Tramadol: a wonder drug for the treatment of chronic pain?

"Nowadays, we should consider tramadol as a 'silver bullet', rather than as a 'wonder drug', for its extreme effectiveness in chronic pain management."

"When the only tool you have is a hammer ... it is tempting to treat everything as if it were a nail."
Abraham Maslow, 1962. The Psychology of

Science: A Reconnaissance

Chronic pain is one of the most prevalent, costly and disabling conditions in both clinical practice and the workplace, yet often remains inadequately treated. Musculoskeletal conditions, such as low-back pain and osteoarthritis (OA), are the leading causes of disability among individuals of working age. The goals of adequate pain management include pain relief, minimizing disability, improving quality of life and preventing progression of the disease [1]. Optimal management requires a combination of nonpharmacological and pharmacological modalities of therapy [2].

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NSAIDs have been widely used in the management of chronic pain. However, patients receiving long-term NSAID therapy may experience severe gastrointestinal (GI) symptoms. NSAID-related ulceration and bleeding is estimated to result in up to 20,000 deaths each year in the USA [3]. Attempts to reduce the serious GI adverse effects of the NSAIDs by the introduction of the highly selective COX-2 inhibitors have only had limited benefit in reducing these untoward actions. COX-2-specific inhibitors, such as celecoxib, may spare gastric mucosal prostaglandin synthesis and, consequently, cause less GI injury. However, both COX-2specific inhibitors and NSAIDs may affect fluid and electrolyte balance in some patients, resulting in fluid retention, edema and hypertension [4]. Moreover, accumulating data have linked COX-2 inhibitors with serious cardiovascular and/or cardiorenal effects and/or serious cutaneous adverse reactions, particularly at anti-inflammatory doses or when used long term. Regulatory authorities in both Europe and the USA have responded to these data with the withdrawal of rofecoxib and valdecoxib, and the strengthening of prescribing advice on all anti-inflammatory drugs [5].

Scientific societies, including the American College of Rheumatology (ACR) [6], American Pain Society (APS) [7] and European League Against Rheumatism (EULAR) [8], have published treatment guidelines to assist clinicians to achieve effective chronic pain management. Safety is a core concern in all these guidelines, especially for chronic conditions such as lowback pain and OA that require long-term treatment. There is a consensus among recommendations that paracetamol should be the first-line analgesic agent due to its favorable side effect and safety profile. Owing to the selective inhibition of COX in the CNS, paracetamol does not impair GI, renal and platelet function [9].

When the anti-inflammatory component is required, the OA Research Society International (OARSI) guidelines recommend NSAIDs, including COX-2 inhibitors, for the treatment of symptomatic OA of the hip or knee at minimal effective doses only; whereas long-term NSAID use should be avoided if possible [10].

All the recent pain management guidelines have shifted their emphasis from the use of NSAIDs and COX-2 inhibitors to opioids. Therefore, when greater analgesia is desired, the addition of weak opioids is recommended, based on a preferable GI and cardiovascular profile, compared with the prolonged use of high doses of NSAIDs [11].

Conversely, opioids are still underused, regardless of their established analgesic efficacy. The fear of adverse effects and the need of risk assessment for scheduled opioids remain problematic



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for many healthcare providers. Pain management guidelines recommend that strong opioids only be used for the management of severe pain in OA in exceptional circumstances, when more conservative methods have failed [12]. The use of opioids requires close supervision, especially in the elderly with cognitive decline, since drug actions on the CNS and peripheral nervous systems can result in significant adverse effects of these agents (e.g., constipation, drowsiness, respiratory and cardiovascular decline) [13].

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The beneficial effects of 'nontramadol opioids', as defined in the last Cochrane systematic review on oral or transdermal opioids for OA of the knee or hip, are outweighed by large increases in the risk of adverse events. Therefore, they should not be routinely used, even if osteoarthritic pain is severe [14].

In light of this consideration, the use of tramadol becomes readily apparent. Tramadol, as an atypical opioid with a low potential for drug tolerance and abuse, is well suited for the management of refractory pain and, as such, is recommended as an alternative to NSAIDs and strong opioids in various treatment guidelines.

Tramadol has been demonstrated to be effective in the treatment of a wide range of acute and chronic pain syndromes, including neuropathic pain, and it is generally well tolerated. The APS recommends tramadol, alone or in combination with acetaminophen or NSAIDs, for the management of OA pain when NSAIDs alone produce inadequate pain relief [15]. Unlike NSAIDs, tramadol does not irritate the GI mucosa, or exacerbate hypertension or congestive heart failure, making it potentially useful for the elderly. For patients awaiting total joint replacement surgery, tramadol may be a good analgesic option if NSAIDs or COX-2-specific inhibitors are not tolerated or provide suboptimal pain relief.

The most recent recommendations of the American Heart Association include tramadol, not NSAIDs or COX-2-specific inhibitors, as first-line therapy for musculoskeletal symptoms in patients with cardiovascular disease or risk factors [16]. The fixed association tramadol/paracetamol is a safe and easy solution for mild-to-moderate chronic pain [17].

Compared with other centrally acting analgesics, tramadol has no clinically relevant cardiovascular effects and insignificant effects on respiration. While μ -opioid agonists have undesirable effects on GI function, resulting in nausea, emesis and especially constipation, these effects are less severe with tramadol and attenuate over time. Tramadol has only a minor delaying effect on colonic transit, and no effect on upper GI transit or gut smooth muscle tone [18].

Despite its favorable profile, it is a conceptual mistake to consider tramadol a 'panacea', a supposed remedy that would cure all types of pain. The research of the so-called 'wonder drugs' failed to give positive results in several medical fields. In particular, owing to the complexity of pain mechanisms, it is unreliable to think that the rule 'one fits all' could be applicable to any analgesic drug.

Although we often think of pain as a homogeneous sensory entity, several distinct types exist. Current analgesic treatment is aimed at suppressing or controlling symptoms; however, a better approach should be a mechanism-based pain management, which includes a diseasemodifying treatment strategy to complement the existing approach of symptom control [19]. The identification of the multiple mechanisms responsible for the production of distinct pain syndromes and their molecular components has been a major advance in our understanding of pain and represent the first step for the development of pharmacologic tools that act specifically on these mechanisms.

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Tramadol is a centrally acting analgesic with two mechanisms of action in a single molecule. Tramadol acts both on the opioidergic system, with an affinity for μ -opioid receptor approximately 6000-fold less than that of morphine, and on the descending monoaminergic inhibitory system that physiologically modulates pain perception. Tramadol hydrochloride exists as a racemic mixture with the (+)-enantiomer and the (-)-enantiomer, and at least some of their metabolites, having different effects. (+)-tramadol and (+)-O-desmethyl-tramadol (M1), the main analgesic effective metabolite, are agonists of the μ -opioid receptor. (+)-tramadol inhibits serotonin reuptake and (-)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The *O*-demethylation of tramadol to the active metabolite M1 is catalyzed by the liver enzyme cytochrome P450 2D6. Therefore, the observed variability in the pharmacokinetic properties of tramadol can partly be ascribed to cytochrome P450 polymorphism [18].

This dual mechanism of action by which analgesia may be achieved with tramadol includes, in a 'single drug', the concept of multimodal analgesia, which involves the use of different classes of analgesics and/or different sites of administration to provide synergistic analgesic effects and minimize adverse drug effects.

These different, complementary mechanisms of action could be of particular relevance in some types of pain that are generally considered to be relatively unresponsive to opiates, such as neuropathic pain syndromes.

A novel, centrally acting analgesic with two mechanisms of action, termed tapentadol, is currently under evaluation. Its analgesic activity is achieved through micro-opioid receptor agonism and noradrenaline reuptake inhibition in the CNS. Tapentadol represent a new alternative drug for moderate-to-severe pain, to be located in the 'third step' of the analgesic ladder [20].

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Chronic pain is still far from being a solved problem. The search for a 'magic wand' does not represent the right solution. Rather, we should focus on drugs with an appropriate balance between analgesic efficacy and tolerability in order to improve patient adherence to long-term treatments.

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