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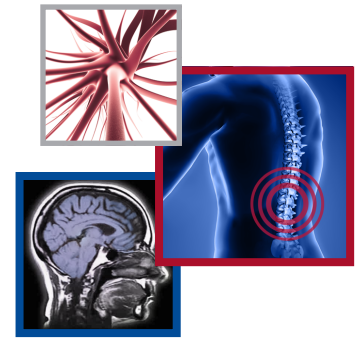
Pain Management



A comparison of transdermal over-the-counter lidocaine 3.6% menthol 1.25%, Rx lidocaine 5% and placebo for back pain and arthritis

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Aim: Transdermal lidocaine therapy has become a gold standard as part of a treatment regimen for patients who suffer from localized pain. We compared transdermal patches: over-the-counter (OTC) lidocaine 3.6% combined with menthol 1.25%, prescription lidocaine 5% (Rx) and placebo. **Methods:** In a double-blind, placebo-controlled trial, 87 patients were randomized to: OTC, Rx or placebo. **Results:** OTC met primary end points of noninferiority compared with Rx for efficacy, side effects and quality of life. Versus placebo, OTC proved superiority for efficacy, general activity and normal work. Side effects were similar. **Conclusion:** It is theorized that menthol's ability to increase skin permeability facilitated more efficient drug delivery to the site of pain causing higher than expected efficacy. Decreased cost and resource utilization could benefit patients and payers.

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KEYWORDS
• arthritis • back pain
• lidocaine • local anesthetic
• osteoarthritis • patch
• transdermal

Back pain and arthritis are among the most prevalent and costly disease states throughout the world. The second most frequent medical complaint is back pain and related symptoms, and disability from back pain is behind only the common cold as a leading cause of lost work time [1]. More strikingly, back pain is the most common cause of disability in people under age 45 [1]. There is approximately an 80% lifetime prevalence of back pain in the USA, with a 15–20% 1-year prevalence rate and with the highest prevalence in the 45–64 age group [1]. While most causes of back pain are unknown [2], most episodes are short-lived, and 80–90% of attacks of back pain are resolved in about 6 weeks [3]. Osteoarthritis is one of the primary conditions leading to disability in the elderly, particularly in developed countries, and the prevalence of osteoarthritis is on the rise [4]. Osteoarthritis is expected to be an increasingly common problem as the population ages and as risk factors such as obesity increase [4]. Currently, in the USA, one out of every two people over the age of 65 is affected by arthritis [5]. While back pain and osteoarthritis can limit an individual's activity and with back pain cited as the primary reason for work absence [2], both conditions result in a significant burden on individuals, families, communities, health systems, social care systems and governments [2,4].

Options for over-the-counter (OTC) analgesics (in both internal and external forms) remain limited. OTC internal analgesics are among the most popular medicines used throughout the world, however they are not without limitations. The two of most popular options are nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Nonselective NSAIDs (Rx and OTC combined) can cause upper gastrointestinal symptoms such as dyspepsia in up to 60% of patients and peptic ulcer

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disease in up to 30% of patients [6], and in the USA, the annual rate of individuals being hospitalized for NSAID-induced gastrointestinal damage is one of 175 [7]. Furthermore, they include a black box warning by the US FDA in the USA, indicating that NSAID use can increase the chance of a heart attack or stroke, either of which is potentially fatal, and noting that patients with cardiac risk factors such as high blood pressure and cholesterol should be particularly careful. Moreover, it has been reported [8] that acetaminophen is responsible for over 100,000 emergency room visits per year in the USA because of acetaminophen-related toxicity.

OTC external analgesics are available as creams, gels, plasters and patches. Topical agents have the dual advantages of local drug delivery [9] and avoidance of adverse systemic effects [10–12]. Indeed, adverse side effects resulting from topical pain treatments are reported to be generally mild and limited to the local site of application with less than 5% of patients reporting adverse reactions [11,13–14]. However, creams and gels have a short duration of action requiring high dosing frequencies and, thus, are often not effective for those who suffer from ongoing back pain and arthritis. While transdermal patches offer increased duration of action, the vast majority of the OTC analgesic patch market is comprised of simple menthol patches [15].

Prescription external analgesics are primarily represented in the market by lidocaine 5% patches [15]. Lidocaine has no significant risk of systemic absorption and toxicity when applied transdermally in both the short and longer term [16,17]. Lidocaine does not carry a black box warning and has little systemic bioavailability as all NSAIDs do. However, prescription lidocaine patches can have limited use because of its relatively narrow indication for postherpetic neuralgia [18]. Additionally, its cost and reimbursement from third parties often limit payment to only those patients suffering from postherpetic neuralgia. Finally, although transdermal lidocaine is effective, the current delivery systems are inefficient; over 95% of the active lidocaine remains in the patch even after use [18]. This keeps lidocaine 5% for optimal efficacy.

In the USA, lidocaine 3.6%, menthol 1.25% (LidoPatch®) has recently entered the market as an OTC. The patch is labeled for back pain, arthritis and muscle sprains and strains. In an effort to improve the efficiency of drug delivery the OTC patch was developed with menthol, a known permeation enhancer [19–21]. In addition, menthol provides an immediate soothing sensation, and this combines well with topical lidocaine, which does not have an immediate effect.

Thus, if effective, an OTC lidocaine/menthol patch would be of benefit to countless people suffering in pain and to physicians who struggle with third-party reimbursement of prescription patches for their patients. Therefore, the objective of this study was to compare the efficacy, safety and impact on quality of life of LidoPatch lidocaine patch (3.6% lidocaine, 1.25% menthol), prescription lidocaine patch (lidocaine 5%) and placebo to determine if OTC lidocaine patches can provide similar benefits as prescription lidocaine patches while also providing the advantages of using a lower dose of lidocaine and being available without a prescription.

Materials & methods

This was a randomized, double-blind study to compare effectiveness, safety and the quality of life of various transdermal patches: lidocaine 3.6% and menthol 1.25% combined into a single patch, lidocaine 5% and placebo. Each was administered for 12 continuous hours followed immediately by a 12-h period of not wearing any patch to provide anesthesia for adult subjects with back pain or arthritis.

Eligible subjects were adults 18 years of age or older of any race and gender who had pain from knee or hip arthritis or back pain for at least 3 months and did not meet any of the following exclusion criteria: known allergies or sensitivity to lidocaine, menthol or methylparaben; damaged or broken skin at the site of designated pain; pregnant, plan to be pregnant in the next month or breastfeeding; suffering from any pain other than arthritis or back pain; pain in an area of the body that was not conducive for a transdermal patch; or an average pain score of 1, 2, 9 or 10 on a scale of 0–10. Pain ratings of nine and ten were excluded because of the potential for randomization to placebo. Subjects were instructed to place the patches at the site of pain (or as close as possible to the site of pain) and to apply the patches at the same site throughout the treatment period. All patches could be cut to fit the area of pain. All osteoarthritis subjects used the patches on a single hip or knee. A summary of subject baseline characteristics can be seen in **Table 1**.

Using a simple randomization method, subjects were randomized to one of the three treatment arms. Each arm followed the same protocol of

Table 1. Day 10 study patients' baseline characteristics.

	Lidocaine 5%	Lidocaine 3.6%, menthol 1.25%	Placebo	Overall
Day 10 cohort	n = 24	n = 27	n = 26	n = 77
Sex				
– Female	58 (14)	56 (15)	54 (14)	56 (43)
– Male	42 (10)	44 (12)	46 (12)	44 (34)
Type of pain				
– Back pain	79 (19)	81 (22)	65 (17)	75 (58)
– Arthritis	21 (5)	19 (5)	35 (9)	25 (19)
Age (years, mean)	55	55	56	55
Weight (kg, mean)	79	78	81	79
Average pain intensity at baseline	6.5	7.2	6.6	6.8
Aggregate pain at baseline (mean)	5.1	5.5	5.2	5.3
Duration of treatment (days, mean)	9.8	9.7	9.2	9.5

applying patches as instructed by the study nurse for 10 days. After days 2 and 10, the subjects completed a follow-up survey comparing their baseline responses to questions regarding efficacy, safety and quality of life. Subjects were required to keep a pain diary chronicling exactly when and for how long the patch was worn each day. If a subject were more than 6 h tardy in applying the next scheduled patch, the subject was removed from the trial.

Placebo patches were constructed exactly the same as the lidocaine 3.6%, menthol 1.25% patch except there were no active ingredients. To maintain the blind, the airtight pouch of each patch was covered in order to avoid any identifying marks or symbols. All patches were the same size. Subjects were randomized to receive ten patches of lidocaine 3.6%, menthol 1.25% (JAR Laboratories, IL, USA) or lidocaine 5% (various manufacturers) or placebo (JAR Laboratories).

• Efficacy ratings

Pain intensity was assessed using an electronic horizontal 0–10 Numeric Pain Rating Scale. Pain was assessed using four questions: what is your pain: on average, at its worst, at its best, and right now compared with prior assessment at day 2, at day 10, and over the past month at baseline. Data analysis was performed individually on each category and as an aggregate of all efficacy end points.

• Side effect ratings

Side effects were assessed using an electronic horizontal 0–10 Numeric Rating Scale. Side effects were assessed over 14 questions: nausea, vomiting, constipation, lack of appetite, tired, itching, nightmares, sweating, difficulty thinking, insomnia, bruising, redness of skin and swelling. Subjects were also allowed to report spontaneously any other side effects. All questions were measured at baseline, day 2, and day 10. Data analysis was performed individually on each category and as an aggregate of all efficacy end points.

• Quality of life

Quality-of-life impact was assessed using an electronic horizontal 0–10 Numeric Rating Scale. Quality-of-life impact was assessed over eight questions: general activity, mood, normal work, sleep, enjoyment of life, ability to concentrate and relations with other people. Subjects were also allowed to report spontaneously any other impacts on their daily life. All questions were measured at baseline, day 2, and day 10. Data analysis was performed individually on each question and as an aggregate of all efficacy end points.

• Data analysis

The clinical significance (δ) for the noninferiority study is estimated from the definitions shown in **Table 2** and power of the test (β) as 80%. The expected mean difference between lidocaine 3.6%, menthol 1.25% and lidocaine 5% is taken as the observed mean difference of the samples, 0.76042. The minimum value set for the power is matched as we considered

Table 2. The statistical definitions of comparisons used for evaluation.

Test statistics	Alternative hypothesis	Null hypothesis	Design
$Z^{\dagger} = (d^{\ddagger} + \delta^{\S})/sd^{\P}$	Noninferiority	H0:T-S = -δ	Ha: $T^{\#}$-$S^{\dagger\dagger}$ > -δ
Equivalence	H0:T-S = -δ	Ha: T-S > -δ	Z1 = (d + δ)/sd
Statistical superiority	H0:T-S = 0	Ha: T-S > 0	Z = d/sd
Clinical superiority	H0:T-S = δ	Ha: T-S > δ	Z = (d-δ)/sd

†Z obeys standard normal distribution.
‡d is the effectiveness difference between T and S.
§δ is clinically admissible margin of noninferiority/equivalence/superiority.
¶sd is the standard error of d.
#T is new treatment.
††S is standard treatment.

power to be 80%. There is no bias in calculation of clinically significant difference, which is -1.4283. Parametric testing was applied. All the assumptions made are standard, and only the values observed in the study are considered. Hence the study is clinically relevant. Relation between clinical significance and optimal sample size is estimated using the following relation:

$$N = \left(Z_{1-\alpha/2} + Z_{\beta}\right)^2 \sigma^2 / \delta^2$$

N is the sample size, σ is the variance of difference between the groups, δ is the clinical significance, and α and β are the chosen type 1 and type 2 errors, respectively.

Calculation:

$$N = 25, \sigma^2 = 9.357, Z_{1-\alpha/2} = 1.64\,(\alpha = 0.05, \text{one sided}), Z_{\beta}\,(\beta 80\%) = 0.84$$

$$\delta = \left(\left[1.64 + 0.8\right]^2 * 9.357 / 25\right)^{0.5} = -1.5$$

Results

A total of 87 subjects (47 females and 40 males) met all the inclusion and exclusion criteria. Only one patient from the placebo group did not complete treatment due to discomfort wearing a transdermal patch. Four subjects were lost to follow-up and provided no information past the initial screening even though they received the study drug. 80 subjects provided a 2-day follow-up, and 77 provided a 10-day follow-up, with 70 of those subsets completing follow-up at both day 2 and day 10.

The age range was 21–70 years, and the mean age was 55. The racial breakdown was White 55%, Black 30%, Latino 13% and other 2%. Mean duration of treatment was 9.5 days. The cohort comprised 75% back pain and 25% arthritis subjects.

The efficacy comparisons between lidocaine 3.6%, menthol 1.25% and lidocaine 5% and between lidocaine 3.6%, menthol 1.25% and placebo at day 10 are shown in **Figure 1**. The comparisons for the aggregate side effects between lidocaine 3.6%, menthol 1.25% and lidocaine 5% and between lidocaine 3.6%, menthol 1.25% and placebo at day 10 are shown in **Figure 2**. The quality-of-life comparisons between lidocaine 3.6%, menthol 1.25% and lidocaine 5% and between lidocaine 3.6%, menthol 1.25% and placebo at day 10 are shown in **Figure 3**.

• Lidocaine 3.6%, menthol 1.25% compared with lidocaine 5%

The 95% confidence interval of difference between day 0 and day 10 aggregate pain scores between the lidocaine 3.6%, menthol 1.25% and the lidocaine 5% groups are -0.46261 and 1.98344, respectively, and the p-value is 0.214. Hence, the clinical significance (δ) is less than the lower bound of this confidence interval, and the noninferiority of the lidocaine 3.6%, menthol 1.25% arm is achieved. Analyzing individual day 10 efficacy end points shows no statistically significant differences. However, there is a consistent numeric trend favoring lidocaine 3.6%, menthol 1.25%: 'pain at its worst' 2.16 decrease compared with 0.833 (p-value = 0.072), 'pain at its best' 1.32 compared with 0.375 (p-value = 0.28), and 'average pain intensity' 2.04 compared with 1.125 (p-value = 0.176). Day 2 results consistently favored lidocaine 5% with 'aggregate pain intensity' 1.4688 compared with .7935 (p-value = 0.349).

Day 2 side effects showed minimal difference on aggregate: lidocaine 3.6%, menthol 1.25% with a 2.48 decrease compared with a 2.56 decrease for lidocaine 5% (p-value = 0.919). Day 10 results show a strong but insignificant trend toward lidocaine 3.6%, menthol 1.25% with a 3.19 decrease compared with 1.32 (p-value = 0.098).

Quality-of-life results continue the trend of minimal differences of aggregate results with day 2 decreases of 2.57 and 2.72 (p-value = 0.857) and

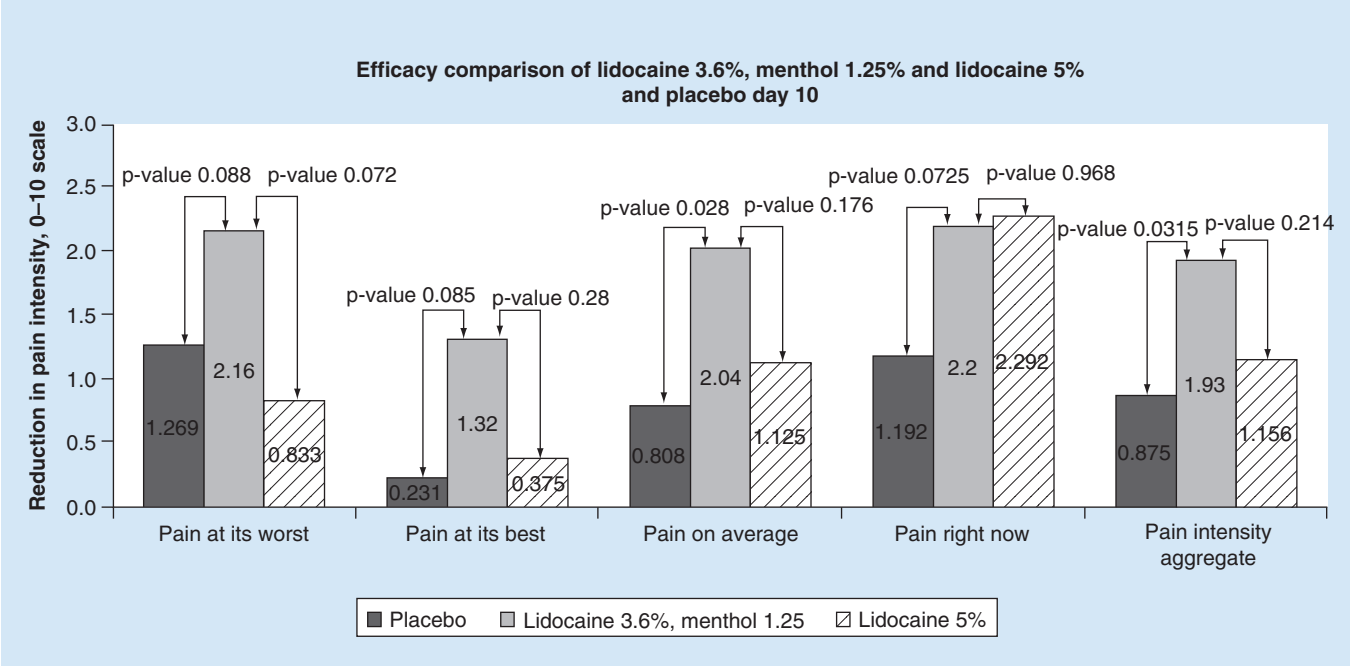

Figure 1. Efficacy comparison of lidocaine 3.6%, menthol 1.25% and lidocaine 5% and placebo day 10.

insignificant trends favoring lidocaine 3.6%, menthol 1.25% at day 10 with decreases of 4.11 and 3.24 (p-value = 0.385).

• Lidocaine 3.6%, menthol 1.25% compared to placebo

Lidocaine 3.6%, menthol 1.25% met its secondary end point by having a significant decrease in aggregate efficacy of 1.93 compared with 0.875 for placebo (p-value = 0.0315) at day 10. Lidocaine 3.6%, menthol 1.25% was also statistically superior to placebo for 'decrease in average pain intensity' with 2.04 decrease versus 0.8077 (p-value = 0.028). Lidocaine 3.6%, menthol 1.25% also showed strong trends to superiority for all other efficacy end points: 'pain at its best' 2.16 compared with 1.27 (p-value = 0.088), 'pain at its worst' 1.32 compared with 0.23 (p-value = 0.085) and 'pain right now' 2.2 compared with 1.19 (p-value = 0.0725).

Day 10 side effect showed insignificant differences on aggregate, lidocaine 3.6%, menthol 1.25% with a 3.19 decrease compared with 3.93

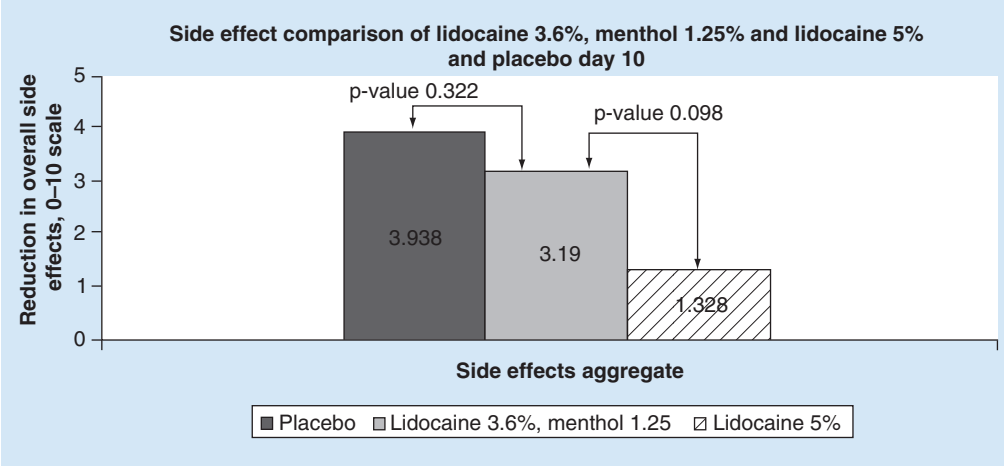

Figure 2. Side effect comparison of lidocaine 3.6%, menthol 1.25% and lidocaine 5% and placebo day 10.

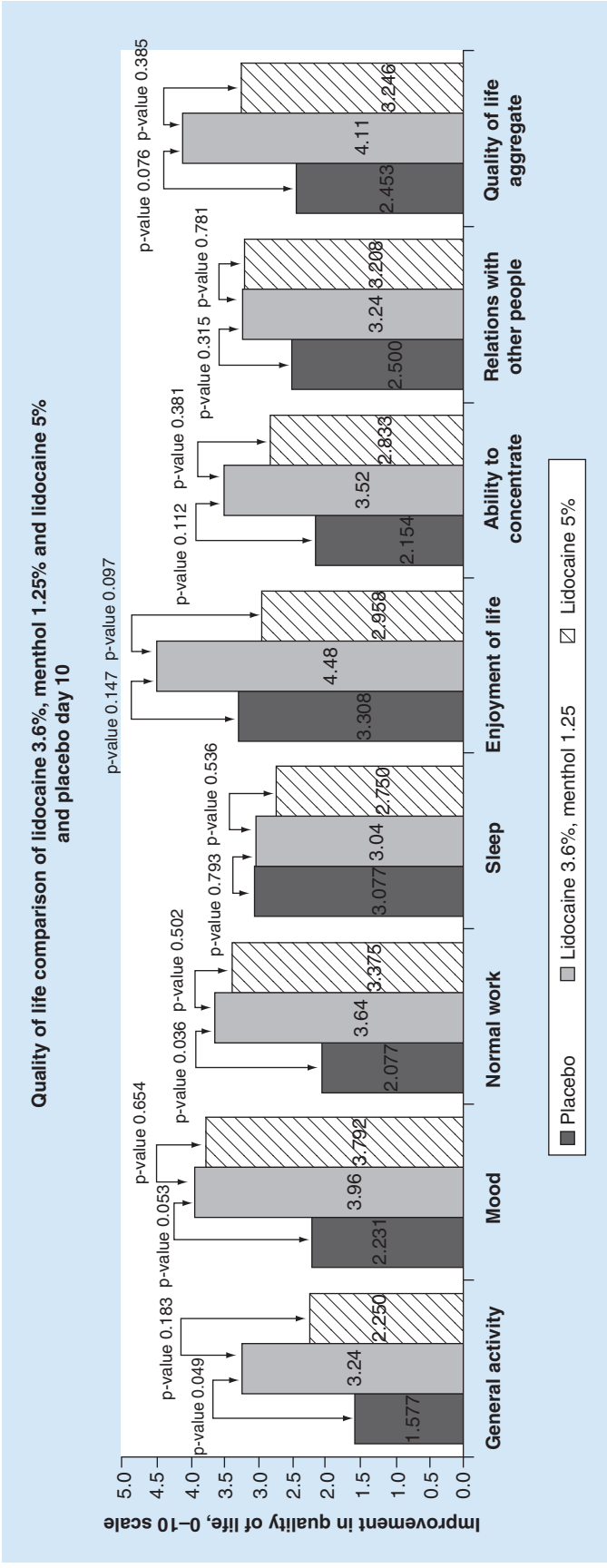

Figure 3. Quality-of-life comparison of lidocaine 3.6%, menthol 1.25% and lidocaine 5% and placebo day 10.

decrease for placebo (p-value = 0.322). Day 2 results showed an insignificant trend toward placebo with a 2.48 decrease compared with 3.83 (p-value = 0.102).

Lidocaine 3.6%, menthol 1.25% demonstrated superiority to placebo for two quality-of-life measures: 'general activity' decrease of 3.24 compared with 1.58 (p-value = 0.047), and 'ability to perform normal work' decrease of 3.64 compared with 2.07 (p-value = 0.036) at day 10. Strong trends at day 10 were also observed for: 'mood decrease' with 3.96 compared with 2.23 (p-value = 0.053) and 'quality of life' aggregate of 4.11 compared with 2.45 (p-value = 0.076).

Discussion

Compared to lidocaine 5%; lidocaine 3.6%, menthol 1.25% met its primary end point by proving noninferiority on all efficacy, safety and quality-of-life measures at day 10. With a score of 1.15 for 'reduction in pain intensity' lidocaine 5% efficacy results were about what we expected based on prior literature [22]. However what was unexpected was the consistent trend to superior efficacy for lidocaine 3.6%, menthol 1.25%. While the exact explanation for this is yet to be determined, our observation is consistent with other studies that have noted the influence of including menthol in topical drug applications. Several studies have reported an increase in drug levels of other actives when used transdermally in conjunction with menthol [19–21,23–35]. Although there is no general consensus on the exact role of menthol in these studies, it is a consistent observation that inclusion of menthol in combination with another active ingredient in topical drug treatment increases the effectiveness of the other active drug. Researchers have focused primarily on how menthol increases tissue temperature [36] at the site of application which results in: an increase in local circulation leading to increased drug delivery [37,38], and increased skin permeability whereby menthol disrupts the lipid structure of the skin barrier allowing for increased accessibility of other drug molecules through the skin [19,33–34].

An increase in skin permeation by lidocaine may generate concern that more lidocaine in the body will lead to increased side effects. Research at JAR Laboratories measured blood levels of lidocaine after using the three patches of lidocaine 3.6%, menthol 1.25% simultaneously over 72 h and showed an average max blood level of 0.2 mcg.ml^{-1} [39]. In a separate but similarly

designed trial [16], data were compiled for lidocaine 5% showing average max blood levels of 0.13 mcg.ml^{-1}. Both of these levels are well below the reported toxic level of lidocaine which starts at 5 mcg.ml^{-1} [40], and neither is clinically significant; however, it is interesting to note that lidocaine 3.6%, menthol 1.25% resulted in a slightly higher systemic concentration of lidocaine than the lidocaine 5% patch. We speculate that higher levels of lidocaine in the bloodstream from the lidocaine 3.6%, menthol 1.25% patch indicate higher levels of lidocaine at the site of pain although this cannot be specifically measured and further study is warranted. These data are in agreement with the above theories regarding the role of menthol in drug delivery.

But it should also be noted that menthol itself has local anesthetic properties [41,42], and thus, we propose that the inclusion of menthol could lead to increased efficacy because of the instantaneous onset of action. This immediate onset of action enables menthol to serve as a bridge until the lidocaine becomes fully effective, and thus, the medication does not have to 'chase the pain'. To test this theory of the bridge-effect, it would be interesting for further prospective trials to evaluate the efficacy of a lidocaine patch that uses a permeation enhancer that does not have its own analgesic properties like menthol does.

These results are particularly encouraging because of a developing trend to encourage the use of OTCs in place of prescription products when appropriate. The Centers for Disease Control in the USA recently released a recommendation [43] that opiates only be used in palliative care situations. Such recommendations point to a growing epidemic of abuse and diversion of these powerful drugs. But also, the new guidelines go on to recommend several drugs that are available OTC in certain doses. In addition, the use of OTCs rather than prescription drugs can save the already taxed US healthcare system money. For every dollar spent on OTCs instead of prescription drugs, the US healthcare system can save $6.00–$7.00 which accumulates to a collective annual savings of approximately $102 billion [44].

Compared to placebo, lidocaine 3.6%, menthol 1.25% also met its end point by proving statistical superiority for an aggregate of overall efficacy. In addition, lidocaine 3.6%, menthol 1.25% proved statistical superiority on 'average pain intensity,' which we consider the most relevant efficacy end point. While this result might have been somewhat expected, what we find rather unexpected was the strength of the quality of life results. Lidocaine 3.6%, menthol 1.25% performed significantly better than placebo in regard to the areas of 'general activity' and 'ability to perform work.' Given that often the primary goal of pain management therapy is to maximize quality of life and not just decrease pain, these results are of significant importance.

By meeting its end points this study demonstrates that lidocaine 3.6%, menthol 1.25% is an effective and safe OTC option for patients suffering from back pain and osteoarthritis. With the FDA's focus on increasing access to OTC medicines [45], combined with the burden of pain throughout the world, lidocaine 3.6%, menthol 1.25% could present a reasonable option for many people while eliminating the physicians' and patients' burdens of attempting to gain third party reimbursement for lidocaine 5%.

Even though 87 subjects allowed us to reach our end point, a larger sample could provide confirmatory data. There are two potential solutions to this challenge. First, obtain further data by enrolling more subjects under the same protocol. Second, conduct a slightly different follow-up trial. Based on the results of this work, we are curious to see the outcome if we changed the primary end point from noninferiority to a head-to-head comparison between the two lidocaine patches with an increased sample size.

Conclusion

Our study demonstrates noninferiority when comparing OTC lidocaine 3.6%, menthol 1.25% in a single transdermal patch with Rx lidocaine 5%. Also, the study shows superiority of the OTC patch compared with placebo for efficacy with similar side effects. Therefore, the combination of lidocaine and menthol in OTC strengths could provide an effective alternative to prescription strength lidocaine 5% patch. Less cost and resource utilization could provide an economic advantage to patients and payers alike and potentially make the product useful.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that this study was conducted in accordance with the Declaration of Helsinki (2008) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use E6 guideline. Approval was obtained from the appropriate Institutional ethics committees, institutional review boards and regulatory authorities, prior to study initiation. Written informed consent was obtained from parent(s)/legal guardian(s) prior to enrollment. For patients of appropriate age and maturity, signed assent forms were obtained in compliance with local laws and regulations.

SUMMARY POINTS

- Over-the-counter (OTC) lidocaine/menthol patch met the primary endpoint of non-inferiority compared to Rx lidocaine patches.
- OTC lidocaine/menthol patch provided quality-of-life benefits compared to placebo.
- Both OTC and Rx lidocaine patches were superior to placebo in regards to efficacy.
- OTC lidocaine patches could provide economic advantages for patients and payers compared to Rx lidocaine patches.

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