Topical 2% Amitriptyline and 1% Ketamine in Neuropathic Pain Syndromes

A Randomized, Double-blind, Placebo-controlled Trial

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Background: A double-blind, randomized, placebo-controlled 3-week study evaluated the efficacy of topical 2% amitriptyline, 1% ketamine, and a combination of both in treating patients with neuropathic pain.

Methods: Ninety-two patients with diabetic neuropathy, postsurgical/posttraumatic neuropathic pain with allodynia, hyperalgesia, or pinprick hypesthesia were randomly assigned to receive one of four creams (placebo, 2% amitriptyline, 1% ketamine, or 2% amitriptyline–1% ketamine combined). The primary outcome measure was change in average daily pain intensity (baseline week vs. final week) using an 11-point numerical pain rating scale. Secondary outcomes included the McGill Pain Questionnaire, measures of allodynia and hyperalgesia, and patient satisfaction.

Results: A reduction in pain scores of 1.1–1.5 units was observed in all groups, and there was no difference between groups. Blood concentrations revealed no significant systemic absorption. Minimal side effects were encountered.

Conclusion: This randomized, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination in the treatment of neuropathic pain revealed no difference between groups. Optimization of doses may be required, because another study has revealed that higher concentrations of these agents combined do produce significant analgesia.

NEUROPATHIC pain is now understood to involve neural responses in which both peripheral and central mechanisms contribute to the generation of spontaneous pain and evoked aspects of pain, including allodynia and hyperalgesia.1–4 The involvement of peripheral mechanisms suggests the use of topical approaches in the treatment of neuropathic pain. Both capsaicin5,6 and local anesthetics2–9 can be useful in the relief of neuropathic pain when administered locally to peripheral sites as a cream or a patch, respectively.

Additional novel drug classes may also be effective in alleviating neuropathic pain after topical administration.10 Therefore, tricyclic antidepressants have been shown to produce a peripherally mediated antinociception in preclinical models of ongoing and neuropathic pain11–14 and to produce analgesia in humans in placebo-controlled studies involving patients with mixed neuropathic pain.15,16 Peripheral excitatory amino acid receptor antagonists also might be useful in reducing pain of peripheral origin.17 Local injections of ketamine, which blocks N-methyl-D-aspartate receptors, produce antinociception in a preclinical model of ongoing pain18 and lead to antihyperalgesic and some analgesic actions in human experimental models of inflammatory pain.19,20 There also are case reports of pain relief after topical administration of ketamine in sympathetically maintained pain21,22 and cancer pain,23 but there are no published controlled trials demonstrating such efficacy.24

In a previous pilot trial, we examined the potential analgesic effects of a topical formulation of a cream containing 1% amitriptyline and 0.5% ketamine.25 Although there was no acute treatment effect during the 2-day placebo-controlled part of the trial, in 11 patients who took part in the 7-day open phase of the trial, there was a significant analgesic effect by day 3 of treatment, which continued to increase to day 7. The results of the open phase trial suggested that a longer treatment period was necessary to observe a beneficial effect. In studies using topical doxepin for neuropathic pain of mixed etiology, pain relief was observed primarily 10–28 days after drug application.15,16 The purpose of the current study was to examine the efficacy of topical preparations of 2% amitriptyline, 1% ketamine, and a combination of amitriptyline with ketamine for the treatment of neuropathic pain over a 3-week treatment period in a randomized placebo-controlled trial. Patients with mixed neuropathic pain were chosen for study because they reflect the reality of clinic populations, and previous studies have demonstrated that patients with neuropathic pain from different diagnostic categories exhibit a response to peripheral doxepin (another tricyclic antidepressant)15,16 and peripheral ketamine.21,22

Materials and Methods

Subjects
Study subjects were recruited from three hospital outpatient pain management units in eastern Canada. The study took place from September 2001 to December 2002. Inclusion criteria and exclusion criteria are presented in table 1. Subjects were permitted to continue...
Normal cognitive and communicative ability as judged by clinical assessment and ability to complete self-report questionnaires.

Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant adult</td>
<td>Evidence of another type of pain as severe as the pain under study.</td>
</tr>
<tr>
<td>Established diagnosis of postherpetic neuralgia,* diabetic neuropathy,† or postsurgical/posttraumatic neuropathic pain‡</td>
<td>Evidence of another type of neuropathic pain not included in this study.</td>
</tr>
<tr>
<td>Moderate to severe pain all or most of the time persisting despite other treatment modalities</td>
<td>Major depression requiring treatment.</td>
</tr>
<tr>
<td>Pain has persisted for 3 months or longer</td>
<td>Allergy to amitriptyline or ketamine</td>
</tr>
<tr>
<td>Presence of dynamic tactile allodynia or pinprick hyperalgesia in the area of pain</td>
<td>Ongoing use of a monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>Normal cognitive and communicative ability as judged by clinical assessment and ability to complete self-report questionnaires</td>
<td></td>
</tr>
</tbody>
</table>

*Postherpetic neuralgia: chronic pain precipitated by an episode of acute herpes zoster which persists after the vesicles have healed. †Diabetic neuropathy: symptoms and signs of diffuse, painful, predominantly sensory neuropathy or single or multiple mononeuropathy related to diabetes. ‡Postsurgical/posttraumatic neuropathic pain: symptoms of spontaneous pain for 3 months or longer after a surgical procedure or trauma.

Subjects were instructed to clean the area and then apply 4 ml cream to the site of maximum pain (size of the area of pain varied) three times per day for 3 weeks. Subjects returned to the study site 2 and 3 weeks after initiation of treatment, at which time pain levels were documented using measures described below (Outcomes section), and blood samples were taken for assay of amitriptyline and ketamine concentrations. The used tubes of cream were collected, weighed, and recorded to assess compliance with treatment.

**Objectives**

The primary objective of the study was to determine whether topical creams containing amitriptyline, ketamine, or a combination exhibited analgesic efficacy for treatment of neuropathic pain. Secondary study objectives included identifying patient satisfaction with the cream and determination of whether systemic absorption occurred.

**Outcomes**

**Spontaneous Pain.** The primary outcome measure consisted of an 11-point numerical rating scale for pain intensity (NRS-PI) with the anchors “no pain” and “severe pain.” The short-form McGill Pain Questionnaire was included as an additional measure of spontaneous pain; this generates subscales that assess sensory and affective dimensions of pain experience. These measures have been developed and validated as measures of clinical pain.26,27 The baseline level of pain consisted of the average of NRS-PI scores taken daily over the 5 days before the start of treatment, and subsequent scores were completed daily during treatment. Subjects completed the McGill Pain Questionnaire at the first visit before the initiation of treatment and again at the end of 3 weeks of treatment.

**Evoked Pain.** All subjects had a sensory examination completed by study physicians at the time of screening. Dynamic tactile allodynia was tested using 1-in-wide foam brushes,28 whereby strokes of 3–5 cm in length and of 1 s in duration were applied over the site of pain, and patients were asked to grade the magnitude of unpleasantness using a visual analog scale. Anchors at each extreme stated “not unpleasant” and “extremely unpleasant.” Pinprick hyperalgesia was tested using an autoclaved standardized safety pin applied over the painful site, and subjects were asked to grade the magnitude of hyperalgesia on a visual analog scale by comparing the evoked sensation caused by the pin in the area of their pain with that experienced in a corresponding normal site (usually contralateral). Pinprick hypesthesia was tested using the same pin over the entire affected limb or body region near the pain, and hypesthesia was documented as present or absent. Testing for evoked pain...
was done on the first visit prior to treatment, and again after 2 and 3 weeks of treatment.

**Perceived Disability.** The Pain Disability Index assesses the degree to which respondents perceive themselves to be disabled in 7 different areas of daily living (home, social, recreational, occupational, sexual, self-care, and life support). For each life domain, respondents are asked to provide perceived disability ratings on 11-point scales with the endpoints 0 (no disability) and 10 (total disability). The Pain Disability Index has been shown to be internally reliable and significantly correlated with objective indices of disability. The Pain Disability Index was included to examine treatment effects on pain-related disability.

**Patient Satisfaction.** An 11-point numerical rating scale for patient satisfaction was given at the completion of week 3. Subjects were asked to rate their satisfaction with the treatment. Verbal anchors included “not at all” or “completely satisfied.”

**Measurement of Plasma Concentrations**

Amitriptyline was measured by reverse-phase high-performance liquid chromatography with ultraviolet detection. The lower limit of detection was 15.7 ng/ml or 20 ng/ml for amitriptyline and nortriptyline. Ketamine and norketamine concentrations were determined by liquid chromatography–mass spectrometry; this method was validated in human serum for a range of 5–5,000 ng/ml for ketamine and 2.5–2,500 ng/ml for norketamine. Blood was collected for drug concentrations after 2 and 3 weeks of treatment. For patients already taking oral amitriptyline, pretreatment plasma amitriptyline concentrations were also measured before initiation of treatment.

**Randomization**

Subjects were randomly assigned to one of four treatment groups using a computer-generated randomization list. The randomization list was used at the manufacturing site to assign a study number to each allotment of cream. The study medication containers were numbered sequentially. The manufacturing site (Pharmaform LLC, Austin, TX) was separate from the study site. At the study site, successfully screened patients were entered into the trial and were provided the next allotment of medication according to the sequential numbers. Study staff

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Two different laboratories were used for the amitriptyline concentrations. The lower limit of detection was 15.7 ng/ml at the Queen Elizabeth II Health Sciences Centre laboratory, Halifax, Nova Scotia, Canada, and 20 ng/ml at ACM Labs, Rochester, New York.

The ketamine analysis is an internally validated method at ACM Labs, Rochester, New York, and was performed under Good Laboratory Practice conditions.

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saw only the sequential numbers on the containers of cream, thus achieving double-blind randomization.

**Data Analysis**

The study was estimated to have 83% power to detect a difference of 1.0 on the pain diary scale as statistically significant ($P_{0.05} < 0.05$, two sided), based on an estimated SD of 1.1 and a sample size of 20 evaluable patients per group. The study recruited 92 subjects with a SD of 1.4, giving 80% power to detect the specified difference.

Statistical analyses on the primary outcome measure (NRS-PI) consisted of intent-to-treat analysis conducted on all subjects initially randomly assigned to treatment condition, with the last pain rating carried forward. Pain severity ratings were transformed to change-from-base-line scores. Change scores were analyzed as a two-way mixed factorial analysis of variance (ANOVA) with treatment (placebo, amitriptyline, ketamine, amitriptyline-ketamine) as the between-groups factor and time (week 1, week 2, week 3) as the within-groups factor.

Two-way (treatment × time) ANOVAs were conducted separately for McGill Pain Questionnaire sensory and affective subscales. Because the McGill Pain Questionnaire was administered only before and after treatment, the time factor was reduced to two levels. Two-way (treatment × time) ANOVAs were conducted separately for evoked pain measures allodynia and pinprick hyperalgesia. One-way ANOVAs were performed on patient ratings of perceived disability on the Pain Disability Index and patient satisfaction at the end of treatment.

**Results**

**Subject Profile**

The study design and conduct is summarized in figure 1. Ninety-two subjects were randomized, and 80 subjects completed the protocol. Adverse events prompted five withdrawals: two in the placebo group, two in the ketamine group, and one in the amitriptyline group. Patient characteristics at baseline are summarized in tables 2 and 3.

Neuropathic pain conditions represented in the study sample were diabetic neuropathy (n = 20), postherpetic neuralgia (n = 14), and postsurgical/posttraumatic pain (n = 58). The mean age of patients included in the study was 54 yr for men (range, 26–84 yr) and 50 yr for women (range, 24–82 yr); age did not vary significantly as a function of sex. Sex distribution, duration of pain, pain severity at baseline, and number of concurrent analgesics did not vary significantly as a function of diagnostic classification or treatment condition. However, there was a significant difference in age across different diagnostic classifications in that patients with postherpetic neuralgia were older than patients with diabetic neuropathy, who in turn were older than patients with postsurgical/posttraumatic neuropathy ($F_{2,89} = 27.8, P < 0.001$).

Spontaneous pain duration ranged from 3 months to 22 yr, with a mean duration of pain of 69.6 months (SD = 68.5). All subjects exhibited dynamic tactile allodynia, pinprick hyperalgesia, pinprick hypesthesia, or a combination of allodynia, hyperalgesia, and hypesthesia at the affected area.

**Pain Severity**

Intent-to-treat analysis was conducted including all patients initially randomly assigned to treatment condition, with the last pain rating carried forward. The results of a two-way (treatment × time) repeated-measures ANOVA on NRS-PI scores revealed only a significant main effect for time ($F_{3,264} = 27.2, P < 0.001$). There was no significant effect for treatment ($F_{3,264} = 1.3, P = 0.27$) and no significant interaction ($F_{9,264} = 0.25, P = 0.95$). These results are presented in figure 2.

Analyses conducted on the individuals who completed the study protocol again revealed a significant main effect of time where all groups showed decreased pain...
the analysis revealed a significant main effect for time. No other effects emerged.

For the McGill Pain Questionnaire sensory subscale, the analysis revealed a significant main effect for amitriptyline, 16% for ketamine, 40% for the combination, and 27% for placebo (chi-square (3) = 28.4, P < 0.001). Pairs of values with different symbols differ at P < 0.05.

Secondary Measures

Dynamic tactile allodynia and hyperalgesia were assessed before treatment and at the end of the second and third weeks of treatment. The pattern of means shows no discernible pattern associated with treatment. From the first to the third assessment, all conditions showed an overall decline in allodynia (F(2, 102) = 7.21, P < 0.001). A similar pattern of findings was observed for ratings of hyperalgesia. Again, there was a significant main effect for amitriptyline; Ket = ketamine.

Adverse Events

Adverse events were reported by 30% of the entire sample of the 92 patients randomized. Reporting of adverse events was evenly distributed across treatments (amitriptyline, 26%; ketamine, 30%; ketamine-amitriptyline, 35%; placebo, 27%) (chi-square (3) = 1.1, P = 0.76).

Plasma Drug Concentrations

Plasma drug concentrations for subjects who were taking oral amitriptyline concurrently are presented in Table 4. Three subjects who were not taking oral amitriptyline exhibited detectable amitriptyline concentrations (table 5); two of these values were false positives only, because there was no amitriptyline present in the assigned treatment cream. Three subjects exhibited detectable ketamine concentrations (20, 22, and 33 ng/ml), over the course of the study (F(3,228) = 28.4, P < 0.001).
but not the second (r = −0.25, P < 0.05) and third weeks (r = −0.24, P < 0.05) but not the second (r = −0.19, P = 0.08) week of treatment. The number of concurrent analgesics did not differ significantly as a function of treatment (F_{3,76} = 1.0, P = 0.50). With specific reference to oral amitriptyline, there was no significant difference in response.

### Concurrent Analgesics and Treatment Response

The numbers of concurrent analgesics according to treatment group are presented in table 2. All subjects were stabilized on their concurrent analgesics for 30 days before the study but continued to report pain of sufficient intensity to meet the inclusion criteria. The majority of patients (80%) were using at least one concurrent analgesic, and 53% were using two or more concurrent analgesics. Correlational analysis was conducted to address whether the number of concurrent analgesics was associated with lack of response to treatment. The analysis revealed that the greater number of concurrent analgesics was associated with lack of response to treatment during the first (r = −0.25, P < 0.05) and third weeks (r = −0.24, P < 0.05) but not the second (r = −0.19, P = 0.08) week of treatment. The number of concurrent analgesics did not differ significantly as a function of treatment (F_{3,76} = 1.0, P = 0.50). With specific reference to oral amitriptyline, there was no significant difference in treatment response between patients taking oral amitriptyline and those who were not. The mean dosage of oral amitriptyline in all groups was 53 mg/day.

### Table 4. Plasma Amitriptyline/Nortriptyline Concentrations (ng/ml) in Patients Taking Oral Amitriptyline Concurrently

<table>
<thead>
<tr>
<th>Subject No. (Treatment Group)</th>
<th>Pretreatment</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>003 (AK)†</td>
<td>19/61</td>
<td>72/16</td>
<td>89/21</td>
</tr>
<tr>
<td>006 (A)†</td>
<td>ND</td>
<td>25/ND</td>
<td>25/ND</td>
</tr>
<tr>
<td>015 (AK)†</td>
<td>50/16</td>
<td>64/18</td>
<td>28/ND</td>
</tr>
<tr>
<td>016 (P)†</td>
<td>150/37</td>
<td>119/47</td>
<td>50/24</td>
</tr>
<tr>
<td>018 (AK)†</td>
<td>22/ND</td>
<td>—</td>
<td>17/ND</td>
</tr>
<tr>
<td>019 (A)†</td>
<td>ND</td>
<td>—</td>
<td>19/ND</td>
</tr>
<tr>
<td>023 (P)†</td>
<td>17/21</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>024 (AK)†</td>
<td>19/29</td>
<td>28/ND</td>
<td>ND</td>
</tr>
<tr>
<td>038 (A)†</td>
<td>19/13</td>
<td>31/21</td>
<td>ND</td>
</tr>
<tr>
<td>039 (P)†</td>
<td>86/34</td>
<td>105/50</td>
<td>108/47</td>
</tr>
<tr>
<td>041 (K)†</td>
<td>28/47</td>
<td>19/45</td>
<td>19/40</td>
</tr>
<tr>
<td>043 (AK)†</td>
<td>19/ND</td>
<td>22/ND</td>
<td>22/ND</td>
</tr>
<tr>
<td>048 (A)†</td>
<td>58/45</td>
<td>61/63</td>
<td>50/58</td>
</tr>
<tr>
<td>050 (AK)†</td>
<td>ND/92</td>
<td>ND/90</td>
<td>ND/65</td>
</tr>
<tr>
<td>053 (P)†</td>
<td>—</td>
<td>17/16</td>
<td>19/16</td>
</tr>
<tr>
<td>073 (P)</td>
<td>ND/29</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>088 (AK)</td>
<td>56/34</td>
<td>53/30</td>
<td>51/31</td>
</tr>
<tr>
<td>089 (P)</td>
<td>64/21</td>
<td>57/ND</td>
<td>40/ND</td>
</tr>
<tr>
<td>094 (AK)</td>
<td>ND/20</td>
<td>35/33</td>
<td>41/35</td>
</tr>
<tr>
<td>116 (K)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>117 (A)</td>
<td>28/ND</td>
<td>42/20</td>
<td>31/22</td>
</tr>
</tbody>
</table>

The only side effects reported in this group were local irritation in subject 94 and tinnitus in subject 117. Missing values are due to unavailable blood plasma concentrations.

* Nortriptyline is an active metabolite of amitriptyline. † The lower limit of detection was 20 ng/ml at ACM Labs, Rochester, New York, and 15.7 ng/ml at the Queen Elizabeth II Health Sciences Centre laboratory, Halifax, Nova Scotia, Canada; the asterisk designates values obtained at the Queen Elizabeth II Health Sciences Centre laboratory. ‡ Subject 027 was taking oral amitriptyline or any other tricyclic or similar medication; he reported no side effects that would be unusual at this plasma concentration. The concentration detected therefore reflects a false positive value. † Subject 102 was using placebo cream; the concentration detected therefore reflects a false positive value. § Subject 104 reported no side effects.

### Table 5. Detectable Amitriptyline/Nortriptyline Concentrations (ng/ml) Exhibited in Three Subjects Not Taking Oral Amitriptyline

<table>
<thead>
<tr>
<th>Subject No. (Treatment Group)</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>027 (K)†</td>
<td>111/416</td>
<td>144/540</td>
</tr>
<tr>
<td>102 (P)‡</td>
<td>24/ND</td>
<td>ND</td>
</tr>
<tr>
<td>104 (A)§</td>
<td>73/ND</td>
<td>92/24</td>
</tr>
</tbody>
</table>

Discussion

This study examined topical formulations of novel peripheral analgesics containing 2% amitriptyline, 1% ketamine, and a combination of both in the treatment of neuropathic pain. The study involved a 3-week, double-blind, placebo-controlled trial. Pain levels at the end of the study revealed no significant differences in changes in pain scores between treatment groups.

The dose of amitriptyline (2%) was selected on the basis of a previous trial, efficacy of topical doxepin in human trials (3.3–5%), and plasma concentrations of amitriptyline and ketamine. In preclinical studies using the formalin test (a model involving inflammation and ongoing pain), both amitriptyline and a combination of amitriptyline with ketamine produced antinociception of a similar magnitude. However, there is no preclinical data examining effects of this combination of drugs in a model of neuropathic pain where the neurobiology of pain is known to be altered from the uninjured state. Therefore, there is scope for optimization of doses of both agents.

Plasma concentrations of amitriptyline and ketamine indicated no or minimal detectable concentrations of either active agent or metabolite, indicating a lack of systemic effect. Only three subjects exhibited any evidence of plasma ketamine, and the concentrations were generally less than 30 ng/ml (20, 22, 30 ng/ml). The lack of a systemic effect with topical ketamine at these concentrations.
centrations is supported by a recent study that demonstrated that plasma concentrations of ketamine in the range of 126–362 ng/ml were required to increase pain thresholds in patients with neuropathic pain; lower concentrations of ketamine exhibited no significant effect.35

A recent randomized placebo-controlled trial examined a higher dose of topical amitriptyline and ketamine (4% and 2%, respectively) using an enriched enrollment design.34 That study identified a 52% responder rate in 250 subjects with postherpetic neuralgia after 1 week of open treatment with the drug combination; 118 subjects were then randomly assigned to receive 4% amitriptyline–2% ketamine, 2% amitriptyline–1% ketamine, or placebo for 2 weeks.34 Mean average daily pain intensity using the NRS-PI went from 6.4 at baseline to 3.28 for the higher-dose cream, 4.08 for the lower-dose cream, and 4.34 for placebo, with the higher-dose cream effect being statistically significant. The number of subjects attaining a 30% reduction in pain intensity was 46% for the higher-dose cream, 26% for the lower-dose cream, and 19% for the placebo; again, the higher-concentration cream effect was statistically significant. Plasma concentrations of either drug were minimal.34 These results indicate that the higher-concentration cream leads to a greater responder rate than was observed with the lower-concentration cream, without significantly increasing the risk of systemic absorption in the majority of subjects.

Conclusion

In conclusion, this randomized, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination of both in the treatment of neuropathic pain revealed no differences between groups. Optimization of doses may be required, because another study has revealed that higher concentrations of these agents combined do produce significant analgesia.

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