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Associations between treatment with melatonin and suicidal behavior: a nationwide cohort study

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Abstract

Study Objectives: Melatonin is often prescribed to patients with sleep disorders who are known to have elevated suicide risks. Yet, melatonin's association to suicidal behaviour remains to be examined. We investigated whether individuals prescribed melatonin had higher rates of suicide and suicide attempts when compared to individuals who were not prescribed this drug, including both those with and without known mental disorders.

Methods: A cohort design was applied to longitudinal, register data on all persons aged 10+ years in Denmark during 2007-2016. Based on data from the National Prescription Register, periods of being in treatment with melatonin were defined using information on number of tablets and daily defined dose. We calculated IRR for suicide and suicide attempts, as identified in register records, comparing those in treatment with melatonin to those not in treatment.

Results:
Among 5,798,923 individuals, 10,577 (0.2%) were treated with melatonin (mean treatment length 50 days) during the study period. Of those, 22 died by suicide and 134 had at least one suicide attempt. People in treatment with melatonin had a 4-fold higher rate of suicide (IRR: 4.8; 95% CI, 3.0-7.5) and a 5-fold higher rate of suicide attempt (IRR: 5.9; 95% CI,4.4-8.0) than those not in treatment and when adjusting for sex and age-group.

Conclusions:
Treatment with melatonin was associated with suicide and suicide attempt. While there are several possible explanations, attention to suicide risk is particularly warranted for people with mental comorbidity who are in treatment with melatonin.

Keywords:
Suicide, Melatonin, Sleep disorder, Suicide Prevention, Melatonin Treatment.

Brief Summary

Current Knowledge/Study Rationale:
Melatonin is being prescribed over the counter in several countries and its use among vulnerable groups, including in children and adolescents as well as people with mental disorders, is increasing. Still, little evidence exists regarding its possible association with suicidal behaviour.

Study Impact:
Using longitudinal national and complete data on all redeemed prescriptions in Denmark, an association between treatment with melatonin and suicidal behaviour was established, which largely may be assumed to be related to mental disorders and/or sleep disturbance. Considering the high proportion of patients with co-existing mental comorbidity receiving melatonin, it would in general be relevant to be attentive towards their mental wellbeing and any suicidal ideation.

Introduction

Nearly 700,000 individuals die by suicide every year,[1] making it a major public health issue.[2] Suicide is associated with mental disorders.[3] While sleep disorders are relatively common among people with mental disorders, they are also often a reason for health care contact in their own right.[4] Sleep disorders have been associated with suicidal ideation and behaviour, including suicide.[5-8] Further complicating the issue, links between medications often used as hypnotics (e.g., benzodiazepines, non-benzodiazepines) and suicide have been observed.[9-12] Melatonin is increasingly prescribed for sleep/wake disturbances[13] and is available for sale over the counter in several countries. We are unaware, however, of studies investigating whether melatonin use is associated with suicidal behaviour. This is concerning, given its increased prescription rate, particularly among children and adolescents.[14-16]

Melatonin is an endogenous hormone produced in the pineal gland. It has a variety of neuroendocrine regulatory roles by determining and regulating circadian effects throughout the body, including maintenance of a stable sleep-wake schedule.[17] Orally taken melatonin might be linked to suicidal behaviour through different pathways. First, melatonin is prescribed for disturbances of the circadian rhythm,[18] but subsequently can also be prescribed for homeostatic sleep problems, both of which are often disturbed in psychiatric patients.[19] Suicidal behaviour is well known to peak in spring and autumn and rates of suicide and suicide attempts have been reported to vary according to circadian changes (morning vs. evening); thus, it is plausible that changes in melatonin levels may have an impact on risks of suicidal behaviour.[20,21] Secondly, levels of endogenous melatonin have been found to vary in patients with depression, leading to the use of melatonin as a treatment for depression, for instance in the form of the melatonin receptor agonist Agomelatine.[22-24] It is, therefore, possible that those people who are taking melatonin and suffer from depression may represent a sub-group with an excess risk of suicidal behaviour.[3] Based on the existing evidence, it seems likely that individuals in treatment with melatonin have an increased risk of suicidal behaviour, but that this could in part could be related to underlying conditions, such as mental or sleep disorders.[25]

Pharmaceutical companies began marketing melatonin in Denmark in 2007.[26] Prior to this, melatonin was prescribed by magistral ordination (products produced specifically for the individual who had received a prescription, i.e., ad. hoc production) at pharmacies. In Denmark, melatonin can only legally be acquired through prescription from a doctor. In contrast, in many other countries, melatonin is sold over-the-counter with little to no regulation.[27] This lack of regulation complicates its systematic study in these environments, and emphasizes the need for a careful assessment of possible risks. Combined with the availability of national health registries, the regulated access to melatonin makes Denmark an ideal country for systematically studying its use and associated health outcomes.

Serious adverse effects related to treatment with melatonin have not previously been reported.[28,29] One systematic review found that there were low to few adverse events related to melatonin treatment, but that more careful analyses were warranted.[25] The common use of melatonin and its multiple indications (i.e., ranging from dietary supplementation to support mental health to treatment of sleep disorders), underscores the importance of assessing whether melatonin is linked to increased risk of suicidal behaviour.

We examined whether people in treatment with oral melatonin had higher rates of death by suicide and suicide attempt compared to people not in treatment We hypothesised that risk of suicidal behaviour might be related to underlying conditions, such as mood and sleep disorders, and therefore examined this in the analyses. In addition, we examined whether rates of suicide attempts varied with respect to onset of melatonin treatment. We used longitudinal national linkage data on all melatonin prescriptions filled at Danish pharmacies to define individual treatment periods based on number of tablets and standard dosages.

Methods

Data sources

We applied a retrospective cohort study design to longitudinal data on all individuals living in Denmark at some point between Jan 1st, 2007, and Dec 31st, 2016. A unique identification number is assigned to all people living in the country at birth or upon immigration.[30] Using this identification number, data from the Civil Registration System were linked to complete information on all prescriptions redeemed at pharmacies since 2007, as listed in the National Prescription Registry.[31] Additional linked registries included the National Patient Registry[32] and the Psychiatric Central Registry,[33] which list information on all hospital contacts, as well as the Cause of Death Registry.

Participants

We studied all individuals aged 10 years or older. Individuals who turned 10 years or immigrated to Denmark during the follow-up period were included on the date of the respective event.

Exposure

Data on redeemed melatonin prescriptions were obtained from the National Prescription Registry. This register contains information on specific drugs, number of tablets, strength, and date of purchase. Medication is categorized according to the Anatomical Therapeutic Chemical Classification System (ATC) and melatonin was identified as ATC: N05CH01. Based on these data, we considered individuals as being in treatment from the date of redeeming a prescription with melatonin. Using information on the total number of tablets, the strength of the drug, and the Daily Defined Doses, we estimated the number of days each prescription would last and identified the date when a new prescription would be expected to be filled. This treatment period was extended by 50% to account for variation in dosages. If a new prescription had not been redeemed prior to the estimated end date, the person was considered as having ended treatment on that date. If the individual filled a new prescription prior to the estimated end date, they were considered to have continued melatonin treatment, and a new end date was calculated based on the new prescription. A ‘carry-over’ of up to 21 days of unused tablets to a new treatment period could account for vacation closures at pharmacies or primary care and also holiday periods.

Additional measures

Information on sex *(male, female)* was obtained from the Civil Registration System. Analyses were stratified by age groups by using two broad categories (10-59 years, ≥60 years), as there were few observed events. Furthermore, in Denmark, melatonin is in general only supposed to be prescribed for older people with sleep problems. Covariates denoting any previous mental disorder before exposure to melatonin, and any current or previous mood disorders, were based on data from the Psychiatric Central Registry (eTable 1). We included a separate measure for mood disorders in general because of awareness that melatonin is fairly often prescribed for people with this group of mental disorders compared to all mental disorders.[34] Sleep disorder diagnoses were identified in the National Patient Registry and pooled into one group of "any sleep disorder." Somatic disorders were used for calculation of score for the Charlson Comorbidity Index,[35,36] which served as a weighted index of somatic comorbidity. All diagnoses (mental or somatic) were coded according to the *International Classification of Diseases, 8th revision* (*ICD-8*) prior to 1994 and according to the 10th revision (*ICD-10*) thereafter. People were considered to have a disorder (mental or somatic) from the date a diagnosis was first recorded.

Outcomes

The primary outcome was death by suicide, which was identified by the following ICD-codes: ICD-10: X60-X84, Y87.0, or where the manner of death was listed as 'suicide' in the Cause of Death Register.

Suicide attempt was examined as a secondary outcome. This was identified as presentations to either psychiatric or somatic hospital, including emergency departments, as recorded in National Patient Registry or Psychiatric Central Registry, with one of the following ICD diagnoses: ICD-8: E950-E959, and ICD-10: X60-X84, or when the reason for contact was listed as suicide attempt.

Statistical analyses

Incidence rates for suicides and suicide attempts per 100,000 person years were calculated separately. Using logistic regression models, we estimated Incidence Rate Ratios (IRR) for suicide and suicide attempt for individuals in treatment with melatonin

relative to those not in treatment. We assessed for overdispersion and opted for a negative binomial distribution, to compensate for this. IRRs were reported with 95% confidence intervals. We examined whether IRRs differed with respect to *any comorbidity using stratified analysis* (defined as a mental disorder, sleep disorder, or conditions identified by the Charlson comorbidity index), *mental disorder*, *mood disorders*, *sleep disorders*, and the *Charlson comorbidity index*, as well as *time since start of treatment with melatonin* (not in treatment, <1 month, 1-<3 months, 3-<6 months, ≥6). In models assessing suicide attempt, persons were censored after a first suicide attempt. Analyses were adjusted for sex and age group. All variables were included as time-varying covariates and updated either on the exact date of change or on a yearly basis.

Data management and regression analysis were conducted using SAS Institute Inc; version 9.4.

Ethical considerations

The project was approved by the Danish Data Protection Agency and the Danish National Board of Health (RHP-2012-021). All data processing and analysis were conducted on Statistics Denmark's servers in accordance with Danish and EU legislation.

Results

In all, 5,798,923 (49.7% males) individuals aged 10 years and over were observed over 45,826,519 person-years. During the 12-year study period, 10,577 (0.2%) individuals had been in treatment with melatonin, with a median treatment time of 35 days (IQR=20 - 45) and mean treatment time of 50 days (SD =77) per prescription.

Suicides

A total of 5,952 individuals aged 10 years and over died by suicide, of whom 22 (0.4% of all; 63.6% males) were being treated with melatonin at the time of suicide. The rate of suicide among those in treatment with melatonin was 53.7 per 100,000 person-years, compared with 13.0 for those not in treatment (Table 1). After adjustment for sex and age group differences, individuals in treatment with melatonin had an IRR for suicide of 4.8 (95% CI, 3.0-7.5) when compared to those not in treatment. When

examined separately by sex, IRRs of 4.3 (95% CI, 2.6-7.3) and 4.3 (95% CI, 2.1-8.6) were found for males and females, respectively.

Suicide attempts

In the full sample of individuals aged 10 years and older, 25,136 (0.4%) persons had a first suicide attempt. Of these, 134 (0.5% of all; 28.4% males) were in treatment with melatonin. The rate of suicide attempt was 346.6 per 100,000 person-years for those in treatment with melatonin and 55.5 for those not in treatment. An IRR of 5.9 (95% CI, 4.4-8.0) for suicide attempt was found among individuals in current treatment with melatonin when compared to those not in treatment when adjusting for sex and age group. Elevated rates of suicide attempt were found in separate analyses for both males (IRR, 6.1; 95% CI, 4.4-8.4) and females (IRR, 7.4, 95 CI, 6.1-9.1) compared to those not in treatment within the respective sex group.

Comorbidity

Among the 134 individuals who had a suicide attempt while being in treatment with melatonin, 124 (92.5%) had an underlying comorbid disorder (defined as any mental, mood or sleep disorder and/or the presence of any of the diseases present in the Charlson Comorbidity index) (Table 2). Those in treatment with melatonin who also suffered from a comorbid condition had a 29-fold higher rate of suicide attempts (IRR: 29,4, 95% CI, 21.2-40.9) when compared to those not in treatment and without any comorbidity. Those in treatment with melatonin but no history of comorbidity had an IRR of 3.2 (95% CI, 1.6-6.3), although this estimate was based on few suicide attempts (n=10). Lastly, people not in treatment with a comorbid disorder had an IRR of 8.8 (95% CI, 6.9-11.2), also compared to those with no disorders and not in treatment.

In all, 120 (90%) melatonin users with a suicide attempt had a history of mental disorders. Individuals who were in treatment with melatonin and had earlier been diagnosed with a mental disorder had an IRR of 39.8 (95% CI, 28.1-56.5) for suicide attempts, which was higher than those with mental disorders and not in treatment with melatonin (IRR, 17.7 95% CI, 13.6-23.1), both measured relative to persons who were neither in treatment nor had mental disorders. Compared to this group, those who

had no mental disorder but were in treatment with melatonin also had higher rates of suicide attempts (IRR, 3.2 95% CI, 1.6-6.3), although based on few suicide attempts (n=14). Being in treatment with melatonin and having a prior diagnosis of a mood disorder was associated with a higher suicide attempt rate (IRR, 28.2 95% CI, 19.3-41.2) than in those in treatment with melatonin but not diagnosed with mood disorders (IRR, 5.9 95% CI, 4.1-8.4), when using the group with none of these exposures as the reference.

Despite individuals who were in treatment with melatonin and diagnosed with a sleep disorder having an elevated rate of suicide attempt (IRR, 3.7 95% CI, 1.3-10.2), the estimated confidence intervals overlapped with those of persons in treatment but with no diagnosis of sleep disorders (IRR, 7.4 95% CI, 5.4-10.2) when compared to those with neither. Amongst melatonin users with a suicide attempt, 33 (24%) had a chronic somatic disorder, as identified by Charlson Comorbidity Index. The IRR of individuals with somatic comorbidity who were in treatment with melatonin (IRR, 8.3 95% CI, 5.5-12.5) was comparable to that of those who were in treatment with melatonin but had no somatic comorbidity (IRR, 7.4 95% CI, 5.4-10.3) when compared to those with neither of these factors.

Although not significantly different from other groups in treatment, individuals who had initiated treatment with melatonin 3-6 months earlier were found to have the highest rate of suicide attempt (IRR, 8.5 95% CI, 4.6-15.4) when compared to those not in treatment (Figure 1). Elevated IRRs for suicide attempt were also noted among those who had initiated treatment within the past month (IRR 7.1 95% CI, 4.7-10.7), 1-3 months ago (IRR, 5.7 95% CI, 3.6-9.2) as well as those who had been in treatment with melatonin for more than 6 months (IRR, 3.3 95% CI, 1.7-6.5).

Users aged 10-59 years had a higher rate of suicide attempt compared to users 60 years and over (Table 3). In contrast, melatonin users aged 60 years and over seemed to have a higher suicide rate than users aged 10-59 years.

Discussion

To our knowledge, this is the first study to examine the association between melatonin treatment and suicidal behaviour. We found that individuals who were in current treatment with melatonin had higher rates of suicide and suicide attempt, albeit based on relatively few events, than non-users. We also found that the majority of melatonin users who had suicide attempts suffered from co-existing conditions, mainly in the form of mental and sleep disorders. Keeping the potential benefits of sleep medication in mind, it is possible that the excess risk of suicidal behaviour experienced by those people who were in treatment with melatonin might have been related to symptom severity of co-existing conditions rather than the melatonin treatment.

With regard to sex differences, the higher number of suicide attempts among females coincides with the general finding that suicide attempts are more frequent among females in Denmark.[37] The majority of fatal suicide events occurred among males and the relation between the male and female suicide rates among melatonin users resembled the distribution seen for suicide in the Danish general population.[38]

Furthermore, those who had mental disorders and received melatonin treatment had higher suicide attempt rates than those who had a mental disorder but were not in treatment with melatonin. Melatonin users who had been diagnosed with any type of comorbidity (i.e., as measured by the Charlson Comorbidity Index, anyone with *any* mental or *any* sleep disorders) had the highest rate of suicide attempts of all examined groups. In fact, 92.5% of melatonin users who had a suicide attempt suffered from comorbid disorders, thus strongly suggesting that the main drivers of risks of suicidal behaviour might be carried by comorbid disorders. The impact of underlying disorders is underscored by the fact that the majority of individuals with suicide attempts had comorbid mental disorders, i.e., mood disorders or other mental disorders. In contrast, relatively few had somatic comorbidities, including somatic hospital diagnosed sleep disorders. Thus, it seems likely that the main factor influencing the excess risk of suicidal behaviour in those with mental health disorders might have been sleep disorders.

Melatonin is often prescribed to people who suffer from sleep (insomnia or circadian) disturbances.[18] It is, therefore, possible that the association with suicidal behaviour could be driven by sleep disorders.[6,8,39] Sleep disturbances are, however, also

common in patients suffering from depression,[34,40] schizophrenia, and other mental disorders.[41] These disorders could also convey an increased risk of suicide.[42] Although it is likely that these factors are responsible for, at least in part, the higher rates among people taking melatonin, we cannot exclude a direct causal association between melatonin and suicidal behaviour. For this reason, it might be more important to directly address mental disorders, which have been demonstrated to have stronger associations to suicidal behavior, rather than the association studied here. Nevertheless, when evaluating whether patients should be prescribed melatonin it might be worthwhile assessing for underlying mental health disorders, considering that 90% of those with suicidal behaviors had a history of mental disorders.

Strengths and limitations

Strengths of the study include a large national cohort with a long follow-up period. The National Prescription Registry and the National Patient Registry have in general been evaluated to have high levels of validity.[30,32] Furthermore, the CPR register is continuously validated. The data on prescriptions allowed us to continuously monitor, those who were in treatment with melatonin. Characteristics of users might differ between countries. The ones identified as being in treatment in this study had been in contact with a doctor to obtain a prescription, which might imply that they represent a more vulnerable group. Register data enabled us to follow a large group of individuals in treatment, which might not be feasible in countries where melatonin is sold over the counter. The outcome measures, suicide and suicide attempt, were identified using robust register data.[32,43]

This study had several limitations. Firstly, we cannot exclude that individuals may have acquired the drug in other ways, such as international mail orders, although this is illegal in Denmark. Secondly, the number of observed outcomes were low. Death by suicide is relatively rare; and, although suicide attempts are more frequent, they are known to be underreported in Denmark.[37] Thirdly, the results might not be indicative of a direct effect of melatonin, but rather of other characteristics of the population receiving melatonin, given this drug is often prescribed to individuals with underlying mental health conditions and/or sleep disorders. Fourthly, confounding by underlying sleep issues in those with mental or mood disorders cannot be excluded, thus it is hard to establish if it is mental health disorders driving these observed higher IRR or deteriorated sleep, which is often seen in

individuals with mental health disorders, when considering melatonin as a proxy for deteriorated sleep. Therefore, any conclusion from this study concerning melatonin as a predictor of suicide risk should be considered with caution. It would have been preferable to have data from primary care so that one might have identified diagnoses given by patients' general practitioners. Fifthly, it would also have been desirable to account for potential confounders, such as insufficient sleep, polypharmacy, and seasonality, but it was only feasible to include a limited number of covariates due to the relatively small exposure group. Sixthly, melatonin is often prescribed to individuals with underlying mental health conditions, including substance misuse, depression and/or sleep disorders. Thus, it cannot be excluded that the observed association might have been moderated by other medication that the individual was taking. Seventhly, the small size of the group of melatonin users who engaged in suicidal behavior compared with the very much larger group of individuals with suicidal behavior who were not receiving melatonin, limited the extent to which subgroup analyses could be performed.

Clinical implications

The benefits of offering sleep medication, such as melatonin, for people experiencing sleep difficulties related to mental health problems are obvious as this could increase quality of life and thereby potentially reduce suicidality. This is likely to outweigh the disadvantages, including a possible higher risk of suicide. However, when choosing a hypnotic to treat insomnia in a person with mental disorder, it is also important to consider the relative toxicity of the drug, given the potential risk of intentional self-poisoning. The findings from this study do not warrant changes or warnings regarding melatonin. Most cases of suicidal behaviour are likely to be related to mental health problems rather than the melatonin treatment. Considering the high proportion of individuals with mental comorbidity among melatonin users, it would in general be relevant to be attentive towards mental wellbeing and any suicidal ideation, as well as adjunctive drug therapies.

Conclusion

In this national register study, treatment with melatonin was associated with both suicide and suicide attempt. While there are several possible explanations, attention to suicide risk is warranted for people with mental health problems who are in treatment

with melatonin. Given that the majority of suicide cases were observed among melatonin users who suffered from mental disorders, it is plausible that the observed increased suicidality was related to presence of mental disorders and, potentially, also sleep disorders not diagnosed in a hospital setting. While a direct effect is uncertain, our results suggest that risks of suicidal behaviour were higher among melatonin users with mental disorders than those not in treatment with melatonin who suffered from mental disorders. Thus, treatment with melatonin might potentially be an indicator of suicide risk, especially in individuals with mental health and/or sleep disorders.

Abbreviations:

IRR – Incidence Rate Ratio

IR – Incidence Rate

CI – Confidence Interval

SD – Standard Deviation

IQR – Interquartile Range

ATC – Anatomical Therapeutic Chemical Classification System

CPR - Central Personal Registry / Civil Registration System

NPR - National Prescription Registry

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