Melatonin - Potential Dosing Strategies and possible side effects, other strategies.

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ABSTRACT

Background: Insomnia is a very common sleep disorder which is encountered to a greater extent in cohorts of the population as they get older. The author of this paper has suffered from the effects of insomnia. He has performed some experimentation on himself with a number of publicly available supplements including Melatonin with a view to ameliorating the insomnia with some success. He will be writing papers which report his conclusions. This is the first.

Methods: Over a period of 3 years the author has tried a range of different strategies for reducing the effects of insomnia with supplements including Melatonin and measured the effects on his sleep using a sleep monitor and otherwise.

Results: It is clear for the test subject that relatively substantial doses of Melatonin (15-110mg) taken during the night can assist with the failure of sleep maintenance and thereby improve the ability of the subject to function intellectually during the day rather than suffer from afternoon fatigue. There may be other people that this approach could benefit. Caution and further research is, however, needed as there may be side effects. An alternative strategy is to clear down the melatonin system and restart it.

INTRODUCTION

Sleep patterns change in normal ageing, but the operation of the sleep wake cycle is complex and the causes of disturbances to the cycle are multifactorial. [4] There is wide recognition that the first step in treating insomnia should be CBT-i (Cognitive Behavioural Therapy for Insomnia) [5] However, treatment should not always stop at that point. The neural circuits that control the sleep wake cycle are complex involving neuronal activity, sleep pressure and the secretion of melatonin on a circadian basis. [6] Melatonin ($C_{13}H_{16}N_2O_2$ - N-acetyl-5-methoxy tryptamine) is produced in many parts of the body, but that produced for the circadian cycle is produced in the pineal gland. [2] This injects melatonin into the third ventricle of the Cerebral Spinal Fluid. A view is commonly held that melatonin is mainly a chronotherapeutic and its sleep-promoting effects are weak [6] , but the author disagrees, having concluded after experimentation that in certain circumstances it can induce sleep directly.

Experiments with sheep have concluded that pineal melatonin transferred into the CSF is the only melatonin that gets to cerebral tissue in high concentrations [7] The concentration of melatonin in the CSF is materially higher than that in blood serum. Melatonin also has a short half life of the order of 30 minutes. The turnover of fluid from the blood is such that it takes around 5 hours. [13] [11] Hence the concentration of melatonin in blood serum will have to be materially higher than that in the CSF in order to increase the concentration in the CSF sufficiently to impact on cerebral tissue.

Melatonin is safe even in the short term in extreme doses [1] [8] What is not known, however, is what impact higher doses have in the long term. This particular experiment was designed to see if sleep could be induced by abnormally high concentrations of melatonin in blood serum.

MATERIALS AND METHODS

Melatonin was sourced from three manufacturers: Natrol Advanced 10mg -chosen because it may have some delayed release, Eurovital Fast Dissolve 5mg and 10mg - chosen to be dissolved in the mouth and available on a sublingual basis and Spray Melatonine from Abiocom (a French company) chosen for rapid absorption. An Omron M2 basic arm sphygmomanometer, a Fitbit HR and Vesync Fit weighing machines the latter two of which linked via bluetooth to a Samsung Android Mobile phone. Records were taken when going to bed as to heart rate, blood pressure, weight and the supplements taken during the day as well as food eaten and alcohol consumption. On waking records were taken and details of when melatonin was taken to track the time taken to return to sleep.

The objective of the experimentation was to deal with a recurrent problem of insomnia which was undermining the test subject's ability to rapidly handle technical issues within the Fintech that he had founded. The test subject was born in 1960 and is, therefore, older than many people still active in writing software.

It is recognised that Fitbit HR is not as reliable as specialist

polysomnograms. However, given that the objective is to work out how to improve sleep rather than necessarily to precisely measure sleep and given that records were taken over a period of multiple years the view was taken that its unobtrusive nature and the ability to check the accuracy on waking meant that it was a useful and objective measurement. Heisenberg's uncertainty principle is relevant here and the chosen sleep monitor did not interfere with sleep.

The sleep monitor sleep analysis records a time asleep, a balance between REM and other sleep and a score for restoration based upon heart rate changes during the night. This was recorded both as a sleep period and a combined sleep score. Again this was found to be useful as a measurement in that it predicted the ability of the test subject to work effectively on complex technical issues.

Success in sleeping was defined as having sufficient restoration so that the test subject could work continually on complex technical problems during the day without being tired until the evening. It was found that a total period identified by the sleep monitor as being asleep in excess of 6 hours was normally sufficient to achieve this. It should be noted that the sleep analysis ignores periods of time that sleep monitor software concluded the test subject was awake.

A set of standard CBT protocols for improving sleep were implemented in terms of sleep hygiene - keeping the bedroom dark, avoiding looking at blue light during the night, having a regular sleep schedule. Attempts were made to vary only one supplement from time to time in an attempt to work out what the effect from each supplement. Menaquinone (Vitamin K2) was found to impact on the ability of melatonin to return the test subject to sleep. At times supplements with four, seven and nine isoprene residues were taken.

The variation in sleep pressure and its impact was recorded in a qualitative manner.

Melatonin was taken when sleep maintenance failed. If this happened it was often in the period after 3am or potentially 4am. The test subjects daily cycle started after 6am and adding between 30 and 90 minutes additional sleep had a material positive effect.

A dose of berry melatonin was taken masticated and held sublingually immediately after the delayed release melatonin was swallowed. That was in order to have an immediate increase in serum levels followed by the maintenance of serum levels as that would result in a longer period of sleep. Potentially further doses of berry melatonin were taken sublingually, but keeping the tablets whole in order to delay release.

An alternative strategy is to clear down the melatonin system and restart it without the use of exogenous melatonin. This involved getting up and reading using a computer with blue light then returning to bed.

RESULTS

Results are analysed for the period 10th August 2020 to 21st May 2021

For doses under 15mg melatonin return to sleep did not happen.

For 15mg melatonin there were three successes and one failure to return to sleep. The successes were after 9, 17 and 88 minutes.

For 20mg Melatonin there were two successes after 5 and 113 minutes and two failures, both when the test subject went to sleep having consumed unreasonably large quantities of ethanol (mixtured with natural flavourings)

For 25mg Melatonin there was one failure caused by over consumption of ethanol.

For 30mg Melatonin there was a success at 90 minutes and a success at 34 minutes where the test subject had taken both ethanol and menaquinone (vitamin K2). Otherwise there were three failures caused by ethanol and one other failure.

For 35mg Melatonin there were 33 successes at 9, 14, 24, 34, 40, 47, 48, 51, 53, 53, 53, 55, 57, 63, 65, 71, 71, 74, 79, 82, 83, 83, 87, 88, 90, 95, 99, 99 minutes without ethanol and 153, 120, 83, 64, 63 and 35 minutes with excessive ethanol consumption and one with menaquinone at 35 minutes. One failure without ethanol and 6 failures with ethanol one of which also had menaquinone.

At 40 mg there were three successes at 75, 84 and 86 minutes, one at 64 minutes with menaquninone and ethanol.

At 45mg there was one success at 35 minutes. One success with ethanol at 68 minutes, a failure, three failures with ethanol and one failure with menaquinone.

At 50mg there were successes without ethanol at 9, 40, 51, 80 with ethanol only at 11 with menaquinone only at 40, 55 and 87. With ethanol and menaquinone at 13, 47 and 106 minutes.

At 60mg there were two successes at 5 and 80, one wih ethanol at 32 and one with menaquinone at 40. There were 7 failures with alcohol, or other unusual things. There was one failure without unusual things.

At 65mg there were two successes at 40 and 76 minutes and no failures.

At 80 mg there were two sucesses both with menaquinone, one of which also had ethanol and two failures both with menaquinone, but no alcohol.

At 110mg there was one success after 4 minutes.

Restarting the system: Restarting the system produced a better subjective quality of sleep than exogenous melatonin,

but it took longer to return to sleep (potentially 3 hours) and so was not practical on days on which the test subject had to take children to school.

This strategy was only tried three times in the above period.

Conclusions: Taking large doses of melatonin during the night frequently returned the test subject to sleep. Drinking a lot of ethanol or taking menaquinone made this less likely although a larger dose of melatonin would be more likely to have an effect. Drinking ethanol and taking menaquinone made sleep more likely than one in isolation. Doses under 15mg did not return the test subject to sleep.

Side Effects: The amounts of melatonin taken do exceed normal serum levels even for younger people who normally have higher melatonin levels. Hence it would not be surprising if there were some other effects. One noticeable side effect is the growth of a small number of dark hairs on an area of scalp that has not seen hair for perhaps 20 years. There is also at times a short hangover of the effects on the brain, but dosing can be managed to stop this occurring at times when the subject is supposed to be out of bed.

There may be other side effects which will come to light.

Part way through the experimentation period the test subject decided to lose weight. On 12th August 2022 he was 129.80kg (BMI 36.4) on 5th May 2021 he was 85.65kg (BMI 24.2). There are suggestions that exogenous Melatonin assists weight loss. This experience would be consistent with that thesis as being a side effect.

DISCUSSION

There has been a debate about what the appropriate dosing of melatonin is and whether or not it has a therapeutic benefit. Concerns have been expressed at dosing levels beyond those normally found in the blood serum. There are receptors for Melatonin around the body and it is not possible to predict what will happen with a long term high dosage of melatonin. That creates an ethical problem for research with a particular need for particularly well informed consent. This particular research project does not have that ethical problem as it has a primarily therapeutic objective and the test subject has designed the project.

One set of melatonin receptors is on the suprachiasmatic nucleus (SCN). There is a debate as to what feedback effect occurs between the SCN and the Pineal Gland. [14] [10] [12] [9] The author has concluded on the basis of his research that one effect is to reduce the production of pineal melatonin. This means that once there is a substantial amount of serum melatonin the pineal gland ceases melatonin production and any melatonin going into the CSF has to be exogenous.

Hence if sleep maintenance fails there are only really two options. One is to using blue light and waking to clear melatonin from the CSF and blood serum and then recommence melatonin generation. This has a material time requirement. The other is to dose with exogenous melatonin in sufficient quantities to increase blood serum levels so they increase the concentration in the CSF sufficiently to enable sleep.

It is clear that the latter does work for the test subject. It is also clear that there are circumstances (high levels of menaquinones, particularly long chain and prior night consumption of high levels of ethanol in which the same dosage and structure of dosage does not work).

The side effect on the scalp raises a question as to whether hair colour and density can be seen in some way as a proxy for melatonin levels. Research on melatonin levels and hair colour and density could identify if this is the case.

Melatonin has a number of potential benefits [3] further research is needed as to the long term impact of melatonin.

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All the research is self funded by the author. He has no financial interest in any manufacturing of supplements. He has an interest in reducing insomnia.

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