

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association Between Initial Opioid Prescription Diagnosis Type and Subsequent Chronic Prescription Opioid Use in Rhode Island: A Population-Based Cohort Study
<b>AUTHORS</b>	Hallowell, Benjamin; Chambers, Laura C.; Barre, Luke; Diao, Nancy; Onyejekwe, Collette; Banks, Alexandra; Bratberg, Jeffery; Weidele, Heidi; Viner-Brown, Samara; McDonald, James

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Franklin, Gary University of Washington, School of Public Health & Community Medicine
<b>REVIEW RETURNED</b>	19-Apr-2021

<b>GENERAL COMMENTS</b>	<p>This is a good study on an understudied question-does the incidence/prevalence of persistent opioid use differ by diagnosis and other key characteristics? While the overall manuscript is well reasoned, it could be improved by addressing the following issues:</p> <p>Major</p> <ol style="list-style-type: none"> <li>1. The biggest issue to address here is the conservative definition of persistent opioid use, resulting in quite low proportions of patients defined as receiving persistent opioids. WA state has published definitional metrics that were created with strategic policies and practicality in mind. Please see "Fulton-Kehoe et al, Surveillance of opioid prescribing as a public health intervention: Washington state Bree opioid metrics. J Public Health Manag Prac 2020; 26: 206-213", and <a href="https://www.qualityhealth.org/bree/wp-content/uploads/sites/8/2018/06/Bree-Opioid-Prescribing-Metrics-Final-2017.pdf">https://www.qualityhealth.org/bree/wp-content/uploads/sites/8/2018/06/Bree-Opioid-Prescribing-Metrics-Final-2017.pdf</a> These metrics are now part of the WA DOH reporting dashboard, and are being used by select health plans. The definition of new chronic use is 60 days use in any quarter, preceded by little/no use in the prior quarter. No one would argue that 60 days of opioids in a quarter is only intermittent use. You've gone to a lot of trouble in doing this study, and I would recommend it will have larger impact by using a somewhat less conservative definition of persistent opioid use.</li> <li>2. The authors could do a somewhat better job of more specific recommendations for policy improvement, or of guideline development by specific professional societies. For example, the peri-operative opioid prescribing issue for musculoskeletal procedures associated with adverse events is mentioned but could be expanded upon. Similarly, I would breakdown the neurologic category into 2-3 subgroups if possible, such as headache (not broken down by types) and painful neuropathy, likely mostly related to diabetes. This is important b/c tramadol is likely overused in the painful neuropathy group and opioids should</li> </ol>
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	<p>probably almost never be used for headaches. As the authors suggest, these are the types of examples that such analyses could lead to important policy and guideline developments.</p> <p>3. The prescriber type analysis is interesting. However, for dentists, if the vast majority of dental opioid prescribing is for extractions, maybe dental diagnostic information isn't that critical.</p> <p>4. P9 lines 253-255-yes it's possible that legacy patients came from a different diagnostic mix, but that's not likely. Are there any references to support this?</p> <p>Minor</p> <p>The language in the Table headers should be consistent: Initial opioids, initial opioid initiates, opioid initiates</p>
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<b>REVIEWER</b>	Zhang, Yongkang Cornell University Joan and Sanford I Weill Medical College
<b>REVIEW RETURNED</b>	22-Apr-2021

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this interesting paper. In this study, the authors examined the association between the diagnosis of the initial opioid prescription and subsequent persistent opioid use, using a comprehensive dataset from Rhode Island. They found certain diagnoses, such as musculoskeletal system and connective tissue, are associated with increased risk of persistent opioid use. I found this paper important and of great policy implications. My major comments include:</p> <p>(1) Outcome: this paper focused on the subsequent persistent prescription opioid use, defined as at least 90 days of prescription opioid use without a gap of more than seven days starting from the fill date of the initial opioid prescription. As the authors explained in the discussion section (the 2<sup>nd</sup> paragraph in page 9), the incidence of the outcome is pretty low in this study (0.7%), and one of the reasons is that the persistent opioid use is defined as 90-day use without &gt;7 day gap immediately following the initial opioid prescription, if my reading is correct.</p> <p>I feel like this is different from many previous studies, which usually specified a follow-up period (e.g., 12-month or 18-month after the initial opioid prescription) and identified the persistent use or high-risk use during this period. Some examples I encountered include PMC6258623 and <a href="https://bmjopen.bmj.com/content/9/7/e027203">https://bmjopen.bmj.com/content/9/7/e027203</a>. I don't think what they did is wrong, but some patients may not have instant use after the initial prescription. I wonder how the definition used by this study contributes to the field, as compared with other studies.</p> <p>(2) Exposure: the independent variable of interest is the initial opioid prescription, defined as either</p> <p>a. the patient's first opioid prescription or b. an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. I wonder if there is a look-back period to</p>
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	<p>ensure it was the first opioid prescription, such as no any opioid prescription 6 months before it?</p> <p>(3) Potential confounders: the authors controlled for age and sex in the logistic regression. I feel like there are many other potential confounders, including insurance type, the clinical setting of the initial prescription, and socioeconomic status (e.g., individual patient level or neighborhood level). If they decided not to control for these variables, an explanation is needed.</p> <p>(4) Table 4 presented the results from the logistic regression. It compared the likelihood of having persistent opioid prescription between seven diagnosis types with Other. However, in the methods section, they mentioned that they classified all ICD-10 codes into 20 major groups. Why only eight groups in table 4? The discussion section is thoughtful. I have no other comments.</p>
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<b>REVIEWER</b>	Jani, Meghna The University of Manchester, ARUK Centre for Epidemiology
<b>REVIEW RETURNED</b>	03-May-2021

<b>GENERAL COMMENTS</b>	<p>The aim of this study is to identify initial diagnoses/ indications associated with persistent opioid use. The majority of administrative databases/ EHRs do not record indications for opioid use and this specific datsource/ Prescription Drug Monitoring programme allows a unique opportunity to evaluate this. For that reason, this study is an important piece of work. Over a third of patients have a missing diagnosis code (36%), which unfortunately leads to a lot of missing outcome data. The authors do discuss this as a limitation of their work. Some additional suggestions below:</p> <ul style="list-style-type: none"> <li>- The proportion of persistent use seems rather small. How does the figure in the study compare to others US or international studies (bearing in mind the different definitions used widely and the stricter definition here). Suggest these figures are quoted in the discussion.</li> <li>- Suggest removal of p values in table 1. These are likely to be significant given large numbers compared.</li> <li>-An interesting result is that neoplasms (cancer), is a less frequent indication for initial opioid use in comparison to diseases other systems (2.3% overall, Table 2). Is there a reason why this proportion is so modest specific to this dataset? If not, important to highlight in the discussion that pain due to cancer is a far less common initial diagnosis for opioids and how this compares to other work.</li> <li>- Are the higher odds of persistent use in MSK patients/ nervous system disease patients likely because they simply are the most frequent groups of patients prescribed opioids? Are the authors able to discern any patterns with individual diagnoses that may be of interest?</li> <li>- In Table 4, whilst higher odds of persistent use are demonstrated with several groups of conditions, the confidence intervals seem wide. The numbers of patients for each system (who developed persistent use) would be useful to record here to gain an idea of numbers</li> </ul>
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	- What are the 3-4 most frequent diagnoses within each system type (Table 4)? Whilst the broad systems associated with higher ORs are of general interest, from a practical/ public health standpoint specific diagnoses information is likely to be most valuable to prescribers of opioids and when developing future interventions. Table 5 gives information about individual ICD-10 codes but not specific conditions (which may have several ICD-10 codes for instance).
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### VERSION 1 – AUTHOR RESPONSE

This is a good study on an understudied question-does the incidence/prevalence of persistent opioid use differ by diagnosis and other key characteristics? While the overall manuscript is well reasoned, it could be improved by addressing the following issues:

RESPONSE: We appreciate your positive comments!

Major

The biggest issue to address here is the conservative definition of persistent opioid use, resulting in quite low proportions of patients defined as receiving persistent opioids. WA state has published definitional metrics that were created with strategic policies and practicality in mind. Please see "Fulton-Kehoe et al, Surveillance of opioid prescribing as a public health intervention: Washington state Bree opioid metrics. J Public Health Manag Prac 2020; 26: 206-213", and [https://urldefense.com/v3/\\_\\_https://www.qualityhealth.org/bree/wp-content/uploads/sites/8/2018/06/Bree-Opioid-Prescribing-Metrics-Final-2017.pdf\\_\\_;!!KKphUJtCzQ!bDwxpRvwMRBS0FgMZkN2NUmjsHrXSL9XvJM788g1\\_lkFQBSFYVLhjE pHploXcSbtjq9Ql447Bw\\$ \[qualityhealth\[.\]org\]](https://urldefense.com/v3/__https://www.qualityhealth.org/bree/wp-content/uploads/sites/8/2018/06/Bree-Opioid-Prescribing-Metrics-Final-2017.pdf__;!!KKphUJtCzQ!bDwxpRvwMRBS0FgMZkN2NUmjsHrXSL9XvJM788g1_lkFQBSFYVLhjE pHploXcSbtjq9Ql447Bw$ [qualityhealth[.]org]) These metrics are now part of the WA DOH reporting dashboard, and are being used by select health plans. The definition of new chronic use is 60 days use in any quarter, preceded by little/no use in the prior quarter. No one would argue that 60 days of opioids in a quarter is only intermittent use. You've gone to a lot of trouble in doing this study, and I would recommend it will have larger impact by using a somewhat less conservative definition of persistent opioid use.

RESPONSE: Thank you for your feedback. We agree that our definition of persistent opioid use was very conservative and that a somewhat less conservative definition may improve the impact of our analysis. We appreciate you sharing your definition with us and have revised our manuscript to utilize your definition. We have updated all findings accordingly. We now define our primary outcome as follows, including a reference to your paper:

“Our primary outcome was subsequent chronic prescription opioid use, defined as  $\geq 60$  days’ supply of opioids dispensed in the 90 days following the fill date of an individual’s initial opioid prescription (including the days’ supply of the initial prescription).<sup>21</sup>”

2. The authors could do a somewhat better job of more specific recommendations for policy improvement, or of guideline development by specific professional societies. For example, the peri-operative opioid prescribing issue for musculoskeletal procedures associated with adverse events is mentioned but could be expanded upon. Similarly, I would breakdown the neurologic category into 2-3 subgroups if possible, such as headache (not broken down by types) and painful neuropathy, likely

mostly related to diabetes. This is important b/c tramadol is likely overused in the painful neuropathy group and opioids should probably almost never be used for headaches. As the authors suggest, these are the types of examples that such analyses could lead to important policy and guideline developments.

RESPONSE: Thank you for these suggestions. We agree that certain diagnoses or groups of diagnoses can best be targeted with interventions based on particularly high risk of chronic opioid use and more appropriate alternative therapies. We have edited our manuscript to highlight the following specific diagnoses: intraoperative/postprocedural complications and disorders of the musculoskeletal system, polyosteoarthritis, rheumatoid arthritis, and spondylosis. We selected these diagnoses due to the particularly high risk of chronic opioid use and availability of more effective management approaches.

Specifically, we have edited the discussion as follows:

“A primary benefit of categorizing diagnosis type through ICD-10 codes in this population-based study is the ability to systematically review opioid prescribing patterns among patients with different diseases or sources of pain. Previous studies have shown the dangers of inappropriate prescribing, but effectively targeting interventions and prescribing guidelines to minimize risk of chronic opioid use while appropriately managing pain is challenging.<sup>17</sup> Our study identified a few diagnosis types on initial opioid prescriptions that are associated with greater odds of subsequent chronic prescription opioid use in Rhode Island, which allows our state to prioritize interventions that target specific practice areas. For instance, we found that diseases of the musculoskeletal system and connective tissue were highly associated with subsequent chronic prescription opioid use, and initial opioid prescriptions with ICD-10 codes for polyosteoarthritis, rheumatoid arthritis, spondylosis, and intraoperative/postprocedural complications and disorders of the musculoskeletal system had a particularly high percentage of patients develop chronic use after initiation. Given that many patients with musculoskeletal pain can improve over time independent of treatment, prior work has suggested that non-pharmacological treatments be utilized first (e.g., physical therapy, acupuncture, massages), followed by or with anti-inflammatory medications, and if patients are still experiencing pain, prescription opioids.<sup>18,19</sup> Importantly, as the pathophysiology of musculoskeletal diseases is inflammatory, a prescription opioid to block pain is not clinically appropriate, and if pharmacological therapy is necessary, anti-inflammatory medications may be more efficacious than opioids.<sup>20</sup> This is true for diagnoses of polyosteoarthritis, rheumatoid arthritis, and spondylosis, which are generally inflammatory in nature, and depending on the diagnosis standard treatment guidelines recommend treatment with non-steroidal anti-inflammatory drugs, corticosteroids, muscle relaxants, steroids, disease-modifying antirheumatic drugs, biologics, anti-seizure medications, warming therapy, exercise, and/or antidepressants rather than opioid pain management.<sup>22</sup> By focusing interventions and prescribing guidelines on specific types of diagnoses that carry a high risk of chronic opioid use and benefit equally or more for alternative management approaches, states and health care organizations may efficiently decrease inappropriate opioid prescribing while improving the quality of patient care. Our study suggests that interventions focused on appropriate management of musculoskeletal conditions, including polyosteoarthritis, rheumatoid arthritis, and spondylosis, may be particularly beneficial given the overall association with chronic use and the high percentage of patients who develop chronic use after an initial opioid prescription for one of these diagnoses.”

Unfortunately, we are not able to create subgroups of diagnoses within the neurologic category. The level of specificity in the ICD-10 codes reported to the Rhode Island PDMP varies greatly across prescriptions, making it very difficult to group them into specific diagnoses. We initially attempted to group ICD-10 codes in this way but were concerned that the resulting information would not be informative because many ICD-10 codes were too broad to be classified with that level of specificity

and omitting the many broad ICD-10 codes from our classifications would likely introduce bias into our results.

Because RI does not have an all drug PDMP, another approach we are considering is utilizing Medicaid medical records for these diagnoses to evaluate if treatment is being escalated appropriately (non-pharmacological, non-inflammatory medications, and then opioids) or if opioids are being prescribed as a first response.

3. The prescriber type analysis is interesting. However, for dentists, if the vast majority of dental opioid prescribing is for extractions, maybe dental diagnostic information isn't that critical.

RESPONSE: Thank you for this comment. We hypothesize that most opioid prescribing by dental professionals in Rhode Island is probably for surgical procedures. Studies using data from 2010-2015 suggest that roughly two of every three opioid-associated dental visits were "invasive" or "surgical" visits; however, the remaining one third of opioid-associated visits were non-invasive or non-surgical visits [Gupta N et al., J Am Dent Assoc 2018; Obadan-Udoh E et al., J Am Dent Assoc 2019]. We also expect that this may have changed over time based on our analyses of opioid prescribing by dental professionals from 2017-2019. Nonetheless, we would like to be able to confirm the diagnoses associated with opioid prescriptions by dental professionals in our PDMP data and explore which diagnoses are associated with opioid prescriptions provided for non-post-operative diagnoses. We are working with prescribers, including dental professionals, and pharmacies to improve the reporting of ICD-10 codes to the Rhode Island PDMP.

4. P9 lines 253-255-yes it's possible that legacy patients came from a different diagnostic mix, but that's not likely. Are there any references to support this?

RESPONSE: Thank you for raising this point. Our concern that legacy patients may have come from a different diagnostic mix stems from evidence of substantial changes in opioid prescribing patterns over the past five years in Rhode Island. For example, the number of unique people receiving new opioid prescriptions decreased by 38% from Quarter 1 of 2017 (January-March, n=41,820) to Quarter 1 of 2021 (n=26,025). Moreover, the number of prescriptions for high-dose opioids decreased by 47% during this same period from 20,511 in Quarter 1 of 2017 to 10,804 in Quarter 1 of 2021. Additional data on opioid prescribing trends in Rhode Island are available at <https://preventoverdoseri.org/prescribing-data/>.

Unfortunately, our PDMP data are only considered to be complete starting in April of 2016, so we are not able to evaluate prescribing trends over a longer time-period. Nonetheless, this suggests to us that interventions to change prescribing practices since 2014 have had some impact on prescribing practices in Rhode Island. Some of these interventions promoted responsible prescribing, regulated prescribing, and incentivized use of non-opioid pain management strategies, which each may have changed the diagnostic mix of people receiving opioid prescriptions over time.

Minor

The language in the Table headers should be consistent: Initial opioids, initial opioid initiates, opioid initiates

RESPONSE: Thank you for identifying this inconsistency. We have made all table headers consistent, using the phrase "initial opioid prescription."

Reviewer: 2

Dr. Yongkang Zhang, Cornell University Joan and Sanford I Weill Medical College

Comments to the Author:



Thank you for the opportunity to review this interesting paper. In this study, the authors examined the association between the diagnosis of the initial opioid prescription and subsequent persistent opioid use, using a comprehensive dataset from Rhode Island. They found certain diagnoses, such as musculoskeletal system and connective tissue, are associated with increased risk of persistent opioid use. I found this paper important and of great policy implications. My major comments include:

RESPONSE: Thank you for the supportive comments!

(1) Outcome: this paper focused on the subsequent persistent prescription opioid use, defined as at least 90 days of prescription opioid use without a gap of more than seven days starting from the fill date of the initial opioid prescription. As the authors explained in the discussion section (the 2nd paragraph in page 9), the incidence of the outcome is pretty low in this study (0.7%), and one of the reasons is that the persistent opioid use is defined as 90-day use without >7 day gap immediately following the initial opioid prescription, if my reading is correct.

I feel like this is different from many previous studies, which usually specified a follow-up period (e.g., 12-month or 18-month after the initial opioid prescription) and identified the persistent use or high-risk use during this period. Some examples I encountered include PMC6258623 and <https://bmjopen.bmj.com/content/9/7/e027203>.

I don't think what they did is wrong, but some patients may not have instant use after the initial prescription. I wonder how the definition used by this study contributes to the field, as compared with other studies.

RESPONSE: We agree with your feedback and, based on input from reviewer 1, have changed our outcome measure to define chronic use following the initial prescription as:

"... ≥60 days' supply of opioids dispensed in the 90 days following the fill date of an individual's initial opioid prescription (including the days' supply of the initial prescription).21"

This "new" definition aligns with how Washington State reports chronic opioid use and allowed our definition to be somewhat more inclusive. While the proportion of patients developing chronic use has substantially increased with the new definition (now 3.7% chronic users vs. 0.7% with our prior definition), nearly all findings/patterns remain the same.

(2) Exposure: the independent variable of interest is the initial opioid prescription, defined as either a. the patient's first opioid prescription or b. an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. I wonder if there is a look-back period to ensure it was the first opioid prescription, such as no any opioid prescription 6 months before it?

RESPONSE: Thank you for the comment. We did incorporate a look-back period in our analysis and have clarified this in the methods section. While the primary analysis used initial opioid prescriptions dispensed between April 1, 2019 and March 31, 2020, we utilized data from January 1, 2019 -June 30, 2020 to (1) ensure there were no opioid prescriptions filled in the 90 days before every initial opioid prescription in our analysis and (2) look at chronic use in the 90 days following the initial opioid prescription for those that were filled as late as March of 2020.

The new initial opioid prescription definition is below.

"We defined an initial opioid prescription as either (1) the patient's first opioid prescription or (2) an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. When defining initial opioid prescriptions, we utilized prescriptions filled on/after January 1, 2019 to ensure there was a "look-back" of at least 90 days for all patients."

(3) Potential confounders: the authors controlled for age and sex in the logistic regression. I feel like there are many other potential confounders, including insurance type, the clinical setting of the initial prescription, and socioeconomic status (e.g., individual patient level or neighborhood level). If they decided not to control for these variables, an explanation is needed.

RESPONSE: Thank you for noting this important point. While there are many other potential confounding variables, such as those you mentioned, these are not recorded in the Rhode Island Prescription Drug Monitoring Program database, and therefore could not be utilized. While insurance type is included, this variable was not utilized because individuals over 65 who have supplemental Medicare coverage are frequently coded as “private insurance,” making it difficult to ascertain who is on Medicare vs. private insurance in this population. To respond to this comment, we did re-run the analysis adjusting for insurance type and results were near identical, with most odds ratios remaining within 0.01 of the initial value, and largest adjustment was a change of 0.1.

To address the lack of other potential confounders included in the model, we have added the following sentence to the methods section

“While other sociodemographic and clinical factors likely impact chronic prescription opioid use (e.g., socioeconomic status), these variables are not recorded in the Rhode Island PDMP database.”

(4) Table 4 presented the results from the logistic regression. It compared the likelihood of having persistent opioid prescription between seven diagnosis types with Other. However, in the methods section, they mentioned that they classified all ICD-10 codes into 20 major groups. Why only eight groups in table 4?

RESPONSE: Thank you for raising this point. Per our methods section, “... diagnosis categories with fewer than fifteen chronic opioid users were collapsed and used as the reference group.” This was primarily done to improve interpretability and allow us to generate a comparison group utilizing diagnosis categories with a low likelihood of chronic opioid use. As this type of analysis has not been done before, there was no precedent for which group to use as the comparator. While our sample size of chronic users has substantially increased with the new definition, this approach was also used due to the extremely low frequency of chronic users in many diagnostic groups, as can be seen in Table 2. We have also clarified the referent group in our abstract, noting “...the referent group included all diagnosis types with fewer than 15 chronic opioid users.”

The discussion section is thoughtful. I have no other comments.

RESPONSE: Thank you for the positive comment and helpful feedback.

Reviewer: 3

Dr. Meghna Jani, The University of Manchester Comments to the Author:

The aim of this study is to identify initial diagnoses/ indications associated with persistent opioid use. The majority of administrative databases/ EHRs do not record indications for opioid use and this specific data source/ Prescription Drug Monitoring programme allows a unique opportunity to evaluate this. For that reason, this study is an important piece of work.

RESPONSE: Thank you!

Over a third of patients have a missing diagnosis code (36%), which unfortunately leads to a lot of missing outcome data. The authors do discuss this as a limitation of their work. Some additional suggestions below:



- The proportion of persistent use seems rather small. How does the figure in the study compare to others US or international studies (bearing in mind the different definitions used widely and the stricter definition here). Suggest these figures are quoted in the discussion.

RESPONSE: We thank you for the feedback and agree. Importantly, we modified our definition of chronic prescription opioid use based on feedback from Reviewer 1 and Reviewer 2. The percentage of patients who experienced subsequent chronic prescription opioid use is now 3.7% vs. the 0.7% with our prior definition. We have modified the following paragraph of the discussion section based on our revised analysis and your feedback:

“While prior work has focused on chronic prescription opioid use following specific diagnoses or procedures, our population-based study evaluated chronic prescription opioid use among all patients receiving initial opioid prescriptions in Rhode Island.<sup>4-6</sup> Despite differences in methodology, other studies estimating the frequency of chronic prescription opioid use after childbirth (1.7-2.2%), dental procedures (2.4-4.1%), elective surgeries (3.0-8.0%), or cancer treatment (8.3%) identified a similar percentage of patients with chronic use compared to our study of all patients receiving initial opioid prescriptions (3.7%).<sup>4-7,9-12</sup> In the absence of similar population-based studies, these comparisons suggest that the percentage of patients experiencing subsequent chronic prescription opioid use was generally similar to what might be expected based on prior studies.”

- Suggest removal of p values in table 1. These are likely to be significant given large numbers compared.

RESPONSE: Thank you for this suggestion. We have removed the p-values from Table 1 and adjusted the interpretation of the comparisons to be more cautious in the text. For example, we included statements like “... patients with versus without subsequent chronic prescription opioid use following the initial prescription were somewhat older (median 63 vs. 53 years), somewhat more likely to have paid for their initial opioid prescription with Medicare (27.5% vs. 14.4%), and somewhat less likely to have paid with private insurance (44.3% vs 60.9%).”

We also made similar adjustments to Table 3, as the statistical tests have the same limitations for those comparisons.

-An interesting result is that neoplasms (cancer), is a less frequent indication for initial opioid use in comparison to diseases other systems (2.3% overall, Table 2). Is there a reason why this proportion is so modest specific to this dataset? If not, important to highlight in the discussion that pain due to cancer is a far less common initial diagnosis for opioids and how this compares to other work.

RESPONSE: We appreciate you raising this point and agree that the low percentage of initial opioid prescriptions for neoplasm diagnoses is surprising. We hypothesize that three factors are contributing to this low percentage. First, the Rhode Island PDMP only receives the primary ICD-10 diagnosis code with each prescription, and it is possible that cancer patients had a primary ICD-10 diagnosis code for general pain and a secondary diagnosis code for cancer. In that case, the prescription would be recoded as pain related (unless they used the cancer specific pain ICD-10 code). When reviewing other studies that documented elevated opioid prescribing among cancer patients, we could not find another study that utilized prescription ICD-10 codes, and it appears most used medical records, administrative claims, or the cancer registry to identify cancer patients which are likely more inclusive of cancer patients. (e.g. in Zin et al, all opioid prescriptions received after a document diagnosis of cancer in the medical record were deemed cancer related).

Second, previous work has shown that many individuals with cancer receive opioids as part of their end of life care. However, work by Zielgler et al, found that they started on strong opioid prescriptions at a median of 9 weeks before death – which would not satisfy our definition of 60 days for chronic

use (additionally this would need to be an initiate script with no prior opioids in the prior 90 days to meet our chronic definition).

Third, the absolute number of cancer patients in Rhode Island is relatively low (Incidence ~5,000 cases a year, Deaths ~2,100), so even if opioid prescribing were relatively common among cancer patients these might make up a low percentage of the total opioid prescriptions.

Ziegler, Lucya,\*; Mulvey, Matthewa; Blenkinsopp, Alisonb; Petty, Duncanb; Bennett, Michael I.a  
 Opioid prescribing for patients with cancer in the last year of life: a longitudinal population cohort study, PAIN: November 2016 - Volume 157 - Issue 11 - p 2445-2451 doi:  
 10.1097/j.pain.0000000000000656

Zin, C. S., Chen, L. C., & Knaggs, R. D. (2014). Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain*, 18(9), 1343-1351.

To help clarify this in the manuscript we have modified the following section of the methods section to align with our first factor discussed.

“In 2018, Rhode Island began requiring that prescribers include the primary ICD-10 code on all prescriptions for a controlled substance.<sup>16</sup> In this study, our primary exposure was the diagnosis type associated with the primary ICD-10 code on the initial opioid prescription.”

- Are the higher odds of persistent use in MSK patients/ nervous system disease patients likely because they simply are the most frequent groups of patients prescribed opioids? Are the authors able to discern any patterns with individual diagnoses that may be of interest?

RESPONSE: Thank you for raising this important question. Diseases of the musculoskeletal system and connective tissue (MSK/CT) and diseases of the nervous system (NS) were the most common diagnoses in our population of patients receiving initial opioid prescriptions; however, you can also see evidence of the disproportionate risk of subsequent chronic prescription opioid use among people with those diagnosis types in crude comparisons. For example, 36% of patients who developed chronic use had an initial MSK/CT diagnosis compared to only 17% of patients who did not develop chronic use. Similarly, 19% of patients who developed chronic use had an NS diagnosis compared to only 9% of patients who did not develop chronic use. In other words, the MSK/CT and NS diagnoses were both over-represented among people with chronic use. If these diagnoses were not associated with chronic use, then we would expect the percentage of patients with that diagnosis type in each group to be roughly similar (even with the high overall percentage of patients with that diagnosis type).

As we describe in more detail below in response to your final comment, there are unfortunately limitations to our ability to report on specific diagnoses based on the available data and small numbers. Based on Table 5, some specific diagnoses within MSK/CT that stood out to us due to relatively high percentages of patients who progressed to chronic use:

- Intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified (31/89, 34.8%)
- Polyosteoarthritis (38/205, 18.5%)
- Rheumatoid arthritis (15/84, 17.9%)
- Spondylosis (69/407, 17.0%).

We highlight these conditions at the end of the results section, as follows:

“Notably, specific diagnoses that had a relatively high percentage of patients that progressed to chronic use following the initial opioid prescription included: intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified (31/89, 34.8%);

polyosteoarthritis (38/205, 18.5%); rheumatoid arthritis (15/84, 17.9%); and spondylosis (69/407, 17.0%).”

We have expanded upon our discussion of these types of MSK/CT diagnoses in the discussion, as noted above to Reviewer 1.

- In Table 4, whilst higher odds of persistent use are demonstrated with several groups of conditions, the confidence intervals seem wide. The numbers of patients for each system (who developed persistent use) would be useful to record here to gain an idea of numbers

RESPONSE: Thank you for this suggestion. With the modified definition of our outcome, our chronic use population has notably increased resulting in a narrowing of the confidence intervals. The number of patients for each system who developed chronic use is available in the third column of the Table 4 under the subheading Subsequent Chronic Prescription Opioid Use: Yes.

- What are the 3-4 most frequent diagnoses within each system type (Table 4)? Whilst the broad systems associated with higher ORs are of general interest, from a practical/ public health standpoint specific diagnoses information is likely to be most valuable to prescribers of opioids and when developing future interventions. Table 5 gives information about individual ICD-10 codes but not specific conditions (which may have several ICD-10 codes for instance).

RESPONSE: Thank you for this suggestion. We chose not to report the individual diagnoses or ICD-10 codes within each diagnosis type category for two main reasons. First, the Rhode Island Department of Health Small Number Policy prohibits the display of any counts of less than five. We included Table 5 to provide a sense of the ICD-10 codes with the most chronic opioid users, as well as the associated distribution of chronic use, while meeting our state’s reporting requirements. Second, the level of specificity in the ICD-10 codes reported to the Rhode Island PDMP varied greatly across prescriptions, making it very difficult to group them into specific diagnoses. We initially attempted to group ICD-10 codes in this way but were concerned that the resulting information would not be informative because many ICD-10 codes were too broad to be classified at the diagnosis-level and omitting the many broad ICD-10 codes from our classifications would likely introduce bias into our results.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Franklin, Gary University of Washington, School of Public Health & Community Medicine
<b>REVIEW RETURNED</b>	03-Aug-2021
<b>GENERAL COMMENTS</b>	The authors have been very responsive to the submitted critiques
<b>REVIEWER</b>	Zhang, Yongkang Cornell University Joan and Sanford I Weill Medical College
<b>REVIEW RETURNED</b>	22-Aug-2021
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