

INTEGRATIVE MEDICINE SECTION

Herbal Topical Analgesic for Pain Management: Perspectives from Cancer Patients

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Abstract

Objective. Herbs and natural products are increasingly used by cancer patients for pain management, but few studies have examined their integration within conventional cancer care. This study describes the characteristics, experiences, and perspectives of cancer patients who were prescribed an herbal topical analgesic for pain management. Design and Setting. Program evaluation of a pilot herbal dispensary at a National Cancer Institute-designated comprehensive cancer center. Subjects. Cancer patients who were prescribed the Tibetree Pain-Relieving Plaster (PRP) by an integrative medicine physician. Methods. Sociodemographic and clinical characteristics of patients were abstracted from medical records. Semistructured phone interviews were conducted 1-2 weeks after PRP prescription to evaluate patient experiences with using PRP for pain. Interviews were analyzed through thematic content analysis. Results. From February 2019 to February 2020, 50 patients were prescribed PRP. Median age (range) was 63 years (21-86), 37 patients (74%) were female, 14 (28%) were non-White, and 38 (76%) were using oral analgesics. During interviews, the majority of patients reported that the PRP improved pain and health-related outcomes, was convenient to use, and addressed pain management needs that were not fulfilled by oral analgesics. However, a few patients described adverse experiences with PRP, including skin irritation. Conclusions. Understanding patient experiences and perspectives is a critical step toward evidence-based integration of herbs and natural products into cancer pain management. Findings from this program evaluation will inform the design of a randomized clinical trial on the efficacy and safety of PRP for pain in patients with cancer.

Key Words: Cancer; Pain Management; Integrative Medicine; Herbs; Natural Products

Introduction

In 2019, an estimated 1.8 million people were newly diagnosed with cancer, joining the 16.9 million patients living with cancer in the United States [1, 2]. Pain is one of

the most common symptoms in the cancer population, affecting up to 60% of patients undergoing treatment and persisting in a third of patients who had completed cancer treatment [3, 4]. Pain disrupts physical function, 1436 Liou et al.

impairs quality of life, and potentially worsens cancerrelated outcomes and overall survival [5]. Unfortunately, approximately 50% of cancer patients do not receive adequate treatment for their pain symptoms [4, 6].

Cancer patients are more likely than the general population to seek complementary and alternative therapies to address their pain management needs [7]. Prior research has estimated that up to 87% of cancer patients use complementary and alternative therapies, and approximately a third of these cancer patients report the use of herbs [8]. Although research on herbal medicine for cancer-related pain is growing, the majority of studies have been limited to Chinese populations, and trials with rigorous designs are still lacking [9]. These evidence gaps pose significant challenges to integrating herbal medicine into cancer pain management in the United States.

The ongoing opioid crisis, coupled with growing concerns about polypharmacy in the cancer population, has renewed interest in other forms of pain management that do not involve taking analgesics orally [10–12]. Tibetree Pain-Relieving Plaster (PRP) is a topical herbal medicine widely used in China for the treatment of acute and chronic musculoskeletal pain conditions [13]. In a recent systematic review conducted by our group, the PRP demonstrated promising effects on osteoarthritic pain with minimal adverse events; however, the strength of this evidence was deemed low to moderate because of methodological limitations [13]. Given that none of the studies on PRP were conducted in oncology settings, the findings are not generalizable to the cancer population. The PRP is currently available as an over-the-counter medicine in the United States, but its acceptability, patterns of use, and perceived benefits and harms among cancer patients remain unclear.

To address unmet cancer symptom management needs and to promote research on the evidence-based integration of herbal medicine into cancer care, the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center (MSK) launched a pilot herbal dispensary program in February 2019. The PRP was one of several herbal medicines that could be prescribed by integrative medicine physicians to patients receiving care at MSK. The present study describes the clinical characteristics of patients who received PRP prescriptions and aims to understand their experiences with and perspectives on the use of PRP for cancer pain management.

Methods

Study Setting, Design, and Participants

The study took place at MSK, a National Cancer Institute-designated Comprehensive Cancer Center, and was part of a program evaluation of MSK's pilot herbal dispensary. The study included patients who were prescribed PRP by integrative medicine physicians at MSK between February 2019 and February 2020. The

program evaluation protocol was approved by MSK's Institutional Review Board.

Program Evaluation Procedures

We abstracted sociodemographic information (age, gender, race/ethnicity) and clinical characteristics (cancer type, analgesic use, and pain location) from the medical records of patients who received PRP prescriptions between February 2019 and February 2020. We also conducted semistructured phone interviews until thematic saturation was reached [14]. We contacted patients 1-2 weeks after they received the PRP prescription and asked them whether they were interested in participating in a phone interview with regard to their use of the PRP. If patients agreed to participate, we asked them about the perceived impact of the PRP on pain severity and then followed up with open-ended probes to elicit more specific information and feedback about their experiences with the PRP [15]. Phone interviews lasted 25-90 minutes. Transcripts of phone interviews were deidentified.

Data Analysis

Sociodemographic and clinical characteristics were summarized descriptively.

We analyzed interviews by using an iterative process of independent and collaborative thematic content analysis [16]. Three members of the research team (CC, NE, KAL) independently coded each transcript in Microsoft Excel according to a set of a priori and interpretive codes and then met regularly to build consensus and resolve discrepancies in coding. After all transcripts had been coded, the research team engaged in a secondary analysis, coding quotes within categories of interest to identify primary themes and subthemes. Primary themes were observed across a majority of transcripts, whereas subthemes constituted key divergences between patient subgroups. As themes were identified, they were discussed among research team members (CC, NE, KAL) and substantiated with supporting quotes.

Results

Patient Characteristics

From February 2019 to February 2020, 50 patients were prescribed PRP. The median age was 63 years (range 21 to 86 years). Of the 50 patients, 37 (74%) were female, and 14 (28%) were non-White. The most common cancer types were breast (40%), prostate (8%), and gastrointestinal (8%). Thirty-eight patients (76%) were using oral analgesics for pain management. The most common pain location was the back, which was reported by 19 patients (38%). Patient characteristics are summarized in Table 1.

Table 1. Patient characteristics

| Characteristics | N = 50 |
|-----------------------------|------------|
| Age, y, median (range) | 63 (21–86) |
| Gender, n (%) | |
| Female | 37 (74) |
| Male | 13 (26) |
| Race/ethnicity, n (%) | |
| White | 36 (72) |
| Black | 5 (10) |
| Asian | 5 (10) |
| Hispanic | 4 (8) |
| Cancer type, n (%) | |
| Breast | 20 (40) |
| Prostate | 4 (8) |
| Gastrointestinal | 4 (8) |
| Genitourinary | 3 (6) |
| Sarcoma | 3 (6) |
| Myeloma | 3 (6) |
| Lymphoma | 3 (6) |
| Leukemia | 2 (4) |
| Lung | 2 (4) |
| Gynecological | 2 (4) |
| Melanoma | 1 (2) |
| Adenocarcinoma, unspecified | 1 (2) |
| Glioblastoma | 1 (2) |
| Mixed | 1 (2) |
| Analgesic use, n (%) | |
| NSAIDs | 14 (28) |
| Acetaminophen | 2 (4) |
| Opioid | 15 (30) |
| Gabapentin | 5 (10) |
| Other | 2 (4) |
| None | 12 (24) |
| Pain location, n (%) | |
| Back | 19 (38) |
| Shoulder | 3 (6) |
| Leg | 2 (4) |
| Abdomen | 1(2) |
| Hip | 1(2) |
| Generalized muscular pain | 5 (10) |
| Multiple joints | 15 (30) |
| Unknown | 4 (8) |

NSAID = nonsteroidal anti-inflammatory drug.

Semistructured Telephone Interviews

Interviews were conducted from October 2019 to December 2019. Thematic saturation was reached after interviews with 15 patients, consistent with literature on exploratory qualitative studies [17]. The following primary themes were identified from interviews: 1) reduction in pain severity after using the PRP, 2) additional benefits of the PRP beyond pain reduction, 3) unmet pain management needs fulfilled by the PRP, 4) convenience and functionality of the PRP, and 5) feedback on improving the patient experience with the PRP. The primary themes, along with accompanying subthemes, are summarized in Table 2 with illustrative quotes from patients.

Theme 1: Reduction in Pain Severity After Using the PRP Nearly 75% of patients reported a reduction in pain severity after using the PRP. However, the magnitude of improvement appeared to vary. As a 61-year-old patient

with lung cancer described, "The patch definitely helped me. I've used two so far on my knee, and it definitely relieved the pain there ... I also noticed it even reduced the swelling too. Before the patch, the pain would be around 6/10 and I definitely noticed a difference. After the patch, it's around a 2/10." Another 75-year-old patient with prostate cancer stated, "The patch is amazing ... I have no more pain! The pain was a 4/10, and now, it is less than one or zero." However, a subset of patients (n = 4 [26.7%]) did not notice any improvements in pain severity after using the PRP patch. These patients stopped using the PRP after several tries, and a few started to use oral analgesics for pain relief.

Theme 2: Additional Benefits of the PRP Beyond Pain Reduction

Several patients noted that the pain relief from the PRP contributed to additional benefits in other aspects of their daily lives. These reported benefits included better sleep, greater mobility, and increased ability to tolerate and engage in physical activity and other health-related activities. As a 67-year-old patient with breast cancer stated,

"The pain in my knee use to be excruciating, night after night I couldn't sleep ... now, I can sleep through the night because the patches were a big relief. When I lie in my bed the pain is almost gone, maybe one out of ten or nothing. It is almost not there ... I [also] go to physical therapy. Because of my radiation treatment I have so much pain all over and haven't been able to move as much, but because of the patch, I have so much less pain in my knee when I walk now."

Theme 3: Unmet Pain Management Needs Fulfilled by the PRP

Many patients reported that their pain symptoms were inadequately treated with conventional oral or topical analgesics. These patients commented that the PRP was helpful in addressing some of their unmet pain management needs. A 75-year-old patient with prostate cancer stated, "Oh my gosh, I used to be on a lot of pain killers, it was a nightmare ... I was prescribed so much, oxycodone, gabapentin, celecoxib, Lyrica [pregabalin] ... it was terrible and it didn't work ... but this patch helped." Another 74-year old patient with breast cancer commented, "Before the patch I tried everything for the pain, like lidocaine ... I developed a reaction with those ... I also didn't feel good. I don't have that with the patch. Even though I got a rash, I would use the patch over anything they gave me."

Theme 4: Convenience and Functionality of the PRP

The majority of patients commented that the PRP was convenient and easy to use. Most patients used the PRP as needed for pain episodes, rather than applying it on a daily basis. As a 46-year-old patient with glioblastoma noted, "I've used around ten patches over the course of two months, I don't need it all the time, but I use it when

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Table 2. Themes and illustrative quotes from semistructured telephone interviews

Primary Theme 1: Reduction in pain severity after using the PRP

"The patch definitely helped me. I've used two so far on my knee, and it definitely relieved the pain there ... I also noticed it even reduced the swelling too. Before the patch, the pain would be around 6/10 and I definitely noticed a difference. After the patch, it's around a 2/10." (61-year-old, lung cancer)

"The patch is amazing ... I have no more pain! The pain was a 4/10, and now, it is less than one or zero." (75-year-old, prostate cancer)

"I think Tylenol helps with general pain. Because of my radiation, I have aches and pain all over my body, but it [Tylenol] doesn't help with specific pain in my shoulder or knee. The patch, I can use just for my knee and the pain is much less." (67-year-old, breast cancer)

Subtheme 1: No changes in pain severity after using the PRP

- "I tried the patch and it was okay. I didn't really notice that it made a huge difference ... I take two Advil every time after a long run, and I still had to take them even with this patch." (33-year-old, breast cancer)
- "I used the patch for 6 days, and I didn't notice any pain relief, so I stopped it." (67-year-old, adenocarcinoma, unspecified)
- "The patch wasn't helping that much, so I took Naproxen. I don't like popping pills, and I know they have risks, but I appreciate that Naproxen allowed me to walk." (77-year-old, breast cancer)

Primary Theme 2: Additional benefits of the PRP beyond pain reduction

- "The pain in my knee used to be excruciating, night after night I couldn't sleep ... now, I can sleep through the night because the patches were a big relief. When I lie in my bed the pain is almost gone, maybe one out of ten or nothing. It is almost not there ... I [also] go to physical therapy. Because of my radiation treatment I have so much pain all over and haven't been able to move as much, but because of the patch, I have so much less pain in my knee when I walk now." (67-year-old, breast cancer)
- "I got the knee injury four years ago, and since then, I have not been able to walk on my own. I have to always use a walker, and I walk a lot slower now. But after using the patch, I am able to walk now. I was even able to do an echo stress test . . . I was able to stay on the treadmill for 7 mins." (46-year-old, glioblastoma)
- "The patch has really helped me be able to accomplish everyday tasks. The pain in my lower back would flare up unexpectedly, the most worrisome time was when I was driving, and I would have to pull over. Now, I would prepare and use the patch when I'm about to do something that might give me my back pain, and it has helped with that." (46-year-old, melanoma)
- "I would get really bad pain in my chest when I get scans for my breasts, and this [PRP] has really helped me be able to tolerate that more." (47-year-old, breast cancer)

Primary Theme 3: Unmet pain management needs fulfilled by the PRP

- "Oh my gosh, I used to be on a lot of pain killers, it was a nightmare ... I was prescribed so much, oxycodone, gabapentin, celecoxib, Lyrica [pregabalin] ... it was terrible and it didn't work ... but this patch helped." (75-year-old, prostate cancer)
- "Before the patch I tried everything for the pain, like lidocaine ... I developed a reaction with those ... I also didn't feel good. I don't have that with the patch. Even though I got a rash, I would use the patch over anything they gave me." (74-year-old, breast cancer)
- "I am very sensitive to medications. I've been through so much in the last 12 years, I have taken so many medications, and those meds did so many bad things to my body . . . it caused me so many trips to the hospital and to the emergency room because I had all these different reactions . . . so, now, I am very cautious about using medications. I don't care if I'm dying. I don't like taking any more medications. I tried this patch because I wanted to try something different. I've used seven patches, it works slowly, not like it takes the pain away right away . . . but when the pain is really bad . . . I will use it." (62-year-old, gynecological cancer)

Primary Theme 4: Convenience and functionality of the PRP

- "I've used around ten patches over the course of two months, I don't need it all the time, but I use it when the pain in my hip is really bothering me."
 (46-year-old, glioblastoma)
- "I like that I can put it on whenever I need and wherever I need it, and it works pretty quickly." (78-year-old, gynecological cancer)
- "What I like about the patch the most is that it works, it's fairly comfortable, it doesn't restrict movement, and it doesn't interfere with my life." (64-year-old, prostate cancer)

Primary Theme 5: Feedback on improving the patient experience with the PRP

- "It would be nice if the patch came in assorted sizes. The area I use it for is not that big, so I cut the patch in half, but it's hard to save the liquid portion ... When I use half, there is one side without an adhesive and I have to use a Band-Aid to keep it in place." (64-year-old, prostate cancer)
- "I would like the patch to be bigger. It should cover more area, like if I want to use it for my shoulder pain, the patch should be bigger to cover it. Other than that, it works well. It sticks on and peels off, but there should be an option to be bigger." (67-year-old, breast cancer)

Subtheme 5: Adverse experiences with the PRP

- "I used it [PRP] for three days, and it was wonderful ... but after the third day, I had redness on the skin and it was itchy, so I stopped using it." (75-year-old, prostate cancer)
- "The overall experience is very good, except it turns my hands yellow-green." (64-year-old, prostate cancer)
- "I used the patch for my right thumb, and every piece of that area was stained, and the stain didn't go away until the skin started to peel, which took a week or two. It wasn't the painful kind of peeling like a sunburn, but the top layer did come off, leaving a fresh layer of skin." (67-year-old, adeno-carcinoma, unspecified)
- "The smell of the patch was very strong and quite unpleasant. It has a very strong herbal smell, maybe it was the turmeric, but it was quite overbearing." (67-year-old, adenocarcinoma, unspecified)
- "It's a little messy. Since you have to pour the liquid onto the patch, that can be messy. But other than that, I think it's fine." (61-year-old, lung cancer)

the pain in my hip is really bothering me." A few patients commented that the fast-acting effects of the PRP contributed to its convenience. A 78-year-old patient with gynecological cancer noted, "I like that I can put it on whenever I need and wherever I need it, and it works pretty quickly."

Theme 5: Feedback on Improving the Patient Experience with the PRP

Despite these positive comments, some patients offered feedback on how to improve the functionality of the PRP. A 64-year-old patient with prostate cancer

suggested, "It would be nice if the patch came in assorted sizes." A few patients also highlighted negative experiences with using the PRP. Skin irritation or rash was the most commonly reported adverse event related to PRP use. Others commented that the PRP caused a "yellow-green" stain on their skin. A few patients disliked the odor of the PRP and noted that the application process was "messy" because a separate liquid packet had to be opened and poured onto the patch to activate the PRP.

Discussion

Pain is a prevalent, disabling, and undertreated symptom among patients with cancer [4, 6]. Herbs and natural products represent one of the most used complementary and alternative therapies in the cancer population [7, 8], but research on their optimal integration with cancer pain management remains limited. The present study is the first study to understand the characteristics and experiences of patients who were prescribed a topical herbal medicine for pain management at a National Cancer Institute-designated comprehensive cancer center. Whereas prior research on the PRP was limited to Chinese non-cancer populations [13], the present study shed light on the use of PRP among racially diverse patients with various cancer types and pain conditions. The majority of patients reported that the PRP produced benefits for pain, physical function, and health-related quality of life while addressing unmet pain management needs; however, a few patients also highlighted adverse side effects and shortcomings of the PRP that warrant further investigation. These findings can help to guide rigorous trials on the PRP and other natural products for cancer pain management.

Nearly three in four patients in our study reported a reduction in pain severity after using the PRP. The PRP consists of camphor 3% (active ingredient), Zanthoxylum bungeanum Maxim. (Chuan Lamiophlomis rotate (Benth.) Kudo (Du Yi Wei), Curcuma longa L. (Jiang Huang), Myricaria germanica (L.) Desv. (Shui Bai Zhi), Carthamus tinctorius L. (Hong Hua), and Oxytropis falcata Bunge (Ji Dou). According to in vitro and in vivo studies, these ingredients have anti-inflammatory and anti-nociceptive properties, which are hypothesized to contribute to their analgesic effects [18, 19]. Multiple studies, all conducted in China, have shown that PRP use is associated with reduced chronic nonmalignant pain; however, to the best of our knowledge, no randomized controlled trial has been conducted in an oncology population [13]. Our qualitative findings on the PRP, demonstrating its acceptability and perceived effectiveness among diverse cancer patients, provide support for a future randomized controlled trial of PRP to establish the specific efficacy for pain in an oncology population.

In our study, the majority of patients commented on the convenience of using the PRP as needed for

intermittent pain episodes. This pattern of use is consistent with other qualitative research on the use of topical analgesics. In a qualitative study comparing topical versus oral nonsteroidal anti-inflammatory drugs (NSAIDs), patients preferred the topical formulation for transient pain and the oral formulation for constant pain [20]. Patients also viewed the topical formulation of NSAIDs as weaker and less potent than the oral formulation, which shaped their preference to use topical NSAIDs for mild pain and oral NSAIDs for moderate-severe pain [20]. By contrast, patients in our study appeared willing to use the PRP for more severe pain intensities, and some even commented that the PRP was more effective than oral analgesics. Our findings suggest greater acceptability among patients toward using topical herbal formulations for a wide range of pain intensities, whereas other research demonstrates that patients tend to view topical NSAIDs as weaker versions of oral NSAIDS and thus suitable only for mild pain intensities [20]. Given that the PRP exists only as a topical formulation, future research should examine whether the lack of an alternative oral formulation may enhance patient perceptions of potency.

In addition to pain reduction, patients reported that the PRP improved sleep, physical functioning, and engagement in health-related activities. These perceived global benefits of the PRP stand in contrast to other qualitative studies showing that topical analgesics are viewed as producing localized effects limited to the area of application [20]. Prior research has shown that integrative and complementary therapies are often viewed as more "holistic" than conventional treatments [21], and this preconception could potentially shape patient perceptions of global benefits of using natural products such as the PRP. Future clinical trials on PRP should incorporate measures of sleep, physical function, and health-related quality of life as secondary outcomes in addition to pain.

Patients who had prior negative experiences with oral analgesics appeared to prefer using the PRP for pain management. This finding is aligned with other qualitative studies demonstrating that patients viewed topical analgesics has having fewer side effects than oral analgesics [20]. As polypharmacy emerges as a growing concern in the cancer population [12], the PRP could potentially help to address unmet pain management needs, particularly among patients who are hesitant to use oral analgesics because of potential adverse side effects.

Although most patients reported positive experiences with the PRP, it is important to note that natural does not mean safe. Herbs and other natural products are not regulated by the Food and Drug Administration in the United States, and manufacturers are not required to prove efficacy and safety before making natural products available to the public. A few patients in our study reported adverse experiences related to PRP use. Some side effects, such as skin irritation, have been reported with other topical analgesics [22], whereas other adverse experiences (e.g., skin discoloration, unpleasant odor)

appear to be unique to the PRP and warrant further investigation to ensure safety, acceptability and tolerability, particularly among cancer patients with cosmetic concerns. The required application of a separate liquid packet onto the topical patch is another unique aspect of the PRP that may cause barriers for some patients. Other negative feedback from patients, such as the lack of different patch sizes, should be addressed in future intervention development to ensure that the PRP and other topical herbal analgesics remain patient centered and easy to use.

Our research findings have some limitations. This study was designed as a qualitative program evaluation and did not include any quantitative, longitudinal measures of pain-related outcomes. A randomized clinical trial will be required to determine the efficacy or safety of the PRP for pain management in oncology settings. Guided by the findings from this program evaluation, our group plans to conduct a randomized, placebo-controlled trial on the PRP for chronic musculoskeletal pain in patients with cancer. Another limitation of this study is that the participants were cancer patients who had received integrative medicine consultations at a tertiary academic cancer center. Thus, these patients may favor complementary approaches to pain management, and their experiences and perspectives may not be generalizable to all patients with cancer and pain.

Despite these limitations, this study of diverse cancer patients provides novel insight into the integrated use of a topical herbal medicine for cancer pain management at a National Cancer Institute–designated comprehensive cancer center. Patient experiences, perspectives, and values, such as those described in our study, represent important aspects of evidence-based practice [23]. Our findings will help to inform the design of randomized controlled trials to test the efficacy and safety of the PRP. Rigorous research, combined with an understanding of patients' health beliefs and values, will support the evidence-based integration of herbs and natural products into comprehensive cancer pain management.

References

- Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA: Cancer J Clin 2019;69 (5):363–85.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: Cancer J Clin 2019;69(1):7–34.
- van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Ann Oncol 2007;18(9):1437–49.
- van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence

- of pain in patients with cancer: Systematic review and meta-analysis. J Pain Symptom Manag 2016;51(6):1070–90.e9.
- Zylla D, Steele G, Gupta P. A systematic review of the impact of pain on overall survival in patients with cancer. Support Care Cancer 2017;25(5):1687–98.
- Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol 2008;19(12):1985–91.
- Mao JJ, Palmer CS, Healy KE, Desai K, Amsterdam J. Complementary and alternative medicine use among cancer survivors: A population-based study. J Cancer Surviv 2011;5 (1):8–17.
- 8. Judson PL, Abdallah R, Xiong Y, Ebbert J, Lancaster JM. Complementary and alternative medicine use in individuals presenting for care at a comprehensive cancer center. Integr Cancer Ther 2017;16(1):96–103.
- Xu L, Lao LX, Ge A, et al. Chinese herbal medicine for cancer pain. Integr Cancer Ther 2007;6(3):208–34.
- Paice JA. Managing pain in patients and survivors: challenges within the United States opioid crisis. J Natl Compr Canc Netw 2019;17(5):5):595–8.
- 11. Paice JA. Navigating cancer pain management in the midst of the opioid epidemic. Oncology 2018;32(8):386–90. 403.
- Murphy CC, Fullington HM, Alvarez CA, et al. Polypharmacy and patterns of prescription medication use among cancer survivors. Cancer 2018;124(13):2850–7.
- Chen C, Li SQ, Bao T, et al. A systematic review of cheezheng pain relieving plaster for musculoskeletal pain: implications for oncology research and practice. Integr Cancer Ther 2020;19: 153473542091893.
- 14. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. Oual Res 2008;8(1):137–52.
- Creswell JW, Poth CN. Qualitative Inquiry and Research Design: Choosing Among Five Approaches. Los Angeles: Sage Publications; 2017.
- Saldaña J. The Coding Manual for Qualitative Researchers. London: Sage Publications; 2016.
- 17. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field Methods 2006;18(1):59–82.
- Duan WR, Lu J, Xie YK. Mechanisms of topical analgesics in relieving pain in an animal model of muscular inflammation. Pain Med 2013;14(9):1381–7.
- 19. Wang YZ, Dong FH, Zhong HG, Zhang WQ. [In vivo effects of Qizheng-xiaotong plaster on soft tissue injury of rabbit ears]. Zhongguo gu Shang = China Journal of Orthopaedics and Traumatology 2008;21(5):356–8.
- 20. Underwood M, Ashby D, Carnes D, et al. Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study. Health Technol Assess 2008;12(22):iii–v. ix-155.
- Bao T, Li SQ, Dearing JL, et al. Acupuncture versus medication for pain management: A cross-sectional study of breast cancer survivors. Acupunct Med 2018;36(2):80–7.
- 22. Cameron M, Chrubasik S. Topical herbal therapies for treating osteoarthritis. Cochrane Database Syst Rev 2013;5(5):Cd010538.
- Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: Incorporating patient preferences in practice guidelines. JAMA 2013;310(23):2503–4.