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Buprenorphine for pain management vs. chronic hydrocodone-acetaminophen therapy when comorbidities increase the risk of opioid-related side effects

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ABSTRACT A clinical decision report using:

Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther.* 2010;32(5):844-860. <https://doi.org/10.1016/j.clinthera.2010.04.018>

for a patient on long-term opioid therapy with high risk factors for adverse effects.

Keywords: *chronic opioid use, opioid therapy, chronic pain, buprenorphine*

Clinical-Social Context

Daniel Porch (pseudonym) is a 62-year-old African American man with a long-standing history of spinal stenosis following a lumbar decompression 23 years ago who presented to the clinic following a history of multiple falls at home in the past 2 months. He is unable to ambulate independently and uses a walker and wheelchair. Due to the extent of his pain, he has been on chronic opioid therapy with hydrocodone-acetaminophen, which he uses every day. Additionally, Mr. Porch has significant medical history of end-stage renal disease on hemodialysis, chronic obstructive pulmonary disease, and congestive heart failure. He is a current every-day cigarette smoker with marijuana use 2-3 times a week. Mr. Porch requires transportation assistance, which sometimes makes it difficult to arrive to appointments due to availability. During the visit, Mr. Porch did not report any neurological or musculoskeletal symptoms. He stated that he recently ran out of his opioid medication and that his pain has been uncontrolled. His request for a refill was declined by his pain specialist as the clinic practiced non-opioid methods to managing pain. He had tried physical therapy, steroid injections, and other medications, all of which did not relieve the pain. He appeared frustrated as he stated that opioids were the only source of relief. The frustration could have been added by the fact that opioid usage for pain control has a stigma associated with it. Garcia et al. discussed a case about a patient who refused a treatment due to the stigma associated with it.¹ They talked about information management where patients spend time and energy in hiding stigmatizing attributes. In Mr. Porch's case, his desire to try alternative treatments to relieve the pain, running out of opioid medications, and going to a non-opioid pain management clinic might speak to his desire to hide his use of opioids for pain management. Due to the futile efforts of other pain management options, he presented to our clinic seeking options for his pain

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management.² Although he expressed desire to continue with his hydrocodone-acetaminophen therapy, there were risks of its continued use given his COPD, ESRD, and heart failure. After further discussion regarding the high risks of adverse effects such as respiratory depression given his risk for respiratory decompensation with his comorbidities, he expressed that he would be open to trying alternative methods except for surgery to his current regimen as long as his pain was controlled. Dahan et al. showed that partial opioid agonists, such as buprenorphine, has a limit on the respiratory depression they cause, but not on pain control with increasing dose.³ Therefore, the alternative methods for treatment included anything, including other opioid medications (with a preference for partial agonists), besides treatment with hydrocodone-acetaminophen alone.

Clinical Question

What is an effective alternative to chronic oral full agonist opioid therapy in a patient with a history of spinal stenosis with moderate pain and comorbidities that increase the risk of adverse effects from full opioid agonist therapy?

Research Article

Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther.* 2010;32(5):844-860. <https://doi.org/10.1016/j.clinthera.2010.04.018>⁴

Description of Related Literature

An UpToDate search regarding “long-term opioid use” and “chronic pain” was performed to look at pain management recommendations with opioids in patients with chronic pain. Typically, patients are started on an immediate-release/short-acting opioid with initial opioid therapy and converted to an extended-release/long-acting opioid if necessary.⁵ Buprenorphine can also be used for chronic pain management, especially for patients who have been on chronic opioid therapy.⁵ With the consideration of the patient’s advanced kidney disease, current opioid treatments should be kept to short-acting opioids due to decreased clearance.⁶

To look more into alternatives to hydrocodone-acetaminophen, a search on PubMed was conducted using search terms “opioid alternative” and “chronic back pain”. Searches were filtered by clinical trials and randomized controlled trials, yielding 17 results. 11 studies were excluded because they did not address the clinical question, or they did not fit the clinical context for Mr. Porch.

Of alternatives, other opioids were most studied as an alternative to control back pain. Simpson Jr et al. studied transdermal fentanyl as an alternative to oral opioids.⁷ 50 patients with chronic low back pain and each patient was maintained on transdermal fentanyl for one month. They then resumed oral opioid therapy after the one-month trial and patients were assessed for pain relief and disability. Results of the study showed significant improvement in pain relief and disability on transdermal fentanyl compared to oral opioids. However, some patients experienced more frequent headaches and lightheadedness on the transdermal fentanyl patch. This study is not suitable for Clinical Appraisal because fentanyl is a highly potent opioid that may not be suitable for Mr. Porch given his comorbid conditions.

Mitra et al. compared buprenorphine to fentanyl transdermal patches in their efficacies at treating chronic pain.⁸ 46 opioid-naive adults were recruited and assigned randomly to buprenorphine or fentanyl treatment. Both groups reported pain relief in the initial 6 months with 50% being in the buprenorphine group and 43% in the fentanyl group. However, 30% of the patients discontinued treatment prior to the end of the study. Buprenorphine patients also experienced relatively fewer side effects. This study was less relevant to Mr. Porch as he has already been on opioid therapy for almost 2 years. In addition, Mr. Porch had never been on transdermal fentanyl patches; therefore, this study was not suitable for Clinical Appraisal.

One study did study low-dose amitriptyline to control for back pain. Urquhart et al. performed a double-blind, randomized clinical trial comparing low-dose amitriptyline with benzotropine mesylate, an active comparator.⁹ 146 randomized patients were recruited, and follow-up was performed at 3 and 6 months. There was no significant improvement at 6 months in both pain and disability though disability improved at 3 months in the amitriptyline group. This did not seem to be an appropriate alternative for Mr. Porch



as there is not significant evidence that this may relieve his pain. However, since Mr. Porch has significant disability with requiring transportation to get from place to place, this study could be looked at in addressing his disability, but it is unrelated to the Clinical Question.

Gordon et al. was chosen as buprenorphine appears to be the most suitable for Mr. Porch. In this study, the safety and efficacy of transdermal buprenorphine was studied in a randomized, double-blind, placebo-controlled crossover study.⁴ 78 patients who were already taking oral opioid therapy for back pain were recruited and randomized to buprenorphine or placebo patches. Buprenorphine was effective in pain management throughout the duration of the 8-week trial, which also sustained in the 6 month, open-label extension. This study is the best match for addressing the Clinical Question because it offers the best alternative to oral opioids in patients with back pain. This article was chosen because it offers the most suitable alternative to controlling for Mr. Porch's back pain, while at the same time, avoiding full agonist opioids for therapy. Based on the SORT criteria, the Strength of Recommendation for this study is Level 2.¹⁰

Critical Appraisal

Gordon et al. studied the safety and efficacy of buprenorphine as a transdermal patch.⁴ Prior studies with transdermal buprenorphine have shown decreased pain intensity in adult patients with chronic back pain of moderate or greater severity. This study specifically studied a higher initial dose (10 ug/h) and higher maximum dose (40 ug/h) of buprenorphine throughout an 8-week trial in patients who were currently on opioid analgesic tablets.

Inclusion criteria for patients included adults who had chronic back pain of low to moderate pain intensity for >3 months who were currently taking 1 or more tablets of opioids. Patients with allergies to acetaminophen or opioids were excluded. Additionally, any patient with abnormal liver enzymes, electrolyte imbalances, organ dysfunction, head injury or seizures, chronic obstructive pulmonary disease, asthma, respiratory depression, or cardiovascular disease was excluded. 78 patients were selected for the study.

The study was a randomized, double-blind, placebo-controlled crossover study. Patients underwent a 2-to-7 day washout of opioids before being randomized to receive buprenorphine at 10 ug/h or matching placebo patches. A block-randomization pattern was used and a randomization code was generated. Investigators were also blinded to treatment allocation. Patches were worn for 6-8 days. The initial dose was titrated weekly to 20ug/h up to a maximum of 40 ug/h. Acetaminophen (325 mg) was provided as needed for unmanageable pain. Patients were given 4 weeks of assigned treatment, and then crossed over to alternative treatment for 4 weeks. If patients completed the full 8-week trial, they were eligible to receive buprenorphine in a 6-month, open-label extension.

Assessment of pain was done through patient self-report twice daily, once at 8 AM and once at 8 PM using an unmarked 100-mm visual analog scale, as well as through a 5-point ordinal scale. Patients also completed the Pain and Sleep Questionnaire, Pain Disability Index, Quebec Back Pain Disability Scale, and 36-item Short Form Health Survey to measure secondary outcomes.

Baseline visual analog scale pain score was 60.9 and baseline 5-point ordinal scale was 2.6. Patients receiving buprenorphine showed a significantly lower score on the visual analog scale (45.3) compared to patients receiving placebo (53.1) with a p-value of 0.022. On the 5-point ordinal scale, pain intensity was also significantly decreased in patients receiving buprenorphine (1.9) versus placebo (2.2) with a p-value of 0.044. Pain and Sleep scores were also significantly lower in the buprenorphine group compared to placebo. However, all other measurements showed significant improvement from baseline in both groups. Patients who received buprenorphine reported more adverse effects, with the most common being nausea, dizziness, and pruritus. At the end, 49 patients completed the full 8-week trial, and 27 completed the open-label extension study. Of those 27 patients, pain scores continued to be improved.

Limitations of this study included withdrawals due to adverse effects experienced by patients. 19 patients withdrew in the buprenorphine group compared to 10 in the placebo study. However, the authors state that this is a similar rate of withdrawal compared to other studies of opioids. Additionally, the sample size was relatively smaller compared to similar studies, but the authors stated the study was adequately powered as it was consistent with power calculations for crossover studies. Finally, this study was funded by Purdue Pharma and some authors were employed by the company at the time of the study, which may have led to bias.



Clinical Application

Dahan et al. demonstrated that partial opioid agonists, like buprenorphine, exhibit a ceiling effect for respiratory depression but not for analgesia as the dose increases.³ Mr. Porch came to the clinic looking for sufficient pain management. Given his comorbidities, he is at high risk of opioid adverse effects from full agonist opioids, but since he has been on opioids for over a year, he has developed tolerance to his current regimen. As Gordon et al. had demonstrated, buprenorphine, a partial opioid agonist, may be a suitable alternative.⁴ Although Mr. Porch met the exclusion criteria for the study, the limits on respiratory depression, which was the main concern with continued hydromorphone therapy, with buprenorphine justified applying this study to him. Mr. Porch was recommended that he start buprenorphine, though he should also be given naloxone to prevent risk of overdose. Mr. Porch was recommended that he also continue seeing his pain specialist to consider weaning off opioids in the long-term.

New Knowledge Related to Clinical Decision Science

Pain management is often difficult and subjective. Providers should use their clinical judgment as well as take a comprehensive medical history to choose the best therapy for their patients. Often, patients have many comorbidities with many prescriptions that may affect their pain. It's important for providers to focus on modifiable risk factors and continue to educate patients, but also pay attention to other medications that patients may be on to avoid adverse interactions. In addition, for patients with disability who require transportation, treatment should be tailored to providing long term care without frequent visits to the office. Therefore, patients with medical comorbidities and difficulties with transportation are more willing to attempt using transdermal buprenorphine to minimize opioid use in chronic pain settings.

Social prescribing refers to changing the patient's social context to address medical care needs. In Mr. Porch's care, he attends dialysis three times weekly. Given that type of schedule, it is unrealistic to add further transportation burdens to his care. Yet, prescribing opioids or any other pain management requires a trusting relationship. This case highlights the opportunity to perform video visits for pain management while the patient is in dialysis and under the direct care of medical professionals. It would require the cooperation of multiple providers that are currently siloed, but might reimagine what optimum care for Mr. Porch would look like.

Conflict Of Interest Statement

The authors declare no conflicts of interest.

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