Decreased Pain Following use of a Compounded Topical Analgesic: Interim Results from the Optimizing Patient Experience and Response to Topical Analgesics (OPERA) Observational Study

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Introduction

Chronic, noncancer pain affects over 100 million Americans and is one of the most frequent reasons for individuals to seek medical care.[1] Although achieving pain relief and improved quality of life are the primary clinical goals, most patients and healthcare professionals recognize, and the literature supports, 30% pain improvement to be clinically significant—a success level that would be unacceptable in other areas of medicine.[2] Despite a wealth of treatment options, as many as 40% of patients treated for chronic pain do not attain adequate analgesia, which can lead to physical and social dysfunction and diminished quality of life.[1]

Further compounding the issue, patients who experience chronic pain often have multiple comorbidities and take multiple medications. Unfortunately, most pain therapies, including opioids and NSAIDs, are associated with adverse effects and the addition of further systemic medications to control pain increases the risk of drug-drug interactions and side effects.[3,4] Moreover, opioids are subject to regulatory control due to the risk of abuse, misuse, and/or diversion, and therefore may not be appropriate for all patients. Successful pain management must provide adequate analgesia without excessive adverse effects or risk.

Topical analgesics have the advantage of local application with limited systemic levels of drug.[3] Because of the lower systemic exposure observed with topical therapies, there may be a benefit from reduced side effects, a lower risk of drug-drug interactions, and improved tolerability.[1,3] Therefore, evaluation of opioid-sparing treatments including topical compounded formulations is critical to identification of safer and more effective approaches to the treatment of pain.

Purpose

OPERA is an ongoing observational survey study of patients ages 18-64 who experience chronic neuropathic or musculoskeletal pain and who have been prescribed a topical analgesic (Flurbiprofen 20%, Amitriptyline 5%, Magnesium Chloride 10%, Gabapentin 6%, Bupivicaine 2% or other pain-relieving transdermal gel). The study protocol did not dictate the treatment decisions for the patients (i.e., number of applications per day). Most of the patients had been prescribed opioids or other oral analgesics, or were taking over-the-counter medications for chronic pain.

The purpose of the pre-planned interim analysis of the OPERA study reported here was to:

1. Validate findings from a previous 2015 interim analysis (n= 417)
2. Evaluate the efficacy of the topical analgesic in reducing pain in patients experiencing either neuropathic or musculoskeletal pain, using the Brief Pain Inventory (BPI) Short Form,[5]
3. Assess changes in the percentage of patient-reported primary pain complaints/symptoms,
4. Assess patient satisfaction with the topical analgesic, and
5. Identify any adverse effects.

Methods

Following IRB approval and patient consent, data were collected beginning in 2014 via paper survey forms completed by study participants from 85 physicians who treat patients with chronic pain. The top four physician specialties were: anesthesiology, general medicine, pain management, and podiatry. Physician practices were in 12 different states across the USA.

Observation Study Design

Survey 1 (at first patient visit before use of topical analgesic):

- Questions regarding primary pain complaint/symptoms (and location)
- The BPI Short Form (Severity and Interference components)—used with permission from MD Anderson.
- Current medication usage

Survey 2 (at second patient visit—approximately 45 days since starting use of the topical analgesic):

- Data not used for this interim analysis. Study designed called for an analysis at approximately half way through the entire study (at Survey 3). A more in-depth summative analysis will be conducted at study conclusion.
- Same questions as used for Survey 3 below

Survey 3 (at third patient visit—approximately 90 days since starting use of the topical analgesic):

- All Survey 1 questions
- Questions related to use of the topical analgesic

All Surveys included queries on any side effects of the topical analgesic.

Completed forms were collected and entered into Microsoft *Excel*.

- For patients with days between Survey 1 and Survey 3 ≥40 and ≤140, Survey 1 and Survey 3 records were matched using a unique identifier = 723 records.
- Records were removed due to incomplete/misaligned data = 92 records.
- Total records used in this interim analysis = 631 paired records.

Data were transferred from *Excel* into the *Statistics Package for the Social Sciences* (*SPSS*, IBM, version 23) for statistical analysis. Descriptive statistics were run for all questions. Statistically significant differences between Survey 1 and Survey 3 results were calculated using the McNemar test for binomial data and the Wilcoxon Signed Ranks test for scale data. Alpha was set at .05.

Results

Table 1. Patient Characteristics (n= 631 for each)

	Mean ± SD	Range
Female/Male (n)	383/248	
Age at Survey 1 (years)	46.3 ± 11.1	18.2 – 64.3
Days between Surveys 1 & 3	75.5 ± 22.5	40 - 140

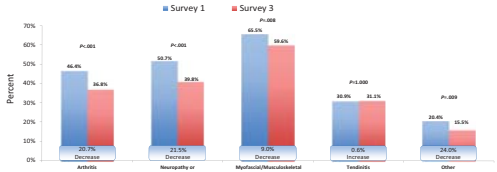
SD = standard deviation

Table 2. Patient-Reported Side Effects Associated with Topical Analgesics

Side Effect	%	n
No side effect	99.5%	628
Rash	0.5%	3
"Other"	0.0%	0
Total	100%	631

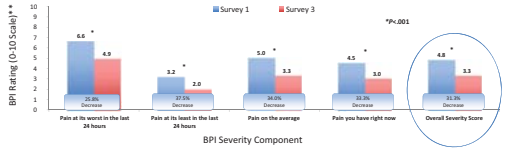
None of the side effects reported were serious adverse events

Figure 1. Changes in Percentage of Patient-Reported Primary Pain Complaints/Symptoms from Survey 1 to Survey 3 (n= 631 for each, paired data)



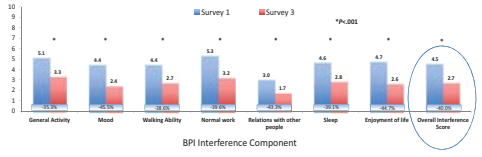
Further analysis is needed, as 55% of patients reported more than one primary complaint (Survey 1 mean = 2.1 complaints, Survey 3 mean = 1.8 complaints, statistically significant decrease: *P*<.001, n= 631, paired data).

Figure 2. Change in Mean Overall BPI Severity Score and 4 Components of the BPI Severity Score from Survey 1 to Survey 3 (n= 631 for each, paired data)



**Average score on a scale of 0 = No pain, to 10 = Pain as bad as you can imagine.

Figure 3. Change in Mean Overall BPI Interference Score and 7 Components of the BPI Interference Score from Survey 1 to Survey 3 (n= 631 for each, paired data)



**Average score on a scale of 0 = Does not Interfere, to 10 = Completely Interferes

Figure 4. Change in Reported Use of Oral Pain Medications from Survey 1 to Survey 3 by Type (n= 631 for each, paired data)

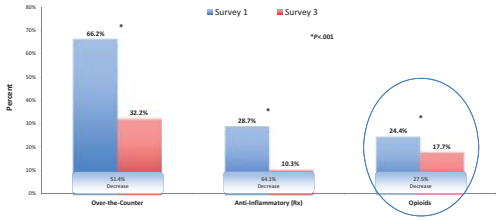
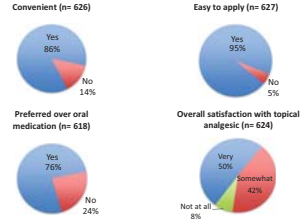


Figure 5. Patient-Reported Observations on the Use of Topical Analgesics



Conclusions

- **Results from this interim analysis suggest that the topical analgesics used in this study may:**
  - **Reduce BPI Severity and Interference scores for adult patients with neuropathic and musculoskeletal pain.**
  - **Reduce the number of primary pain complaints for each of arthritis, neuropathy or radiculopathy, and myofascial/ musculoskeletal pain or spasm.**
  - **Reduce the use of oral OTC, anti-inflammatory and opioid analgesics.**
- **Overall patient satisfaction with topical analgesics was high.**
- **Topical analgesics were safe and well-tolerated.**
- **Findings were consistent with previous interim analysis results, and include 32 more investigators and 214 more patients.**
- **Results from the interim analysis warrant and justify continuation of the OPERA trial.**

Limitations

- This was an interim analysis. A more detailed analysis will be conducted at the conclusion of the study.
- Results include all respondents, regardless of number/types of complaints/symptoms and regardless of number/types of oral pain medications currently being taken.
- This is an observational study; Changes observed cannot definitively be attributed to the topical analgesic. Further study is therefore required.

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