

Observed Hypnotic Effects with a Continuous-Release Ion-Powered Pump Melatonin Delivery System: Self-Reported Patient Outcomes Study Results Demonstrating Improvement in Sleep Duration and Quality

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Introduction

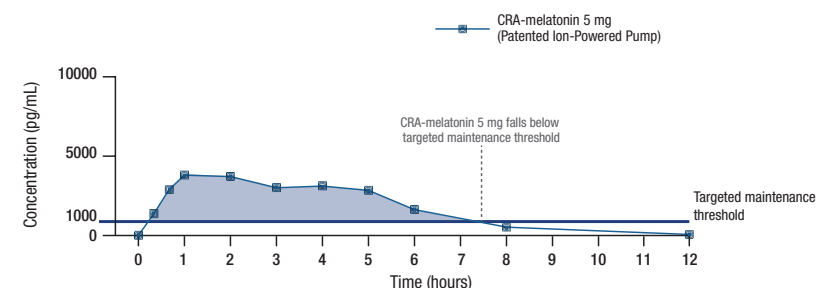
Melatonin, with its soporific action effects¹ and benign safety profile, could be an effective and well-tolerated sleep agent with an appropriate delivery system. Melatonin promotes sleep in a way that resembles the natural onset of sleep, through quiet wakefulness to the sleep state, while maintaining normal sleep architecture.²

Clinical use of exogenous melatonin as a drug-free hypnotic in initiating and maintaining sleep, is limited since no formulation has been shown to maintain critical blood levels for more than a few hours.³

A 2 mg prolonged-release melatonin (PR-M) has been approved as a prescription therapy for primary insomnia in Europe, based upon RCT sleep studies⁴ demonstrating improvements in sleep quality, wake time after sleep onset, and behavior following waking. While an improved formulation over previous attempts, a lower than anticipated plateau time for PR-M (4.4 hours)⁴ resulted from limited absorption in the distal GI tract.^{5,6}

Continuous Release and Absorption Melatonin (CRA-melatonin), with its IPP (Ion-Powered Pump) delivery system, has shown an extended 7-hour pharmacokinetic (PK) plateau time, which may offer a new low-dose, drug-free alternative to prescription hypnotics to treat chronic sleep disturbances.⁷

Figure 1. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin



The **REM** Absorption Kinetics Trial (**REMAKT**) was a randomized, crossover, clinical (PK) evaluation in 10 healthy, non-smoking adults. CRA-melatonin levels showed a median plateau time of 6.7 hours and no TEAEs were seen. The usage of 5 mg IR-melatonin for comparison with 5 mg CRA-melatonin was chosen as it is the most common melatonin product taken by US consumers and, unlike the 2 mg form, was readily available in the marketplace for comparator access purposes.

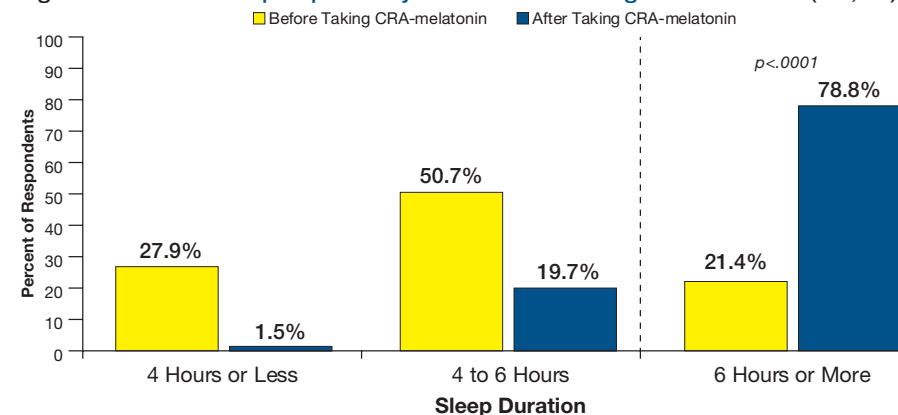
Methods

The **REM**fresh Duration Validation (**REMAVAL**) study was designed to validate the results from the first PRO Study, **REMDUR**, including obtaining clinically relevant information about patients' past usage of melatonin and non-melatonin sleep aids, sleep patterns prior to taking CRA-melatonin, sleep duration before and after taking CRA-melatonin, frequency of CRA-melatonin usage, improvement in sleep onset, sleep maintenance and sleep quality after taking CRA-melatonin, and overall satisfaction with CRA-melatonin.

Patients with sleep disturbances in the general population who received a sample of CRA-melatonin (REMfresh) from their physicians, were invited to complete a 13-question online survey.⁸ The authors noted that there may be inherent bias in these types of open-label studies.

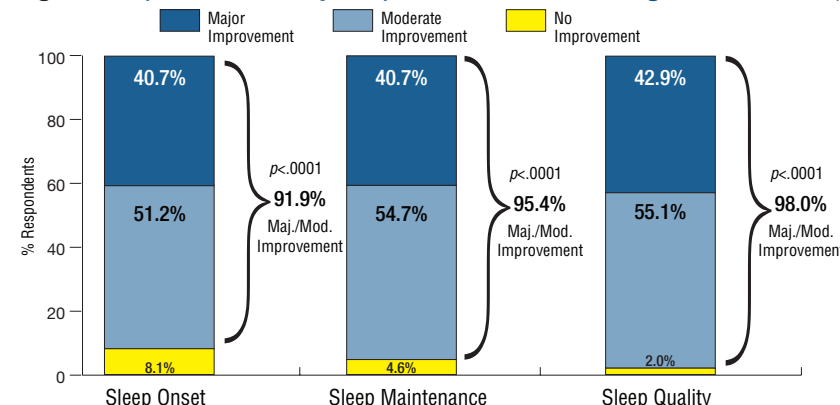
Results

Figure 2. Hours of Sleep Reported by Patients After Taking CRA-melatonin (n=1,116)



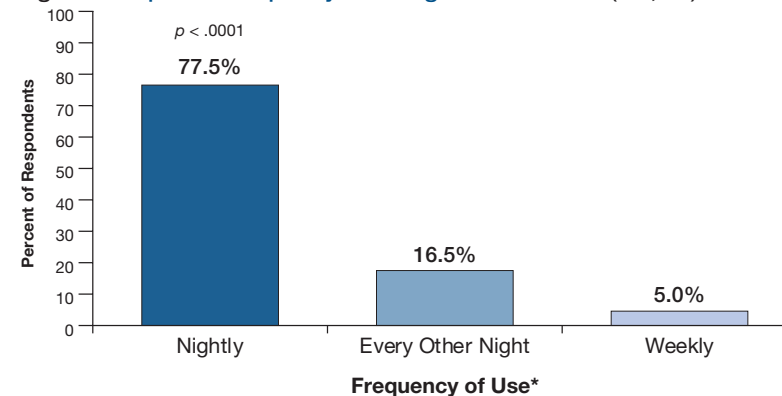
Patients were asked how many hours of sleep per night did you get before and after taking CRA-melatonin? Survey responses were received from 1,116 patients in the general population who had taken CRA-melatonin. 78.8% of patients reported sleeping 6 hours or more after taking CRA-melatonin compared with 21.4% before taking CRA-melatonin ($p < .0001$).

Figure 3. Improvement in Key Sleep Parameters After Taking CRA-melatonin (n=1,116)



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 patients reported a major/moderate improvement for each of the three sleep parameters measured, as compared to no improvement ($p < .0001$).

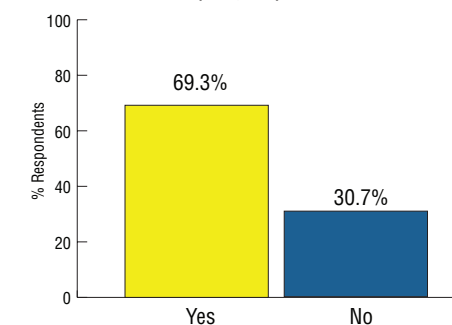
Figure 4. Reported Frequency of Taking CRA-melatonin (n=1,116)



*monthly=1.0%

When asked how often do you take CRA-melatonin?, 77.5% of patients indicated they take CRA-melatonin nightly, 16.5% take it every other night, and 5.0% take it every other night. The proportion of patients reporting nightly CRA-melatonin use was statistically greater as compared with the proportion of patients using CRA-melatonin less frequently ($p < .0001$).

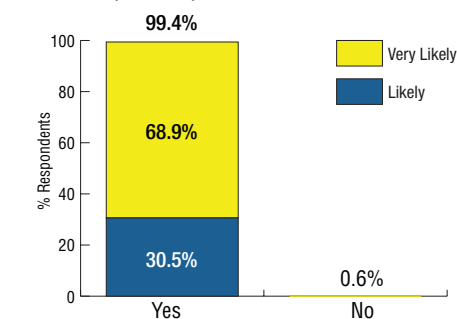
Figure 5. Patients Reporting Having Taken Other Brands of Melatonin Prior to Taking CRA-melatonin (n=1,116)



While the vast majority of patients had taken other brands of melatonin prior to trying CRA-melatonin, over 30% of patients (342 in total) reported never having taken other brands of melatonin.

99.4% of those 342 patients reported being either very likely or likely to continue taking CRA-melatonin for their sleep issues ($p < .0001$).

Figure 6. Patients Indicating They Will Continue Taking CRA-melatonin for Sleep Issues (n=1,116)



Conclusions

After taking CRA-melatonin, the vast majority of patients (78.8%) achieved a sleep duration of ≥ 6 hours ($p < .0001$).

More than 91% of patients reported a major/moderate improvement in sleep onset, maintenance and sleep quality ($p < .0001$ for each parameter).

Of those patients who had never taken melatonin before, 99.4% indicated they were likely or very likely to continue taking CRA-melatonin ($p < .0001$).

In spite of the inherent bias, the differences reported are very substantial.

REMAVAL provides further real-world evidence of a correlative relationship between the 7-hour PK profile and observed hypnotic effects of CRA-melatonin (improvements in sleep duration, onset, maintenance, and quality).

The results of this second PRO study closely validate the findings of the first 500-patient PRO study, **REMDUR**, peer-reviewed and presented at SLEEP 2018.

References

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4. European Medicines Agency. Assessment Report for CIRCADIN. 2007.
5. Zisapel N, inventor; Neurim Pharmaceuticals Ltd., assignee. Method and Pharmaceutical Formulation for Treating Benign Prostatic Hyperplasia. US patent 5,750,557. May 12, 1998. Column 10, lines 21-25.
6. Zisapel N, inventor; Neurim Pharmaceuticals Ltd., assignee. United States Patent Application Publication: Methods for Treating Patients Suffering from Drug Dependencies which lead to Plasma Melatonin Deficiencies. Pub. No. US 2003/0040539. February 27, 2003.
7. 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.
8. Survey Monkey® was the online delivery platform.

DISCLOSURES

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