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REVIEW

The role of tramadol in pain management in Latin America: a report by the Change Pain Latin America Advisory Panel

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ABSTRACT

Objective: Change Pain Latin America (CPLA) was created to enhance chronic pain understanding and develop pain management improving strategies in this region. During its seventh meeting (August 2016), the main objective was to discuss tramadol's role in treating pain in Latin America. Furthermore, potential pain management consequences were considered, if tramadol was to become more stringently controlled.

Methods: Key topics discussed were: main indications for prescribing tramadol, its pharmacological characteristics, safety and tolerability, effects of restrictions on its availability and use, and consequent impact on pain care quality.

Results: The experts agreed that tramadol is used to treat a wide spectrum of non-oncological pain conditions (e.g. post-surgical, musculoskeletal, post-traumatic, neuropathic, fibromyalgia), as well as cancer pain. Its relevance when treating special patient groups (e.g. the elderly) is recognized. The main reasons for tramadol's high significance as a treatment option are: its broad efficacy, an inconspicuous safety profile and its availability, considering that access to strong analgesics – mainly controlled drugs (classical opioids) – is highly restricted in some countries. The CPLA also agreed that tramadol is well tolerated, without the safety issues associated with long-term nonsteroidal anti-inflammatory drug (NSAID) use, with fewer opioid-like side effects than classical opioids and lower abuse risk.

Conclusions: In Latin America, tramadol is a valuable and frequently used medication for treating moderate to severe pain. More stringent regulations would have significant impact on its availability, especially for outpatients. This could cause regression to older and frequently inadequate pain management methods, resulting in unnecessary suffering for many Latin American patients.

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Pain management; tramadol; Latin America; abuse; prescription control

Introduction

The management of pain represents an important public healthcare issue. The Declaration of Montreal, Canada (2010) states that access to pain management is a fundamental human right, and this has been endorsed by the International Association for the Study of Pain (IASP), the European Pain Federation (EFIC) and the World Health Organization (WHO)[1–3]. It also established that any person with pain has the right to be evaluated and treated properly, without any kind of discrimination[1]. However, in many Latin American countries pain management is currently still perceived to be inadequate, mainly owing to severe restrictions on the availability of controlled analgesic drugs[4].

The United Nations Single Convention on Narcotic Drugs[5] of 1961 was held in order to ensure the availability of controlled medications for the relief of pain and to prevent diversion and abuse[6]. Nevertheless, the use of controlled medications remains low in many parts of the world. Developing countries (including Latin American countries) account for 80% of the world's population, but the consumption of strong opioids (e.g. morphine) for pain relief hardly reaches 6% of the global total[7]. A recent article stated that barriers to the use of opioids include absence of prescriber

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Table 1. Change Pain Latin America (CPLA) Advisory Panel members.

CPLA members	Country	Specialist in
Argelia Lara-Solares	Mexico	Anesthesiology, pain management and palliative care
José Alberto Flores Cantisani	Mexico	Anesthesiology, pain management and palliative care
César Amescua-Garcia	Mexico	Anesthesiology, pain management and palliative care
María del Rocío Guillén Núñez	Mexico	Anesthesiology, pain management and palliative care
Aziza Jreige Iskandar	Venezuela	Physical rehabilitation
Patricia Bonilla	Venezuela	Anesthesiology, pain management and palliative care
João Batista Santos Garcia	Brazil	Anesthesiology, pain management and palliative care
Osvandré Lech	Brazil	Orthopedics
Durval Campos Kraychete	Brazil	Anesthesiology and pain management
María Antonieta Rico	Chile	Anesthesiology, pain management and palliative care
John Jairo Hernández-Castro	Colombia	Neurosurgery, pain management and palliative care
Frantz Colimon	Colombia	Anesthesiology and pain management
Carlos Guerrero	Colombia	Anesthesiology, pain management and palliative care
William Delgado Barrera	Costa Rica	Anesthesiology
Manuel Sempértegui Gallegos	Ecuador	Anesthesiology and pain management
María Berenguel Cook	Peru	Anesthesiology, pain management and palliative care
Concepción Pérez Hernández	Spain	Anesthesiology, pain management and palliative care

training, fear of producing dependence on opioid analgesics, financial constraints, and problems sourcing or importing opioid medicines. Cultural attitudes toward pain management, fear of diversion, and fear of criminal prosecution were also frequent impediments[8].

Inadequate pain treatment because of the limited use of opioids appears to be highly prevalent in Latin America, and is directly linked to patient dissatisfaction[9,10]. Countries in the region have stringent laws and restrictions regulating the storage and distribution of opioids[11]. This limits their accessibility and delivery, and negatively affects their prescription. Additional limitations come from a lack of knowledge regarding opioid use and efficacy amongst both patients and healthcare professionals (opioignorance)[12,13], and from the fear of possible abuse and addiction (opiophobia).

The Change Pain Latin America Advisory Panel (CPLA) was created in 2012 to enhance the understanding of chronic pain and to develop strategies for improving pain management in this region. It comprises 17 experts from Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru, Venezuela and Spain, who work across a variety of clinical pain-related specialties and were selected for their research activity and clinical experience (Table 1). Panel members apply their knowledge and experience to highlight and address the unmet medical needs associated with chronic pain treatment in Latin America, and to overcome obstacles in order to improve best practice and outcomes[9].

The CPLA objectives include: i) to improve the management of pain, ii) develop solutions based on research data and expert opinion, iii) increase knowledge and provide appropriate tools to improve pain diagnosis, and iv) eliminate opiophobia via the education of healthcare professionals and patients, based on reliable evidence[9].

At one of its earlier meetings, the CPLA formulated a table of analgesics with opioid activity currently available in Latin America. The centrally acting analgesic with the most widespread availability and versatility in the region appears to be tramadol[10,14].

This is supported by the retail, i.e. mainly pharmacy, sales of tramadol (on its own or in combination with other analgesic medications) in Latin and Central America (Table 2).

Table 2. Retail sales: standard units (in thousands) of tramadol and other opioid medications in Latin and Central America countries (Brazil, Chile, Colombia Ecuador, Mexico, Peru and Central America).

Medication	Retail sales standard units, in thousands
Tramadol	135,064 (247,851)
Morphine	21,369 (22,347)
Hydrocodone	(4414)
Codeine	22,344 (231,869)
Oxycodone	4703 (4955)
Fentanyl	243
Buprenorphine	3900
Tapentadol	493

The IMS standard unit defines a single dose of tramadol. Numbers reflect the total sales of the medications, either on their own or (in parentheses) in combination with other analgesic medications (paracetamol, NSAIDs, gabapentin, etc.).
Source: IMS MIDAS MAT September 2016.

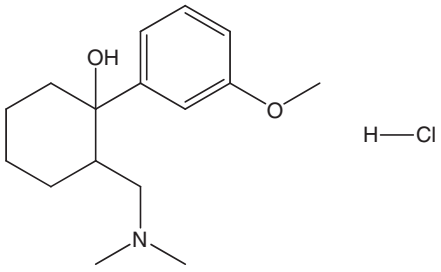
The total almost equals the combined retail sales of all classical opioids available in this region (data published by IMS MIDAS MAT September 2016).

At the CPLA meeting in August 2016, the main objective was to discuss the role of tramadol for the management of pain in Latin America[10]. During this meeting, 13 of the 17 experts (from Chile, Colombia, Peru, Ecuador, Mexico and Brazil) were present. The discussion centered on their clinical experience with tramadol and its use in daily practice. The importance and relevance of tramadol in Latin American countries were also considered, focusing on the most relevant indications, advantages and benefits it offers compared to other analgesics (such as classical opioids and NSAIDs). The potential impact that higher restrictions on the availability and use of tramadol might have on the quality of patient care was also explored.

Pharmacology and characteristics of tramadol

Tramadol (Figure 1) is a centrally acting analgesic with opioid and non-opioid mechanisms of action. It was introduced in 1977 by the German pharmaceutical company Grünenthal GmbH.

Pharmacologically, tramadol is unique in its dual pain control action. Tramadol binds to the human μ-opioid receptor but its activity at this receptor is negligible. The M1



2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexan-1-ol hydrochloride

Figure 1. Chemical structure of tramadol.

metabolite has relevant binding and activity at the human μ-opioid receptor (EC_{50} 860 nM) although lower than for morphine (EC_{50} 118 nM)[14]. In addition, tramadol has also been shown to inhibit the reuptake of norepinephrine and serotonin (i.e. non-opioid activity)[15], thereby enhancing the descending inhibitory pathways associated with pain transmission in the CNS[16]. The opioid and non-opioid mechanisms of tramadol seem to contribute about equally to the analgesic effect of tramadol in humans[17,18].

After oral administration tramadol is absorbed rapidly and reaches maximum serum concentrations within two hours[19]. The oral absolute bioavailability is about 70% after a single dose and approaches 100% after repeated dosing[20]. Extensive first-pass metabolism occurs via O- and N-demethylation catalyzed by the enzymes cytochrome P450CYP2D6 and CYP3A4[20,21]. The active metabolite (+)-M1 depends upon CYP2D6 for its generation; it is the main carrier of the opioid activity of tramadol and has a half-life of 8 hours[19,20]. Subjects deficient in CYP2D6 activity (so called poor metabolizers) are confined to the non-opioid analgesia of tramadol and may need higher doses[22]. Subjects with multiple copies of the CYP2D6 gene and subsequently higher than normal CYP2D6 activity (ultra-rapid metabolizers) have on average 30% higher concentrations of (+)-M1 and hardly lower tramadol concentrations than normal[23]. There is a considerable variability in the CYP2D6 allele distribution among different ethnic groups[24]. The frequency of poor metabolizers among Hispanics is 2.2–6.6%[25].

The (+)-M1 is deactivated by glucuronidation which reaches maturity at about the age of 1 year. Therefore, (+)-M1 may accumulate in children below the age of 1 year and should not be administered to these young children[26]. Ninety per cent of tramadol is excreted by the kidneys and 1% in bile[20].

Clinical use of tramadol in Latin America

Tramadol is widely prescribed for treating moderate to severe pain in Latin America. The recommended indications for use are in line with those described in the international literature[19,27].

Published clinical evidence shows that tramadol has, as a result of its dual pain control action, a wide range of applications in both acute (trauma, post-operative) and chronic (cancer and non-cancer) moderate to moderately severe pain[20,28–31]. Cochrane meta-analyses have concluded that tramadol is efficacious in neuropathic pain[32] and in pain related to osteoarthritis[29]; the assessment of tramadol's efficacy for the treatment of low back pain and rheumatoid arthritis gave similarly positive results[28,33]. The meta-analysis in low back pain concluded that tramadol was superior to placebo for pain and function[33]. The meta-analysis in rheumatoid arthritis concluded that treatment of patients with rheumatoid arthritis with weak opioids (including tramadol) for up to six weeks may offer clinically relevant improvement in pain.

Furthermore national and international pain societies recommend tramadol in their evidence-based treatment guidelines, e.g. in neuropathic pain[34], acute and chronic low back pain[35], and osteoarthritis pain[36].

Following discussion, the CPLA Advisory Panel unanimously agreed that in Latin America tramadol is frequently used to treat: (i) non-cancer patients with severe acute pain (post-operative, post-traumatic and lower back pain), (ii) moderate to severe chronic pain (neuropathic, osteoarthritic, chronic low back pain), (iii) elderly patients with moderate pain who are not candidates for treatment with non-steroidal anti-inflammatory (NSAID) medications or COX2 inhibitors, (iv) opioid-naïve patients, as a first choice analgesic, (v) cancer pain patients, and (vi) fibromyalgia – use in this disease is controversial but might be beneficial for short periods of time.

Members of the Advisory Panel also rated the importance of tramadol (high, moderate or low) as a treatment option in their own countries, when treating cancer pain, acute or chronic non-cancer pain, and neuropathic pain. The general consensus was that tramadol is moderately to highly significant in the management of pain caused by almost every condition for which it is indicated. In treatment for acute post-surgical pain and cancer pain, tramadol was considered highly significant, more so than for neuropathic pain and acute musculoskeletal pain. Their conclusion was that tramadol is an extremely useful agent in the pain management armamentarium.

Discussion extended to the use of tramadol in patients suffering from fibromyalgia. Ultimately, the Panel endorsed the use of tramadol for this condition (because of its dual action effect), which agrees with the recommendations of the National Opioid Use Guideline Group[37]. These state that tramadol is indicated for managing pain during fibromyalgia crises for short periods of time, usually concomitantly with other analgesic medications that are similarly indicated.

Special emphasis was given to the small group of patients who have obstructive sleep apnea and severe chronic obstructive pulmonary disease (COPD). Tramadol has a lower risk of respiratory depression compared with classical opioids and respiratory depression does not normally occur when the drug is used in the therapeutic range. Published literature suggests that it might be useful in situations in which the risk of respiratory depression is increased[19,20,38,39]. However, it should be noted that in patients with additional risk factors such as respiratory center or function disorders, including obstructive sleep apnea syndrome, the risk of developing respiratory complications can increase and

therefore may only be used with particular caution in such patients including children[40].

With respect to different patient groups (adults, children or the elderly), the CPLA Advisory Panel discussed that tramadol is highly significant in the management of acute and chronic pain in adults, and moderately significant in elderly patients when treating moderate persistent pain (e.g. osteoarthritis, lower back pain). Managing pain in the elderly can be complex and challenging, as they often have multiple nutritional and medical problems. These might limit treatment options because of the increased risk of drug interactions and adverse effects, and individual differences in the metabolism of drugs[41]. Tramadol has been recommended as a second-line option for neuropathic pain in elderly patients[41]. Treatment should be initiated at a low dose and then titrated as required[42]. A randomized, double-blind, placebo-controlled trial showed that the tolerability profile of a tramadol–acetaminophen combination for osteoarthritis pain in elderly patients makes this combination an attractive therapeutic option[43], especially when the side effects of NSAIDs are taken into account[44].

Tramadol has also been approved for use in the pediatric population in some Latin American countries. As with many medicines, tramadol is dosed in children according to body weight. The availability of appropriate formulations allows for body weight adjusted dosing in patients under twelve years of age. Respiratory depression is rare in the pediatric population; however, in overdose situations it can occur[45–47]. Therefore, dosing recommendations for children should be strictly followed and only suitable formulations should be used that allow appropriate dosing in patients under 12 years.

In conclusion, the clinical use of tramadol in Latin America extends over a broad range of indications covering acute and chronic, moderate to severe pain. Its broad use is also reflected by its recommendation in national guidelines[48,49]. Thus, in Latin America tramadol has established a clear and important position in therapy between NSAIDs/COX-2 inhibitors and strong opioids.

Safety and tolerability of tramadol

The safety and tolerability profile of tramadol was evaluated by the experts in comparison to NSAIDs and also to classical opioid analgesics.

Since selective COX-2 inhibitors and especially NSAIDs are associated with an increased risk of severe gastrointestinal, renal and cardiovascular side effects, which further increases with the duration of treatment[50–53], the experts emphasized the suitability of tramadol for longer term treatment of chronic pain patients compared with NSAIDs. The experts' opinion reflects current recommendations regarding the use of NSAIDs in guidelines that the lowest dose of these agents to control symptoms should be prescribed for the shortest time[54].

Extensive discussion of the safety and tolerability profile of tramadol compared to classical opioids led to the following consensual conclusions:

- tramadol has a lower incidence of typical opioid side effects, such as respiratory depression
- the risk of dependence and addiction is lower with tramadol
- tramadol has been described to have a lower immunosuppressive effect
- tramadol is available in multiple formulations and can be easily titrated, thereby reducing the incidence of opioid-typical side effects especially at treatment initiation or dose increase.

The experts' view is supported by published data. Vazzana *et al.* reported that the advantages of tramadol over other opioid medications are its unique pharmacological profile, and that the incidence of side effects and the abuse potential are lower[15].

Special attention was paid to the incidence of constipation, nausea and vomiting. Based on their clinical experiences the incidence of constipation was rated by the Panel to be lower than with classical opioids, but nausea and vomiting appear to be more prevalent with tramadol. However, the occurrence of nausea and vomiting with tramadol can be minimized by: (i) intra-operative administration in surgical patients, (ii) titrating the dose slowly, and (iii) concomitantly administering anti-emetics[55].

Respiratory depression is a typical serious side effect of μ-opioid receptor agonists. Due to its multiple modes of action, tramadol has a lower propensity to cause respiratory depression compared to pure μ-opioid receptor agonists. This has been demonstrated in several clinical trials comparing tramadol to conventional opioids such as morphine, oxycodone, pethidine or nalbuphine[39,56–62]. However, the risk is increased in adults or children if recommended doses are considerably exceeded, other centrally depressant substances are administered concomitantly, or in patients with additional risk factors such as respiratory center or function disorders.

A further potential advantage of tramadol was seen in the lack of immunosuppressive effects of tramadol as described by Sacerdote in animal studies compared to classical opioids[63]. In contrast, tramadol may even possess an immune-enhancing effect most likely linked to its serotonergic component[64]. However, it was emphasized that the current clinical evidence is still limited.

The CPLA experts experienced only a few cases of tramadol abuse in their clinical practice. Abuse is a well known risk with opioids. In these days, the increasing misuse and abuse of prescription opioids and related harms have become matters of severe concern and public controversy, especially following the opioid crisis in the US[65].

The abuse potential of tramadol has been investigated in various preclinical and clinical models, as well as post-marketing surveillance studies, and was shown to be relatively low compared to opioids such as morphine, oxycodone or hydrocodone[66–72]. When abuse of tramadol was recorded, this was predominantly in persons with a history of substance abuse[67]. The WHO Expert Committee on Drug Dependence (WHO ECDD) last reviewed tramadol's worldwide abuse risk and related harms in 2014 and came to the conclusion that international control of tramadol is not appropriate[73].

Overall, the CPLA experts noted that it is important to follow guidelines that provide guidance on patient selection and risk stratification for opioid prescribing in chronic pain. Guidelines, such as those published by the National Opioid Use Guideline Group (NOUGG) of Canada[74], give strategies to use opioids in the best way, i.e. after thorough diagnosis, assessment of alternative therapeutic options in the context of a multimodal treatment concept, periodic re-assessments and close follow-up. Safe and effective long-term opioid therapy requires clinical skills and knowledge of the principles of opioid prescribing, and of the assessment and management of risks associated with opioid abuse, addiction, and diversion.

Potential pharmacokinetic and pharmacodynamics interactions of tramadol with other medications were also addressed. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported. Induction of CYP3A4 may reduce the analgesic effect and shorten the duration of action of tramadol.

The concomitant administration of tramadol with other centrally depressant medicinal products – or alcohol – may potentiate the CNS effects. Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), MAO (monoamine oxidase) inhibitors, and tricyclic antidepressants may cause serotonin toxicity. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

The Advisory Panel concluded that tramadol is well tolerated overall, without the safety issues related to the (long-term) use of NSAIDs, and with fewer opioid side effects than classical opioids.

Further features of tramadol of value for physicians and patients

In addition to the efficacy and safety profile of tramadol, its diversity of formulations and routes of administration (tablets, drops, injections, suppositories, etc) were regarded by all the Panel members as a valuable feature.

Further characteristics highlighted by the CPLA experts include: ease of dose titration, reasonable cost, good adherence to treatment, and simple prescription making it readily accessible by the patient.

Potential consequences of implementing more stringent regulations on the use of tramadol

With respect to the potential implementation of more stringent regulations for tramadol, the CPLA experts expressed concern that the quality of pain management in the Latin American region would be severely negatively affected, unnecessarily increasing the suffering of patients.

Currently, especially for physicians in the community, tramadol offers some unique advantages over classical opioids: accessibility, no requirement for controlled prescriptions, and a limited risk of abuse. Often, tramadol is the only available option to treat pain requiring a centrally acting analgesic, as classical opioids are either unavailable or strictly controlled.

According to the CPLA Advisory, only few healthcare professionals (HCPs) – predominantly pain specialists in hospitals – prescribe controlled drugs. In some countries, HCPs must obtain a license to prescribe strong opioids and maintain records of patients' consumption of them. This complex and time-consuming process can deter HCPs from prescribing controlled drugs. In addition, these prescriptions have very short validity periods (typically 5 days) and cover a limited period of treatment (maximum of 30 days' supply). The consequent need for frequent repeat prescriptions may also result in poor compliance according to the experts.

In addition stricter storage regulations may have an impact on the availability of tramadol on a pharmacy level. The reduced availability of tramadol would most likely result in an increase in the use of paracetamol and NSAIDS with the consequence of a higher rate of inadequate pain relief and increase in complications, increasing patients' dissatisfaction with their treatment.

The CPLA experts therefore concluded that tramadol is often not just one valuable treatment option, but the only option available for treating moderate to severe pain. More stringent regulations producing decreased availability and limited access to tramadol would therefore lead to a significant deterioration in the quality of pain management – especially in the out-patient setting – and a significant increase in suffering, particularly in countries where controlled strong opioids are rarely used.

Conclusions

After reviewing and discussing the use of tramadol in depth, the Advisory Panel of experts have concurred that tramadol is a valuable and frequently used component of the analgesic armamentarium in Latin America. It is very often chosen in preference to NSAIDs, paracetamol and strong opioids for treating moderate to severe pain. Effective across a wide spectrum of acute and chronic pain conditions, tramadol is well tolerated and without the safety issues related to NSAIDs, with fewer opioid-like side effects and a lower risk of abuse than classical opioids.

The potential consequences of more stringent regulations of tramadol on the management of pain in Latin America are a concern of the CPLA Advisory Panel. Fears were expressed that tighter global control, in combination with the lack of access to controlled opioid analgesics in many areas of the region, might lead to inadequate pain control and the unnecessary suffering of many patients with pain.

Transparency

Declaration of funding

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Declaration of financial/other relationships

J.B.S.G., O.L., D.C.K., M.A.R., J.J.H.-C., F.C., C.G., M.S.G., A.L.-S., J.A.F.C., C.A.-G., M.R.G.N., M.R.B.C., A.J.I. and P.B.S. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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