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Efficacy of Omega-3 in Improving Sleep Quality of Healthcare Workers with Shiftwork Sleep Disorder: Phase III, Double-blind, Placebo-controlled Trial Study Protocol (SLEEP-O3 Trial)

María Lucía Sequeira[1], Maria Isabel Bojorquez Ortiz[2], Camila Bernardes de Faria[3], Vitor Yukio Yonekura[1], Aline Aparecida Lacerda Gruber[1], Igor Malheiros Assad[4*], Luciano Hurtano Peña[5], Lukas Rudzevicius[6], Marilia Ribeiro de Azevedo Aguiar[7], Ahmad G. A. Khater[8], Agustín Pérez Londoño[9], Bisher Sawaf[10], Dongwoo Nam[11], Francisco Espinoza Aguayo[12], Franja Dugar[13], Guilherme de Araujo Gomes[14], Luis Angel Rivera Quinto[15], Rawan Mohammad AlMuhanna[16], Stalin Canizares[1], Vanesa Scholl[17]

[1] Principles and Practice of Clinical Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [2] Universidad Francisco Marroquín, Ciudad de Guatemala, Guatemala; [3] D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil; [4] Universidade Federal de São Paulo, São Paulo, Brazil; [5] Emergency Department, Dávila Clinic, Santiago, Chile; [6] Department of Neurosurgery, Klinikum Chemnitz gGmbH, Chemnitz, Germany; [7] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [8] Faculty of Oral and Dental Medicine, Egyptian Russian University, Cairo, Egypt; [9] Division of Urologic Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA; [10] Department of Internal Medicine, Hamad Medical Hospital, Doha, Qatar; [11] Department of Acupuncture and Moxibustion Medicine, Kyung Hee University College of Korean Medicine, Seoul, Korea; [12] Medicine Faculty, Universidad del Desarrollo, Clinica Alemana, Santiago, Chile; [13] Department of Radiology and Nuclear Medicine, University Hospital Basel, Basel, Switzerland; [14] Hospital São Vicente de Paula, Passo Fundo, Brazil; [15] Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA; [16] Saudi Commission For Health Specialties, Riyadh, Saudi Arabia; [17] Conciencia Clinic, Neuquén, Argentina.

Abstract

Introduction: *Healthcare workers are especially vulnerable to sleep disturbances, including shift work sleep disorder (SWSD). Even though omega-3 supplementation has been studied to enhance sleep quality in different populations, there is lack of evidence to support its effectiveness in SWSD. This trial aims to evaluate this compound potential benefits towards health care personnel suffering from SWSD.*

Methods: *This study protocol consists of a phase III, single-center, double-blind, placebo-controlled randomized clinical trial. Participants will receive sleep hygiene orientation in addition to either omega-3 dietary supplementation or placebo for 8 weeks. The primary outcome will be sleep quality as measured by the Pittsburgh Sleep Quality Index and one of the secondary outcomes would be actigraphy as a reliable sleep assessment. The sample size will be 136 subjects.*

Discussion: *The importance of improving sleep quality of health care workers relies on its impact on their wellness, and on patient safety. Sleep deprivation and disorders are responsible for multiple workplace errors and worse health outcomes alike. This trial can help determine if omega-3 supplementation can contribute to ameliorate sleep disturbances in health care professionals.*

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Introduction

Sleep disorders are currently considered a major public health problem, with some populations deserving special attention (Hirshkowitz et al, 2015). Among such populations, healthcare workers are prone to sleep conditions, including shift work sleep disorder, whose main symptoms include insomnia and excessive sleepiness (Jang et al., 2021) . The US Bureau

of Labor Statistics Standard Occupational Classifications classify healthcare professionals as shift workers, since they regularly work extended, rotating, irregular, or consecutive shifts (Wickwire et al., 2017; Thorpy, 2012). It is well established that sleep disturbances deeply impact physical and mental well-being, quality of life, and daytime functioning, (Szentkirályi et al., 2009). There is also robust evidence in the literature that sleep deprivation is related to errors in patient care by health professionals (Ramadan & Al-Saleh, 2014; Trockel et al., 2020). Poor sleep quality measured by the Sleep Hygiene Index (Booker et al., 2020) was related to an elevated risk of excessive daytime sleepiness (EDS) among medical students (Mastin et. al, 2019), with decreased discrimination and inattention on continuous performance tasks in doctors of Physical Therapy (Coffyn, & Siengsukon, 2020), and as a risk factor for the shift work disorder between nurses (Booker et. al, 2020). Also, poor sleep hygiene was associated with deterioration of quality of life in shift work healthcare professionals (Hattatoğlu et. al, 2020).

In recent years, investigators have studied therapeutic options to ameliorate sleep conditions. Among such options, omega-3 supplementation has drawn special attention. A recent meta-analysis showed that several populations demonstrated benefits on sleep quality with omega-3 supplementation (Dai & Liu, 2020). Shift workers, however, have been consistently excluded from such protocols. Therefore, there is still uncertainty whether omega-3 dietary supplements might be a valid alternative for this population, particularly those suffering from SWSD.

Due to scarce literature on the impact of omega-3 supplementation on shift workers' sleep quality, specifically health care professionals, this protocol aims to explore its potential benefit for this subpopulation. Positive findings would contribute to alleviate the burden of night shift sleep disorders on health professionals and, equally important, increase patient safety. The investigated intervention is a low cost, widely available compound that could help public authorities and health systems ameliorate professional's wellness while potentially improving their quality of care.

Materials and Methods

This trial is designed as a randomized, double-blinded, parallel, placebo-controlled, single-center, phase III clinical trial among healthcare professionals with SWSD to evaluate the efficacy of omega-3 supplementation on their sleep quality. This study will take place in an academic hospital located in a metropolitan area in the United States of America, which displays a large workforce of healthcare professionals who work on shift schedules. To ensure a representative sample, healthcare professionals from various professions will be recruited.

The study inclusion criteria are: (a) professionals including emergency medical service personnel, nurses, nursing assistants, physicians, technicians, therapists, phlebotomists, pharmacists, students and trainees; (b) age of 18 years old or older; (c) ability to provide written consent; (d) work on shift schedules including from two to four night shifts a week during the six months prior to enrolment; (e) clinical symptoms compatible with the diagnosis of night shift sleep disorder such as insomnia and excessive sleepiness, adding an overlap of usual sleep hours with work (Jang et al., 2021) ; (f) a score of 5 or higher in the Pittsburgh Sleep Quality Index questionnaire (Buysse et al., 1989). Workers from the intended center will be recruited to participate via an email invitation explaining the study.

Our exclusion criteria are: (a) alcohol consumption of more than 20 g/day; (b) intermediate to high risk of obstructive sleep apnea assessed by the STOP-BANG questionnaire (Chung et al., 2016); (c) diagnosis of hyperlipidemia (total cholesterol > 200 mg/dl, LDL cholesterol > 100 mg/dl, triglycerides > 150 mg/dl); (d) pregnancy or lactation; (e) other sleep disorders diagnosis defined by the ICSD-3 sleep disorder categories; (f) consumption of any supplement containing omega-3 fatty acids for the last three months; (g) previous diagnosis of major depressive disorder; (h) current prescription of approved medications for sleep disorders including benzodiazepines, Z-drugs intended for sleep amelioration, melatonin agonists, tricyclic antidepressants, barbiturates, suvorexant and any other off-label medication including antidepressants and atypical antipsychotics, over-the-counter medication that may be used for the same purpose including melatonin, herbal compounds, and antihistamine will also be excluded; (h) Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension; severe bleeding disorders); (i) traveling to a different time zone in the month previous to enrollment or intention to do so during the duration of the trial; (j) individuals engaging in high intensity physical activity assessed by the PRETIE-Q questionnaire with a result of 24 points or more (Ornelas et al., 2020).

Participants who match our inclusion criteria will be randomly assigned to either the intervention or placebo group using a centralized simple randomization method via REDCap platform (Harris et al, 2009).

1. Optimize regularity activity and sleep schedule, when possible: according to work schedule, make an effort to minimize discrepancies in sleep timing every day.
2. Create a sleep-friendly environment: control for a comfortable environment, preferably a dark, temperature-controlled room.
3. Reduce exposure to bright light before daytime sleep.
4. Focus on pleasant activities and avoid lights in the room in the last hour before sleep.
5. Avoid consumption of alcohol within 3 hours before sleep.
6. Avoid smoking and other drugs.
7. Exercise, but avoid such activities and warm baths 1.5 hours before bedtime.
8. Avoid consuming more than 250 milliliters of liquids and empty bladder before sleep time.
9. Avoid caffeinated products, tea, chocolate, and sodas six hours before bedtime.

Table 1: *Sleep hygiene adapted for shift workers.*

The randomization list and allocated codes will be kept anonymous, and the recruiter will be unaware of the allocation of each participant until the trial is completed. Each participant will have an equal chance of being randomly assigned to the treatment or control groups. In order to minimize any potential biases, our study will be double-blinded. Neither the investigators, participants, data collectors, researchers administering treatments or collecting data and outcome assessors will be aware of patient allocation.

The Informed Consent Form (ICF) will be signed before the beginning of the trial. All participants will be provided with general sleep hygiene orientation, adjusted for shift workers routine, as outlined in Table 1. One group will receive omega-3 LC-PUFA at a higher dose of 3,300 mg (1 omega-3 capsule contains 675 mg of DHA and 975 mg of EPA) administered orally on a daily basis (2 oil capsules of 1, 650 mg per day). The second group will receive placebo, with the administration of 2 inert pills daily for blinding purposes. The omega-3 oil capsule will be supplied by Nordic Naturals, Watsonville, CA, and the placebo pill will be supplied by Meda Pharma, Bad Homburg, Germany. All participants will be given instructions to take pills daily, combined with their main meal during the day. Participants will not be asked to alter dietary patterns for study purposes.

Necessary precautions will be taken during manufacturing and packaging to ensure that there is no visual identification of each compound. Both the investigational drug supplement and the placebo capsule will contain lemon to mask potential taste associated with omega-3 supplements. The placebo will consist of a soft layer of gelatin oil capsule which contains encapsulated corn oil ethyl esters and lemon flavor to match the treatment pill. Each treatment will have symbols with a unique barcode to register with the computerized system for randomization.

The Bang's Blinding Index will be used to assess the effectiveness of blinding (Bang et al, 2004). Participants will be asked to answer questions on a 5-point scale ('Strongly believe the treatment is a new treatment,' 'Somewhat believe the treatment is a new treatment,' 'Somewhat believe the treatment is placebo,' 'Strongly believe the treatment is placebo,' or 'Don't know'), rating their belief on whether the treatment being administered is a new treatment, a placebo, or if they are unsure. If a participant reveals unblinding during the survey, they will not be notified. All instances of unblinding will be reported.

Given the nature of the intervention and the implications of the disease in the target population, this study is considered to have an overall low risk of dropout. In-home behavior will consist of assessing how the patient is adapting to medical advice through scheduled visits. General recommendations regarding scheduling methods for pill intake, location of medication, and testing accuracy in remembering dosing and other associated characteristics should be performed in each visit. Furthermore, participants will be continuously notified via telephone and email of all advances in the study and future scheduled visits to avoid delay or dropouts. Adverse events, difficulties keeping track of the medication and study reasons for lack of adherence will be evaluated by fulfilling a questionnaire. Patients will be asked to log in their pill counting each day to promote adherence. Additional advice regarding diet, exercise and any other behavior that may confuse our findings will be clearly presented in each visit. To increase compliance activities including appointments, follow-up and any additional complementary exams the team might find appropriate, we will elaborate

Activity	Screening	Period of treatment			
Day	-	0d	30d ±3	56d ±3	84d±3
Visit	V1	V2	V3	V4	V5
Clinical evaluations					
Signature of ICF	x				
Eligibility Criteria	x				
PRETIE-Q	x				
Medical history	x				
Blood test (triglyceride, cholesterol levels, pregnancy, coagulation tests)	x		x		
Concomitant medication	x	x	x	x	
Sleep Hygiene Orientation		x	x	x	
PSQI		x		x	x
Actigraphy		x	x	x	
Omega-3 levels		x		x	
Bang´s Blinding		x	x	x	x
Administration of the IP					
Randomization		x			
IP (omega-3 or placebo)		x	x	x	

Visits 1 and 2 may take place in the same day, if possible.

Table 2: *Timeline of clinical of trial components.*

an informative pamphlet with advantages, risks and expected practices during participation. The timeline of activities (Table 2) is displayed below.

Participants will be instructed on how to proceed if adverse reactions arise. Allergic reactions are described to be rare. However, if this is suspected, the trial medication will be withdrawn from the patient and it will be reported as an adverse event. Gastrointestinal disturbances are the most common side effects expected for participants under this study, namely nausea and eructation. In such cases, participants will be offered to take the formulation after freezing. Ultimately, patients will be able to exit the study protocol if intolerance to formulations jeopardizes participation. Considering the intervention safety profile, emergency unblinding is not expected. However, if required, emergency unblinding will be performed in case of life-threatening events. The principal investigator will be notified, and the subject will be discontinued from the trial.

Sleep quality would be measured as the primary outcome. The differences in sleep symptoms between the two treatment arms participants will be measured after 8 weeks of intervention. Intervention effects will be measured using Pittsburgh Sleep Quality Index (PSQI). The questionnaire will be done the day after the second night shift of the week during the visits that would be prescheduled. Assuming normality due to the sample size according to the central limit theorem, for primary analysis, we will perform a paired t-test to compare the difference (at baseline and after intervention) in sleep quality (measured by the PSQI) between the omega-3 intake and placebo groups.

The sample size was calculated based on the primary hypothesis using a power of two means as follows: alpha (α) of 0.05, power (1 - Beta) of 0.80, dropout rate of 0.20 (20%) and effect size of 1, derived from clinical experience. Based on available literature (Nourosi et al., 2021) a conventional standard deviation of 3.4 was used. After calculation, the sample size is 136 patients.

With the aim of measuring more objective symptoms and dealing with self-report measures issues, actigraphy will be used as a secondary measure. Even though polysomnography is the gold standard criterion to identify sleep stages objectively (Chen et al., 2017), actigraphy has approximately 90% agreement with polysomnography (Sadeh & Acebo, 2002). Actigraphy has also been established by the American Academy of Sleep Medicine as a reliable sleep assessment to evaluate sleep and circadian rhythm abnormalities (Chen et al., 2017). Based on this, this method was chosen as it is more convenient, less invasive, and less costly than polysomnography. Also, as a secondary outcome, omega-3 levels will be measured before the intervention and after 8 weeks of intervention. Finally, we will include a second mea-

surement at 12 weeks using the PSQI also measured after the second nightshift.

For secondary outcomes, we have chosen to measure total sleep time, sleep efficiency, wake after sleep onset and sleep latency using actigraphy each week for the total duration of the trial. The data will be analyzed using descriptive statistics. Additionally, as a secondary outcome, we will perform a paired t-test to compare the difference (at baseline and after intervention) of blood omega-3 index.

Up-to-date versions of STATA (StataCorp, 2023) will be used to conduct analyses. For all tests, we will use 2-sided p-values with alpha = < 0.05 level of significance.

For data entry, we plan to record all pertinent information in an electronic format using REDCap at the center site; this includes the participants' medical history, concomitant medications, primary and secondary outcomes, and omega-3 levels. To enhance data quality, range checks for data values will be performed.

There will be a clinical research associate by the designated investigator for data monitoring. The fact that omega-3 has been well-established in regard to safety profile and the nature of the trial, short duration, the decision has been made to not include a Data Monitoring Committee for safety. However, monitoring will be performed throughout the trial to ensure data quality.

We will not perform an interim analysis to evaluate safety. Furthermore, the mechanism of action of omega-3 supplementation relies on the slow rise in melatonin levels within the body. Given that the response is time-dependent, we will also not perform an interim analysis to evaluate efficacy and futility.

We consider missing data as missing data at random (MAR) because we suspect the pattern of missing data to be related to independent variables. We propose handling MAR with multiple imputation using the following covariates: age (since melatonin levels decrease with increasing age), baseline omega-3 and rescue medication.

This study protocol will be reviewed and approved by the local Institutional Review Board (IRB). All procedures performed in this study involving human participants will be conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before participating in the study, all participants will be provided with a detailed explanation of the study objectives, procedures, potential risks, and benefits. Written informed consent will be obtained from all individual participants included in the study. Participants will be assured that their participation is voluntary, and they may withdraw from the study at any time without any consequences.

Discussion

Night-shift workers often struggle with demanding schedules, requiring them to work at unconventional hours and leading to poor sleep quality. Shift work sleep disorder is a condition characterized by insomnia, sleep deprivation and excessive sleepiness due to an irregular sleep schedule (Akerstedt, 2003). It is estimated that 32% of night-shift workers suffer from SWSD (Brito et al., 2021). One of the major consequences of sleep deprivation on this population is its effect on workspace safety, including medical errors (Shaik et al., 2022). In fact, medical errors cause losses of billions of dollars annually in the United States alone in addition to accounting for the third-leading cause of death in the country (Makary & Daniel, 2016).

In this context, omega-3 long chain polyunsaturated fatty acids have been studied as a possible treatment option for sleep disorders. Omega-3 derived supplementation commonly consists of two long-chain omega-3 PUFA, which are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They enhance the regulation of serotonin and play an important role in brain function and sleep regulation (Hansen et al., 2014). Other studies found levels of these fatty acids persistently lower among those with very short sleep relative to normal sleep (Shaik et al., 2022) and that consumption of oily fish has been associated with an improvement in sleep quality (Del Brutto et al., 2016). Additionally, administration of omega-3 orally has been proven safe. In the search for cardiovascular benefits, daily doses up to 4000 mg/d have been tested with only mild adverse effects (Hu et al., 2019) while research on sleep has employed 1800 mg and found no significant side effects (Cohen et al, 2014).

Due to unavailability of standard medical treatment for night shift sleep disorder, it is feasible to conduct a placebo-controlled trial. All patients nonetheless should receive instructions on how to improve sleep hygiene, which nowadays comprehends the only available standard treatment. It is important to highlight that working night shifts by itself can deeply jeopardize sleep routine. However, special orientations employed in our protocol have been developed and validated specifically for patients who work shift schedules.

Our study protocol does present limitations. Due to the subjective nature of the primary outcome, there is increased risk of bias in outcome reporting. The follow-up period might also be considered short, even though it is in line with similar previous studies

in the field. Scarce literature on this topic in specific for the health care workers population might also make sample size calculations more imprecise. Finally, supplementation dosages have been extrapolated from available literature, even though there are no consensual regimens for omega-3 supplementation in sleep disorders.

This study will be the first clinical trial to evaluate the effect of omega-3 supplementation on sleep quality in healthcare workers with shift work sleep disorder. The study will also use a higher dosage of omega-3 within acceptable limits, compared to other clinical trials that have used such intervention for the treatment of sleep disorders, in order to investigate possible dose-dependent benefits. If the study fails to provide positive results regarding omega-3 supplementation for sleep quality in healthcare workers, it would still provide valuable information regarding the diagnosis and natural history of shift work sleep disorder, mainly through data collected for the protocol's secondary outcomes. Positive findings from this study on the other hand will help build a path toward improved well-being and enhanced performance for night shift workers.

Conclusion

In conclusion, night shift sleep disorder is a common sleep disorder associated with health care professionals accounting for a high burden on workers' wellness and patient safety. Our protocol aims to investigate the validity of known benefits of omega-3 supplementation on sleep quality for this specific condition. Findings will help clarify therapeutic options, potentially benefiting workers and patients alike.

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Conflicts of Interest

The authors declare no conflict of interest.

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