Scoping Review Protocol: The Effect of Mandibular Advancement Devices on the Autonomic Nervous System in Obstructive Sleep Apnea Patients

by

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# Abstract

BACKGROUND: Obstructive sleep apnea (OSA) is a type of disordered breathing defined by repetitive airflow obstruction during sleep due to upper airway collapse. Each obstructive event contributes to decreased blood oxygen (i.e., hypoxia). OSA is associated with vascular damage and dysfunction of the cardiac autonomic nervous system. Increased sympathetic nervous activity (SNA) is a type of cardiac autonomic dysfunction observed even in mild OSA. SNA can be measured using a variety of indirect and direct techniques. To our knowledge, only indirect techniques have been published to measure SNA during a mandibular advancement device (MAD) intervention, such as heart rate variability (HRV) and urine catecholamines. There appears to be no published literature directly measuring SNA in a MAD intervention with microneurography.

OBJECTIVE: We aim to conduct a scoping review to map the direct and indirect techniques used to measure autonomic nervous activity in OSA patients managed with MAD therapy. Secondly, we aim to assess the extent of current knowledge regarding changes in SNA in patients using MADs and determine the appropriateness of a systematic review of the topic.

DESIGN: Under librarian guidance, relevant databases were identified, and an initial search strategy was built and later refined considering initial search results. The final search was confirmed with all team members and applied in Ovid MEDLINE In-Process & Other Non-Indexed Citations (1946 to the present), Ovid Embase (1974 to the present), CINAHL Plus with Full Text (1937 to the present), Scopus, Cochrane Library and Google Scholar (limited to 2016-2022 and first 100 results).

RESULTS: Our search identified 233 results, 82 duplicates were removed, leaving 151 results for screening.

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# Rationale

Obstructive sleep apnea (OSA) is a type of disordered breathing defined by repetitive airflow obstruction during sleep due to upper airway collapse. Each obstructive event contributes to decreased blood oxygen (i.e., hypoxia). OSA is associated with vascular damage and dysfunction of the cardiac autonomic nervous system [1]. The degree of hypoxia plays a role in the development of cardiac autonomic dysfunction and has been associated with an increased risk of sudden cardiac death [2]. As a result, OSA is strongly and independently associated with increased cardiovascular mortality, stroke, heart failure and arrhythmia [3]. Continuous positive airway pressure (CPAP) is the most accepted treatment for OSA. Unfortunately, fewer than 50% of patients adhere to CPAP therapy over the long term [4]. Mandibular advancement devices (MAD) are an accepted alternative treatment [5]. Despite their decreased efficacy in lowering

hypoxic events, they are suggested to improve disease progression through increased compliance

compared to CPAP [6]. Further research is needed to understand the effect of MADs on the cardiac autonomic nervous system [7].

Increased sympathetic nervous activity (SNA) is a type of cardiac autonomic dysfunction observed even in mild OSA [8]. Increased SNA is a cause of hypertension which may also increase

subsequent cardiovascular risk in OSA [9]. To our knowledge, no studies exist directly measuring SNA in a MAD intervention with microneurography. However, heart rate variability (HRV) and urine and blood catecholamine concentrations have been used to reflect cardiac autonomic modulation indirectly during MAD interventions. Our purpose is to conduct a scoping review to map the direct and indirect techniques used to measure autonomic nervous activity in OSA patients managed with MAD therapy. Secondly, we aim to assess the extent of current knowledge regarding changes in SNA in patients using MADs and determine the appropriateness of a systematic review of the topic.

# Definitions

Indirect markers of SNA were defined as blood or urine norepinephrine or epinephrine concentrations. Indirect markers of sympathetic and parasympathetic balance were defined as heart rate variability, both time and frequency domain techniques. Direct assessment of SNA was defined as the measurement of sympathetic nervous activity to muscle (mSNA) using microneurography.

# Methods

The five-step method for scoping reviews published by Arksey and O’Malley was followed with additional guidance from “PRISMA Extension for Scoping Reviews” to map the key concepts in the literature surrounding how autonomic nervous activity has been measured in OSA patients using MADs.

### **Step 1: The research question**

Our research question was: *Is there any literature assessing the effect of MAD therapy on SNA directly using microneurography in OSA patients? If not, what measurement tools have been used to quantify autonomic changes during MAD therapy? What is known in the existing literature on the impact of MAD therapy on the autonomic nervous system in mild to severe OSA patients? Does adequate literature exist to justify a formal systematic review and meta-analysis?*

Our primary aim was to complete a formal search strategy to identify any potential publications using microneurography. However, the parasympathetic and sympathetic components of the autonomic nervous system may also be assessed using various prospective or retrospective, direct or indirect techniques. Therefore, our secondary aim was to use a comprehensive approach to identify all existing literature to inform our response to whether a systematic review of the available literature would provide a meaningful conclusion regarding the effects of MADs on autonomic nervous activity.

### **Step 2: Identifying relevant studies**

Our search strategy involved searching several electronic databases, reference lists and grey literature (google scholar). However, due to time and resource constraints, unpublished and non-English studies were excluded from our search and hand-searching of key journals was also not performed. A librarian from the University of Alberta worked with us to identify relevant databases and aided us in building an initial search strategy. The initial search strategy was refined under librarian guidance, considering initial search results. The final search was applied in Ovid MEDLINE In-Process & Other Non-Indexed Citations (1946 to the present) (Table 1) and was then revised to appropriate syntax and database-specific subject headings for Ovid Embase (1974 to the present) (Table 2), CINAHL Plus with Full Text (1937 to the present) (Table 3), Scopus (Table 4), Cochrane Library (Table 5) and Google Scholar (Table 6). Each search strategy was reviewed with the librarian. Searches were conducted in April 2022.

We identified 233 articles, 82 of which were duplicates, leaving the remaining 151 results for further review. All citations were entered into Endnote to facilitate data management and then transferred into Covidence to facilitate paper selection within the research team. The references of the final paper selection will be checked to ensure that all relevant studies within them are also included in our initial list of citations, and we will make a note of any studies missed by our search.

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| **Table 1:** Ovid Medline <1946 to April 05, 2022>  Date searched: 05-Apr-2022  Results: 11 |
| |  |  | | --- | --- | | 1. | sleep apnea syndromes/ or exp sleep apnea, obstructive/ or OSA | | 2. | Snoring/ | | 3. | (obstructive sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)).mp. | | 4. | ("upper airway resistance" or “SDB” or "sleep disordered breathing" or snor\*).mp. | | 5. | or/1-4 | | 6. | Mandibular Advancement/ | | 7. | oral appliance therapy.mp. | | 8. | (panthera or prosomnus or Orthoapnea or BTI or Narval or Noa or somnodent or snore rx or HERBST).mp. | | 9. | (mandibular adj3 (advanc\* or reposition\*) adj3 (appliance\* or therap\* or device\*)).mp. | | 10. | or/6-9 | | 11. | 5 and 10 | | 12. | parasympathetic nervous system/ or ganglia, parasympathetic/ or parasympathetic fibers, postganglionic/ or exp vagus nerve/ or exp ganglia, sympathetic/ or sympathoadrenal system/ or exp vasomotor system/ | | 13. | (parasympathetic or vagus nerve or sympathetic or sympathoadrenal or vasomotor).mp. | | 14. | heart rate variability.mp. | | 15. | exp Autonomic Nervous System/ and exp Arrhythmias, Cardiac/ | | 16. | (Cardiac autonomic adj2 (dysfunction or activity or neuropathy)).mp. | | 17. | (sympathoexcitation or sympathetic activation).mp. | | 18. | Norepinephrine/an, bl, ur or catecholamine.mp. | | 19. | (mSNA or microneurography).mp. | | 20. | or/12-19 | | 21. | 11 and 20 | |

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| **Table 2**: Ovid Embase <1974 to April 05, 2022>  Date searched: 05-Apr-2022  Results: 53 |
| |  |  | | --- | --- | | 1. | OSA.mp. | | 2. | Snoring/ | | 3. | (obstructive sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)).mp. | | 4. | ("upper airway resistance" or "sleep disordered breathing" or snor\*).mp. | | 5. | or/1-4 | | 6. | sleep apnea appliance/ or sleep apnea device/ | | 7. | oral appliance therapy.mp. | | 8. | (panthera or prosomnus or Orthoapnea or BTI or Narval or Noa or somnodent or snore rx or HERBST).mp. | | 9. | (mandibular adj3 (advanc\* or reposition\*) adj3 (appliance\* or therap\* or device\*)).mp. | | 10. | or/6-9 | | 11. | 5 and 10 | | 12. | cholinergic system/ or autonomic nervous system/ or parasympathetic ganglion/ or parasympathetic nerve/ or vagus nerve/ or vasomotor reflex/ or vasomotor system/ or adrenergic system/ or sympathetic ganglion/ or sympathetic innervation/ or sympathetic nerve/ or sympathetic trunk/ | | 13. | (parasympathetic or vagus nerve or sympathetic or sympathoadrenal or vasomotor).mp. | | 14. | heart rate variability.mp. | | 15. | heart disease/ or cardiac autonomic neuropathy/ or ecg abnormality/ or heart arrhythmia/ or heart stress/ or major adverse cardiac event/ or myocardial disease/ | | 16. | (Cardiac autonomic adj2 (dysfunction or activity or neuropathy)).mp. | | 17. | (sympathoexcitation or “sympathetic activation”).mp. | | 18. | (noradrenalin or catecholamine or catecholamine).mp. | | 19. | (mSNA or microneurography).mp. | | 20. | or/12-19 | | 21. | 11 and 20 | |

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| **Table 3:** CINAHL Plus with Full Text <1937 to April 03, 2022>  Date searched: 05-Apr-2022  Results: 10 |
| S22 S20 AND S21  S21 S5 AND S9  S20 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19  S19 (MH "Norepinephrine/BL/UR/DU")  S18 (MH "Heart Rate Variability") OR (MH "Heart Rate+")  S17 “microneurography”  S16 “sympathoexcitation”  S15 (MH "Vagus Nerve+") OR parasympathetic or “vagus nerve” or sympathetic or sympathoadrenal or vasomotor  S14(MH "Parasympathetic Nervous System+")  S13 (MH "Sympathetic Nervous System") OR sympathetic or sympathoadrenal or vasomotor OR (MH "Receptors, Adrenergic+") OR (MH "Autonomic Nervous System Diseases+") OR (MH "Epinephrine+")  S12 "Cardiac autonomic dysfunction"  S11 (MH "Autonomic Nervous System+")  S10 "muscle sympathetic nerve activity"  S9 S6 OR S7 OR S8  S8 panthera or prosomnus or Orthoapnea or BTI or Narval or Noa or somnodent or "snore rx" or HERBST  S7(MH "Orthodontic Appliances+") OR "oral appliance therapy" OR (MH "Surgery, Oral+")  S6 (MH "Device Removal+") OR (((Mandibular advance\*) OR (mandibular reposition\*)) N2 (device\* OR appliance OR therap\*)) OR mads  S5 S1 OR S2 OR S3 OR S4  S4 sdb OR “sleep disordered breathing"  S3 (MH "Snoring")  S2 "OSA"  S1(MH "Sleep Apnea, Obstructive") OR (MH "Sleep Apnea Syndromes") |

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| **Table 4:** Scopus  Date searched: 05-Apr-2022  Results: 49 |
| ( ( TITLE-ABS-KEY ( "mandibular advancement device" OR "mandibular advancement devices" OR "mads" OR "mandibular advancement appliance" OR "mandibular advancement therapy" OR "mandibular repositioning device" OR "mandibular repositioning appliance" OR "mandibular repositioning therapy" OR panthera OR prosomnus OR orthoapnea OR bti OR narval OR noa OR somnodent OR "snore rx" OR herbst ) AND TITLE-ABS-KEY ( "obstructive sleep apnea" OR "osa" OR "obstructive sleep apnea syndrome" OR "osas" OR "sleep disordered breathing" OR "sdb" OR "upper airway resistance syndrome" OR "uars" ) ) ) AND ( "autonomic nervous system" OR "sympathetic nervous system" OR "heart rate variability" OR "norepinephrine" OR "microneurography" OR "msna" OR "heart rate" OR "cardiac autonomic dysfunction" OR "cardiac autonomic activity" OR "cardiac autonomic neuropathy" OR "sympathoexcitation" OR "sympathetic activation" OR "parasympathetic nervous system" ) |

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| **Table 5:** Cochrane Library  Date searched: 05-Apr-2022  Results: 10 |
| #1 “Obstructive sleep apnea” OR osa OR “sleep disordered breathing” OR SDB  #2 (((Mandibular advance\*) OR (mandibular reposition\*)) NEAR/2 (device\* OR appliance\* OR therap\*)) OR mads OR panthera OR prosomnus OR orthoapnea OR bti OR narval OR noa OR somnodent OR "snore rx" OR herbst  #3 "autonomic nervous system" OR "sympathetic nervous system" OR "heart rate variability" OR "norepinephrine" OR "heart rate" OR "cardiac autonomic dysfunction" OR "cardiac autonomic activity" OR "cardiac autonomic neuropathy" OR "sympathoexcitation" OR "sympathetic activation" OR "parasympathetic nervous system"  #4 microneurography OR mSNA OR "muscle sympathetic nervous activity"  #5 #1 AND #2 AND ( #3 OR #4) |

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| **Table 6:** Google Scholar  Date searched: 05-Apr-2022  Results: 388\* |
| With all of the words: autonomic “mandibular advancement”  With the exact phrase: obstructive sleep apnea  With at least one of the words: sympathetic  Since 2018\*\* |

\*Only the first 100 results were downloaded as search specificity was limited in Google Scholar.

\*\*Articles were restricted to 2016-2022 in the Google Scholar search as a systematic review was found in previous searches published in 2018 and was presumed to contain relevant articles from dates later than 2016.

### **Step 3: Study selection**

The initial selection will be extended to articles whose title or abstract mentioned the use of MADs in mild to severe OSA patients who were at least 18 years of age and included the assessment of any autonomic nervous activity, including parasympathetic and sympathetic, by indirect or direct methods. Studies that were explicitly about individuals with central sleep apnea, cardiovascular disease, pulmonary disease, neurologic disease, or kidney disease were excluded unless they contained an OSA control group free of these fully diagnosed comorbidities. These conditions were excluded as they are known to influence autonomic function.

Two researchers will independently appraise all identified citations using the inclusion and exclusion criteria. If uncertainty arises regarding the relevance of a citation, the complete article will be obtained for further discussion until consensus is reached. After the initial selection is complete, copies of all the selected articles will be obtained. The same two researchers will then independently review these complete articles to finalize the paper selection. If a disagreement occurs, the study will be discussed with a third researcher until a consensus is reached.

### **Step 4: Charting the data**

Two independent researchers will record the following data from the selected studies into a data abstraction table: Author(s); year of publication; country of publication; sample size, age and sex; study aim; study design, instruments or approaches used to assess autonomic nerve activity in subjects; arms of the intervention, if applicable, and results.

### **Step 5: Collating results**

The data abstraction table and initial drafts of the review will be circulated to all research team members for continuous revision until all agree that it reflects the results of the reviewed articles.

# Results

A flowchart diagram will be included, mapping the paper selection, inclusion, and exclusion process. The review will then follow in a narrative format structed by headings for each question outlined in step one. Under each heading there will be mention of the study types used (ex: randomized control trial, review, etc.) and the number of studies used to support the answer. The relevant results of individual sources of evidence will be summarized, including methodologies used to measure autonomic activity and findings pertaining to autonomic activity. The characteristics of sources of evidence, including main results, will be included in summary tables as described in step four.

# Discussion

The main findings will be summarized and linked to our review questions and objectives. Insights will be expanded upon where applicable. The quality of the sources of evidence may be expanded upon in general terms, although not critically appraised.

# Limitations

The limitations of our search strategy and any deviations from PRISMA guidelines will be discussed and rationale or future suggestions will be provided.

# References

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3. Narkiewicz, K. and V.K. Somers, *Cardiovascular variability characteristics in obstructive sleep apnea.* AUTONOMIC NEUROSCIENCE-BASIC & CLINICAL, 2001. **90**(1-2): p. 89-94.

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5. Yeghiazarians, Y., et al., *Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association.* Circulation, 2021. **144**(3): p. e56-e67.

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9. Lopez-Jimenez, F., et al., *Obstructive sleep apnea: Implications for cardiac and vascular disease.* Chest, 2008. **133**(3): p. 793-804.