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Impact of an over-the-counter "sleep lotion" on human salivary melatonin levels and sleep quality: a randomized controlled trial.

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Abstract

OBJECTIVE: To compare the impact of a commercial "sleep lotion" versus a placebo control lotion on salivary melatonin and sleep quality.
METHODS: The presence of melatonin in the lotion was confirmed and quantitated with High Performance Liquid Chromatography (HPLC). In this randomized, controlled, double-blind crossover trial, undergraduate student participants applied lotions on two separate nights and we quantitated melatonin in saliva samples with enzyme linked immunosorbent assays. We also assessed sleep quality with a modified Pittsburgh Sleep Quality Index. Clinicaltrials.gov ID NCT06053385.
RESULTS: Sixty-three participants (age 20.5 ± 1.2 years; 81% female) enrolled in the study and provided at least one saliva sample. The sleep lotion contained 0.24 ± 0.01% melatonin (g/100 g lotion) which dramatically impacted salivary melatonin levels, increasing them up to ~1000 fold compared to the placebo lotion (n = 36 participants with all six timepoints). The lotion improved sleep quality in a subsample of the poor sleepers (n = 18). However, the sleep quality in the overall sample was not significantly different on the active versus placebo lotion nights.
CONCLUSION: In a small undergraduate student sample, a commercial melatonin-containing lotion improved sleep in those with poor sleep quality. Caution should be taken by consumers using over-the-counter melatonin lotions because the undisclosed dosage can be high and well absorbed by the skin.

Abbreviations:
HPLC - High Performance Liquid Chromatography
PSQI - Pittsburgh Sleep Quality Index

BRIEF REPORT

INTRODUCTION

Melatonin has been shown to improve sleep quality (Fatemeh *et al.* 2022), and its use in the United States has dramatically increased in the last decade (Li *et al.* 2022). Unlike the United Kingdom, Europe, Japan, Australia and Canada where it must be prescribed (Grigg-Damberger & Ianakieva 2017), melatonin is available over-the-counter in the United States, and it is not classified as a drug (Skrzelowski *et al.* 2021). In addition to oral supplements, melatonin can be purchased in lotions and bubble baths for which the efficacy is unknown. "Dr. Teal's" (PDC Brands, Stamford, CT) is a popular maker of melatonin-containing aromatherapies, lotions, and bath products that claim to "calm the mind for a good night's sleep" (https://www.drteals.com/products/). In 2018, Dr. Teal's was the leading brand for bubble bath in the United States with $104 million USD in sales (Statista 2022), and the products are exported internationally. We hypothesized that melatonin absorbed through the skin from Dr. Teal's Sleep Lotion would improve sleep. Our goals in this study included: quantitating the amount of melatonin in this over-the-counter lotion that has no dosage listed on the label, assessing whether the melatonin would be absorbed through the skin, and comparing the impact of melatonin lotion versus a placebo control lotion on sleep quality.

MATERIALS AND METHODS

Trial design

This randomized, controlled, double-blind crossover trial (Fig. 1) was approved by our Institutional Review Board (approval number 2021-37-REDLANDS) and registered with clinicaltrials.gov (NCT06053385). Participants were undergraduate students at a small liberal arts university in California, USA between the ages of 18-24. Exclusion criteria included pregnancy, use of sleep medications in the previous two weeks, and allergies/sensitivity to scented lotion. Data collection occurred from 2/2022 to 2/2023. Participants (n = 63) provided informed consent, and the experiment was performed according to the Declaration of Helsinki. If participants completed the study, they received a gift worth less than $5. After providing consent, participants answered an electronic questionnaire on demographic information, exercise, and the Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality in the last month (Buysse *et al.* 1989). The PSQI is scored between 0 – 21; scores above the cutoff of 5 indicate poor sleep.

We tested two lotions that are widely available over-the-counter: Dr. Teal's Sleep Lotion with Melatonin and Essential Oils and Dr. Teal's Soothing Lavender Essential Oil Body Lotion as a scent-matched placebo control (PDC Brands, Stamford, CT). At home, participants applied 7 g lotion to their hands and arms one hour before bedtime on two separate nights approximately one week apart. The order of which lotion was applied on the first versus the second night was randomized and allocated by author L.E.O. (Urbaniak & Plous 2013); both participants and researchers doing the analysis were blinded to lotion type. Participants took their own saliva samples three times per night: 1) immediately prior to lotion application, 2) 30 minutes following application, and 3) 1 hour following application. Passive drool samples obtained with collection aids (Salimetrics, State College, PA) were frozen until analysis. The following morning, participants completed an electronic PSQI modified to ask questions about the quality of the previous night's sleep only. Changing question wording from *"How often in the past month…"* to *"Last night,* did you have trouble sleeping due to…" yielded possible scores from 0 to 14.

Saliva analysis

Reagents for enzyme-linked immunosorbent assays, including plates coated with rabbit anti-melatonin monoclonal antibodies, were purchased from Salimetrics (State College, PA) and manufacturer instructions were followed. Optical density at 450 nm was assessed using an AgileReader (ACTGene, Piscataway, NJ). Standards from 0.78 to 50 pg/mL were used for a standard curve with mycurvefit.com software. Participant samples were diluted to 10x, 100x, or 1000x if necessary to fall within the standard curve, and all samples were tested in at least duplicate. Samples with absorbances slightly out of the standard curve (n = 7 samples) were assigned the value of the nearest sample within the curve in order to be cautious. The average intraassay coefficient of variation was 3% and interassay coefficient of variation for this study was 18%.

High performance liquid chromatography (HPLC)

We adapted a protocol to prepare lotion extracts (Usher *et al.* 2015) for HPLC analysis. A solution of 0.5 g lotion and 5 mL 20% NaCl was vortexed for 30 seconds, centrifuged for 6 minutes at 4000 rpm, and the aqueous layer was filtered using a syringe disc filter containing a 0.22 μm polyvinylidene difluoride membrane. For recovery studies, melatonin (99% pure, ThermoFisher Scientific, Waltham, MA) was added to lotion samples at 50 μg melatonin/mL solvent prior to beginning the extraction protocol. All extractions were performed in triplicate. Melatonin standards (10 – 100 μg/mL) were prepared in ultrapure water. HPLC analyses were performed using an Agilent 1220 LC System (Agilent, Santa Clara, CA) equipped with a C18 reverse-phase analytical column (Phenomenex Prodigy ODS(2), 4.6 x 150 mm, 150 Å) at a flow rate of 1 mL/min. The gradient began at 1 min and was 15 – 35% solvent B over 20 min. Solvent A was ultrapure water containing 0.1% trifluoroacetic acid; solvent B was acetonitrile containing 0.1% trifluoroacetic acid. All standards and lotion samples were analyzed in triplicate using an injection volume of 20 μL, and melatonin was

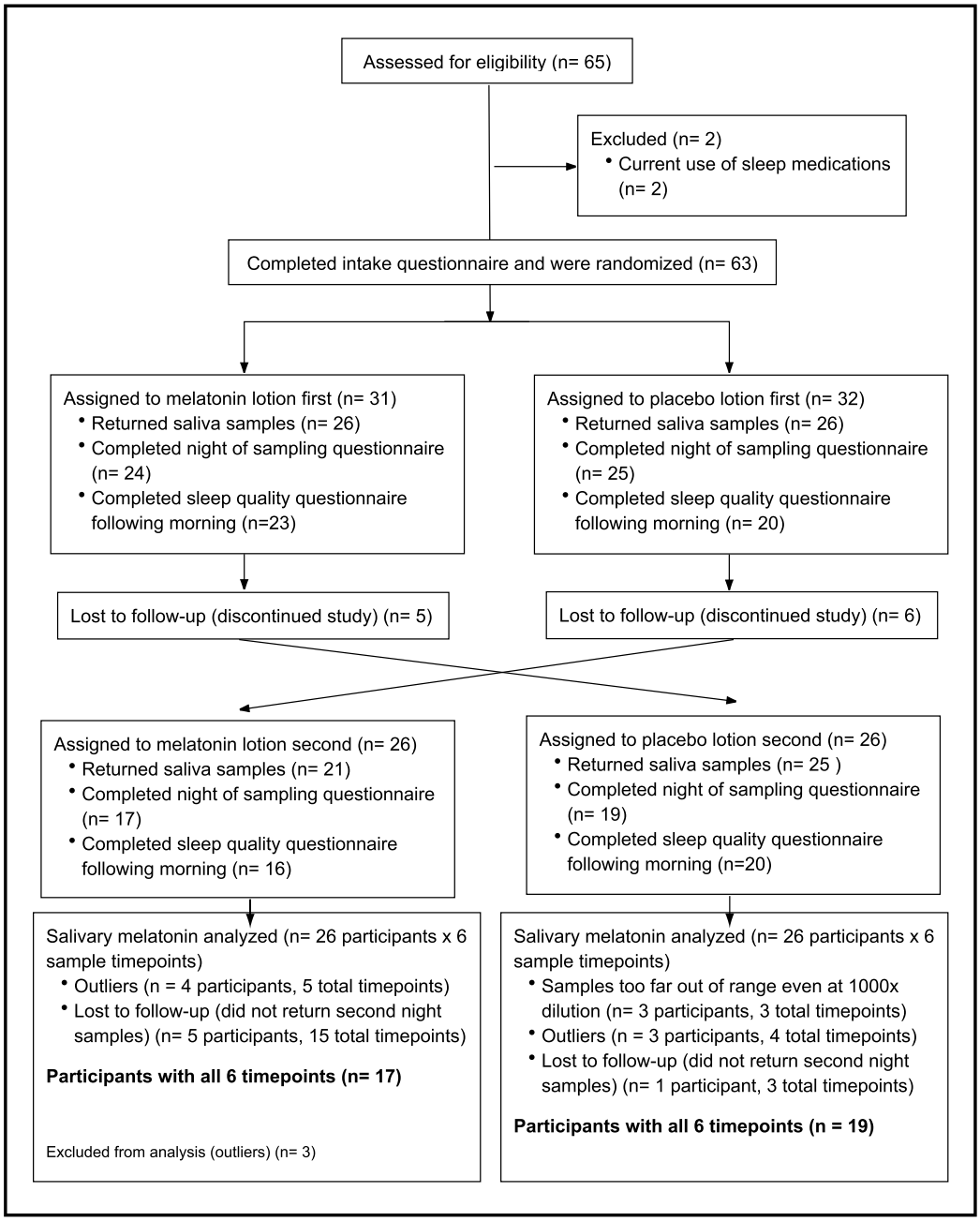

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for the study.

quantified using absorbance at 215 nm. Ultrapure water (>18 MΩ-cm) was obtained from a Barnstead E-PURE system (ThermoFisher Scientific, Waltham, MA); HPLC-grade acetonitrile from VWR (Radnor, PA); and trifluoroacetic acid from ThermoFisher Scientific (Waltham, MA).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistical software (IBM, Armonk, NY). Extreme outliers as identified by SPSS (± 3x interquartile range) were removed. Data were transformed by log10 or square root to achieve a normal distribution if necessary; when this was unsuccessful, non-parametric analyses were used. Exploratory analyses comparing race (White vs. Non-White), ethnicity (Hispanic/Latino vs. Non-Hispanic/Latino), first-generation status (yes vs. no), and gender (male vs. female) were performed with independent samples t-tests or Mann-Whitney-U tests as appropriate with an alpha of 0.05. When multiple tests were conducted on the same dependent variable, the Benjamini-Hochberg correction for multiple testing was used to control the false discovery rate to 0.05 (McDonald 2014) and only those *p* values significant after correction are reported. Salivary melatonin levels were compared using a two-way repeated measures ANOVA with an alpha level of 0.05. This 2 x 3 ANOVA tested treatment (within subjects factor: placebo control lotion vs. sleep lotion) and sampling time (within subjects factor). Assumptions of ANOVA

Tab. 1. Demographics of participants N = 63

Age	
Mean ± std dev	20.5 ± 1.2 years
Race	**n (%)**
White	28 (44%)
Asian	5 (8%)
Black or African-American	4 (6%)
American Indian or Alaska Native	1 (2%)
Multiracial	4 (6%)
Other	16 (25%)
Prefer not to disclose	5 (8%)
Ethnicity	
Hispanic or Latino	37 (59%)
Non-Hispanic or Latino	26 (41%)
First generation	
in their family to pursue a four-year college degree	30 (46%)
Gender	
Female	51 (81%)
Male	10 (16%)
Non-binary/third gender	1 (2%)
Prefer not to disclose	1 (2%)

were checked and appropriate corrections applied when necessary.

RESULTS

Of the 63 college students who participated in this study, approximately half were non-White (Table 1). Due to small samples sizes, race was only analyzed by comparing White to Non-White participants, excluding those who preferred not to disclose. More participants were Hispanic or Latino (59%) than were not (41%). Approximately half of the participants were in the first generation in their family to pursue a four-year college degree. The majority (81%) of participants were female (Table 1). Due to the small sample size in the non-binary/third gender category, gender was analyzed by comparing to males versus females only.

Exploratory analysis of baseline variables and demographics

In the month prior to the study, the mean sleep quality as measured by the PSQI was 6.3 ± 2.7; 65% of the participants scored above the Global PSQI cutoff of 5, indicating poor quality sleep. Global PSQI was not different by race, ethnicity, first-generation student status, or gender (p's > 0.05). Global PSQI was better in participants who vigorously exercised more than once per week for at least 30 minutes (5.4 ± 2.3, n = 37) compared to those who did not (7.7 ± 2.7, n = 26, $p < 0.001$, Cohen's d = 0.97).

Participants reported that they typically slept 7.1 ± 0.13 hours per night; this was not different by race, ethnicity, first generation student status, or gender (p's > 0.05). On average, participants went to bed at 00:03 ± 01:11, and this was different by race with White participants going to bed 42 minutes (95% CI 7 – 78 minutes) earlier than non-White participants ($p = 0.01$, Cohen's d = -0.64). Bedtime was not different by ethnicity, first generation student status, or gender (p's > 0.05).

Salivary melatonin levels

We compared the impact of Dr. Teal's Sleep Lotion with Melatonin and Essential Oils versus Dr. Teal's Soothing Lavender Essential Oil Body Lotion as a placebo control on salivary melatonin levels. Participants provided saliva samples just before applying lotion (one hour prior to bedtime) and then 30 and 60 minutes later (at bedtime). Average melatonin levels on the placebo control night did not differ by race, ethnicity, first generation student status, gender, exercise, or caffeine (p's > 0.05). Repeated measures 2 x 3 ANOVA showed main effects of treatment, $F(1, 35) = 330.92$, $p < 0.001$, $\eta p^2 = 0.91$; sampling time, $F(2, 70) = 241.75$, $p < 0.001$, $\eta p^2 = 0.87$; and the interaction effect, $F(2, 70) = 191.48$, $p < .001$, $\eta p^2 = 0.85$. On the placebo control lotion night, melatonin levels rose from a median of 34.1 pg/mL one hour before bedtime to 54.8 pg/mL at bedtime, as expected due to circadian effects (Figure 2). The application of Dr. Teal's Sleep Lotion dramatically increased participants' salivary melatonin levels up to ~1000-fold compared to the placebo control (Figure 2).

Impact of lotion on sleep quality

The morning after lotion application, participants completed a PSQI questionnaire modified to ask questions about the quality of the previous night's sleep only. Instead of scores from 0 to 21, the possible scores on the modified questionnaire were 0 to 14. In an analysis of all participants, the average modified PSQI score on the night after placebo control lotion application was 3.25 ± 2.27, and on the night after sleep lotion application was 3.63 ± 2.54 ($p > 0.05$). We were particularly interested in the impact of lotion on sleep quality in the participants who were poorer sleepers, and thus we analyzed participants who scored at or above the median of 3.0 out of 14 on the modified PSQI after application of the placebo control lotion. In this subsample of 18 participants, the average modified PSQI score on the night after placebo control lotion application was 4.83 ± 1.72, and on the night after sleep lotion application was improved to 3.33 ± 2.22 ($p = 0.02$, Cohen's d = 0.81).

HPLC analysis of lotions

We measured the amount of melatonin in Dr. Teal's Sleep Lotion with Melatonin and Essential Oils and

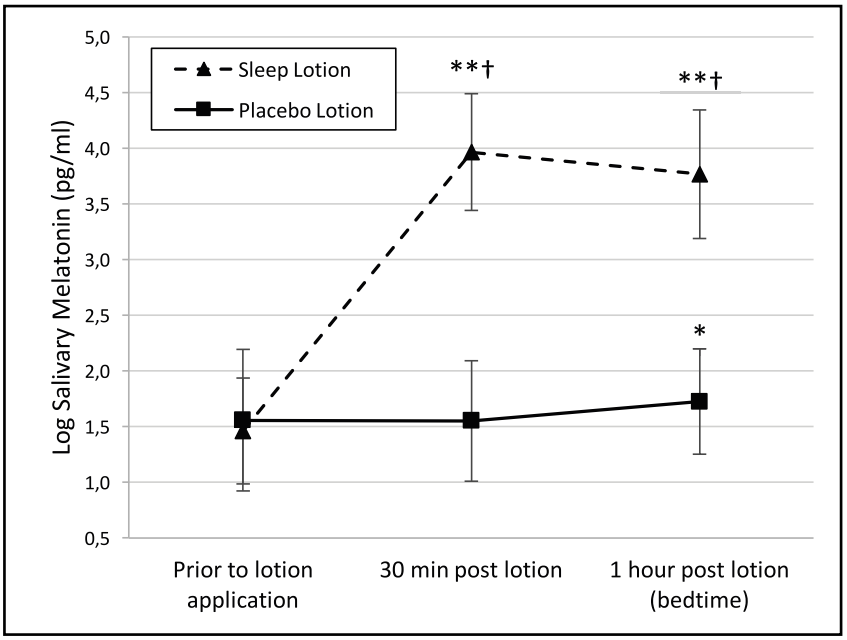

Fig. 2. The impact of Dr. Teal's Sleep Lotion with Melatonin and Essential Oils on salivary melatonin levels. Lotion was applied to hands and arms immediately after the first saliva sample, one hour prior to bedtime. Data were log transformed due to violations of normality; log10 of 10,000 pg/ml = 4. *$p < 0.05$ compared to prior to lotion application; **$p < 0.001$ compared to prior to lotion application; †$p < 0.001$ compared to placebo. n = 36 participants with all six timepoints.

Dr. Teal's Soothing Lavender Essential Oil Body Lotion (placebo control) using HPLC. Melatonin standards at 10, 25, 50, 75, and 100 μg/mL displayed a distinct peak with a retention time of 12.4 minutes; the peak areas for these standards were used to create a linear calibration curve. Samples extracted from Dr. Teal's Sleep Lotion had a matching peak and were determined to contain 46.5 ± 1.7 μg melatonin/mL extract. To calculate the percent recovery in our extraction method, we spiked an additional 50 μg melatonin/mL into the same amount of Dr. Teal's Sleep Lotion. We recovered an additional 9.9 ± 1.1 μg melatonin/mL extract in our spiked samples compared to the non-spiked samples. Thus, our extraction method recovered 20% of the spiked melatonin, and presumably a similar percent from the original lotion sample. Taking this recovery rate into account, we estimate that Dr. Teal's Sleep Lotion contains 2.4 ± 0.1 mg melatonin/g lotion for a 0.24 ± 0.01% formulation (g/100 g lotion). Given that our participants were supplied with 7 g of lotion and instructed to use it all, their dose was approximately 17 mg transdermal melatonin. Dr. Teal's Soothing Lavender Essential Oil Body Lotion (placebo control) did not contain any detectable melatonin.

DISCUSSION

We have shown here that Dr. Teal's Sleep Lotion, a very common non-prescription transdermal formulation with no specific dosage listed on the label, contains 0.24 ± 0.01% melatonin that was readily absorbed up to ~1000-fold higher than physiological levels. In a small undergraduate student sample, this lotion also improved sleep in those with poor sleep quality. Consumers should be aware of the potency of such over-the-counter products.

Average sleep duration, bedtime, and quality of sleep in our sample were similar to a previous study in a university population (Lund *et al.* 2010), although that study found that exercise frequency was not related to PSQI scores. However, our results that exercisers had higher sleep quality than non-exercisers would add to the weight of the evidence for this relationship (Wang & Biro 2021). Our finding that White participants went to bed 42 minutes earlier than non-White participants is intriguing. Although reported typical total sleep time was not different by race in our study, the shift of sleep to a later clock time in non-White participants could compromise optimal function. Such delayed sleep phase has been associated with depression in some populations (Combs *et al.* 2021). Our data was collected by self-report; future work to confirm this finding would benefit from more objective actigraph data.

Previous studies have examined over-the-counter melatonin oral formulations (liquids, pills, tablets, and gummies) and found startling inconsistencies in the amount detected, up to almost five times the dosage listed on the label (Erland & Saxena 2017; Cohen *et al.* 2023). Dr. Teal's lotions, bubble baths, and sprays have no information on the labels about the amount of melatonin in the products, how much of the products consumers should use, or how often consumers should use them. This includes Dr. Teal's products specifically designated for children (https://www.drteals.com/products/?product-type=kids). Our data show that the sleep lotion from this product line contains a high level of melatonin. Interviews with caregivers have identified a common belief that melatonin will have fewer side effects because it is "natural" (Lee *et al.* 2023). However, from 2012 – 2021, the number of oral melatonin overdoses in children reported to U.S. poison control centers per year increased over five-fold (Lelak 2022). There

were over 53,000 cases regarding melatonin ingestion in the U.S. poison control data system in 2022 (Gummin *et al.* 2023). About 10% were treated in a health care facility, and while most outcomes were of no or minor effect, there were 149 outcomes of moderate or major effect (Gummin *et al.* 2023). Thus, although melatonin is generally considered safe (Besag *et al.* 2019), new formulations such as transdermal administration would benefit from assessments for side effects. Our data show extremely high salivary melatonin levels in response to sleep lotion application, and it complements appeals for increased regulation of this hormone (Grigg-Damberger & Ianakieva 2017) and research on long-term safety (Li *et al.* 2022).

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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