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Peer Review File

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Reviewer A

Comment 1: The timing of those visits is not illustrated in the manuscript

Reply 1: We agree that would it be helpful to know this information. It is now provided in both the methods and results section.

Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days." (P5, L3-4)

The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 2: I believe the responders analysis that is the number of patients who have a 30% reduction in pain is more clinically relevant than the mean/ median change of the entire group. I believe that that should be the primary endpoint.

Reply 2: The authors considered this change. To assist in comparison of rotation effects, data from non-rotated visits are now included. Due to pain scores being the sole indicator for whether a rotation was considered "successful" or "adverse", the authors wanted to keep pain scores as the primary outcome. Discussion about clinical relevance is now also included.

Changes in the text: Discussion now reads: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR in patients that may benefit."(P13, L1-11)

Comment 3: The authors should clarify the (in the PRE rotation and post rotation columns)

Reply 3: This has been clarified in the tables. Due to the addition of non-rotated data.

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The visits are now identified as "pre-visit" and "post-visit" with adjustment in the methods.

Changes in the text: The following statement has been included into the methods section: The "pre-visit" is defined as the first of two subsequential visits and the "post-visit" is the second of two subsequential visits" The rest of the manuscript reflects changing of this definition.

Comment 4: It is unlikely that methadone works via NMDA receptors by Affinity studies

Reply 4: Appreciate this comment with a chance to clarify to effects of methadone. Methadone also works by NMDA antagonism which has been demonstrated.

Changes in the text: Sentence now reads "Methadone has agonist activity at both the mu-opioid receptors and antagonist activity at the N-methyl-D-aspartate (NMDA) receptors with contributions of both effects demonstrating contribution to analgesia" with addition of references. (P10, L7-10)

Comment 5: The relative potency of methadone increases with MEDD. This cohort had a high initial MEDD (> 400mg/d) which may be the reason for the unique relative reduction in MEDD with rotation.

Reply 5: We agree with the reviewer's comment that the conversion ratio of morphine to methadone is non-linear. While there is no standardized conversion[i], several studies show conversion ratios that vary depending on dose range. However there are differences among these studies, with a ratio of about 4:1 for <90 mg morphine[ii] [iii] [iv]and between 4.6:1[4] and 6:1[2] for morphine doses between 90 and 300mg. An earlier study concluded a dose <1165 mg morphine had a conversion ratio of 5.42 for methadone[v]. Doses higher than 300mg are noted to have higher ratios in these particular studies; however, the reasons for rotation (side-effects vs uncontrolled pain) are also factors for influencing conversion[vi]. A switch for pain at >300mg/day was associated with a median conversion of 4.9:1 vs 9.1:1 for side effects. Since our population were ambulatory clinic patients typically reporting inadequate pain control prior to rotation and were unlikely to be experiencing side effects such as sedation, or delirium we chose a ratio of 5:1. This ratio is used in a prior publication about opioid rotation in cancer pain[vii], nevertheless, we recognize that this may be an important limitation to our study and have emphasized this aspect in the manuscript text.

Changes in the text: The following has been added to the discussion: "In addition, the conversion ratios for methadone are not standardized, and variable. Conversion ratios of morphine to methadone are non-linear; they vary with dose and the reasons for rotation (side effects are 9:1 vs 5:1 for uncontrolled pain) (44). In our population of

ambulatory clinic patients, inadequate pain control prior to rotation is a more likely reason for rotation than side effects such as sedation. Evidence for conversion ratios from methadone to morphine are even more limited and may not vary with increasing dose (42)." (P11, L18-23, P12 L1)

Reviewer B

Comment 1: My main issue with this paper is the conversion ratio that it has adopted for methadone. It is a wide consensus that the conversion ratio for methadone is a non-linear, dose-dependent one.

Reply 1: We agree with the reviewer's comment that the conversion ratio of morphine to methadone is non-linear. While there is no standardized conversion[viii], several studies show conversion ratios that vary depending on dose range. However there are differences among these studies, with a ratio of about 4:1 for <90 mg morphine[ix] [x] [xi]and between 4.6:1[4] and 6:1[2] for morphine doses between 90 and 300mg. An earlier study concluded a dose <1165 mg morphine had a conversion ratio of 5.42 for methadone[xii]. Doses higher than 300mg are noted to have higher ratios in these particular studies; however, the reasons for rotation (side-effects vs uncontrolled pain) are also factors for influencing conversion[xiii]. A switch for pain at >300mg/day was associated with a median conversion of 4.9:1 vs 9.1:1 for side effects. Since our population were ambulatory clinic patients typically reporting inadequate pain control prior to rotation and were unlikely to be experiencing side effects such as sedation, or delirium we chose a ratio of 5:1. This ratio is used in a prior publication about opioid rotation in cancer pain[xiv], nevertheless, we recognize that this may be an important limitation to our study and have emphasized this aspect in the manuscript text.

Changes in the text: The following has been added to the discussion: "In addition, the conversion ratios for methadone are not standardized, and variable. Conversion ratios of morphine to methadone are non-linear; they vary with dose and the reasons for rotation (side effects are 9:1 vs 5:1 for uncontrolled pain) (44). In our population of ambulatory clinic patients, inadequate pain control prior to rotation is a more likely reason for rotation than side effects such as sedation. Evidence for conversion ratios from methadone to morphine are even more limited and may not vary with increasing dose (42)." (P11, L18-23, P12 L1)

Comment 2: Was there any reason why smoking history was specifically mentioned in the baseline patient characteristics?

Reply 2: It was part of the data collected but agree that it has limited utility in this retrospective study. Smoking data has been removed from Table 1 and methods/results.

Changes in the text: Smoking data has been removed from methods, results, and Table

1.

Comment 3: What was the usual interval between the pre-rotation and post-rotation visits?

Reply 3: We agree that would it be helpful to know this information. It is now provided in both the methods and results section.

Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days." (P5, L3-4)

The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 4: Why did you choose a universal conversion factor of 5 for methadone instead of a dose-dependent one?

Reply 4: Please see reply to comment 1. Ultimately the authors chose to follow the conversion factors utilized studies with designs most similar to the retrospective study.

Changes in the text: The following has been added to the discussion: "In addition, the conversion ratios for methadone are not standardized, and variable. Conversion ratios of morphine to methadone are non-linear; they vary with dose and the reasons for rotation (side effects are 9:1 vs 5:1 for uncontrolled pain) (44). In our population of ambulatory clinic patients, inadequate pain control prior to rotation is a more likely reason for rotation than side effects such as sedation. Evidence for conversion ratios from methadone to morphine are even more limited and may not vary with increasing dose (42)." (P11, L18-23, P12 L1)

Comment 5: How did you deal with the prn opioid doses taken by the patients? How did you estimate that in this retrospective chart review, as that would also cause under- or over-estimation of the MEDD?

Reply 5: The authors were unable to perform pill counts or accurately determine how much of PRNs were being taken. It was decided to include all PRN doses available. For example if a patient had a prescription for oxycodone 5mg every 6 hours PRN, that would be calculated as 20mg daily prescribed oxycodone.

Changes in the text: The methods section now includes the sentence: "Doses included in the analysis were determined by prescriptions in the EMR at the time of the visits and included the full PRN or "as needed" doses available within a 24-hour period." (P6, L13-15)

Comment 6: Are there any significant differences in patient characteristics between the patient groups with and without opioid rotation?
Reply 6: There are no significant differences in terms of demographics. There was a significant difference in time between visits and the manuscript was updated to reflect this.
Changes in the text: The results section now includes the following: "There were no differences in demographic data. Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18)

Comment 7: Would you consider to report the baseline opioid drug, mean MEDD and mean pain scores of the two patient groups in table 1 as well?
Reply 7: Yes, we agree that a comparison between rotated visits and non-rotated visits will be helpful. The data has been included in Tables 2,3,4 and discussed throughout the paper.
Changes in the text: The methods, results, tables, and discussion sections all have updated text to reflect this major revision.

Comment 8: Although the drop in mean pain score was statistically significant after opioid rotation, a difference of 0.5 in a 11-point scale would not translate to a clinical significance. It would be better to present this more clearly.
Reply 8: Agree that a discussion of clinical relevance is important.
Changes in the text: Discussion now reads: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR in patients that may benefit."(P13, L1-11)

Comment 9: Again, for the significant decrease in pain scores after rotations to morphine, oxycodone and methadone, all the absolute drops in pain score were not more than 1 point, which did not confer any clinical significance. It would be better to

present this more clearly.

Reply 9: Agree with this comment as above. Please see response to comment 8.

Changes in the text: Discussion now reads: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR in patients that may benefit."(P13, L1-11)

Comment 10: What did you mean by "standardised dosing"? This might not be a term commonly used to refer to MEDD.

Reply 10: The goal of utilizing MEDD is to standardize the dose of an opioid analgesic in terms of agonism and analgesia by converting all doses to a morphine standardized dosing. This is made clearer in the text

Changes in the text: The methods section now reads: "MEDD calculations standardize dosing across the various opioid analgesic agents to compare total opioid dose with morphine as the standard". (P6, L6-8) Several sentences remove the phrase standardized dosing.

Comment 11: Opioid rotation only correlated with clinically significant improvement in pain scores in ~30% of cases, others were only statistically significant differences. Thus, we might not be able to draw the conclusion that "opioid rotation correlated with improved pain scores". The "significant decreases in pain scores" in patients being rotated to methadone was only statistically significant, but not clinically significant, this should be expressed more clearly.

Reply 11: The clinical significance of these findings and discussion about defining "success" utilizing only pain scores is addressed

Changes in the text: Discussion now includes: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, disease progression, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a "successful" OR (11)." (P12, L9-14) and

"While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR (P13, L1-11)

Reviewer C

Comment 1: Since this is a retrospective study, we can only show correlation and we cannot prove causality. Hence, we probably should not be using the word "effect" of opioid rotation on outcomes. A better way is probably to rephrase it as the association between opioid rotation and symptoms, and daily opioid use, etc

Reply 1: We agree with this point. The title has been changed.

Changes in the text: The title now reads: "Comparison of opioid rotation on pain, symptoms, and daily opioid dose in a supportive care clinic." (P1 L1)

Comment 2: Notably, no studies compare rotations to a particular opioid and the effect on overall pain scores, other symptoms, or morphine equivalent daily dosing (MEDD)." I am not sure if this is accurate. There have been multiple other studies by Reddy et al, Mercadante et al. You might want to verify this assertion.

Reply 2: Appreciate this comment, this sentence was adjusted to clarify how this study is different from others.

Changes in the text: While several studies have determined equianalgesic ratios and effects of OR on pain, symptoms assessments, and morphine equivalent daily dosing (MEDD) (11, 14, 17), there is limited data comparing OR across several specific opioids that utilize subjective but quantitative outcomes such as pain scores and symptom assessment tools. (P4, L3-7)

Comment 3: how was post-rotation visit defined.? What was the time frame? For example, was it 28 days +/- 7 days. It will be nice to define the time period in order to standardize comparison of results.

Reply 3: We agree that would it be helpful to know this information. It is now provided in both the methods and results section.

Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days." (P5, L3-4)
The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 4: "For clarity, the drug rotated to would be the opioid analgesic the patient was on between the pre-rotation and post-rotation visit." This is still unclear. What if patient was on the drug between pre-rotation and post-rotation visits, but was not on it at the time of the post-rotation visit? Please clarify
Reply 4: We have attempted to clarify this point.
Changes in the text: The methods section now reads: "For clarity, the drug rotated to would be the opioid analgesic the patient was on between the pre-rotation and post-rotation visit with an active prescription at the date of the post-rotation visit. A rotation to one opioid did not exclude its analysis if a second opioid rotation occurred during the same visit." (P6, L18-23)

Comment 5: First column sub-heading "Patients undergoing rotation": should probably be deleted, since on that same row, we have 328 (100%) who did not undergo an opioid rotation.
Minor comment- it might be easier for readers if you round up figures to whole numbers, or at most to 1 decimal place instead of the 2 decimal places, unless this is a journal style/requirement
Reply 5: Agree, this has been deleted from Table 1.
Changes in the text: Table 1 has this above mentioned component deleted for increased clarity.

Comment 6: Table 3. Title is also unclear. I am sure you meant to say 'Total ESAS scores". Also, you might want to describe a little bit in the methods section how you calculated the total ESAS scores, or the total symptom distress scores as other articles describe it. Please mention if you excluded the total scores which had incomplete scores of some of the individual ESAS items.
Reply 6: Agree with this comment, the titles have been changed and revision of data/methods to reflect missing data which was not included if a component of ESAS was not recorded.
Changes in the text:
Titles in the tables are now:

Table 2: Association of opioid rotation and pain scores
Table 3: Association of opioid rotation and ESAS
Table 4: Association of opioid rotation and MEDD
Tables now reflect appropriate descriptive data included number of rotations with full data included and are reflected as mean with 95% CI.
The following sentence has been added to the methods section: "If data from either the pre-visit or post-visit were not available with regards to pain scores, ESAS, or MEDD, it was not included for analysis. " (P5, L5-7)

Comment 7: Page 7, line 7: please add the word 'individual' to symptoms.
Reply 7: Believe reviewer is referring to page 7, line 17.
Changes in the text: 'individual' has been added. It now reads:" Further sub-analysis demonstrated no significant improvement with any of the individual symptoms captured within the ESAS questions following opioid rotation (data not shown)" (P8, L13-15)

Comment 8: page 9, line 19: "The final reason may be attributed to concerns by clinicians or patients regarding the adverse effects of methadone (41), the stigma surrounding its use for opioid use disorder (42), or a combination of the two." How does this explain the fact that successful OR to Methadone correlated with lower MEDD?
Reply 8: These reasons may contribute to prescribes writing for lower doses of methadone compared to other opioid analgesics. authors attempted to address this comment,
Changes in the text: Discussion now reads: "The final reason may be attributed to concerns by clinicians or patients regarding the adverse effects of methadone such as QT prolongation (45), the stigma surrounding its use for opioid use disorder (46), or a combination of the two with prescribers writing for artificially lower doses of methadone than the other opioid analgesics." (P12, L1-6)

Comment 9: "We also based the MEDD on the clinician's prescribed dose, because pill-counts were not consistently performed" This is a major concern. There is usually a significant discrepancy between what the provider prescribes and what the patient actually takes. Hence, I am worried that in the analysis, we are using the clinician's prescribed dose to suggest patent's actual opioid intake. These are 2 different measures.
Reply 9: Agree that there may be a discrepancy in this true value and is the reasons it is being addressed in the limitations section. In order to limit the effect of potential error in measurements, rotations were only included if it was PRN to PRN or non-PRN to

non-PRN in an effort to reduce this bias. In addition, the authors hope that inclusion of non-rotated data assist in reducing the impact of this error as MEDD was calculated the same way.

Changes in the text: "Our study size limits a full comparison of drug effects, as only within-subject analyses were performed. We also based the MEDD on the clinician's prescribed dose, because pill-counts were not consistently performed. Patients may actually be taking medications (particularly as needed or PRN) less frequently than prescribed." (P12, L14-18)

Reviewer D

Comment 1: Within the abstract, and throughout the text, recommend the reduction in pain scores is presented as a "statistically significant" reduction in "mean" pain scores.

Reply 1: Agree with this comment. The abstract and manuscript has been updated.

Changes in the text: Abstract now reads: "Following opioid rotation, there was a statistically significant reduction in mean pain scores from 6.25 at the pre-visit to 5.75 following opioid rotation." (P2, L20-21).This also has been rectified throughout the manuscript.

Comment 2: Recommend clarifying in the abstract that 217 rotations occurred in 128 patients.

Reply 2: Authors have added this to abstract.

Changes in the text: Abstract now reads: "Study included 676 patients with 217 rotations identified in 128 patients a supportive care clinic at a National Cancer Institute (NCI) Cancer Center. OR were identified and analysis compared the pre-visit data with the subsequent post-visit data following rotations using paired t-tests" (P2, L14-15)

Comment 3: Did the MEDD at baseline and follow up include scheduled (around the clock), PRN agents, or both?

Reply 3: It could include both, depending on the patient. The authors have attempted to clarify this point.

Changes in the text: The methods section now includes the sentence: "Doses included in the analysis were determined by prescriptions in the EMR at the time of the visits and included the full PRN or "as needed" doses available within a 24-hour period." (P6, L13-15)

Comment 4: From where were the MEDD doses collected (medication list of prescriptions, palliative notes, prescription monitoring program, or some combination

of all?)

Reply 4: Agree, we have attempted to address.

Changes in the text: The methods section now includes the sentence: "Doses included in the analysis were determined by prescriptions in the EMR at the time of the visits and included the full PRN or "as needed" doses available within a 24-hour period." (P6, L13-15)

Comment 5: How were PRNs treated (calculation of maximum possible use based on dose and PRN frequency? calculated as a 30 day prescription? some other way

Reply 5: The authors were unable to perform pill counts or accurately determine how much of PRNs were being taken. It was decided to include all PRN doses available. For example if a patient had a prescription for oxycodone 5mg every 6 hours PRN, that would be calculated as 20mg daily prescribed oxycodone.

Changes in the text: The methods section now includes the sentence: "Doses included in the analysis were determined by prescriptions in the EMR at the time of the visits and included the full PRN or "as needed" doses available within a 24-hour period." (P6, L13-15)

Comment 6: that this was a "statistically" significant decrease in "mean" pain scores.

Reply 6: Agree with reviewer that this a more appropriate way to discuss results. As with comment 1, this has been updated.

Changes in the text: Abstract now reads: "Following opioid rotation, there was a statistically significant reduction in mean pain scores from 6.25 at the pre-visit to 5.75 following opioid rotation." (P2, L20-21).This mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 7: Suggest addition of balancing measure - did any % of patients have a 2 point or 30% INCREASE in pain scores at post rotation visit?

Reply 1: Greatly appreciate this comment, not only have analysis of non-rotated patients been included, but "adverse" visits are now included to aid in comparison effects.

Changes in the text: Table 2 now includes "adverse" visits. Methods now reads "An "adverse" visit was defined as a 30% or 2-point increase in pain scores at the post-rotation visit."

Comment 8: suggest reporting average and range of time to post-rotation visit in days.

Reply 8: We agree that would it be helpful to know this information. It is now provided

in both the methods and results section.

Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days."

The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)."

Comment 9: Within discussion, recommend addition of discussion point regarding statistical versus clinical significance of mean pain scores. In particular, even though only statistically significant change in mean pain scores was seen with morphine, oxycodone, and methadone, all agents had a similar rate of "successful rotation". As a clinician, this would be significant to me, in that you can anticipate (based on your data) that somewhere between 1/4 and 1/3 patients will have improved pain with a rotation to any alternative opioid.

Reply 9: Agree, discussion about clinical significance is now included.

Changes in the text: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR (P13, L1-11)

Comment 10: Add to limitations discussion that this was a single post-rotation follow up investigation. It is unknown if the positive effects are sustained over time. This discussion will also be informed by the addition of the "time to follow up" data that is recommended to be added to the results section.

Reply 10: Agree with this comment.

Changes in the text: Discussion now reads: "This study was also limited in that only one subsequent visit was included for analysis and it is unknown to what extent these results are sustained over longer intervals of time." (P12, L18-20)

Reviewer E

Comment 1: Introduction, page 3 line 17: The sentence is inaccurate. Several studies have examined this before including pain score changes, ESAS, MEDD, etc. Please

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find some of the studies below, some which were already a part of the references.1-6

Reply 1: Appreciate this comment, this sentence was adjusted to clarify how this study is different from others.

Changes in the text: While several studies have determined equianalgesic ratios and effects of OR on pain, symptoms assessments, and morphine equivalent daily dosing (MEDD) (11, 14, 17), there is limited data comparing OR across several specific opioids that utilize subjective but quantitative outcomes such as pain scores and symptom assessment tools. (P4, L3-7)

Comment 2: Why did the authors not include "the continuation of the new opioid at subsequent visit" as part of the definition of successful OR? If the patient is not taking the new opioid at the time of follow-up, that would mean the OR was unsuccessful.

Reply 2: All patients who were rotated were on the rotated opioids at the "post-visit". However data was limited in many cases to determine if the patient continued on the rotated medications moving forward. The decision was made to consider opioid rotations successful with regard to purely a pain-score outcome as the primary endpoint of this retrospective study was pain scores. While others in the field have included other metrics as mentioned for "successful OR", unfortunately, availability of additional data precluded this assessment. The authors believe that with additional criteria for "success" that the % of opioid rotations would be higher than reported in this study.

Changes in the text: The methods section now reads: "Additional criteria such as reduced side effects, lack of worsening of pain score with change of route of administration, and continued use of new opioid at subsequent visit were not included in the definition of "successful" rotation for this study due to unavailability of data to assess." (P5 L17-20)

Comment 3: Do the authors have information on history of substance abuse or screen pts with CAGE, SOAPP or other such tools? It appears only smoking history was presented here.

Reply 3: While this data was collected, it was in too few of the patients analyzed (6-11% of patients) and the authors felt the lack of availability of these assessments precluded their inclusion in this manuscript.

Changes in the text: Smoking data has been removed from the Tables, methods, and results.

Comment 4: As the indication of Opioid rotation was not recorded, the definition of success as 30% or 2-point reduction of pain score may not be applicable to all patients. Patients may have a good pain control but still need OR for other reasons such as

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wanting a change in route, or minimize symptoms of opioid induced neurotoxicity, or OR may be due to a potential interaction with a new antineoplastic regimen. For these patients, success of OR would be different than 2-point reduction of pain score as their pain was well managed to begin with. Please add this as a limitation. If possible, can the reason for OR be obtained and the definition of success be changed for these patients?

Reply 4: The authors certainly wish this information was available and additional components have been added to this discussion to address this. Overall, this is the reason that the endpoints are focused on pain scores and endpoints that were adequately measured in the data available.

Changes in the text: The discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR" (P12, L9-14)

Comment 5: Under results, please include the median time to follow-up between OR and the subsequent clinic follow-up. Palliative care patients often have changes in treatment plan, disease progression, improvement of pain after radiation and other such factors which can influence the pain score if the time to follow-up is beyond 2-4 weeks.

Reply 5: We agree that would it be helpful to know this information. It is now provided in both the methods and results section.

Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days." (P5, L3-4)

The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 6: The minimal clinically significant difference for improvement of symptoms on ESAS is approximately a reduction by 1 point. Please see the references for more information on MCID for individual symptoms and total ESAS scores.7-9 Please include that although there was a statistically significant improvement in pain it may not be clinically significant. Please also refer to studies above where both a clinical and statistical difference in ESAS scores was achieved after OR. Include this information and discuss why the results may be different with your study and the previous studies.

Reply 6: Agree, discussion about clinical significance is now included.

Changes in the text: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-

point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR (P13, L1-11)

Comment 7: Is there any information on why 70% of the patients did not experience OR? Most ORs have a success rate of at least 60%. Please include in discussion that due to defining success as 2-point reduction in pain, many pts who otherwise underwent OR for reasons other than uncontrolled pain, were placed in the category of unsuccessful rotation due to no change or <30% reduction in pain score.

Reply 7: The data collected was in a snapshot of time for many patients. Some patients this time period included their initial visit to the supportive clinic, and others may have had their initial visit prior to initiation of this data collection. OR occurred when a need arose in patients (although that reason why data is unavailable) and it is possible rotations occurred prior to or after this study period for many patients.

Changes in the text: The discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a "successful" OR." (P12, L9-14)

Comment 8: Can the authors compare change in MEDD in pts with successful OR vs. unsuccessful OR? MEDD decreased in pts with successful OR in previous studies and in those that had OR due to symptoms of opioid induced neurotoxicity. Please tone down MEDD related information all over the manuscript as the authors did not collect the actual MEDD used by the patient and only included prescribed MEDD, which may be significantly different.

Reply 8: We agree this is a limitation in the study. No formal assessment of how many PRNs were taken was available for this study. This could potentially be looked at with a prospective study that included a validated tool to assess dosage used by the patient. Additional limitation comments have been added to the discussion as well as calculations of MEDD for non-rotated visits which was substantially lower. Additionally, opioid-side effects profiles were not formally assessed at these visits with

ESAS scores being the symptom tool used.

Changes in the text: The discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a "successful" OR." (P12, L9-14)

Comment 9: Page 8, line 22: Please correct the sentence. Although methadone has a long half-life, its duration of action is only 6-12 hours. Many patients may do well on Q 12-hour dosing schedule but a significant number will need a Q 8 hour dosing schedule.

Reply 9: This correction has been made

Changes in the text: Discussion now reads: "Methadone also has favorable pharmacokinetics with a half-life of 24 hours (in non-opioid naïve individuals) that typically requires only twice a day dosing which is favorable to patients (32) while some benefit from every 8 hour dosing." (P10, L10-12)

Comment 10: In this previous study, the median reduction of ESAS pain score was -2 in pts who had OR to methadone and -1 in pts who had OR to other opioids.6

Reply 10: This reference and inclusion in the discussion has been added

Changes in the text: Discussion now reads: "Our findings regarding methadone are consistent with a recent systematic review reporting increased MEDD following opioid rotations, with only rotation to methadone correlating in a decreased MEDD (21) and with a study that demonstrated enhanced reduction in pain scores with OR to methadone compared to other ORs." (P9 L14-18)

Reviewer F

Comment 1: It is unclear why the authors present a control cohort (patients that were not rotated) in the patients characteristics (table 1), but do not report outcomes of the controls later (e.g. what was the change of pain scores in the controls?). Reporting this is important because it hints at the clinical relevance of the data.

Reply 1: Yes, we agree that a comparison between rotated visits and non-rotated visits will be helpful. The data has been included in Tables 2,3,4 and discussed throughout the paper.

Changes in the text: The methods, results, tables, and discussion sections all have updated text to reflect this major revision.

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Comment 2: An ANOVA could have been more appropriate to interpret the data, but I understand if the authors want to leave the analysis rather exploratory. However, the authors should correct for multiple testing (e.g. Bonferroni correction)
Reply 2: Due to the within-subject design of the study, paired-t tests were utilized. Each data set (pain, ESAS, MEDD) were unique and multiple comparisons were not performed. For data not-shown with regard to individual ESAS symptoms, Bonferroni correction was performed but no statistically significant changes were noted.
Changes in the text: No changes to methods.

Comment 3: Please add eligibility criteria in more detail (e.g. age, cancer types)
Reply 3: Unfortunately, cancer type information is not available. Available data is presented in table 1.
Changes in the text: The methods now read: "Patients, ages 18 years or older with at least two consecutive visits were included (n=456)." (P4 L17-18)

Comment 4: Please state how you handled missing data
Reply 4: Missing data in the paired-t tests were not analyzed. Methods and tables now accurately reflect change to missing data.
Changes in the text: Methods now reads: "If data from either the pre-visit or post-visit were not available with regards to pain scores, ESAS, or MEDD, it was not included for analysis." (P5 L5-7)

Comment 5: How was the rotations conducted? Reduction of dosage and titration?
Reply 5: Agree this would be useful information but was unavailable for this study. Reasons and rationale were not included in data from the EMR.
Changes in the text: Discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR." (P12, L9-14)

Comment 6: Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage 2009; 38:418.). If the dosage was not reduced as suggested by guidelines, please discuss that in the manuscript. Not reducing the dosage could explain why MEDD stayed the same.
Reply 6: Agree with this assessment,
Changes in the text: The discussion now reads: "This may largely be attributed to the primary purpose of an opioid rotation in the outpatient clinic: improving pain

management and mitigating the risk of adverse effects, however prescriptions in this cohort of patients did not result in decreases MEDD that are often encouraged with OR (39).” (P11 L4-7)

Comment 7: Institutional Review Board?
Reply 7: IRB from Virginia Commonwealth University approved this study under HM14594. The authors did not see a place in the instructions to include this information. We are happy to include it where appropriate
Changes in the text: None at this time but can include “IRB from Virginia Commonwealth University approved this study under HM14594”

Comment 8: 14b: missing data: “indicate missing number of participants for each variable of interest”; the authors refer to table 1 which does not include missings.
Reply 8: This is in reference to the primary and secondary endpoints. This has been clarified in the methods section.
Changes in the text: Methods now reads: “If data from either the pre-visit or post-visit were not available with regards to pain scores, ESAS, or MEDD, it was not included for analysis.“ (P5 L5-7)

Comment 9: Bias: in the specified sections no comment on bias could be found
Reply 9: The authors have no conflicts of interest to declare.
Changes in the text: The above statement was included in the footnotes and the completed ICMJE uniform disclosure forms will be submitted to the editorial office.

Comment 10: Include data on performance status (e.g. ECOG) and cancer-type, pain-type, reasons for rotation (pain control vs. side effects). Reasons for rotation are important because MEDD might be different in patients rotated for neurotoxicity and patients rotated due to insufficient pain control (Reddy and Bruera, Oncologist. 2013;18(2):212-20. Epub 2012 Dec 13.). Without these information it is difficult to put the data into perspective with other publications.
Reply 10: Unfortunately, this information was not available within the EMR to include with this study or present for far few too patients (5-11%). This is included in the discussion regarding limitations.
Changes in the text: Discussion now reads: “Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a “successful” OR”.

(P12, L9-14)

Comment 11: The significance of the percentage of successful rotations is unclear. E.g. rotation to hydromorphone did not significantly change the mean pain scores, but had the highest rate of successful rotations (37%); please discuss the reasons for that finding.
Reply 11: This is now addressed with discussion of clinical significance of findings.
Changes in the text: Discussion now reads: "While this study demonstrated statistically significant reductions in mean pain scores following OR, the effect was relatively small with less than one-point reduction in mean pain scores. In addition, while OR visits resulted in increased "successful" visits and decreased "adverse" visits determined by pain scores, the clinical significance of this improvement following OR remains unclear as supportive care visits alone appeared to be relatively successful in reducing pain scores with over 20% of all visits resulting in decreased pain scores. OR correlated with a minimal, but significant, reduction in mean pain scores without increasing MEDD despite having higher baseline pain scores, symptom burden, and current opioid dosing compared to visits without OR, supports the utility of OR in patients that may benefit."(P13, L1-11)

Comment 12: How much time elapsed between the first and second visit? This is a relevant question, because subgroup differences in this regard might explain why rotating to some opioids reduced pain, but rotating to others did not.
Reply 12: We agree that would it be helpful to know this information. It is now provided in both the methods and results section.
Changes in the text: The methods section now includes the line: "The average time between all visits were 34.47 days." (P5, L3-4)
The results section now includes the line: "Visits in which are rotation occurred had significantly shorter follow-up visits with a mean of 29.55 days compared to mean interval period of 35.32 days for visits in which rotation did not occur (p=0.03)." (P7, L15-18).

Comment 13: Were there certain symptoms from the ESAS that changed after opioid rotations?
Reply 13: No, no significant changes were observed for certain symptoms in the ESAS.
Changes in the text: Results now reads: "Further sub-analysis demonstrated no significant improvement with any of the individual symptoms captured within the ESAS questions following opioid rotation (data not shown)." (P8 L13-15)

Comment 14: Risks of methadone use are not discussed

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Reply 14: Prescribing of methadone is further explored in the discussion.

Changes in the text: Discussion now reads: "The final reason may be attributed to concerns by clinicians or patients regarding the adverse effects of methadone such as QT prolongation (45), the stigma surrounding its use for opioid use disorder (46), or a combination of the two with prescribers writing for artificially lower doses of methadone than the other opioid analgesics." (P12 L1-6)

Comment 15: Discussion of the comparatively low success rate; a similar study Reddy and Bruera (Oncologist. 2013;18(2):212-20. Epub 2012 Dec 13.) had success rates of app. 60%: What are the reasons of this discrepancy: different tumor entities? Different definition of the end point?

Reply 15: Agree with this concern. The authors believe this is due to the criteria for "success" being solely tied to pain scores. The discussion now addresses this point.

Changes in the text: Discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated opioids, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a "successful" OR" (P12, L9-14)

Comment 16: You state "opioid rotations in this cohort of palliative care patient did not correlate with changes to the MEDD (p.9, l.11)". Put this into perspective with other studies that even showed higher MEDD after rotation

Reply 16: To our knowledge, there are no published studies demonstrating an increase of MEDD, but some that suggest a decrease. This is now addressed. The decision to include this point to address the possibility that increased MEDD regardless of OR would cause reduced pain scores.

Changes in the text: Discussion now reads: "This may largely be attributed to the primary purpose of an opioid rotation in the outpatient clinic: improving pain management and mitigating the risk of adverse effects, however prescriptions in this cohort of patients did not result in decreases MEDD that are often encouraged with OR (39)." (P11 L4-7)

Comment 17: Please discuss possible confounders that were not controlled for (e.g. pain type and others)

Reply 17: Agree with the need to address confounders

Changes in the text: Discussion now reads: "Due to the lack of availability of information regarding full profile of opioid-induced side effects, continuation of rotated

opioids, disease progression, and reason for rotation, this study chose to focus the primary endpoint as mean pain scores and as the sole indicator of a successful OR. As a consequence, it is likely the data presented underestimates what many would consider a "successful" OR" (P12, L9-14)

Response specific citations:

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[i] Smith HS, Peppin JF. Toward a systematic approach to opioid rotation. J Pain Res. 2014 Oct 17;7:589-608. doi: 10.2147/JPR.S55782. PMID: 25378948; PMCID: PMC4207581

[ii] Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998;16(10):3216–2

[iii] Mercadante S, Casuccio A, Fulfaro F, Groff L, Boffi R, Villari P, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. J Clin Oncol. 2001;19(11):2898–904.

[iv] Hagen NA, Wasylenko E. Methadone: outpatient titration and monitoring strategies in cancer patients. J Pain Symptom Manag. 1999;18(5):369–7

[v] Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167–73.

[vi] Benítez-Rosario MA, Salinas-Martín A, Aguirre-Jaime A, Pérez-Méndez L, Feria M. Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors. J Pain Symptom Manage. 2009 Jun;37(6):1061-8. doi: 10.1016/j.jpainsymman.2008.05.016. Epub 2009 Jan 25. PMID: 19171458.

[vii] Reddy A, Yennurajalingam S, Reddy S, Wu J, Liu D, Dev R, Bruera E. The Opioid Rotation Ratio From Transdermal Fentanyl to "Strong" Opioids in Patients With Cancer Pain. J Pain Symptom Manage. 2016 Jun;51(6):1040-5. doi: 10.1016/j.jpainsymman.2015.12.312. Epub 2016 Jan 28. PMID: 26826675.

[viii] Smith HS, Peppin JF. Toward a systematic approach to opioid rotation. J Pain Res. 2014 Oct 17;7:589-608. doi: 10.2147/JPR.S55782. PMID: 25378948; PMCID: PMC4207581

[ix] Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998;16(10):3216–2

[x] Mercadante S, Casuccio A, Fulfaro F, Groff L, Boffi R, Villari P, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a

prospective study. J Clin Oncol. 2001;19(11):2898–904.

[xi] Hagen NA, Wasylenko E. Methadone: outpatient titration and monitoring strategies in cancer patients. J Pain Symptom Manag. 1999;18(5):369–7

[xii] Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167–73.

[xiii] Benítez-Rosario MA, Salinas-Martín A, Aguirre-Jaime A, Pérez-Méndez L, Feria M. Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors. J Pain Symptom Manage. 2009 Jun;37(6):1061-8. doi: 10.1016/j.jpainsymman.2008.05.016. Epub 2009 Jan 25. PMID: 19171458.

[xiv] Reddy A, Yennurajalingam S, Reddy S, Wu J, Liu D, Dev R, Bruera E. The Opioid Rotation Ratio From Transdermal Fentanyl to "Strong" Opioids in Patients With Cancer Pain. J Pain Symptom Manage. 2016 Jun;51(6):1040-5. doi: 10.1016/j.jpainsymman.2015.12.312. Epub 2016 Jan 28. PMID: 26826675.