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Different aspects of opioid use in rheumatoid arthritis patients

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Abstract

Background: Rheumatoid arthritis (RA), chronic severe non-cancer pain and the use of prescription opioids are now an increasing and common problem. Both RA and its comorbid pain have different mechanisms and their control can prove challenging, especially when patients are unresponsive to non-opioid analgesics or have side effects.

The aim of the study is to analyze the available results of research and meta-analyzes on the use of opioids among patients with rheumatoid arthritis.

Materials and methods: the literature available on the PubMed platform and published between 2010 and 2020 was analyzed.

Results and conclusions: The use of opioids can cause a number of side effects, including misuse, abuse or addiction to these drugs. These phenomena are becoming more common in European and North American populations, as well as more and more people are using

opioids in long-term therapy, despite the lack of evidence of a positive effect of such treatment in people with RA. In RA patients, frequent combinations of opioids with other drugs, for example benzodiazepines or anti-anxiety agents, are also observed, as well as side effects specific for this group of patients, such as osteoporotic fractures.

Key words: opioids, rheumatoid arthritis, chronic pain

Background

Rheumatoid arthritis (RA) in the adult population has an estimated incidence of 0.5-1%, affects mainly women, and the mean age of onset is 35-50^{1,2}. RA is a chronic autoimmune disease that can damage many joints and cause disability, but pain is the most common reason for seeing a doctor³. A study in Norway indicates that chronic pain associated with RA is also an area where 68.6% of patients expect improvement during treatment^{4,5}, but its control is a challenge. First, more and more research show that pain severity may not necessarily correlate with disease activity^{6,7} because the components of inflammation are not the only factor causing pain^{8,9}. Despite good disease control, joint pain may also persist in remission, which, as shown in animal models, is related to the multifactorial nature of pain in RA, having a source in inflammatory mechanisms that affect nociceptors, as well as neuropathic, central and central mechanisms⁹, but pain may also be associated with mental disorders, disability and poor mental adaptation to the disease¹⁰. The main group of analgesics prescribed to patients with RA are non-selective non-steroidal anti-inflammatory drugs (NSAIDs), which are useful in the first weeks after clinical onset of RA¹¹, but gastrointestinal disorders (including gastric ulcer, dyspepsia, nausea and vomiting), liver and kidney disorders, asthma, allergic rash, hematopoiesis disorders are common side effects¹². Selective COX-2 inhibitors are more and more often used in RA therapy, which have anti-inflammatory and analgesic effects similar to non-selective NSAIDs, but with fewer gastrointestinal complications^{11,13}. However, it turns out that very often pain control with these drugs is insufficient. The increasing and chronic use of opioids in the treatment of chronic non-cancer pain in recent years has led to an "opioid epidemic" with increasing abuse and dependence on these drugs^{14,15}.

Characteristics of opioids

The main function of opioids is analgesic action, which is an effect of drugs' influence on μ , κ and δ receptors, widely distributed in the central and peripheral nervous system¹⁶. In addition to this effect, there are also a number of side effects, ranging from the most common nausea and vomiting¹⁷, behavioral disorders, somnolence, impaired sleep regulation and insomnia, endocrine disorders, sleep apnea, respiratory depression, abuse and addiction¹⁸. The latter, according to the U.S. Food and Drug Administration, are serious adverse events¹⁹. In addition, drug-drug interactions and alcohol-drug interactions, which may exacerbate or cause side effects, are important issues with chronic opioid use¹⁸. The most commonly used chronic

opioids in the US are oxycodone, tramadol, hydrocodone, fentanyl, codeine and morphine³. In Poland, the most commonly used opioids in 2000 were morphine and fentanyl, while in 2015 the first place was taken by tramadol, mainly due to the widespread use of preparations combining both paracetamol and tramadol²⁰.

Changes in opioids use

Numerous studies indicate an increase in the use of opioids among RA patients, as well as an increasing chronic use of these drugs. In a cohort study conducted in the US in 2002-2015, the criterion of chronic opioid use was defined on the basis of documented opioid use during at least two follow-up visits, with the median time between two visits being 156 days. In the study group, the percentage of chronic opioid users more than doubled from 7.4 in 2002 to 16.9 in 2015²¹. Another study found that patients with RA in 2014 were 1.5 times more likely to use opioids than those without RA (40 % vs 24%) and were almost twice as likely to use opioids chronically (12% in RA vs 4% in non-RA patients, the rate index was adjusted for age and gender), with the study assuming that chronic opioid use was considered to be providing the patient with a prescription for 60 days or longer³. Another cohort study completed in 2014 indicates that 41% of RA patients use opioids regularly (chronic use is defined as having at least 3 opioid prescriptions or taking them for at least 90 days), 40% use them sporadically, and 19% do not take them at all²². All the above-mentioned studies also confirm the increase in the incidence of both incidental and chronic opioid use in the RA patients population in the United States in recent years, with the highest percentage in 2010 and a slight decrease by 2014. In addition, more frequent chronic opioid use was reported among women aged 50-67^{3,22}.

Opioids and rheumatoid arthritis

There are few studies on the effectiveness of opioids in the treatment of pain associated with RA, and evidence of their effectiveness is weak²³. Most studies refer to weak oral opioids and identify these drugs as beneficial in treating pain associated with RA, while paying attention to possible side effects, but the results of these studies are also burdened with a high risk of error^{24,17}. Another study indicates that opioid use for less than 1 month may have a positive effect on health-related quality of life (HRQoL) measured by a physical and mental component survey²⁵.

Although there are indications of the efficacy and relative safety of opioids, they only apply to short-term use. There are no clinically relevant data on the use of opioids in patients with RA for more than 8 weeks²⁶. There was also no evidence that the efficacy of analgesia could be sustained after eight weeks of continuous opioid use in any form of chronic non-cancer pain²⁷.

The cohort studies also highlighted the medications that RA patients used concomitantly with chronic opioids. In one of the studies slightly more than 40% of respondents took biological DMARDs, 27% took glucocorticosteroids and almost 18% took antidepressants²¹. To this list other studies add the frequent use of benzodiazepines, antiepileptic drugs²⁶ and the use of non-opioid analgesics such as acetaminophen or NSAIDs²⁸.

The observed relationship between the use of opioids and biological drugs and glucocorticosteroids may result from the fact that people who require biological treatment are characterized by greater disease activity and greater pain intensity²¹. On the other hand, it seems that the low level of parameters and symptoms of inflammation does not equal reduced pain and fatigue⁶. A study in Iceland found that 75% of patients had used opioid analgesics in two years before and/or after starting treatment with a TNF inhibitor, with the proportion of patients taking opioids rising before starting treatment and then falling back to an earlier level²⁹, which may indicate the fact that better control of RA activity does not necessarily lead to a decline in opioid use¹⁴.

A high proportion of patients who take antidepressants and opioids concurrently corresponds to the data indicating that depression occurs in 22.5% of patients with chronic pain³⁰, while in RA patients depressive symptoms were observed in 12-55% of respondents, depending on the kind of questionnaire used and its level of detail³¹. Moreover, it was determined that in the group of patients with mainly moderate or high RA activity measured with DAS23, a depressive episode in the course of recurrent depression is an important factor in the persistence of pain, and tailored antidepressant treatment leads to a lasting reduction in pain intensity³². On the other hand, chronic pain and inflammation increase the risk of depressive symptoms, but it is unclear whether chronic pain is a depressive factor in RA or whether the relationship is bi-directional³¹. Apart from depression, a very common phenomenon in people with chronic pain is anxiety, which, similarly to depressive symptoms, influences the perception of pain and often leads to extreme focus on the symptoms of the disease³³. There is no clinical-based evidence that long-term treatment of pain with opioids is helpful in depressed and anxious patients who may be at greater risk of opioid side effects, including overdose, during the course of treatment²⁷.

Addiction and threats during the COVID-19 pandemic

The increase of opioid use has been observed worldwide, but it is particularly dramatic in the United States, where prescription sales quadrupled between 1999 and 2010³⁴, reaching 38% of American adults taking opioids in 2015, and 17% of these reported disorders related to opioid use²¹, including increasing dependence and opioid abuse¹⁵. The death rates caused by opioid poisoning also more than doubled between 2000 and 2013, with 81% of these deaths being unintentional³. Data on the use of opioids in chronic pain are similarly disturbing – it is believed that 21-29% of patients have abused them¹⁴. Compared to other drugs for chronic pain, opioids have a significantly increased risk of death from overdose²¹. In Poland, in the years 2000-2015, there was a threefold increase in the use of opioid analgesics; there was an increase in the use of both weak and strong opioids, and almost 93% of them were prescription for ambulatory use. These data, however, refer to the general use of opioids, there are no data on the use of opioids only in non-cancer pain, but it is worth emphasizing that the reported increase in opioid use is not only due to the increased incidence of neoplasms²⁰.

In recent years, numerous efforts have been made to reduce the use of opioids and combat addiction, but there are some data that the positive effects of these efforts have been wasted as a result of the COVID-19 pandemic. Some US states report an increase in opioid overdose of

up to 50% compared to the same period a year ago¹⁴. Concern is also raised by the fact that COVID-19 affects people with chronic diseases more often as well as the group of chronic opioids users, and in addition, as a result of the pandemic, the social conditions that led to the opioid epidemic in the US, namely unemployment and isolation, may deteriorate^{14,35}.

Other risks in people with RA

From the point of view of public health, arthritis is a particularly important disease that should be considered separately in terms of opioid use, as the number of patients in the US is projected to increase from 1.5 million in 2007 to 67 million in 2030³⁶, but also complications of opioid use specific to patients with RA are clinically significant. Rheumatoid arthritis is associated with an increased risk of osteoporosis and fractures compared to the general adult population, and osteoporotic fractures are the third leading cause of death in RA patients and the second leading cause of disability³⁷. An additional factor predisposing to fractures is short-term (≤ 1 month) use of strong opioids³⁸. The increased risk refers both vertebral and non-vertebral fractures, but the increase of risk is higher for vertebral fractures^{38,39}.

Summary

RA remains a difficult and challenging disease, especially when it comes to treating NSAID-resistant pain. While there are reliable studies supporting the safety and efficacy of the short-term use of opioids in the treatment of such pain, long-term treatment is still not supported by adequate studies, but is nevertheless often used in clinical practice. It is important to be aware of many dangers of chronic opioid use, also in combination with other medications that are frequently used by RA patients. Social factors and the individual characteristics of each patient should also be taken into account.

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