Pain medicine has come a long way since the now-famous three-rung “pain ladder” proposed by the World Health Organization (WHO) in 1988. The WHO pain ladder recommended treating cancer pain based solely on intensity and although it allowed for combination therapy and adjuvant agents, it stopped short of specifying them or offering guidance on their use [1]. It also did not address non-cancer pain.

Since 1988, novel analgesic products and new formulations of existing products have come to market and our understanding of the multimechanistic nature of many pain syndromes has increased. For example, the American Geriatric Association recently changed its guidance for pain control in the elderly by advocating opioids be used as first-line agents with NSAIDs reserved for short-term use to manage pain exacerbations and flares [2].

Yet, treating chronic nonmalignant pain remains challenging in that multimodal therapy is often required, and the pharmacological regimen should be individualized to meet the patient’s needs. In Mexico, there are two board groups of pain medicine prescribers: those who are experienced with buprenorphine, including a high dose transdermal buprenorphine (TRANSTEC™) for whom the favorable clinical attributes of buprenorphine are well known; and those who have not or do not currently prescribe buprenorphine.

In this setting, low-dose transdermal buprenorphine is worthy of consideration.

**Abstract**

Chronic non-cancer pain is prevalent in Mexico and its pharmacologic treatment requires clinicians to balance the risks and benefits of various analgesic agents. NSAIDs and paracetamol (acetaminophen) can be effective for mild to moderate pain, but safety considerations place limitations on their use. Opioids are safe and effective, but have opioid-associated side effects plus the potential for abuse. Against this background, it is important to appraise other options with regard to favorable efficacy and safety – such as low-dose transdermal buprenorphine. Buprenorphine, both in transdermal and oral formulations, has been available in Mexico for a number of years yet just recently a Low-Dose Transdermal Patch formulation has been available for the management chronic non-cancer pain of moderate intensity in adults. Buprenorphine is an opioid agent with a unique pharmacological profile, such that it has a ceiling effect for respiratory depression, but no ceiling effect for analgesia. It can be used without dose adjustment in the elderly and in patients with impaired kidney function (unique among opioids). Its small lipophilic molecule makes it well suited to transdermal formulations, which offer steady-state round-the-clock analgesia after three days with clinical convenience and easier patient compliance. Buprenorphine is an effective analgesic in chronic non-cancer pain patients, and its good tolerability and lower abuse potential may make low-dose transdermal buprenorphine appropriate for a broad range of patients.
potential[3]. Familial, social, legal, public health, and regulatory concerns make some prescribers reluctant to consider opioids, contributing to “opiophobia”[14]. Other impediments to long-term opioid therapy include possible development of tolerance (where the patient requires increasing doses of the same agent to maintain the equivalent level of analgesia)[3] and opioid-induced hyperalgesia (OIH), a paradoxical condition in which opioid use appears to lower the pain threshold[15]. These drawbacks have prompted many clinicians in Mexico to avoid using opioids for pain management. It has been estimated that only about one in a thousand registered doctors use major opioids in Mexico[7].

Yet, in the last years, significant concerns have arisen for the use of other therapeutic agents for long term pain management in patients with chronic non-cancer pain; in particular recent high quality data on the cardiovascular safety of both paracetamol[13] and NSAIDs[16] has put into question the sustained use of these drugs in patients with relevant cardiovascular risk. This has caused many clinicians, including those formerly reluctant about the use of opioids, to reconsider their use, particularly in the low-dose transdermal formulation.

The case for buprenorphine

Buprenorphine exerts effective analgesic action for multiple pain types, including bone pain, thermal pain (heat and cold-pressor pain), and neuropathic pain and,although it does not have a direct anti-inflammatory effect, it is active against inflammatory and visceral pain[10]. The buprenorphine molecule has very high affinity (in the sub-nanomolar concentration range) for the μ-opioid receptor and the other seven-transmembrane G protein-coupled opioid receptors (delta and kappa), but its intrinsic activity at δ and κ sites is minimal, so its analgesic activity is thought to be mediated primarily by γ-opioid receptors. Buprenorphine exerts a lasting antihyperalgesic effect[11]. In terms of clinical analgesic efficacy, buprenorphine is comparable to morphine, the “gold standard” of opioids[12].

Among the opioid agents, buprenorphine may be described as having a unique pharmacology[10]. Although often described as a partial agonist based on in vitro data, this term is misleading, because buprenorphine exerts a full analgesic effect in most preclinical studies[13,14] and in humans, radio-labeling studies demonstrate that full analgesia can be produced with less than 100% occupancy of the μ-opioid receptor, which is the definition of a full agonist[15]. This is likely due to the contribution of other analgesic mechanisms[8,16].

The dose-response curve for buprenorphine over the therapeutic range of the drug is roughly linear (doses 0.2 to ≤ 7 mg) and at higher doses (8 to 32 mg) continues to offer increased analgesia[17]. On the other hand, buprenorphine demonstrates a ceiling effect for respiratory depression (a ceiling effect is the point at which no further effect is achieved, despite increasing doses), unique among the other opioid analgesics[10]. Since respiratory depression is a particularly serious and potentially life-threatening adverse event, this characteristic makes buprenorphine an important agent in the opioid armamentarium. Buprenorphine is also unique among the opioids in that it alone can be safely used in patients with compromised renal function. Buprenorphine, when given intravenously, is mainly secreted into bile and excreted in urine. Unlike other opioids, the half-lives of the drug and metabolites do not increase in persons with compromised renal function, such as (but not limited to) the elderly[18]. In fact, the analgesic effects and side effect profiles of buprenorphine do not vary in older (> 65 years) versus younger (< 50 years) patients[19]. In an open-label observational study of elderly chronic non-cancer pain patients (mean patient age 73 years, n = 891), transdermal buprenorphine reduced pain intensity by a score of 5.1 (1.7 ± 1.3 from 6.8 ± 1.5), a 76% improvement on the rating scale[20].

Like other opioid agents, buprenorphine may expose patients to potentially serious pharmacokinetic drug-drug interactions when used with other agents. In particular, such drug-drug interactions may occur when buprenorphine is taken concomitantly with cytochrome (CYP)450-3A4 inhibitors (azoles, macrolides, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors, among others) as well as CYP450-3A4 inducers (phenobarbital, carbamazepine, phenytoin, rifampicin) [21]. Buprenorphine may have a potentially life-threatening effect when administered to patients with severely compromised hepatic function when combined with high-dose benzodiazepine therapy[21]. In general, buprenorphine should be used with extreme clinical caution (if at all) in patients taking benzodiazepines, central nervous system depressants, certain antidepressants, anxiolytics, and other opioids. Furthermore, alcohol should be avoided with buprenorphine use[21].

Clinical efficacy of low dose transdermal buprenorphine

Buprenorphine is available as a transdermal system for pain relief; its long duration of action and lipophilic molecule make it well suited to this route of administration. In Mexico, Low Dose Transdermal Buprenorphine (LDTB) is available in 5µg/h and10µg/h systems. The patch allows for continuous delivery of buprenorphine for seven days, achieving steady state by the third day following the initial patch application. An equipotency ratio of oral morphine to transdermal buprenorphine has been proposed as 1:75, but other recent sources suggest 1:70 or 1:115[22-24].

A review of transdermal buprenorphine in the treatment of chronic non-cancer pain found it was significantly more effective than placebo in reducing pain and was well tolerated by patients[25]. A double-blind parallel-group study of 588 chronic non-cancer pain patients found transdermal buprenorphine to be significantly more effective in reducing pain than placebo, with significantly reduced rescue medication consumption versus placebo. It was well tolerated by patients, with the most common adverse events being pruritus at application site, headache, and somnolence (9.3%, 3.9%, 2.3%, respectively)[26].

The transdermal formulation may offer certain clinical advantages in that it reduces compliance issues in outpatients and offers convenience to both patients and clinicians. In a postmarketing study from Poland (n = 4030), 70.1% of chronic cancer and non-cancer pain patients treated with transdermal buprenorphine intended to continue treatment with the transdermal system[27] (Figure 1). In a larger postmarketing study in Europe (n = 13,179), 80% reported good or very good pain relief at the conclusion of the study and only 5% of patients in this study discontinued transdermal buprenorphine for lack of efficacy[28].
The musculoskeletal system is the most common source of chronic non-malignant pain and the efficacy of LDTP has been extensively evaluated in this group of patients. In a non-inferiority study comparing transdermal buprenorphine to tramadol, shown in (Figure 2). 280 patients with moderate to severe musculoskeletal pain were randomized for eight weeks of treatment. Both treatment arms achieved significant pain reduction over baseline and the least squares mean difference of the change from baseline between the arms was 0.45 (95% confidence interval, range -0.02 to 0.91) which met the predefined ± 1.5 threshold for non-inferiority.\(^{[29]}\)

**Efficacy in osteoarthritis**

Osteoarthritis (OA) is considered one of the main causes of chronic non-malignant pain affecting 34% of patients with chronic pain.\(^{[30]}\) Buprenorphine is considered an excellent alternative for pain management in patients with osteoarthritis; in fact, osteoarthritis was the most frequently recorded indication (48.7%) for LDTB was osteoarthritis in a large retrospective cohort study in England.\(^{[31]}\) In a placebo controlled study of 311 patients suffering from knee or hip OA in which NSAIDS had not been effective, LDTP showed efficacy and good tolerability.\(^{[32]}\) In another study of 134 patients suffering from chronic OA pain, patients were randomized to receive a 12-week treatment of LDTB or tramadol. Both agents were effective in reducing pain versus baseline and the use of rescue medication was similar in both groups. However, despite similar findings in terms of pain relief, quality of sleep and awakenings at night, 70.3% of patients in the study preferred transdermal buprenorphine (95% confidence interval, 62 to 78)\(^{[33]}\). In a study of hip or knee OA patients, 220 patients were randomized to be treated for 12 weeks with either a fixed-dose combination product of codeine plus acetaminophen or transdermal buprenorphine plus acetaminophen. Both treatments significantly reduced pain versus baseline, but the transdermal buprenorphine patients used significantly less rescue medication (ibuprofen, \(p = 0.002\)\(^{[34]}\).

**Efficacy in low back pain**

The impact that low back pain (LBP) has in the general population cannot be overestimated as it is a significant cause of disability and increased medical costs in the general population.\(^{[35]}\) LDTB has been proposed as an excellent alternative to deal with pain and loss of function in patients with LBP. Gordon et al.\(^{[36]}\) Evaluated the efficacy of LDTB in patients 78 with LBP that had previously taken major opioids; in this placebo controlled randomized crossover clinical trial LDTP showed significant efficacy when compared to placebo with only 10% of patients withdrawing due to lack of efficacy. Interestingly, different authors have found in other placebo controlled randomized clinical trials that, in patients with LBP, LDTP has a positive impact in activities of daily living\(^{[37]}\), quality of life\(^{[38]}\) and sleep\(^{[39]}\) outcomes (Figure 3).

In a much larger randomized clinical trial Steiner et al.\(^{[40]}\) recruited 660 patients with moderate to severe LBP and compared the efficacy and safety of LDTB versus oral oxycodeone. They found that LDTB was both efficacious and safe in this population with a similar withdrawal rate due to side effects but lower constipation and headache rates.

**Abuse potential**

Clinicians sometimes are faced with treating pain in patients at risk for substance abuse or, in more extreme situations, patients with active addictions. Addictions to non-opioid substances may indicate a risk for opioid abuse.\(^{[41]}\) The literature reports on potential risk factors for opioid misuse and abuse, and screening tools.\(^{[42-46]}\) Buprenorphine is considered to have lower potential for abuse than equianalgesic strong opioids.\(^{[10]}\) In a double-blind, placebo-controlled, inpatient study of morphine-maintained substance abusers, an injection of buprenorphine resulted in little “good effect” reported by the subjects.
who evidenced only a moderate interest in the drug[47]. This low
“likeability” contributes to buprenorphine’s lower abuse potential.
Buprenorphine in other formulations (typically injections or sublingual products) is used as a first-line agent in opioid
detoxification and maintenance programs, in part because of its
relatively lower potential for abuse compared to other opioids[48].
In the US, the Drug Enforcement Agency (DEA) has classified
buprenorphine as a Schedule III drug because it has less abuse
potential than Schedule I (heroin) and Schedule II agents (mor-
phine, oxycodone, fentanyl)[49]. In Mexico, the regulatory body
responsible for drug enforcement and control is the Comisión
Federal para la Protección contra Riesgos Sanitarios. It has
classified buprenorphine as a psychotropic substance inside Frac-
ción II, defined as a drug that has “certain therapeutic value, but
can constitute a public health problem”; this situation makes bu-
prnorphine a less-controlled drug than Fracción I drugs such
as heroin or morphine[47]. When prescribing opioid agents, cli-
nicians must be mindful not only of the risk presented to the
patient but also to the community at large. Transdermal products
are not, technically, “abuse-deterrent formulations,” but the low-
dose buprenorphine patch system makes it difficult to extract the
drug for potential abuse.

Tolerability of transdermal buprenorphine

When the use of any drug is considered in a certain
patient, the physician has to take into account both the efficacy
and safety profile of the drug. When using opioids, safety concerns
are paramount as adverse effects are specially prevalent and are
the most common cause of treatment withdrawal. A classical
metaanalysis by Moore and McQuay showed that 21% to 23%
of patients with chronic non-malignant pain that were started on
opioids withdrew from their treatments due to side effects while
lack of efficacy was the cause of withdrawal in only 5.6% to
7.4% of patients[50]. The most frequently reported adverse effects
associated with transdermal buprenorphine in the United States (≥ 5%)
were nausea, headache, pruritus at application site, dizzi-
ness, vomiting, constipation, somnolence, erythema at application
site, dry mouth, and rash at the application site[25].

When the safety profile of transdermal buprenorphine is evaluated,
it seems to come out favourably when compared to other
polosy and therapeutic alternatives. A study that compared
LDTB with sublingual buprenorphine in 246 patients with knee
or hip OA showed that the general rate of adverse effects was
lower with the transdermal formulation[33]. There were signifi-
cant reductions in the most frequent side effects such as nausea
(37% vs. 47%, p = 0.035), dizziness (27% vs. 41%, p = 0.026)
and vomiting (18% vs. 29%, p = 0.039)[31]. Another study com-
pared the efficacy and safety of LDTB and oral tramadol in 134
patients with OA and found similar decreases in pain lev-
els but an increased satisfaction with treatment in the LDTB
group, with significantly fewer withdrawals than in the tramadol
group (14.5% withdrawals with LDTB vs. 29.2% withdrawals
with oral tramadol, p = 0.032)[33]. Application site related side
effects are a concern with transdermal systems as they might
cause treatment withdrawal. A recent meta analysis has looked
specifically at cutaneous problems with transdermal buprenor-
phine pooled the results of 16 studies with 6566 patients. It
showed that the incidence of cutaneous problems was signifi-
cant as these appeared in 23% of patients. Most of the cutaneous
adverse events were not severe (98%) and resolved upon patch

site change or with local or systemic treatment. Only in 4.4% of
cases, the application site related adverse effects caused product
discontinuation[52]. In a large postmarketing study of transdermal
buprenorphine (n = 13,179), 22% of patients reported some form
of adverse event[32]. These included nausea, dizziness, vomiting
and constipation. In addition, of the 13,179 patients, only one
case of respiratory depression was reported (which was not clas-
sified as serious).

Use in the elderly population

Formulation in transdermal patch makes it particularly
suitable for use in the elderly with chronic non-malignant pain.
In a study of 93 frail patients with a mean age of 79.7 years and
a mix of nociceptive and mixed chronic pain, low to medium
doses of transdermal buprenorphine during a three month period
significantly reduced pain intensity and improved sleep quality
versus baseline without adverse central nervous system (CNS)
side effects or cognitive changes as measured by the Mini-Men-
tal State Examination (MMSE). Furthermore side effects caused
treatment withdrawal in only 13% of patients[33]. Another study
included 891 patients with chronic non-malignant pain (with a
neuropathic component present in 69% of cases) and a mean age of 72.8 years (69% of them were over 70). Treatment with
LDTB for 12 weeks had a positive effect in their mostly elderly
patient population; most experienced improvements their capac-
ity to perform daily activities and quality of life and sustained
pain relief, leading to a substantial reduction in the overall bur-
den of pain[50].

Unlike other opioids, the pharmacological character-
istics of transdermal buprenorphine offer safe and effective
pain relief to the elderly with no need for dose adjustment[19,54].
During normal aging many different metabolic changes develop
that can have a clear impact in the pharmacokinetic profile of a
drug. These changes were evaluated for buprenorphine in 72
healthy individuals. No differences in the pharmacokinetics of
LDTB were observed when a 50 to 60 year-old group was com-
pared to a >75 year-old group[55].

One essential advantage of LDTB in the elderly pop-
ulation is the transdermal route. The incidence of dysphagia in-
creases with age, and dysphagia rates in older adults can be as
high as 60%[56], this is a problem in institutionalized people as
between 15% and 33% of patients in nursing homes report hav-
ing swallowing difficulties in relation to taking solid oral medi-
cations[56].

Summary

Low-dose transdermal buprenorphine can be a good
option for the management of chronic non-cancer pain, Table 1
highlights the various reasons that support this statement.
Analgesia for Moderate Chronic Non-Cancer Pain

TABLE 1: Buprenorphine attributes.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven and reliable safety and efficacy</td>
<td>for moderate/severe pain in various types of non-cancer painful conditions</td>
</tr>
<tr>
<td>Long duration of action resulting in</td>
<td>sustained pain relief</td>
</tr>
<tr>
<td>Multiple dose options allows for</td>
<td>tailoring to patients needs</td>
</tr>
<tr>
<td>Dosing flexibility and 7 day application</td>
<td></td>
</tr>
<tr>
<td>Potential antihyperalgesic effects</td>
<td></td>
</tr>
<tr>
<td>Respiratory-depression ceiling effect</td>
<td></td>
</tr>
<tr>
<td>Fewer typical opioid side effects</td>
<td></td>
</tr>
<tr>
<td>Titration may improve tolerability</td>
<td></td>
</tr>
<tr>
<td>Lower abuse and addiction potential</td>
<td></td>
</tr>
<tr>
<td>Can be used safely in patients with</td>
<td>renal dysfunction and poor hepatic function - good safety profile with elderly</td>
</tr>
<tr>
<td>Nausea and Vomiting side effects</td>
<td>potentially be avoided or managed</td>
</tr>
<tr>
<td>Simple and convenient; Improvements in ADL, QoL, and Function</td>
<td></td>
</tr>
</tbody>
</table>

*ADL - Activities of Daily Living and QoL - Quality of Life.

Conclusion

Chronic non-cancer pain is prevalent in Mexico, with an increasing incidence due to the aging population. In light of the wealth of treatment options, clinicians must carefully weigh risks against benefits when selecting individual pharmacotherapy for pain control. Opioids are safe, effective, and important analgesic agents in the pharmacologic treatment of chronic pain, in particular as NSAID safety appears to be questionable for long-term use and may be contraindicated in patients with heart disease, renal dysfunction, or those with risk factors for gastrointestinal disorders. Likewise, opioidshave their own risks and benefits. In this context, it is worth considering buprenorphine — an opioid agent with certain unique pharmacological characteristics — particularly in a low-dose transdermal formulation.

Favorable characteristics of buprenorphine include morphine-equivalent clinical efficacy, a ceiling effect for respiratory depression, lower abuse liability relative to other opioids, and good tolerability. In the transdermal formulation, buprenorphine offers effective round-the-clock analgesia in a clinically convenient formulation that reduces issues of patient compliance. So for those healthcare providers who are familiar with buprenorphine, this is an additional option to provide good analgesia for moderate chronic non-cancer pain. For those who are not currently prescribing buprenorphine, the low-dose transdermal formulation introduces a new option for their patients who have moderate chronic non-cancer pain, one that can be considered for use in place of long-term NSAIDs, COXIBs, tramadol, or tramadol combinations.

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Analgesia for Moderate Chronic Non-Cancer Pain


