</sup> In a German cohort study, the pooled 1-year prevalence of abuse/addiction of prescribed opioids (defined by hospital stays because of mental and behavioural disorders due to alcohol, opioids, tranquillisers,

**Table 1** Summary of deaths rate across countries

USA (2001–2016) <sup>6</sup>	33.3/million	130.7/million	+345%
England and Wales (200–2014) <sup>8</sup>	15.1/million	16.9/million	+12%
France (2000–2015) <sup>4</sup>	1.3/million	3.2/million	+146%

multiple substances and intoxication by narcotic agents) was 0.56%. Abuse/addiction of prescribed opioids was associated with younger age, diagnoses of somatoform pain disorder, depression and prescription of tranquilisers.<sup>11</sup> Moreover, in an international survey, Morley *et al* investigated opioid analgesic misuse and abuse in participants from the Global Drug Survey 2015 who had used at least one prescription opioid analgesic medication in the past year. In this survey of 5670 participants from UK (N=1199), France (N=1258), Germany (N=866), USA (N=1334) and Australia (N=1013), between 8% and 22% of participants who had not used any illicit drugs or benzodiazepines in the past year reported misuse or abuse of codeine, hydrocodone, oxycodone, or tramadol.<sup>12</sup>

## CURRENT USE, EFFECTIVENESS AND INEFFICIENCY OF OPIOIDS IN MUSCULOSKELETAL PAIN

### Current use in musculoskeletal pain

In an English cohort of 703 patients with chronic musculoskeletal pain, 59% of the participants were prescribed opioids during the 12 months follow-up.<sup>13</sup> For rheumatoid arthritis (RA), a German cohort of 3140 patients showed that 6% with no or mild pain received opioids and 32.6% with severe pain.<sup>14</sup> In spondyloarthritis (SpA), one cohort study reports 21.7% of patients with intermittent opioid use and 9.5% chronic use.<sup>15</sup> For fibromyalgia, cohort studies found that between 11.3% and 12.5% of the patients were treated with opioids.<sup>16 17</sup> For back pain, an evaluation of trends in treatments over a 12-year period showed an increase in the use of opioids from 19.3% to 29.1%.<sup>18</sup> Finally for osteoarthritis, DeMik *et al* showed that approximately 11.5% of patients with osteoarthritis will be prescribed an opioid in a given year.<sup>19</sup>

### Evidence of opioid effectiveness or inefficiency in musculoskeletal pain

Most of the literature reviews in various musculoskeletal conditions are moderate in their conclusions regarding the benefit of opioids in chronic pain. In osteoarthritis, both the Cochrane review in 2014 and Smith *et al* concluded to a small benefit on pain but with questionable clinical relevance, this with contrast to significant risk of adverse effects.<sup>20 21</sup> Smith *et al* even concluded that nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids have comparable pain relief.<sup>21</sup> The 2014 Osteoarthritis Research Society International (OARSI) guidelines for non-surgical management of knee osteoarthritis came to the conclusion of uncertain appropriateness for opioid.<sup>22</sup> In chronic low back pain, reviews

and meta-analysis reach the same conclusion of short-term benefit of opioids with a moderate effect on pain and small effect for function.<sup>23 24</sup> In chronic inflammatory rheumatism the sole review is the Cochrane review from 2011, conclusion is that weak opioids may be effective for painful RA patients but evidence is limited and there is not enough evidence to conclude for long-term opioid therapy or the benefit of strong opioids.<sup>25</sup> In the 2016 SpA ASAS-EULAR recommendations, opioids analgesics, might be considered for residual pain after previously recommended treatments have failed, are contraindicated and/or poorly tolerated.<sup>26</sup> In fibromyalgia (FM), in a large cohort of 1700 patients, no improvement on pain, function and quality of life was shown.<sup>27</sup> In the latest EULAR recommendations, the committee made a 'strong against' evaluation regarding the use of strong opioids in FM.<sup>28</sup>

These results are to be weighed, taking into account the population included in these different trials. In fact, psychiatric pathologies, including depression, are almost always a non-inclusion criterion, and patients with pre-existing risks of abuse or misuse are commonly also excluded. These patients are, however, regularly met in consultation, mandating that we transpose the results of publications for these patients and analyse the benefit-risk balance carefully.

## RECOMMENDATIONS FOR SAFE PRESCRIPTION OF OPIOIDS IN NON-CANCER PAIN

In this context of complex benefit-risk balance with a moderate short term expected benefit on the one hand, and the risk of abuse or misuse with sometimes deadly consequences, several recommendations of good practice have been issued. In 2016, the French Society of Study and Treatment of Pain (SFETD) published French recommendations on good prescribing practices for strong opioids in non-cancer pain<sup>29</sup> and the Centers for Disease Control and Prevention (CDC) published guidelines in the USA,<sup>30</sup> in 2017 European Federation of IASP Chapters (EFIC) published recommendations for a responsible and safe prescription of opioids in CNCP (table 2).<sup>31</sup>

All recommendations remind us to introduce strong opioids only after failure of recommended first-line drug treatments given at maximum tolerated effective doses; and as part of the comprehensive care of the patient, including at least a psychological evaluation in the case of depressive or anxious comorbidities, social, professional and rehabilitative management for osteoarthritis pain and chronic low back pain,<sup>29 31</sup> expected benefits should outweigh risks.<sup>30</sup> French and American guidelines highlight clinical contexts for which expected benefits of opioids are unlikely to overbalance the risks: fibromyalgia and headaches.<sup>29 30</sup>

Some key principles: before any prescription of opioids is given, one must first establish an assessment with a clear and documented diagnosis, a physical examination, a psychological assessment, and finally a determination

**Table 2** Summary of major recommendations for prescribing opioids for non-cancer pain

Recommendation	SFETD <sup>29</sup>	EFIC <sup>31</sup>	CDC <sup>30</sup>
First establish an assessment with a clear and documented diagnosis, a physical examination, a psychological assessment and finally a determination of the impact of pain in all aspects of the patient's life	✓	✓	
Failure of first line recommended treatment given at maximum tolerated dose	✓	✓	✓
Global comprehensive care of the patient (psychological, social, professional and rehabilitative management)	✓	✓	
Expected benefits of opioid treatment should outweigh the risk			✓
In fibromyalgia expected benefits of opioids are unlikely to overbalance the risks	✓		✓
Establish therapeutic goals with the patient and anticipating with clear explanation, the adverse effects and potential inefficiency	✓	✓	✓
Define for the patient the different modes of action of the prescribed treatments and the difference between prolonged release and immediate release forms	✓	✓	
Symptomatic treatment for the most common adverse reactions (constipation, nausea/vomiting) should be systematically prescribed	✓	✓	
Treatment should be initiated at low doses with progressive titration	✓	✓	✓
There is no evidence in the literature to recommend one molecule over another	✓	✓	
Avoid dose greater than (morphine milligram equivalents)	150		90
Avoid co-prescription of benzodiazepines		✓	✓
Regular reassessment (with regard to previously set goals of pain relief, and/or functional improvement, and/or quality of life improvement)	✓	✓	✓
Evaluate risk factors for opioid-related harms	✓	✓	✓

EFIC, European Federation of IASP Chapters; SFETD, French Society of Study and Treatment of Pain.

of the impact of pain in all aspects of the patient's life.<sup>29,31</sup> On the other hand, it is necessary to evaluate pain and function.<sup>29,31</sup> The three publications recommend establishing therapeutic goals with the patient and anticipating with clear explanation, the adverse effects and potential inefficiency.<sup>29-31</sup> It is important to define for the patient the different modes of action of the prescribed treatments and the difference between prolonged release and immediate release forms. Symptomatic treatment for the most common adverse reactions (constipation, nausea/vomiting) should be systematically prescribed.<sup>29,31</sup>

Treatment should be initiated at low doses with progressive titration.<sup>29-31</sup> There is no evidence in the literature to recommend one molecule over another.<sup>29,31</sup> The French and European recommendations differ from the American recommendations in that the latter favour the use of immediate-release form. This differs from EFIC and SFETD which recommend the prolonged release forms<sup>29-31</sup> in particular for a better observance, less paroxysmal pain episodes and less risk of addiction/abuse/misuse.<sup>29,31</sup> For American recommendations, a dose greater than 90mg/day of morphine equivalent is a high dose.<sup>30</sup> The SFETD recommends not to exceed a dose of 150mg/day of morphine equivalent.<sup>29</sup> All the recommendations agree on the imperative of a regular reassessment<sup>29-31</sup> and, for SFETD, in the absence of improvement beyond 3 months of treatment, it is not recommended to continue treatment with a strong opioid.<sup>29</sup>

The risk of abuse should be evaluated before the initiation of treatment. The main risk factors are personal and family history of substance abuse; age; history of preadolescent sexual abuse; and certain psychological diseases. To assess this risk, the Opioid Risk Tool can be used. It is a quantitative tool with a stratification of the risk according to the scores: 0–3 (low risk), 4–7 (moderate risk), ≥8 (high risk).<sup>32</sup>

Once instituted, the treatment must be regularly re-evaluated, especially with regard to previously set goals of pain relief, and/or functional improvement, and/or quality of life improvement. Indicative thresholds of 30% or two out of 10 improvement of pain rating are considered clinically significant for the SFETD.<sup>29</sup> Similarly, at each prescription renewal, it is important to look for signs of abuse or misuse in order to be able to quickly refer the patient for specialist advice. The Prescription Opioid Misuse Index can be used.<sup>33</sup>

## CONCLUSION

Strong opioids can bring a moderate benefit in chronic non-cancer musculoskeletal pain. However, their prescription should be done in a reasoned way with increased monitoring of both efficacy and adverse effects, with special attention to the risk of abuse and misuse.

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