

“I was a little surprised”: Qualitative Insights from Patients Enrolled in a 12-Month Trial Comparing Opioids to Non-Opioid Medications for Chronic Musculoskeletal Pain

Marianne S. Matthias<sup>a,b,c,d</sup>  
Melvin T. Donaldson<sup>e,f</sup>  
Agnes C. Jensen<sup>g</sup>  
Erin E. Krebs<sup>g,h</sup>

<sup>a</sup> VA HSR&D Center for Health Information and Communication, Roudebush VA Medical Center, Indianapolis, Indiana

<sup>b</sup> Regenstrief Institute, Indianapolis, Indiana

<sup>c</sup> Department of Communication Studies, Indiana University-Purdue University, Indianapolis, Indiana

<sup>d</sup> Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

<sup>e</sup> Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN

<sup>f</sup> Medical Scientist Training Program, University of Minnesota, Minneapolis, MN

<sup>g</sup> Center for Chronic Disease Outcomes Research, Minneapolis VA Health Care System, Minneapolis, MN

<sup>h</sup> Department of Medicine, University of Minnesota Medical School, Minneapolis, MN

Corresponding Author: Marianne Matthias (mmatthia@iupui.edu)

Running Title: (45 characters excluding spaces) Qualitative Insights from an Opioid Trial

Conflicts of Interest: None

Disclosures: This work was supported by the Department of Veterans Affairs, Health Services Research and Development (IIR 11-125). The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the United States Government. M. Donaldson was supported by NIH grants F30AT009162 and T32GM008244.

Trial Registration: ClinicalTrials.gov ID: NCT01583985

---

This is the author's manuscript of the article published in final edited form as:

Matthias, M. S., Donaldson, M. T., Jensen, A. C., & Krebs, E. E. (2018). “I was a little surprised”: Qualitative Insights from Patients Enrolled in a 12-Month Trial Comparing Opioids to Non-Opioid Medications for Chronic Musculoskeletal Pain. *The Journal of Pain*.  
<https://doi.org/10.1016/j.jpain.2018.04.008>

### Highlights

- Patients had strong pre-existing beliefs about opioids being effective medicines.
- Many patients were surprised by results of medication treatment.
- Patients highly valued the trial's personalized pharmacist care management model.

ACCEPTED MANUSCRIPT

### Abstract

Chronic musculoskeletal pain is a major public health problem. Although opioid prescribing for chronic pain has increased dramatically since the 1990s, this practice has come under scrutiny because of increases in opioid-related harms and lack of evidence for long-term effectiveness. The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial was a pragmatic 12-month randomized trial comparing benefits and harms of opioid versus non-opioid medications for chronic musculoskeletal pain. The current qualitative study was designed to better understand trial results by exploring patients' experiences, including perceptions of medications, experiences with the intervention, and whether expectations were met. Thirty-four participants who were purposefully sampled based on treatment group and intervention response participated in semi-structured interviews. The constant comparison method guided analysis. Results revealed that participants often held strong beliefs about opioid medications, which sometimes changed during the trial as they gained experience with medications; participants described a wide variety of experiences with treatment effectiveness, regardless of study group or their response to the intervention; and participants highly valued the personalized pain care model used in SPACE.

**Perspective:** SPACE trial results indicated no advantage for opioid over non-opioid medications. Qualitative findings suggest that, for patients in both treatment groups, pre-existing expectations of medications and of anticipated improvement in pain shaped experiences with and responses to medications. In addition, the personalized pain care model was described as contributing to positive outcomes in both groups.

Key words: chronic pain, opioids, non-opioid analgesics, qualitative research, patient-provider communication

ACCEPTED MANUSCRIPT

## Introduction

Chronic musculoskeletal pain is a major public health problem, associated with disabling physical and emotional consequences for patients and with significant costs related to medical treatment and lost worker productivity.<sup>16</sup> Use of opioid analgesics to treat chronic pain has increased dramatically in recent years,<sup>7, 25</sup> paralleled by increases in opioid-related harms, including addiction and death.<sup>1, 23, 34</sup> While harms of opioids have become apparent, evidence for long-term effectiveness of opioids for chronic pain is lacking; a recent systematic review found no randomized trials that examined effects of opioids on pain, function, or quality of life at one year or longer.<sup>10</sup>

Despite the lack of evidence on the long-term effectiveness of opioids, these medications are frequently perceived to be strong, powerful pain relievers.<sup>2,3,8</sup> Such perceptions may have an important influence on patients' responses to opioid medications; evidence suggests that patients' expectations can indeed shape outcomes.<sup>32,40</sup> This may be especially true for pain outcomes, which are subjective and self-reported. For example, in a pooled analysis of four acupuncture trials for migraine, tension headache, low back pain, and osteoarthritis, patients who had higher treatment expectations were more likely to have a clinical response to the intervention.<sup>26</sup> In a secondary analysis of behavioral physical therapy interventions for patients with low back pain, authors found a significant positive association between patient treatment expectations and improvements in pain intensity and disability.<sup>18</sup> Studies such as these suggest that patients' responses to opioids might be similarly influenced by their expectations of the effectiveness or strength of these medications.

The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial was a pragmatic trial comparing the benefits and harms of opioid versus non-opioid medication therapy over 12 months for patients with chronic back pain or hip or knee osteoarthritis pain.<sup>21</sup> Main SPACE trial results indicated that opioid therapy did not differ from non-opioid therapy on the primary outcome of pain-related function over 12 months, although most patients in both treatment groups experienced improved function from baseline to 12-month follow-up. Additionally, non-opioid medications were significantly better than opioids on pain intensity and tolerability outcomes.<sup>20</sup>

Given evidence suggesting that treatment expectations can influence treatment response, we sought to gain a more complete understanding of the potential role of expectations in the SPACE trial. This was particularly important because participants were not masked to their assigned treatment group, and main outcomes were self-reported. To better understand expectations and subjective experiences with the SPACE trial, we conducted a qualitative, post-intervention evaluation. Qualitative evaluations and mixed-methods approaches to clinical trials are increasingly being used to help to understand and interpret clinical trial results. Such approaches can help to elucidate possible reasons underlying quantitative results and can be especially useful for understanding outcomes of complex interventions such as those used in pain management.<sup>11</sup> Qualitative data also have the potential to capture aspects of participants' experiences with an intervention that are not easily measured quantitatively, potentially revealing avenues for future lines of inquiry or important clinical implications.<sup>30, 31</sup>

For this post-intervention evaluation, we conducted in-depth qualitative interviews with purposefully sampled SPACE participants in an effort to understand patients' experiences with the SPACE trial, including their views and anticipated benefits of opioids versus non-opioids, experiences with the intervention, and to what extent expectations were met after completing the study.

## Methods

**The SPACE Study.** The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial was a pragmatic randomized comparative effectiveness trial conducted with patients in multiple VA primary care clinics from 2013 to 2015. The study's objective was to compare benefits and harms of opioid therapy versus non-opioid medication therapy over 12 months for patients with moderate-to-severe chronic back pain or hip/knee osteoarthritis pain who were not already receiving regular opioid therapy. Accordingly, eligible patients were randomized to either the opioid or non-opioid intervention group. Both groups received active "treat to target" medication management delivered by a study pharmacist within a telecare collaborative management model.<sup>22</sup> The two study groups differed only in the medications offered, and multiple medications were available within each group. Medications were tailored to individual patient preferences and adjusted as needed to reach therapeutic targets. After intervention completion, most participants in the opioid group worked with the study pharmacist to taper off opioids and transition to non-opioid pain medications. Participants' medication management was subsequently returned to their primary care provider. Procedures were approved by the Minneapolis VA Institutional Review Board and Research and Development Committee. Informed consent was obtained from all participants. See Krebs et

al.<sup>21</sup> for detailed study protocol, recruitment outcomes, and participant characteristics. Of 240 patients who were randomized, 234 completed the study, and all but one patient received medication treatment in their assigned study group.

**Eligibility and Recruitment.** Participants who completed the 12-month trial and were willing and able to return to the medical center for a qualitative interview were eligible to participate in this qualitative study. Patients were purposefully sampled from trial completers to reflect four subgroups defined by two variables: treatment group assignment (opioid group or non-opioid group) and pain treatment response (responder or non-responder). Pain treatment response was defined as improvement of at least 30% on the Brief Pain Inventory (BPI) Interference scale<sup>19, 38</sup> from baseline to the 12-month follow-up assessment. We sought to obtain at least 5-8 participants in each of the four subgroups; this size is consistent with published recommendations on adequacy of subgroup sample size required for saturation (i.e., sampling to the point of redundancy in the data, when no new theoretical insights emerge) and allows searching for disconfirming evidence.<sup>24</sup> In addition to sampling based on these criteria, we selected a diverse sample in terms of age, sex, and race, in an effort to obtain a wide range of experiences and viewpoints. Patients were invited to participate in the interviews within 2 months of intervention completion, to optimize recall of study experiences. Once patients agreed to participate, arrangements were made for a face-to-face interview. Participants were compensated \$20 after completing the interview.

**Interviews.** All interviews were conducted face-to-face in a private room. Two experienced qualitative interviewers (MD and AJ) conducted several interviews together, to ensure consistency among interviews, before conducting the remainder of the interviews individually.



Interviews took 45-60 minutes, were semi-structured, and followed an interview guide of open-ended questions. The interviews started with general questions about pain and pain management (e.g., how pain first started, past pain treatments) and then shifted focus to experiences in the SPACE trial, including reasons for participation, goals for pain management, preferences for treatment group assignment, opinions about pain medications, and changes in pain since starting the study. All interviews were digitally audio-recorded, professionally transcribed, checked for accuracy, de-identified, and imported into NVivo 10 for analysis.

**Data Analysis.** All authors participated in data analysis, which was led by the first author (MM) and guided by an inductive approach using the constant comparison method.<sup>9, 27</sup> This iterative, consensus-based process consists of two broad phases, open coding and focused coding. During open coding, team members read all transcripts, noting common, recurrent, and salient themes within and between transcripts. This process led to the development and subsequent refinement of a code list. Once the codes were stable and consistent, analysts conducted focused coding, in which codes derived in the first analytic phase were applied to all transcripts. Analysts divided all transcripts evenly, coding every fourth transcript in common and meeting to compare coding. Discrepancies were resolved by consensus. Analysts were masked to the overall quantitative results of the SPACE trial until qualitative data analysis was completed. Because of the nature of the interviews, analysts were not blinded to assigned treatment group.

The analytic team employed procedures established in the literature on qualitative methods to ensure rigor and validity. Procedures included engaging in reflexivity (e.g., questioning interpretations, becoming aware of one's own expectations in the data), depth of

description (i.e., seeking out rich, particular details of participants' words and experiences), and actively looking for alternative interpretations of the data that might challenge study findings and conclusions.<sup>4, 9, 12, 13</sup>

## Results

Thirty-four patient participants were interviewed, at which point saturation was reached. Participants were 6 women and 28 men, ranging in age from 31 to 78 years (mean=58.9, SD=12.5). Demographics for the full SPACE trial are reported in Krebs et al.<sup>20</sup> Two participants self-identified race as black or African-American, 31 as white, and one participant identified with multiple categories. Eighteen participants were in the opioid group, including 10 non-responders and 8 responders, and 16 were in the non-opioid group, including 7 non-responders and 9 responders. In the interviews, participants discussed their expectations of the intervention, including beliefs about opioids and non-opioids, whether they had a preference to receive opioids or non-opioids, and why. Participants discussed the degree of pain relief and other changes they experienced during and after the intervention, and how these results aligned with their original expectations.

The participant quotes that follow are labeled according to the subgroups used for purposeful sampling (i.e., opioid group or non-opioid group; responder or non-responder).

### Expectations of Opioid and Non-Opioid Medications

Interviewers asked patients to recall their preferences for treatment group (i.e., opioids or non-opioids) at the beginning of the study. Several patients indicated a preference for the opioid group because of the perception that opioids are "stronger."

I definitely wanted the opiate [group]... I guess I was just thinking that it would be stronger medicine. (13440, opioid group; responder)

I was kind of hoping that it would be the narcotics because...usually narcotics are stronger than non-narcotics, and I was hoping that I could get something that would be stronger. (11083, non-opioid group; responder)

There's a reason it's controlled—usually because it's better. So in my mind, when you're in serious pain, you need serious medication—which, serious medication is opioids. (12009, non-opioid group; responder)

Others voiced concerns about being randomized to the opioid group. Many feared addiction.

I had hesitations about the opioid group...I was concerned about long-term use, addiction issues, because, you know, if you feel that good, are you really going to want to stop, ever? And I can answer that honestly, no, you don't want to stop. You feel good. (13606, opioid group; non-responder)

I had an opinion that I didn't want to end up on anything that could become addictive. Hydrocodone works. I'm not going to say it doesn't. But if every time I

took one I was afraid, oh my God, would this be the one that makes me addicted? (10882, non-opioid group; responder)

Impairment while on opioids was another worry. One patient indicated that, although he believed opioids might be more effective, he was concerned about how they might affect his job working on school buses:

Narcotics can lead to a lot of trouble. You're driving, you're taking [an opioid medication], and you get behind the wheel because you have to drive somewhere. Now you are driving on an illegal drug...You have to take it because you hurt really bad in the morning, for whatever reason you have to drive... you've put yourself open for a liability of massive proportions. For a non-narcotic, if it only works half as well, it still allows you to retain control and not be as drowsy. It's safer to not be on a controlled substance. Especially when you have a drive like I do. I mean, I work on school buses. I wouldn't even dream about taking [an opioid] at work. (11161, non-opioid group; responder)

Some negative perceptions of opioids were influenced by past personal experiences or those of friends or family.

I had more of like a hallucinogenic type of reaction [to codeine]. It really freaked the hell out of me. And I did not do well. (11790, non-opioid group; non-responder)

I've just seen my friends and family who have those problem, they can't just quit...I've got an Army buddy of mine who still does opioids just because he thinks it makes him a nicer person. That's him. There's always concern about getting addicted to pills. (13103, opioid group; responder)

Some patients reported no concerns about opioids. One patient, when asked if he had any concerns about being randomized to the opioid group, replied,

I wasn't worried about if I ended up in the opiate group. I wasn't worried about the addiction situation because I don't like drugs to begin with. And I don't drink, I don't smoke...so I figured, I looked at it as, you know, it's just a pill you've got to put in your mouth...I mean, I didn't think it was going to kill me or anything.

(10976, opioid group; non-responder)

Another patient believed that her past addictions better equipped her to resist addiction to opioids:

The only concern I had was that I do have a very addictive nature, but I also am a survivor...And so as far as addiction...I've come through that kind of stuff before, and I know that I'll be able to make it through. (11082, opioid group; non-responder)

### Experiences with Opioid Treatment

Participants in the opioid group described a variety of outcomes of their pain medication treatment. Notably, the subjective experience of benefit or lack of benefit that patients reported did not always match their responder status based on change in numeric scores.

Some patients described good results from opioids.

*Patient:* So, my [pain] control has been great.

*Interviewer:* Do you have any long-term concerns about being on opioids?

*Patient:* No. (13413, opioid group; responder)

I don't think I would've had as quick of feel-good results [in the non-opioid group]... When I was on the first med, it really got me energized. It improved my outlook...it got me wanting to do more and be more. (13606, opioid group; non-responder)

I just want[ed] to be able to walk around the block. Then I wanted to [walk] a half mile. And then, you know, I constantly increased that and now I'm up to four miles a day, six days a week... And it was all because of the medication. (10976, opioid group; non-responder)

This participant went on to say later in the interview, "The relief was way better than what I ever thought it would be." (10976, opioid group; non-responder)

Some non-responders in the opioid group described opioids as working in the short term, but losing effect over time.

*Participant:* When I first started, it would take the pain away and it would be great, but now when I take the medications, it still helps with the pain, but there's still pain. It's more tolerable...They're worn off. They are wearing down basically.

*Interviewer:* Did the medications work the way you thought that they would?

*Participant:* They did at first...but then they wore down to where it's not as much as I would've hoped for, but enough to keep me going. (11082, opioid group; non-responder)

I had immunity...it's less effective. But in the beginning, it was much better. (11305, opioid group; non-responder)

I thought the morphine was really working well up until I fell. And...then it didn't cut through the back pain. (11431, opioid group; non-responder)

Other patients, including some classified as responders, reported disappointment with the relief they got from opioids.

I guess I didn't even know what to expect. It helped, but it didn't fix it. (10987, opioid group; responder)

I thought I'd get more relief from [the opioid]... [Now] I'm taking two tablets [of acetaminophen] three times a day, and that seems to be working just as well as [the opioid] did. (11422, opioid group; responder)

Some responders in the opioid group did not want to continue taking opioids because of concerns about addiction or undesirable side effects.

I have a niece that got hooked on opioids, so it scared me. (10987, opioid group; responder)

One patient described how he reduced his opioid dose himself, during the study, because of addiction concerns.

These drugs are addictive, okay? They take control of your life. These opioids are screwing up your mind. You become addicted. Thank God I weaned off of it myself, because I felt that monkey on my back. (13168, opioid group; responder)

Another patient explained that the opioids provided pain relief, but interfered with her quality of life and ability to reach personal goals.

I'm glad I'm not on opiates anymore. They were effective, but it felt like I was living my life in a sleepy stupor. I did not like being tired and, you know, I could lay down on the floor and fall asleep. My quality of life, I thought, diminished because of the opiates. I think, how, why would you want to take these in your right mind? How can you even function? I wanted to be a more active participant



in my life. I wanted to reestablish friendships and I wanted to get projects done around the house. And I felt none of that was going to happen as long as I was on those opiates. All I wanted to do was sleep. (13427, opioid group; responder)

Another opioid responder described undesirable side effects that outweighed benefits of opioids.

They all worked, everything [the pharmacist] gave me worked... But some of the medicines at the beginning, I just didn't like the feeling I had. And I think the first one, which was the morphine, more scared me than anything... All I got was like a woozy feeling. So, I wasn't really on that one too long. A month or two, I think. And I was scared to take—it worked. It worked real good. But it was the constipation. (13981, opioid group; responder)

Other patients, including responders, reported that opioids did not provide much pain relief.

It's almost like it would deaden my mind and make me like I was drunk or loopy. It wouldn't actually affect the pain, because you'd still be all googly, but you still knew you had the pain. (11239, opioid group; non-responder)

I really don't know if it's doing any good. Well, like I say, just like the morphine, they don't eliminate the pain. You know, I'd still be on the morphine if it eliminated the pain. It don't. (13168, opioid group; responder)

### Experiences with Non-Opioid Treatment

Some patients described surprise that non-opioid medications were more effective than expected.

I was hoping to get into [the opioid] group ...But there's always that thought, it's like, well, hopefully, I won't get addicted to the stuff. That's why I was like, I can't believe that ibuprofen, 800 milligrams, solved the problem. (10949, non-opioid responder)

Another patient had hoped for the opioid group because "I knew [opioids] worked." He said after completing the study in the non-opioid group, "We had a little trouble at first, but finally we got them dialed in and it was great. I was really managing my pain well. I was very happy after we had it all dialed in and everything." (13239, non-opioid group; non-responder)

One patient who was treated in the opioid group during the study and transitioned to non-opioid medications after study completion described his experience with both approaches, including his surprise that the non-opioid medications seemed to be as effective as the opioid he had been taking.

*Patient:* Well, the hydrocodone was probably most effective because it was more powerful of any that I've taken. And, you know, it does more than just relieve the pain on my knee, it relieves anxiety and, you know, a few other things.

*Interviewer:* And, now, when you switched over from the hydrocodone to the acetaminophen and lidocaine, were the results any different than what you expected?

*Patient:* No, the results were about what I expected. The extra heat on my knee that provided some relief and the acetaminophen...between the two of them, it did the same about as the hydrocodone. I was a little surprised. (13281, opioid group; non-responder)

A patient in the non-opioid group indicated that he initially believed opioids were stronger, but had a good response to an anti-inflammatory medication.

I thought, I'll give [the non-opioids] a try...You have to take hydrocodone multiple times a day, and after four to six hours the pain's back, then you have to take the meds again. Where with the meloxicam I can take it in the morning and if I forget to take my morning dose the next day, I'm still fine. I can go easily 24 hours on one dose...without noticing any pain. (12009, non-opioid group; responder)

Other patients described positive effects of non-opioid medications on their activities.

For example, the following patient described how his activity improved after he joined the SPACE study:

I wanted to be active again. It was killing me—just as soon as I came home from work, I was completely exhausted from not sleeping, you know, getting two, one to two hours of sleep from just holding my knee, trying to figure out any way to stop the pain. And going through the pain study that took a year, but finally it's like thank goodness.

He went on to explain that ibuprofen turned out to be most effective medication for him.

Smooth sailing. Yep... And I've gone from not being able to exercise to walking five miles a day now, every morning. (10949, non-opioid group; responder)

Other patients similarly noted they were able to be more active and had improved fitness since being treated in the non-opioid group.

I have no problem with the lawn work now. I've increased my walking, and that's pretty good. (11417, non-opioid group; responder)

I can pick my kid up, throw him around, spin him around, whatever, and I feel great....I even feel like getting teary because I'm just so happy. I am. I'm able to do a lot of things that I couldn't. A lot more things than I thought I would be able to even [do]....I'm also a lot more muscular than I was a year and a half ago, too.

He went on to describe how his results surprised him.

I was expecting it not to be 180-degree turn because I went from being just miserable every day to being just, for the most part, happy. I can basically just bounce right out of bed.

In addition, this patient described a change in his beliefs about opioid and non-opioid medications after participating in the SPACE study.

I assumed...opioids were powerful. So they were necessary for extreme pain when that's not the case. So I do have a lot more respect, I guess, for non-opioids. (12009, non-opioid group; responder)

One patient described surprise at the effectiveness of a topical cream:

I didn't really expect the topical cream to work, to be honest. I thought something had to be ingested, [but]...it was a site-specific pain. And I didn't really think about that at the beginning of the study. You start numbing it up, you get the pain receptors used to this burning and eventually once they're used to the burning, they don't—your receptors aren't as active, it doesn't hurt as much. (11161, non-opioid group; responder)

Some patients described insufficient relief from non-opioid medication treatment.

I was hoping that I could get back some of the things that I lost like, because of my pain I had to quit my volunteer job at the food shelf. I was hoping I could get back to that, but so far that's not been the case. I was hoping I would be able to

go out for walks again, but it's been so painful that I've not been able to do that.

(11083, non-opioid group; responder)

Another patient described some improvement in pain, but not enough: "I made progress, but I'm still frustrated with the pain." (11677, non-opioid group; non-responder)

### Experiences with Pain Care Management

Participants in both study treatment groups described the value of the pain care management approach used in the SPACE trial. A number of patients from both study arms commented on the individualized treatment they received from the clinical pharmacist who managed their medication regimen.

*Interviewer:* What was the most important thing that you got from participating in SPACE?

*Patient:* Individual treatment. I mean, [the pharmacist] was great... And she listened to me. I mean, she wouldn't do anything I didn't want to do. She wouldn't coax me into any which way. I had to want to do it. It had to be my choice. (11788, non-opioid group; responder)

[The study pharmacist] was wonderful...It was nice to see her and...it calmed me down a little bit about worrying about taking [opioids] and being on them for year. (10987, opioid group; responder)

Of particular note, one participant attributed his improvement during the trial more to the support of the pharmacist than to the opioid medications he was prescribed. When asked if he thought his results would have been different if he had been in the non-opioid group, he responded, “I think if the physical or the verbal support with [the pharmacist] was the same, I don’t think there would’ve been a difference taking a bunch of Tylenol as opposed to the opioids.” (13103, opioid group; responder)

### Discussion

The goal of this qualitative follow-up study was to further understanding of SPACE trial results by elucidating participants’ expectations of and subjective experiences with the trial interventions. The primary result of the SPACE trial was that opioid therapy did not differ from non-opioid therapy for pain-related function. Notably, most patients in both treatment groups had improvement in function from baseline to 12-month follow-up. In addition, pain intensity and medication-related adverse symptom outcomes were significantly worse for opioids compared with non-opioids, but differences between groups were small.<sup>20</sup> Results of in-depth interviews with patients have several key implications for interpretation of the main SPACE trial results.

#### Beliefs about Opioid and Non-Opioid Medications

First, we found that many patients expressed strongly held beliefs about the relative effectiveness and risks of opioid and non-opioid medications and that some patients noted changes in these beliefs over time, based on experiences during the trial. Participants

frequently described beliefs that opioids were “stronger,” with one participant compellingly describing them as “serious medication” for “serious pain.” Some participants expressed fears of addiction or impairment. Others had concerns based on their past experiences with opioids, or those of friends or family. Interestingly, patients often expressed these concerns while indicating their belief in opioids as effective, powerful medications. These findings corroborate widespread perceptions of opioids as powerful “painkillers,” which is how they are commonly described by public health officials, consumer advocates, and journalists.<sup>2,3,8</sup> These qualitative findings are also consistent with quantitative pre-randomization perceptions of the two treatment arms in SPACE; overall, participants reported perceiving opioids as substantially more effective and somewhat less safe than non-opioid medications.<sup>21</sup>

Interviews also depicted how patients’ perspectives sometimes changed over time, as they gained experience with medications. Some patients in the opioid group expressed disappointment in the results of opioids, describing expectations for greater relief than they experienced or diminishing effectiveness as time went on. Likewise, some patients in the non-opioid group described surprise that non-opioids could work as well as they did. Current opioid prescribing guidelines recommend discussing patient expectations and establishing realistic goals for pain and function prior to initiating therapy.<sup>14</sup> Our findings support this approach.

Because patients and health care providers were not masked to SPACE treatment assignment, expectations about opioid and non-opioid medication interventions may have influenced the primary patient-reported outcomes in the trial. If present, bias due to positive expectations about opioid effectiveness would likely favor the opioid treatment group.<sup>26</sup> Our qualitative results illuminate how preconceptions may have been at least partially countered by



experience over the course of the trial; this phenomenon has been previously described and could hypothetically ameliorate a biasing effect of expectations on reported outcomes over long-term follow-up.<sup>36</sup>

#### Experiences with Treatment Effectiveness

A second important implication for the SPACE main trial results is that participants described a wide variety of experiences with treatment effectiveness, regardless of their treatment group assignment (i.e., opioid or non-opioid) and whether they met the threshold for responder status (i.e., 30% improvement in BPI interference). Some patients who were considered non-responders described improvement in pain and physical function, whereas some of those considered to be responders described inadequate improvement. Because pain, functional impairment, and well-being are inherently subjective concepts, we do not find it surprising that objective and subjective measures of treatment outcomes were incompletely aligned. Furthermore, patients who met the 30% improvement threshold may have been disappointed if this was less improvement than they had anticipated. The mean pre-randomization self-reported rating of “likely personal improvement” during the study was 7.5 on a scale of 0 “no improvement” to 10 “a great deal of improvement.” Although we did not ask patients in this study to quantify acceptable or desirable levels of improvement, prior research has demonstrated that patients’ expectations for the magnitude of improvement are sometimes higher than expected benefits of existing therapies.<sup>33, 35</sup> Interviews also suggested that pain relief alone was not sufficient for some patients to consider medications effective. Several patients indicated they had less pain while taking opioids, but still chose to discontinue them because of concerns about addiction, undesirable side effects, or interference with

function and quality of life. These findings highlight the clinical importance of assessing more than just pain intensity when evaluating effectiveness of prescribed pain treatments. While pain intensity scores provide an important metric by which to gauge a patient's improvement, it is also important to engage patients in a discussion of what such scores mean in the context of their own lives and experiences.

#### The SPACE Pharmacist Care Model

Finally, we found a strong theme of satisfaction with the pain care model—personalized medication management delivered by a clinical pharmacist—used in both arms of the SPACE trial. Many patients described this personalized contact as just as important as the medications they were taking. The views of these SPACE participants are consistent with research indicating that effective patient-provider communication is inextricably linked to important, measurable outcomes, including patient satisfaction, adherence to treatment, and relief of symptoms.<sup>5, 6, 15, 17, 37</sup>

The importance of a caring clinician providing tailored advice and support has been corroborated in other studies of patients with chronic pain. Participants in a randomized trial consisting of medication management, brief cognitive behavioral therapy, and pain self-management education delivered by a nurse care manager identified the nurse as key to successful pain management, fulfilling three specific roles: helping patients find what works for their pain, holding patients accountable for their pain management, and motivating and providing emotional support.<sup>29</sup> In another study involving pain self-management and medication management for patients with chronic pain and depression, the nurse care manager was similarly identified as critical to successful pain management.<sup>30</sup> Patients in both of these

studies emphasized that the self-management, medication management, or other clinical care provided were not the only “active ingredient” in the minds of participants, but that the clinicians delivering the interventions played an integral role as well. In the same way, the personalized care and measurement-based medication management from the pharmacist care manager is likely to be at least partially responsible for the clinical response rates in the SPACE study. Exposing both arms to this care management approach, with similar contact rates and pharmacist time in both arms, effectively controlled for communication and therapeutic alliance factors that could bias findings if one group received more intensive contact than the other.

This study is limited in that all participants were VA patients in one metropolitan area who agreed to enroll in a randomized controlled trial. As a result, qualitative results might not be applicable to other patients with chronic pain taking medications in a non-research environment.<sup>28, 39</sup> In addition, because patients were interviewed at the same medical center where they received the SPACE intervention, it is possible that they felt more comfortable reporting only positive experiences. However, because some were critical of the intervention, and because participants provided rich, detailed descriptions of their experiences with the intervention, rather than speaking in generalities, we believe that such a social desirability bias is unlikely.

### Conclusions

The SPACE trial, the first randomized controlled trial to compare long-term outcomes of opioid versus non-opioid medications for chronic pain, found no advantage of opioids over 12 months. Moreover, opioids caused significantly more medication-related adverse symptoms

than non-opioid medications.<sup>20</sup> The current qualitative study provides important insights that help to enhance our understanding of the SPACE trial results. First, the role of expectations played a prominent role in patients' experiences with SPACE. These included expectations that opioids are strong, powerful medications, and expectations of pain improvement that may or may not have matched the study definition of a clinically-important response (i.e., 30% decrease in BPI interference). Together these expectations seemed to shape patients' experiences with and responses to the intervention, leading to results that surprised some patients, while others perceived little change. In addition to the role of expectation, patients expressed a high degree of satisfaction with the personalized pharmacist care model that patients in both study arms experienced. The presence of a caring, responsive clinician seeking to improve patients' pain may in part help to explain why, although opioids showed no advantage over non-opioids, patients in both study arms improved.

## References

1. 2010 National Survey on Drug Use and Health: Summary of National Findings. Vol HHS Publication No. (SMA) 11-4658, Substance Abuse and Mental Health Services Administration, 2011
2. 5 surprising facts on prescription painkillers: Why you should be concerned about opioids--the most prescribed drugs in America. Available at: <https://www.consumerreports.org/cro/2014/01/5-surprising-things-you-need-to-know-about-prescription-painkillers/index.html>. Accessed February 21, 2018
3. Board, Editorial, New York Times, Putting more controls on painkillers. In: New York Times, New York, NY, October 29, 2013, <http://www.nytimes.com/2013/10/30/opinion/putting-more-controls-on-painkillers.html>. Accessed February 21, 2018
4. Borkan J: Immersion/crystallization. In: Doing qualitative research.(Crabtree BF, M.W., Ed.), Sage, Thousand Oaks, CA, 1999, pp. 179-194
5. Brown J, Stewart M, Ryan B: Outcomes of patient-provider interaction. In: Handbook of Health Communication. (Thompson, T., Dorsey, A., Miller, K., Parrott, R., Eds.), Erlbaum, Mahwah, NJ, 2003, pp. 141-161
6. Buse DC, Lipton RB. Facilitating communication with patients for improved migraine outcomes. *Curr Pain Headache Rep.* 12:230-236, 2008
7. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain.* 109:514-519, 2004
8. CDC, Prescription Painkiller Overdoses in the US, <https://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html>2011, Accessed February 21, 2018

9. Charmaz K: Constructing grounded theory: a practical guide through qualitative analysis, Sage, Thousand Oaks, CA, 2006
10. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 162:276-286, 2015
11. Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. 2 ed., Thousand Oaks, CA, Sage, 2011
12. Davies D, Dodd J. Qualitative research and the question of rigor. *Qual Health Res.* 12:279-289, 2002
13. Denzin N, Lincoln Y: Introduction: the discipline and practice of qualitative research. In: Strategies of qualitative inquiry.(Denzin NK, L.Y., Ed.), Sage, Thousand Oaks, CA, 2003, pp. 1-45.
14. Dowell D, Haegerich T, Chou R: CDC guideline for prescribing opioids for chronic pain--United States, 2016. *Morbidity and Mortality Weekly Report.* 2016; 65:1-49.
15. Dutta-Bergman MJ. The relation between health-orientation, provider-patient communication, and satisfaction: An individual-difference approach. *Health Communication.* 18:291-303, 2005
16. Education Committee: The National Academies Collection: Reports funded by National Institutes of Health. In: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. The National Academies Collection: Reports funded by National Institutes of Health, National Academies Press (US), National Academy of Sciences., Washington (DC), 2011.

17. Fraser P, Freeman TR, Gillis GE, Goldsmith WO, Grace AN. Predictors of outcome in headache patients presenting to family physicians: a one year prospective study. *Headache*. 26:285-294, 1986
18. George SZ, Robinson ME. Preference, expectation, and satisfaction in a clinical trial of behavioral interventions for acute and sub-acute low back pain. *J Pain*. 11:1074-1082, 2010
19. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain*. 20:309-318, 2004
20. Krebs E, Gravely A, Nugent S, Jensen A, DeRonne B, Goldsmith E, Kroenke K, Bair M, Noorbaloochi S. Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA*. 319:872-8882, 2018.
21. Krebs EE, Jensen AC, Nugent S, DeRonne B, Rutks I, Leverty D, Gravely A, Noorbaloochi S, Bair MJ, Kroenke K. Design, recruitment outcomes, and sample characteristics of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial. *Contemporary clinical trials*. 62:130-139, 2017
22. Kroenke K, Krebs EE, Wu J, Yu Z, Chumbler NR, Bair MJ. Telecare collaborative management of chronic pain in primary care: a randomized clinical trial. *JAMA*. 312:240-248, 2014
23. Kuehn BM. CDC: Major disparities in opioid prescribing among states: some states crack down on excess prescribing. *JAMA*. 312:684-686, 2014
24. Kuzel AJ: Sampling in qualitative inquiry. In: *Doing Qualitative Research*.(Crabtree, B.F., Miller, W.L., Eds.), Sage, Thousand Oaks, CA, 1999, pp. 33-45.
25. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012. *Am J Prev Med*. 49:409-413, 2015

26. Linde K, Witt CM, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B, Willich SN, Melchart D. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain*. 128:264-271, 2007
27. Lindlof TR, Taylor BC: *Qualitative Communication Research Methods*, Thousand Oaks, CA, Sage, 2011.
28. Malterud K. Qualitative research: standards, challenges, and guidelines. *The Lancet*. 358:483-488, 2001
29. Matthias M, Miech E, Myers L, Sargent C, Bair M. An expanded view of self-management: patients' experiences with self-management education and support in an intervention for chronic musculoskeletal pain. *Pain Med*. 13:1018-1028, 2012
30. Matthias MS, Bair MJ, Nyland KA, Huffman MA, Stubbs DL, Damush TM, Kroenke K. Self-management support and communication from nurse care managers compared with primary care physicians: a focus group study of patients with chronic musculoskeletal pain. *Pain Manag Nurs*. 11:26-34, 2010
31. Matthias MS, Miech EJ, Myers LJ, Sargent C, Bair MJ. "There's more to this pain than just pain": how patients' understanding of pain evolved during a randomized controlled trial for chronic pain. *J Pain*. 13:571-578, 2012
32. Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. *CMAJ*. 165:174-179, 2001
33. O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchison JW, Price DD, Robinson ME. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Med*. 11:6-15, 2010



34. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 15:618-627, 2006
35. Robinson ME, Brown JL, George SZ, Edwards PS, Atchison JW, Hirsh AT, Waxenberg LB, Wittmer V, Fillingim RB. Multidimensional success criteria and expectations for treatment of chronic pain: the patient perspective. *Pain Med*. 6:336-345, 2005
36. Sherman KJ, Cherkin DC, Ichikawa L, Avins AL, Delaney K, Barlow WE, Khalsa PS, Deyo RA. Treatment Expectations and Preferences as Predictors of Outcome of Acupuncture for Chronic Back Pain. *Spine*. 35:1471-1477, 2010
37. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, Jordan J. The impact of patient-centered care on outcomes. *J Fam Practice*. 49:796-804, 2000
38. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 5:133-137, 2004
39. Tracy SJ. Qualitative quality: Eight “big-tent” criteria for excellent qualitative research. *Qualitative Inquiry*. 16:837-851, 2010
40. Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci*. 25:7754-7762, 2005