

Improvement in Sleep Maintenance and Sleep Quality with Ion Powered Pump Continuous Release and Absorption Melatonin: Results from a Self-Reported Patient Outcomes Study

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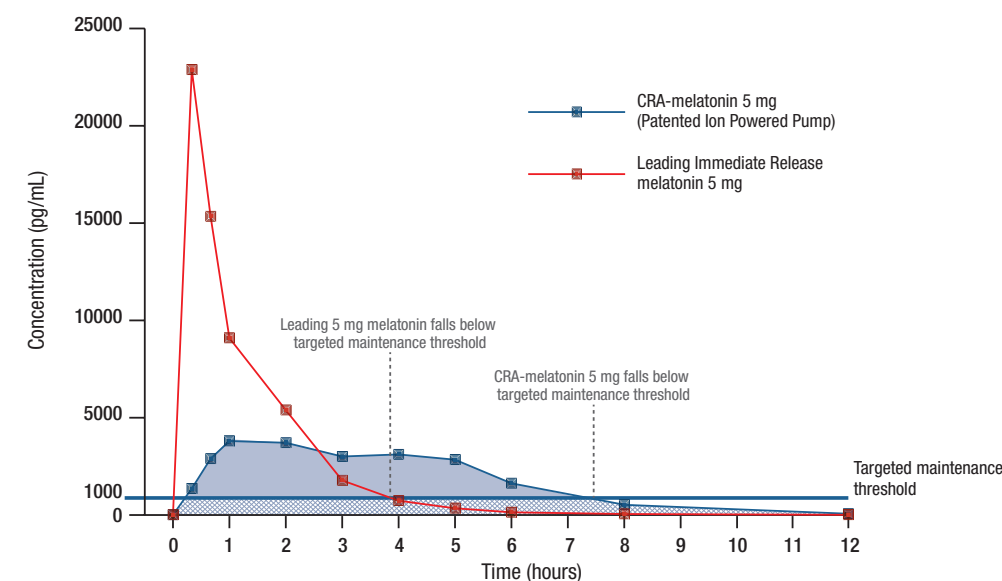
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Introduction

Nearly one-third of US adults sleep less than the recommended 7 hours daily.^{1,2} Increasing evidence suggests an association between sleep duration and adverse health outcomes, making sleep maintenance an important factor in achieving optimal health.³ In a pooled analysis of 16 studies and over 1 million patients, short sleep durations were associated with a greater risk of morbidity and mortality.³ In terms of preventing health consequences, sleeping 6 to 8 hours per night consistently may provide optimal health outcomes.³

Patients are seeking new therapies that are effective in inducing sleep while also achieving optimal sleep duration without residual effects the next day. Endogenous plasma melatonin levels in healthy humans follow a plasma concentration time curve similar in shape to a flat-topped Mesa Wave.⁴ However, mimicking this profile with conventional melatonin has been difficult due to challenges of release and absorption in the gastrointestinal tract.⁵ Continuous Release and Absorption Melatonin (CRA-melatonin) (REMfresh) with its Ion Powered Pump (IPP) delivery technology, provides the desired pharmacokinetic (PK) profile (Figure 1) and is anticipated to yield a relatively fast onset of sleep while providing sleep maintenance for up to 7 hours.⁶ These outcomes support CRA-melatonin as a practical baseline therapy option for patients looking for a hypnotic that has a benign safety and tolerability profile.

Figure 1. Median Concentrations of Plasma Melatonin After 5 mg CRA-Melatonin or 5 mg IR-Melatonin



The **REM Absorption Kinetics Trial (REMAKT)**, peer reviewed and presented at SLEEP 2017, was a randomized, crossover, clinical PK evaluation comparing 5 mg CRA-melatonin with the market-leading 5 mg* immediate release melatonin (IR-melatonin) in 10 healthy, non-smoking adults.⁶ The median C_{max} was 4,690 pg/mL for CRA-melatonin and 23,352 pg/mL for the IR-melatonin. Melatonin levels exceeded the targeted sleep maintenance threshold level of 1,000 pg/mL, for a median of 6.7 hours for CRA-melatonin, compared to 3.7 hours for IR-melatonin.

The post-marketing **REMfresh Patient Reported Outcomes Duration (REMDUR)** study was designed to obtain clinically relevant information about patients' sleep patterns, duration of sleep before and after CRA-melatonin, daily CRA-melatonin use, onset of action, sleep maintenance, quality of sleep, and overall satisfaction with CRA-melatonin.

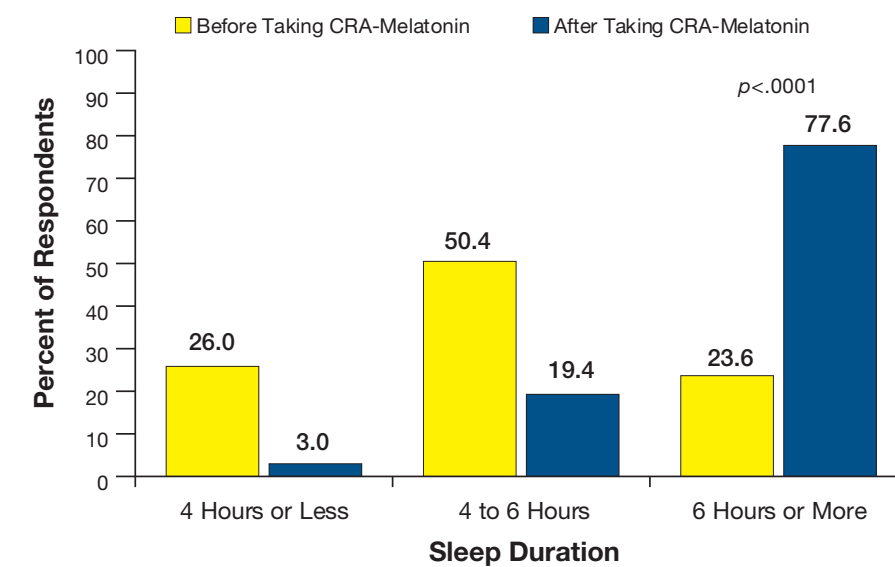
*A direct 2 mg comparison was not possible as there was no commercially established 2 mg presentation of the comparator brand.

Methods

- Patients with sleep disturbances in the general population, who received a sample of CRA-melatonin from their physicians, were invited to complete a 12-question online survey⁷. The authors note that there can be inherent bias in these types of open-label studies.
- Survey questions**
 - Prior to taking CRA-melatonin[†], how often did you suffer from sleep disturbances?
 - Prior to taking CRA-melatonin, on average, how long did it take you to fall asleep?
 - Prior to taking CRA-melatonin, on average, how many times a night did you wake up?
 - Prior to taking CRA-melatonin, how refreshed did you feel when you woke in the morning? (Scale 1-10 with 10 being the most refreshed)
 - Prior to taking CRA-melatonin, how many hours of sleep per night did you get?
 - Since taking CRA-melatonin, how many hours of sleep per night do you get?
 - Since taking CRA-melatonin, on average, how often do you take CRA-melatonin?
 - Overall, how would you rate the improvement in your sleep onset (time it takes to fall asleep) while taking CRA-melatonin?
 - Overall, how would you rate the improvement in your sleep maintenance (staying asleep) while taking CRA-melatonin?
 - Overall, how would you rate the improvement in your total sleep quality while taking CRA-melatonin?
 - Since taking CRA-melatonin, how likely are you to recommend CRA-melatonin to family and friends who have issues with sleep?
 - How likely is it that you will continue taking CRA-melatonin for your issues with sleep?

Results

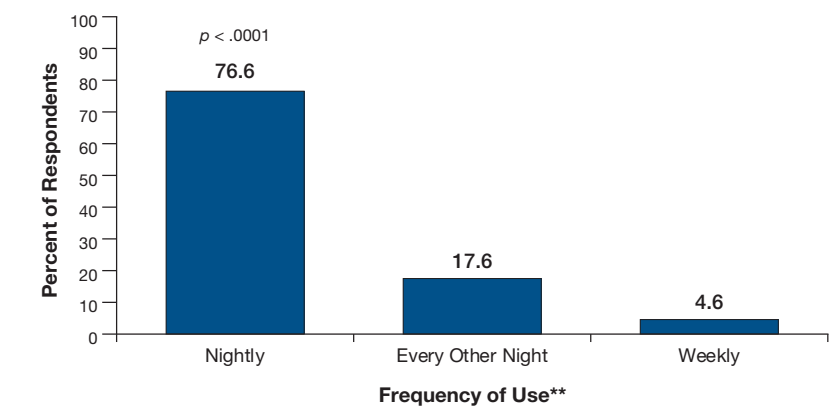
Figure 2. Hours of Sleep Reported by Respondents Before and After Taking CRA-Melatonin (n=500)[‡]



Survey responses were received from 500 patients in the general population who had taken CRA-melatonin. The vast majority (77.6%) of respondents reported sleeping 6 hours or more after taking CRA-melatonin compared with 23.6% before taking CRA-melatonin. The proportion of respondents with 6 hours or more of sleep after taking CRA-melatonin was statistically significantly greater ($p < .0001$) than before taking CRA-melatonin.

[†] To prevent confusion at the consumer level, the brand name was used in the actual surveys.
[‡] After the removal of 3 duplicate responses from the database.

Figure 3. Reported Frequency of Taking CRA-Melatonin (n=500)



When asked "How often do you take CRA-melatonin," 76.6% of survey respondents indicated that they take CRA-melatonin nightly, 17.6% take it every other night, and 4.6% take CRA-melatonin weekly. The proportion of respondents reporting nightly CRA-melatonin use was statistically significantly greater ($p < .0001$) compared with the proportion of respondents with less than nightly use (every other night or weekly).

Figure 4. Improvement in Sleep Since Taking CRA-Melatonin (n=500)



When asked how they would rate their improvement in sleep onset, sleep maintenance, and total sleep quality after taking CRA-melatonin, more than 91% of survey respondents reported a major/moderate improvement for each of the 3 questions. The proportion of respondents with major/moderate improvement was statistically significantly greater ($p < .0001$) compared with the proportion of respondents with no improvement for all parameters: sleep onset, sleep maintenance, and total sleep quality.

Conclusions

- With the use of CRA-melatonin, the majority of respondents (77.6%) achieved a sleep duration of 6 hours or more ($p < .0001$).
- More than 91% of survey respondents reported a major or moderate improvement in sleep onset, sleep maintenance, and total sleep quality after taking CRA-melatonin ($p < .0001$).
- More than 76% of respondents indicated they take CRA-melatonin nightly ($p < .0001$).
- The correlative relationship between a 7-hour Mesa Wave PK profile and real-world evidence of improvements in sleep duration, onset, maintenance, and sleep quality for CRA-melatonin is supported.
- REMDUR** provides confirmatory real-world evidence that CRA-melatonin is a practical baseline therapy option for patients with a variety of sleep disturbances.

References

1. Ford ES, Cunningham TJ, Croft JB. Trends in Self-Reported Sleep Duration among US Adults from 1985 to 2012. *Sleep*. 2015; 38(5):829-32. 2. Watson NF, Badr MS, Belenky G, et al. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the Recommended Amount of Sleep for a Healthy Adult: Methodology and Discussion. *J Clin Sleep Med*. 2015; 11(8):931-52. 3. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*. 2010; 33(5):585-92. 4. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Melatonin rhythm in human plasma and saliva. *J Pineal Res*. 1987; 4(2):177-183. 5. Shah SM, Brodner DC. A Continuous Release Ion Powered Pump Melatonin Delivery System that Overcomes Challenges of Release and Absorption in the Intestines (Abstract 0385). *Poster presented at: SLEEP 2017*; June 3-7, 2017; Boston, MA. 6. Brodner DC, Shah SM. REM Absorption Kinetics Trial: A Randomized, Crossover, Pharmacokinetics Evaluation of a Novel Continuous Release and Absorption Melatonin Formulation versus a Same Strength Immediate-Release Formulation in Healthy Adults (Abstract 0396). *Poster presented at: SLEEP 2017*; June 3-7, 2017; Boston, MA. 7. SurveyMonkey™ was the online survey platform.

DISCLOSURES

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** The monthly use vertical bar of 1.2% is not shown in the above chart.