PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Tolerability of bedtime diuretics: A prospective cohort analysis
AUTHORS	Garrison, Scott; Kelmer, Michael; Korownyk, Tina; Kolber, Michael; Allan, Gary; Bakal, Jeffrey; Singer, Alexander; Katz, Alan; Mcalister, Finlay; Padwal, Raj S; Lewanczuk, Richard; Hill, Michael; McGrail, Kimberlyn; O'Neill, Braden; Greiver, Michelle; Manca, Donna; Mangin, Dee; Wong, Sabrina T.; Kirkwood, Jessica; McCormack, James; Yeung, Jack; Green, Lee

VERSION 1 – REVIEW

REVIEWER	Smolensky, Michael Cockrell School of Engineering, The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA. , Department of Biomedical Engineering
REVIEW RETURNED	20-Oct-2022

GENERAL COMMENTS	According to Garrison et al., Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial. BMJ Open. 2022 and the 2nd paragraph on Page 5 of the submitted manuscript "the BedMed trial randomizes Canadian primary care patients with hypertension to take their existing antihypertensive medications either in the morning, or at bedtime, and examines mortality and morbidity outcomes." The same page and paragraph additionally states "To determine how well diuretics are tolerated at bedtime we conducted a pre-specified prospective cohort study embedded within the ongoing BedMed trial." The authors further state "This paper examines the findings of those participants with a single morning antihypertensive at baseline randomized to switch that antihypertensive to bedtime. Our goal was to compare adherence with bedtime allocation, and self-reported nocturia burden, between those switching a diuretic to bedtime, and those switching other types of blood pressure lowering medication to bedtime. Note, our definition of adherence to allocation time differs from the conventional notion. When we refer to adherence to bedtime allocation, we are talking about the participant's intention to use their antihypertensive at bedtime. This study is NOT evaluating the extent to which individual doses are missed. As such, we did not compare bedtime diuretic use to morning diuretic use because morning medication use was already well established for all participants." Thus, the findings presented in yhis article are based on the differential occurrence and severity of nocturia in patients treated with a single thiazide or hydrocholothiazide diuretic monotherapy or diuretic combination therapy in the morning at baseline that were allocated to switch their therapy to bedtime. However, it is

	stated “If bedtime use was problematic, switching to dinnertime was suggested.” The previously published Garrison et al. paper further stated research assistants (page 3, top paragraph right-hand column): “If morning use is problematic, they ask participants to try taking it with lunch.” Thus, a key element of adherence in the entitled BedMed trial was not entirely a comparison of the enhanced beneficial effects and/or risk for adverse effects of antihypertensive therapy ingested specifcially in the morning vs at bedtime. Collection of information for the BedMed nocturia substudy was obtained by follow-up telephone interviews or email questionnaires according to the authors (bottom of page 9 bottom to top of page 10) “at 6-weeks to obtain self-reported adherence to bedtime antihypertensive use (“Are you taking your blood pressure medication at bedtime?”; and if “no” - the reason for not doing so), and to assess nocturia. Participants could report nocturia as “no”, “minor”, or “major” burden (subjective overall assessment, no itemized criteria), and they were asked to quantify the number of overnight urinations per week by estimating the number of nights they rose to urinate, and the number of times per night they urinated on those evenings. The same follow-up questions were asked again at 6-months, either by telephone or by e-mail questionnaire (participant’s choice), and again every 6-months thereafter.” Criticism 1. The authors propose a unique definition of adherence for the purpose of conducting the BedMed nocturia substudy. This raises questions of the consequence of such a definition on the findings of the substudy. From a circadian medicine perspective, true adherence should be defined as taking the prescribed diuretic medication in the prescribed dose, at the prescribed or allocated time, and taking it consistently at the right time from one day to the next. Criticism 2. The authors indicate the timing of the diuretic medication need not be at bedtime (as indicated by the title of the trial, i.e., BedMed and the title of the submitted manuscript: “If bedtime use was problematic, switching to dinnertime was suggested” and “If morning use is problematic, they ask participants to try taking it with lunch.” Given the fact that the Hygia project, in particular, was designed to compare the effects of antihypertension treatment taken specifically at bedtime to control the asleep blood pressure vs the effects of antihypertension treatment taken specifically upon awakening from sleep to control awake blood pressure, allowed deviation from these two treatments times compromises the pragmatic testing of the findings of the MAPEC and Hygia trials. Thus, since the goal of the trial is to assess the impact of bedtime in comparison to morning-time ingestion of one’s prescribed antihypertension medication(s) on the selected outcomes variables, participants who are allotted to morning-time therapy but ingest their medication at lunch time and participants who are allotted to bedtime therapy but ingest their medications at dinnertime should not be considered properly adherent. Furthermore, the response (measured by occurrence of nocturia and its severity and burden) to a diuretic can vary according to the biological (circadian rhythm) time of its ingestion. This was demonstrated almost 30 years ago for trichlormethiazide in animal models; the diuretic effect is greater when administered around the commencement of the rest than during the beginning or middle of the activity period of the animals (Fujimura et al. Chronopharmacology of trichlormethiazide in rats. Jpn J

	Pharmacol . 1991 Feb;55(2):294-8). Furthermore, of relevance to the outcomes of the BedMed trial, the blood pressure-lowering effect of at least six classes of antihypertension medications are substantially greater when consistently administered as a full daily dose at bedtime than upon awakening (Smolensky et al. Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press Monit. 2010 Aug;15(4):173-80; Hermida-Ayala RG, et al. Ingestion-time differences in the pharmacodynamics of dual-combination hypertension therapies: Systematic review and meta-analysis of published human trials. Chronobiol Int. 2022 Apr;39(4):493-512). Therefore, how can the authors justify the continued inclusion of those participants who do not take their medication at the designated times to which they are allotted to assess any of the outcomes, including occurrence and severity of nocturia? Criticism 3. Page 11, 1st paragraph, states: “Advice from research assistants was to delay the next morning dose until bedtime, and to continue all future doses at bedtime. If bedtime use was problematic, switching to dinnertime was suggested.” The authors should state how many participants elected to take their diuretic medications at dinnertime rather than bedtime and whether the outcome measures -- number of overnight urinations per week, number of times per night of urination, self-perceived burden, and adherence – varied according to the actual allocated ingestion-time schedule. Criticism 4. The design of the prospective nocturia substudy relating to the adherence to the bedtime allocation as an intention to treat paradigm is problematic. The nocturia substudy in actuality entails four different variables relating to adherence to bedtime diuretic therapy: (i) assessment of the use of the diuretic medication at bedtime as allocated, (ii) assessment of the number of nights affected by overnight urinations per week, (iii) assessment of the number of overnight urinations per night, (iv) and assessment of the self-perceived burden of nocturia. These outcomes measures are interdependent. Actual nightly adherence to taking the diuretic medication at bedtime is a key risk factor for occurrence and severity (burden and number of urinations) of nocturia than adherence to allocation of bedtime diuretic therapy as defined by the authors and analyzed by the intention to treat paradigm. Besides the concern about recall basis, absence of information of actual adherence to the bedtime diuretic treatment schedule by each participant from one night to the next makes it impossible to confidentially link the reported information on the number of overnight urinations per week, number of times per night of urinations, and self-perceived burden to one’s allocation to the bedtime diuretic schedule and also the cardiovascular and other outcomes of the BedMed trial. If it is not known if participants took their diuretic medication at every night, how can it be determined if nocturia was due to the consistent ingestion at bedtime of the diuretic? Criticism 5. What was the dose of each participant’s diuretic medication? The authors state the dose of the diuretic medication was unknown. It could have been determined either through the telephone or e-mail questionnaire follow-up interviews or, according to Garrison et al., potentially by “linkable healthcare databases tracking medical services rendered during healthcare interactions …. prescriptions dispensed .....” Thus the authors have neglected to assess whether adherence as well as all of the

	nocturia outcome variables are diuretic dose-dependent, which needs to be done. Criticism 6. The four different study variables relating to adherence to bedtime diuretic therapy -- (i) use of the diuretic medication at bedtime as allocated, (ii) number of nights affected by overnight urinations per week, (iii) number of overnight urinations per night, (iv) and self-perceived burden caused by nocturia -- require different methods of assessment other than the intention to treat one that was used. According to Figure 1, the baseline data concerning the number of nights affected by overnight urinations per week, and the number of overnight urinations per night are representative of 203 participants, while at 6 weeks and 6 months they are representative, respectively, of 203 and 198 participants. How many of these participants took their diuretic medication at lunchtime and how many at bedtime? Should not only those same participants who strictly adhered to the allocation to bedtime (not dinnertime) diuretic therapy, and who actually were consistent in taking the diuretic at bedtime during the six-month span be assessed at baseline and after 6 weeks and 6 months for the variables of the number of overnight urinations per week, number of overnight urinations per night, and self-perceived burden of nocturia? Is not the overall goal of the trial to assess if bedtime antihypertension therapy is more protective of the stated cardiovascular morbidity and mortality outcomes than morning-time therapy? Moreover, the presented information concerning the number of participants who were adherent at the different time points of follow-up is somewhat confusing. As related on Page 17, at 6-Weeks “Change in the number of overnight urinations per week could be calculated for 180 diuretic users, and 330 non-diuretic users (Figure 3). Why only 180 and not the 203 bedtime allocated diuretic users? At 6-months, the number fell to 153 participants. How is possible to properly compare findings at baseline vs those at 6 weeks and 6 months for the variables of number of nights when nocturia occurred, the number of urinations per night and the burden of nocturia when the number of participants is not the same at baseline and each of the follow-up times -- and additionally when information on the actual adherence to taking the medication at bedtime every day is unknown? Criticism 7. If the major research question is whether bedtime ingestion of one’s diuretic poses risk of nocturia and its severity and burden, why do the authors neglect assessing and comparing these variables only in those participants at baseline vs at 6 weeks and 6 months specifically adherent to the bedtime (exclusion of participants who ingested medication at dinnertime or otherwise ceased adherence) diuretic allocation? Moreover, is not the change from the allocated “bedtime” to the “lunchtime” ingestion schedule, itself, nonadherence? Criticism 8. The title of this manuscript is “Tolerability of bedtime diuretics: A prospective cohort analysis”. This reviewer finds the title misleading, since the manuscript describes the comparative differences in the occurrence, severity, and burden of nocturia in those allocated to a diuretic vs those allocated to other classes of blood pressure medications. In this case should not the title be “Differential Occurrence of Nocturia and Its Severity in Participants Allocated to Bedtime Diuretic vs. Other Classes of Antihypertension Therapy”. Moreover, why it is necessary to assess the occurrence of nocturia and its severity in those allocated to a diuretic medication in terms of the occurrence of

	nocturia and its severity of those prescribed antihypertension medications other than a diuretic?

REVIEWER	Gosse , P University Hospital of Bordeaux, Hopital Saint André, Bordeaux, France, Cardiology/Hypertension Department
REVIEW RETURNED	19-Jan-2023

GENERAL COMMENTS	This paper reports the results of a prespecified ancillary study embedded within the Bedmed trial . The objective was to validate or refute the common belief that bedtime diuretics are poorly tolerated due to nocturia. The protocol and results are well described . Adherence to bedtime allocation time was significantly lower in diuretic users. The only concerns I have are about the discussion and conclusion. As pointed out by the authors , the potential selection bias may have reduced the percentage of patients to become non adherent to bedtime allocation. Nocturia as a major burden was tenfold more frequent when diuretic were allocated at bedtime. As adherence to treatment is certainly a major issue in treating hypertensive patients I do not share the conclusion that bedtime use is viable for most hypertensive patients. The last two words of this conclusion are “if indicated”. The TIME study has now been published (Lancet 2022; 400: 1417–25) and show no advantage of evening dosing. The results of this study on adherence and especially for diuretics should be discussed in your paper: “: Reported non adherence to allocated dose timing at any point in the study was more common in those assigned to evening treatment than to morning treatment (4091 [39·0%] vs 2384 [22·5%];p<0·0001). 617 (3·2%) participants reported that they had to change the time of day that a diuretic was administered (546 [5·2%] in the evening group vs 71 [0·7%] in the morning group; p<0·0001.”

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Michael Smolensky, Cockrell School of Engineering, The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA.
Comments to the Author:
According to Garrison et al., Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial. BMJ Open. 2022 and the 2nd paragraph on Page 5 of the submitted manuscript “the BedMed trial randomizes Canadian primary care patients with hypertension to take their existing antihypertensive medications either in the morning, or at bedtime, and examines mortality and morbidity outcomes.” The same page and paragraph additionally states “To determine how well diuretics are tolerated at bedtime we conducted a pre-specified prospective cohort study embedded within the ongoing BedMed trial.” The authors further state “This paper examines the findings of those participants with a single morning antihypertensive at baseline randomized to switch that antihypertensive to bedtime. Our goal was to compare adherence with bedtime allocation, and self-reported nocturia burden, between those switching a diuretic to bedtime, and those switching other types of blood pressure lowering medication to bedtime. Note, our definition of adherence to allocation time differs from the conventional notion. When we refer to adherence to bedtime allocation, we are talking about the participant’s intention to use their antihypertensive at bedtime. This study is NOT evaluating the extent to which individual doses are missed. As such, we did not

compare bedtime diuretic use to morning diuretic use because morning medication use was already well established for all participants."
Thus, the findings presented in yhis article are based on the differential occurrence and severity of nocturia in patients treated with a single thiazide or hydrocholothiazide diuretic monotherapy or diuretic combination therapy in the morning at baseline that were allocated to switch their therapy to bedtime. However, it is stated "If bedtime use was problematic, switching to dinnertime was suggested." The previously published Garrison et al. paper further stated research assistants (page 3, top paragraph right-hand column): "If morning use is problematic, they ask participants to try taking it with lunch." Thus, a key element of adherence in the entitled BedMed trial was not entirely a comparison of the enhanced beneficial effects and/or risk for adverse effects of antihypertensive therapy ingested specifcially in the morning vs at bedtime.
Collection of information for the BedMed nocturia substudy was obtained by follow-up telephone interviews or email questionnaires according to the authors (bottom of page 9 bottom to top of page 10) "at 6-weeks to obtain self-reported adherence to bedtime antihypertensive use ("Are you taking your blood pressure medication at bedtime?"; and if "no" - the reason for not doing so), and to assess nocturia. Participants could report nocturia as "no", "minor", or "major" burden (subjective overall assessment, no itemized criteria), and they were asked to quantify the number of overnight urinations per week by estimating the number of nights they rose to urinate, and the number of times per night they urinated on those evenings. The same follow-up questions were asked again at 6-months, either by telephone or by e-mail questionnaire (participant's choice), and again every 6-months thereafter."

Criticism 1. The authors propose a unique definition of adherence for the purpose of conducting the BedMed nocturia substudy. This raises questions of the consequence of such a definition on the findings of the substudy. From a circadian medicine perspective, true adherence should be defined as taking the prescribed diuretic medication in the prescribed dose, at the prescribed or allocated time, and taking it consistently at the right time from one day to the next.

RESPONSE:
As the reviewer points out, we are examining willingness on the part of the patient to take their medication at bedtime, and not their adherence to individual doses. Patient's will want to know how likely it is they will have problems complying with the suggestion to switch their diuretic to bedtime. Prescribers will want to know the % of patients that will tell them they had problems with their recommendation. From both a clinician, and patient perspective, a global assessment of the patient's experience is highly relevant, and we believe, the best clinical outcome to measure and report.

Criticism 2. The authors indicate the timing of the diuretic medication need not be at bedtime (as indicated by the title of the trial, i.e., BedMed and the title of the submitted manuscript: "If bedtime use was problematic, switching to dinnertime was suggested" and "If morning use is problematic, they ask participants to try taking it with lunch." Given the fact that the Hygia project, in particular, was designed to compare the effects of antihypertension treatment taken specifically at bedtime to control the asleep blood pressure vs the effects of antihypertension treatment taken specifically upon awakening from sleep to control awake blood pressure, allowed deviation from these two treatments times compromises the pragmatic testing of the findings of the MAPEC and Hygia trials. Thus, since the goal of the trial is to assess the impact of bedtime in comparison to morning-time ingestion of one's prescribed antihypertension medication(s) on the selected outcomes variables, participants who are allotted to morning-time therapy but ingest their medication at lunch time and participants who are allotted to bedtime therapy but ingest their medications at dinnertime should not be considered properly adherent.
Furthermore, the response (measured by occurrence of nocturia and its severity and burden) to a diuretic can vary according to the biological (circadian rhythm) time of its ingestion. This was demonstrated almost 30 years ago for trichlormethiazide in animal models; the diuretic effect is greater when administered around the commencement of the rest than during the beginning or middle

of the activity period of the animals (Fujimura et al. Chronopharmacology of trichlormethiazide in rats. Jpn J Pharmacol . 1991 Feb;55(2):294-8). Furthermore, of relevance to the outcomes of the BedMed trial, the blood pressure-lowering effect of at least six classes of antihypertension medications are substantially greater when consistently administered as a full daily dose at bedtime than upon awakening (Smolensky et al. Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press Monit. 2010 Aug;15(4):173-80; Hermida-Ayala RG, et al. Ingestion-time differences in the pharmacodynamics of dual-combination hypertension therapies: Systematic review and meta-analysis of published human trials. Chronobiol Int. 2022 Apr;39(4):493-512).
Therefore, how can the authors justify the continued inclusion of those participants who do not take their medication at the designated times to which they are allotted to assess any of the outcomes, including occurrence and severity of nocturia?

RESPONSE:
We appreciate that a study exploring the physiologic effects of administration time would very much want to control the precise timing of each medication and measurement. However, for a trial evaluating how patients and prescribers will experience the intervention in the real world, it is more important to mirror what we expect to be real world practice. There are some key things to appreciate here:

1. Patients were NOT initially presented with the ability to take their medication at dinnertime. This was only brought up in follow-up visits when patients described to our research assistants that they were struggling with bedtime use and the research assistant thought they might switch back to morning.
2. Patients will struggle with bedtime medications for a variety of reasons. Separate from nocturia, if the pill being switched is the only pill they take at bedtime, they may have trouble remembering it, and prefer to take it at dinnertime when they have other medications to take at the same time. Whatever the reason, allowing individuals to switch to dinnertime to cope with such difficulties mirrors what would likely occur in the real world, which is the goal of a pragmatic trial.

To make it more clear how dinnertime use was introduced to participants, we have made the following alteration to a sentence in the methods section: “If bedtime use proved problematic, and there was concern participants would switch back to morning, switching to dinnertime was suggested.”

Criticism 3. Page 11, 1st paragraph, states: “Advice from research assistants was to delay the next morning dose until bedtime, and to continue all future doses at bedtime. If bedtime use was problematic, switching to dinnertime was suggested.” The authors should state how many participants elected to take their diuretic medications at dinnertime rather than bedtime and whether the outcome measures -- number of overnight urinations per week, number of times per night of urination, self-perceived burden, and adherence – varied according to the actual allocated ingestion-time schedule.

RESPONSE:
Thank you for the suggestion. At 6-months, in the diuretic group, only 6 of 153 individuals considered compliant (3.9%) were not taking their diuretic at bedtime. This includes 5 taking it at dinnertime and 1 taking it twice daily based on their physician’s advice. We have added detailed information on when medications were taken into the first paragraph of the results section where we state: “At 6-months, of those considered compliant with allocation in the diuretic group, 147/153 (96.1%) took their medication at bedtime, 5/153 (3.3%) took it at dinner, and 1/153 (0.7%) had their diuretic split into twice daily dosing. This compares to the non-diuretic group, of whom 282/301 (93.7%) took their medication at bedtime, 12/301 (4.0%) took it at dinner, and 7/301 (2.3%) had been split into twice daily dosing.”
Although the reviewer further suggests we break out our results according to dinnertime versus bedtime administration, this would clearly not be productive given the number of dinnertime users in

the diuretic group is too small for this to be meaningful (i.e. only 6 such participants). Were there more participants with dinnertime use, such a breakdown would still be problematic because participants were not allocated to dinnertime, they CHOSE to take their medication then, which opens up opportunities for selection bias that would confound our findings. To further address the reviewer's point, and incorporate our response, we have added the following statement to the discussion of limitations: "Similarly, while our allowing patients struggling with bedtime use to switch their diuretic to dinnertime might lessen nocturia, this would likely reflect real world practice."
In responding to this point, we realize that our modified intention-to-treat assumptions failed to describe how our analysis handled physicians changing participants to twice daily dosing. As such, we have added the following sentence to that section: "If physicians changed the participant's medication to twice daily (with the second dose at bedtime or dinnertime) we considered them to still experience the effects of an evening dose, and included them in the analysis." We are grateful for the ability to make that addition.

Criticism 4. The design of the prospective nocturia substudy relating to the adherence to the bedtime allocation as an intention to treat paradigm is problematic. The nocturia substudy in actuality entails four different variables relating to adherence to bedtime diuretic therapy: (i) assessment of the use of the diuretic medication at bedtime as allocated, (ii) assessment of the number of nights affected by overnight urinations per week, (iii) assessment of the number of overnight urinations per night, (iv) and assessment of the self-perceived burden of nocturia. These outcomes measures are interdependent. Actual nightly adherence to taking the diuretic medication at bedtime is a key risk factor for occurrence and severity (burden and number of urinations) of nocturia than adherence to allocation of bedtime diuretic therapy as defined by the authors and analyzed by the intention to treat paradigm. Besides the concern about recall basis, absence of information of actual adherence to the bedtime diuretic treatment schedule by each participant from one night to the next makes it impossible to confidentially link the reported information on the number of overnight urinations per week, number of times per night of urinations, and self-perceived burden to one's allocation to the bedtime diuretic schedule and also the cardiovascular and other outcomes of the BedMed trial. If it is not known if participants took their diuretic medication at every night, how can it be determined if nocturia was due to the consistent ingestion at bedtime of the diuretic?

RESPONSE:
We are uncertain as to the point being made here. Our assessment of compliance with allocation time relies on self-report. So far as is discernable from the reporting of the other major antihypertensive timing trials (MAPEC, Hygia, TIME) no other antihypertensive timing trial has used any other method of assessing allocation compliance. It's true that participants could falsely report their medication timing, but that would be a reflection of compliance to a bedtime recommendation in the real world. We are also concerned that the reviewer is suggesting our recommending dinnertime use to struggling participants compromises the evaluation of cardiovascular outcomes. It is BECAUSE the main trial is focused on cardiovascular outcomes that dinnertime use was permitted. This is due to our overall trial having an intention-to-treat analysis for virtually all outcomes. If individuals struggle with bedtime use and switch back to morning, that will make the two groups look more similar. If they can instead manage to tolerate dinnertime use, that is more likely to preserve at least some of the physiologic difference that might be expected from our timing intervention. In an intention-to-treat analysis, a bedtime allocated patient taking their medication at dinnertime is better than the same individual taking it in the morning.

Criticism 5. What was the dose of each participant's diuretic medication? The authors state the dose of the diuretic medication was unknown. It could have been determined either through the telephone or e-mail questionnaire follow-up interviews or, according to Garrison et al., potentially by "linkable healthcare databases tracking medical services rendered during healthcare interactions ….

prescriptions dispensed ....." Thus the authors have neglected to assess whether adherence as well as all of the nocturia outcome variables are diuretic dose-dependent, which needs to be done.

RESPONSE:
We appreciate the suggestion, and agree that it would have been useful to have the information on diuretic dosing available, and to break out results according to diuretic dose in an online supplement. Unfortunately, doing so now is problematic for the following reasons:

1. While we can theoretically make phone calls to participants asking about baseline medication dosage, many of them enrolled in the trial 5-years ago, making such recollection problematic. There are also drop outs and loss to follow-up in every trial, with a resulting survivor bias that would confound such an assessment to some degree. As such we would only be able to meaningfully rely on the administrative claims data to determine baseline diuretic dose. Of our administrative claims data partners, only Alberta Health Services (AHS) can provide us these numbers in a timely manner, and without substantial cost. This would only cover 83% of our study cohort (i.e. provide information on all Alberta residents, but not residents of other provinces).
2. Unfortunately, this would require substantial work on the part of AHS to obtain and process this data, and we have other priorities for the time they are donating to the study. Hence, this is not an easy request to accomodate.
3. The pharmaceutical data available to AHS does not include “directions for use”. Hence, we would not be able to detect tablet splitting, which is common in Canada. This would lessen our certainty of the dose being ingested, and lessen the value of the proposed analysis.
4. Different diuretics were in use in our study. While HCTZ was the most common, 54 of the 203 diuretic cohort (27%) used a diuretic other than HCTZ, which poses problems so far as equating diuretic potency.

In summary: We agree that determining whether or not there is a dose effect would be of interest, but consider such an analysis to be tangential to the main question being addressed in the paper. Given the above limitations/hurdles we would face, and given the suggested breakdown of results would only appear in an online supplement, with a sentence or two in Results, we prefer not to pursue this additional analysis unless requested to do so by the BMJ-Open editors.

Criticism 6. The four different study variables relating to adherence to bedtime diuretic therapy -- (i) use of the diuretic medication at bedtime as allocated, (ii) number of nights affected by overnight urinations per week, (iii) number of overnight urinations per night, (iv) and self-perceived burden caused by nocturia -- require different methods of assessment other than the intention to treat one that was used.

According to Figure 1, the baseline data concerning the number of nights affected by overnight urinations per week, and the number of overnight urinations per night are representative of 203 participants, while at 6 weeks and 6 months they are representative, respectively, of 203 and 198 participants. How many of these participants took their diuretic medication at lunchtime and how many at bedtime? Should not only those same participants who strictly adhered to the allocation to bedtime (not dinnertime) diuretic therapy, and who actually were consistent in taking the diuretic at bedtime during the six-month span be assessed at baseline and after 6 weeks and 6 months for the variables of the number of overnight urinations per week, number of overnight urinations per night, and self-perceived burden of nocturia? Is not the overall goal of the trial to assess if bedtime antihypertension therapy is more protective of the stated cardiovascular morbidity and mortality outcomes than morning-time therapy?

Moreover, the presented information concerning the number of participants who were adherent at the different time points of follow-up is somewhat confusing. As related on Page 17, at 6-Weeks “Change in the number of overnight urinations per week could be calculated for 180 diuretic users, and 330 non-diuretic users (Figure 3). Why only 180 and not the 203 bedtime allocated diuretic users? At 6-months, the number fell to 153 participants. How is possible to properly compare findings at baseline vs those at 6 weeks and 6 months for the variables of number of nights when nocturia occurred, the

number of urinations per night and the burden of nocturia when the number of participants is not the same at baseline and each of the follow-up times -- and additionally when information on the actual adherence to taking the medication at bedtime every day is unknown?

RESPONSE: We believe that we have thoroughly addressed the concern about dinnertime use in our earlier responses and would simply re-iterate here that we have now included the number of individuals to which this applies, and shown that it is too small to meaningfully break out the results in the manner suggested.
The denominators for each analysis are different because a different number of individuals are able to contribute data at each timepoint, according to our modified intention-to-treat assumptions. In reviewing the text, we believe this is already sufficiently clear. I would further point out that, when determining how to deal with missing data or noncompliance we have consistently made the choice that would bias in favour of finding more, rather than less, nocturia. Given our finding that most patients can tolerate bedtime diuretics, we believe those are the correct, conservative, assumptions to have made.

Criticism 7. If the major research question is whether bedtime ingestion of one's diuretic poses risk of nocturia and its severity and burden, why do the authors neglect assessing and comparing these variables only in those participants at baseline vs at 6 weeks and 6 months specifically adherent to the bedtime (exclusion of participants who ingested medication at dinnertime or otherwise ceased adherence) diuretic allocation? Moreover, is not the change from the allocated "bedtime" to the "lunchtime" ingestion schedule, itself, nonadherence?

RESPONSE: There is nobody in this analysis allocated to lunchtime. We presume you mean dinnertime (when the largest meal of the day is taken, typically around 5:00-7:00 PM) and we have already addressed these concerns above. It was important to conduct this analysis only with those who could be considered adherent (or who failed the switch to bedtime because of nocturia) because this was the analytic option that would bias in favor of showing the most nocturia. If you are looking at an adverse effect of medication, a pure intention-to-treat analysis, which would include everyone who was randomized (including those who were noncompliant or for whom there was missing data) would have lessened the ability to detect that adverse effect. Imagine that we had included those who had returned to morning medications for reasons other than nocturia, or who had stopped their antihypertensive altogether. Assuming those individuals are relatively evenly distributed between groups, it would have made the groups look more similar to include them, and lessened the between-group difference in nocturia. Given our finding bedtime diuretics to be better tolerated than expected, analytic assumptions that bias towards finding more nocturia are the conservative, appropriate choice.

Criticism 8. The title of this manuscript is "Tolerability of bedtime diuretics: A prospective cohort analysis". This reviewer finds the title misleading, since the manuscript describes the comparative differences in the occurrence, severity, and burden of nocturia in those allocated to a diuretic vs those allocated to other classes of blood pressure medications. In this case should not the title be "Differential Occurrence of Nocturia and Its Severity in Participants Allocated to Bedtime Diuretic vs. Other Classes of Antihypertension Therapy". Moreover, why it is necessary to assess the occurrence of nocturia and its severity in those allocated to a diuretic medication in terms of the occurrence of nocturia and its severity of those prescribed antihypertension medications other than a diuretic?

RESPONSE: We thank the reviewer for their suggestion but don't see how this title change is better descriptive. The primary outcome of this study is compliance with bedtime allocation time at 6-months between groups, which we think "tolerability" describes. Our nocturia measures are secondary outcomes.
In terms of our choice of comparator, we could have conceivably compared diuretic users to their own baseline (at which point 100% were compliant), but there are reasons other than nocturia that make

switching medications to bedtime problematic – such as remembering to take it, or perceiving that BP control is worse. Other medical considerations beyond hypertension might also lead to a medication change. As such, the best comparator is someone who has been through the same screening process, in the same setting, who is attempting to change a non-diuretic to bedtime. As we believe this is already well described in the text, we have made no changes.

Reviewer: 2
Dr. P Gosse , University Hospital of Bordeaux, Hopital Saint André, Bordeaux, France
Comments to the Author:
This paper reports the results of a prespecified ancillary study embedded within the Bedmed trial . The objective was to validate or refute the common belief that bedtime diuretics are poorly tolerated due to nocturia. The protocol and results are well described . Adherence to bedtime allocation time was significantly lower in diuretic users. The only concerns I have are about the discussion and conclusion. As pointed out by the authors , the potential selection bias may have reduced the percentage of patients to become non adherent to bedtime allocation. Nocturia as a major burden was tenfold more frequent when diuretic were allocated at bedtime. As adherence to treatment is certainly a major issue in treating hypertensive patients I do not share the conclusion that bedtime use is viable for most hypertensive patients. The last two words of this conclusion are “if indicated”. The TIME study has now been published (Lancet 2022; 400: 1417–25) and show no advantage of evening dosing. The results of this study on adherence and especially for diuretics should be discussed in your paper: “: Reported non adherence to allocated dose timing at any point in the study was more common in those assigned to evening treatment than to morning treatment (4091 [39·0%] vs 2384 [22·5%];p<0·0001). 617 (3·2%) participants reported that they had to change the time of day that a diuretic was administered (546 [5·2%] in the evening group vs 71 [0·7%] in the morning group; p<0·0001.”

RESPONSE:
We thank Dr. Gosse for some good suggestions.
1) While we still believe 77.3% of participants being able to adhere to bedtime diuretic use at 6 months makes it reasonable to state that bedtime use is viable for “most” hypertensive patients despite the potential for selection bias, we understand Dr. Gosse’s concern, and have altered the wording of our key conclusion by changing “most” to “many” and by qualifying the “if indicated” statement to suggest bedtime use is not currently indicated. Specifically, our conclusion now states: “Bedtime diuretic use is viable for many hypertensive patients, should it ever become clinically indicated.”
2) We agree that we should discuss the TIME trial, and have added the following to the discussion section: “To our knowledge, our study is the first to prospectively evaluate the link between bedtime diuretic use and nocturia. Our finding the majority of diuretic users able to adhere to bedtime use is consistent with the generally weak and variable association of diuretics and nocturia in cross-sectional studies,11, 13 the inability of baseline diuretics to predict future nocturia (2-year incidence) in 1,289 community dwelling MESA study respondents 60 years and older,26 and the number of participants changing the timing of a diuretic in the TIME antihypertensive timing trial.27 While 22.5% of TIME subjects used a diuretic at baseline, post-randomization diuretic timing changes were made by 5.2% of the evening group vs 0.7% of the morning group (p<0.0001), suggesting 5.2% / 22.5% = ¼ of diuretic users chose not to continue bedtime use.”
We have also updated the wording at the end of the document to describe the TIME trial as having completed its reporting, and having found neither benefit, nor harm, to bedtime antihypertensives.

Reviewer: 1
Competing interests of Reviewer: none

Reviewer: 2
Competing interests of Reviewer: none

VERSION 2 – REVIEW

REVIEWER	Smolensky, Michael Cockrell School of Engineering, The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA. , Department of Biomedical Engineering
REVIEW RETURNED	19-Apr-2023

GENERAL COMMENTS	General Comments: Authors, thank you for the reply to each of my criticisms; they were helpful in answering many of my concerns and clarifying several of the points which were, in my mind, concerning. Specific Comments: 1. With regards to the Authors' Response to my Comment #4, i.e., "Our assessment of compliance with allocation time relies on self-report. So far as is discernable from the reporting of the other major antihypertensive timing trials (MAPEC, Hygia, TIME) no other antihypertensive timing trial has used any other method of assessing allocation compliance." I do not feel the authors' rebuttal statement is accurate. The Methods section of the Hygia Chronotherapy Trial paper published in the European Heart Journal states: "Investigators performed the Morisky-Green test23 at each scheduled ABPM visit during follow-up to assess participant compliance with the prescribed BP-lowering treatment and schedule. Additionally, at every follow-up clinical visit adverse events – including type, duration, seriousness, intensity, and possible relation to hypertension therapy and schedule – were registered when spontaneously reported by the patient and/or revealed through non-direct questioning and physical examination." The results section of the Hygia journal article additionally states: "There were no treatment-time differences in prevalence of patients reporting adverse effects at any visit during follow-up (6.7 vs. 6.0% for the awakening and bedtime-treatment regimen, respectively; P=0.061). Poor adherence (Morisky-Green test) was reported at any visit during follow-up by 2.8 and 2.9%, respectively, of patients of the awakening and bedtime-treatment groups (P=0.813)." 2. Page 49, lines 6-8: Was a change by the physician of the dose of the diuretic an option, or only a change in its timing or the splitting of the dose? 3. Page 53, lines 23-29: The portion of sentence on these lines that states "worsening of BP control (8/34, 23.5%)," is somewhat incomplete. The BedMed trial is designed essentially to assess if targeting the reduction of the asleep blood pressure (although in the pragmatic scenario it is not assessed by an ambulatory device) rather than awake blood pressure that is captured by daytime office blood pressure measurement. Thus, I recommended it prudent to amend that portion of the sentence to read something like "worsening of office assessed daytime blood pressure". Moreover, according to the findings of the Hygia investigation, an enhanced 24-hour blood pressure dipper pattern -- as a result of decreased asleep and somewhat higher daytime blood pressure -- was associated with reduced risk for CVD outcomes.

REVIEWER	Gosse , P University Hospital of Bordeaux, Hopital Saint André, Bordeaux, France, Cardiology/Hypertension Department
REVIEW RETURNED	12-Apr-2023

GENERAL COMMENTS	The authors made acceptable modifications to answer our concerns

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. P Gosse , University Hospital of Bordeaux, Hopital Saint André, Bordeaux, France

Comments to the Author:

The authors made acceptable modifications to answer our concerns

RESPONSE: Thank you for reviewing our manuscript!

Reviewer: 1

Dr. Michael Smolensky, Cockrell School of Engineering, The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA.

Comments to the Author:

Comments on revised version

General Comments:

Authors, thank you for the reply to each of my criticisms; they were helpful in answering many of my concerns and clarifying several of the points which were, in my mind, concerning.

Specific Comments:

1. With regards to the Authors' Response to my Comment #4, i.e., "Our assessment of compliance with allocation time relies on self-report. So far as is discernable from the reporting of the other major antihypertensive timing trials (MAPEC, Hygia, TIME) no other antihypertensive timing trial has used any other method of assessing allocation compliance."

I do not feel the authors' rebuttal statement is accurate.

The Methods section of the Hygia Chronotherapy Trial paper published in the European Heart Journal states: "Investigators performed the Morisky-Green test23 at each scheduled ABPM visit during follow-up to assess participant compliance with the prescribed BP-lowering treatment and schedule. Additionally, at every follow-up clinical visit adverse events – including type, duration, seriousness, intensity, and possible relation to hypertension therapy and schedule – were registered when spontaneously reported by the patient and/or revealed through non-direct questioning and physical examination."

The results section of the Hygia journal article additionally states: “There were no treatment-time differences in prevalence of patients reporting adverse effects at any visit during follow-up (6.7 vs. 6.0% for the awakening and bedtime-treatment regimen, respectively; P=0.061). Poor adherence (Morisky-Green test) was reported at any visit during follow-up by 2.8 and 2.9%, respectively, of patients of the awakening and bedtime-treatment groups (P=0.813).”

RESPONSE: Thank you for the detailed information. The Morisky-Green test assesses compliance by asking participants 8 questions that are expected to correlate with the likelihood for a participant to miss individual doses. It does not assess their willingness to, or success in, taking their medication at the allocated time - which is what is relevant to our study, and which participants would need to be asked about separately.

Towards the point we made earlier (which the reviewer is responding to), given the Morisky-Green test is a questionnaire, and that medication timing would need to be asked about separately, we would still consider that compliance to allocation time in the Hygia trial was self-reported. We thank the reviewer for the information. As there are no suggested changes here, we have made none.

2. Page 49, lines 6-8: Was a change by the physician of the dose of the diuretic an option, or only a change in its timing or the splitting of the dose?

RESPONSE: Outside of the timing change being randomly allocated, physicians were free to prescribe and adjust medications as they saw fit. We had already stated that physicians “…applied their own judgement as to how to make the change…”. To help make this clearer, we have added the sentence “If medication type, dosage, or timing needed to be changed, for any reason, those decisions were at the sole discretion of the prescribing physician.”

3. Page 53, lines 23-29: The portion of sentence on these lines that states “worsening of BP control (8/34, 23.5%),” is somewhat incomplete. The BedMed trial is designed essentially to assess if targeting the reduction of the asleep blood pressure (although in the pragmatic scenario it is not assessed by an ambulatory device) rather than awake blood pressure that is captured by daytime office blood pressure measurement. Thus, I recommended it prudent to amend that portion of the sentence to read something like “worsening of office assessed daytime blood pressure”.

Moreover, according to the findings of the Hygia investigation, an enhanced 24-hour blood pressure dipper pattern -- as a result of decreased asleep and somewhat higher daytime blood pressure -- was associated with reduced risk for CVD outcomes.

RESPONSE: It is common in Canada for patients to use home blood pressure monitors, so BP is not only managed by office readings. Additionally, although it is far less common, ambulatory blood pressure monitoring is available and occasionally utilized to assess BP control. We did not track how patient’s BP was being followed in the community, so stating “worsening BP control”, without specifying the location in which BP was being assessed, seems the most prudent response here. For the reasons given, we feel the wording should not change, but thank the reviewer for their suggestion and insight.

Reviewer: 2

Competing interests of Reviewer: none

Reviewer: 1

Competing interests of Reviewer: None

Editor(s)' Comments to Author (if any):

VERSION 3 – REVIEW

REVIEWER	Smolensky, Michael Cockrell School of Engineering, The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA. , Department of Biomedical Engineering
REVIEW RETURNED	10-May-2023

GENERAL COMMENTS	No further comments to authors

VERSION 3 – AUTHOR RESPONSE