The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 64:7 (2023), pp 1027–1036 doi:10.1111/jcpp.13785

Melatonin use and the risk of self-harm and unintentional injuries in youths with and without psychiatric disorders

Marica Leone,[1,2] Ralf Kuja-Halkola,[2] Tyra Lagerberg,[2] Johan Bjureberg,[3] Agnieszka Butwicka,[2,4,5,6] Zheng Chang,[2] Henrik Larsson,[2,7] Brian M. D'Onofrio,[2,8] Amy Leval,[1,2] and Sarah E. Bergen[2]

[1]Janssen Pharmaceutical Companies of Johnson & Johnson, Solna, Sweden; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden; [3]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden; [4]Child and Adolescent Psychiatry Stockholm, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden; [5]Department of Child Psychiatry, Medical University of Warsaw, Warsaw, Poland; [6]Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland; [7]School of Medical Sciences, Örebro University, Örebro, Sweden; [8]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA

Background: Sleep disorders in youth have been associated with increased risks of injury, including suicidal behavior. This study investigated whether melatonin, which is the most common medication for sleep disturbances in youth in Sweden, is associated with a decreased risk of injury. **Methods:** This population-based cohort study included 25,575 youths who initiated melatonin treatment between ages 6 and 18. Poisson regression was used to estimate rate of injuries in the year prior to and following melatonin treatment initiation. A within-individual design was used to estimate relative risks by comparing injury risk in the last unmedicated month with injury risks in the 12 months after medication initiation. Analyses were stratified by sex, injury type, psychiatric comorbidities and age at melatonin-treatment initiation. **Results:** While body injuries, falls and transport accident rates were comparable in the year before and after melatonin-treatment initiation, the risk of self-harm was highest in the months immediately prior to medication, and decreased thereafter. This was particularly prominent among adolescents with depression and/or anxiety, with females displaying greater absolute risks than males. Compared to the last unmedicated month, the 12 months post medication initiation had decreased relative risks for self-harm, with an IRR [95% CI] in the month following melatonin-treatment initiation of 0.46 [0.27–0.76] among adolescent females with psychiatric disorders, after excluding antidepressant users. **Conclusions:** Decreased risk of intentional self-harm was observed following melatonin-treatment initiation among females with depression and anxiety, suggesting that sleep interventions could be considered in an effort to reduce risk of self-harm in this population. **Keywords:** Melatonin; sleep; injury; self-harm; depression; anxiety.

Introduction

Sleep disorders, such as insomnia, are common in youth, particularly among those suffering from psychiatric disorders (Ophoff et al., 2018). Problems with sleep in children and adolescents can have a significant impact on daytime functioning, health, and development, with negative effects on cognitive skills, emotional regulation and behavior (Cheng et al., 2021; Palmer & Alfano, 2017). Prior research suggests that disrupted sleep in youth is also a risk factor for unintentional injuries, such as falls, sports-related injuries, bicycle and vehicular accidents (Kim, Sim, Kim, & Choi, 2015; Owens & Weiss, 2017), as well as for suicidal and nonsuicidal self-harm (Asarnow et al., 2020; Kearns et al., 2020; Liu, Chen, Bo, Fan, & Jia, 2017; Mars et al., 2019).

Self-harm (intentional nonfatal self-poisoning or self-injury) is of particular concern to child and adolescent psychiatry given its association with a range of adverse outcomes (Bjureberg et al., 2022; Borschmann et al., 2017) including suicide (Hawton et al., 2020; Hawton, Saunders, & O'Connor, 2012). The lifetime prevalence of self-harm in youth has been estimated to be 17% (Gillies et al., 2018), but estimates vary across different study designs and classification systems. There are few empirically supported treatments for self-harm in youth and, although psychosocial treatments appear promising (Fox et al., 2020; Witt et al., 2021), there are no published randomized clinical trials of pharmacotherapy for self-harm (Witt et al., 2021). A recent meta-analysis suggests that researchers should redirect their attention to the causes of self-harm to facilitate progress in self-harm intervention efficacy (Fox et al., 2020). Treating sleep problems has been suggested as a mechanistic target that might decrease the risk of self-harm (Asarnow et al., 2020; Khazaie et al., 2021).

The first-line treatment for youth sleep disorders are behavioral interventions focusing on sleep routine. As for pharmacotherapy, in Sweden, melatonin is the most commonly prescribed drug for sleep

Conflict of interest statement: See Acknowledgements for full disclosures.

disturbances in children and adolescents, and its use has dramatically increased in the last decade (Kimland et al., 2021; Läkemedelsverket, 2014; Wesselhoeft et al., 2021). While melatonin is available as an over the counter drug in some countries, prior to 2020 in Sweden, it was only available as a prescription medicine and fully refundable by the health care system for pediatric patients.

Melatonin is a naturally occurring hormone secreted primarily by the pineal gland in response to darkness. It helps to promote and maintain the normal sleep–wake cycle (circadian rhythm), and it is involved in other biological functions as a result of its chronobiotic, antioxidant, antiinflammatory and free radical detoxification properties (Esposito et al., 2019). Administration of exogenous melatonin in the afternoon or evening can improve sleep–wake rhythm disturbances and reduce sleep latency. Studies among children and adolescents indicate that melatonin can be safe and effective in treating sleep problems (Blackmer & Feinstein, 2016; Wei et al., 2020).

Given the established link between sleep disorders, injuries and self-harm in youth, it is possible that melatonin treatment could reduce the risk of these negative outcomes among young patients with sleep disturbances through the improvement of sleep problems. To date, there are no studies investigating such associations, which could have important public health implications for children and adolescents.

The aim of this study was to examine the risk of self-harm and unintentional injuries in periods before and after melatonin-treatment initiation, among youth with and without psychiatric disorders, and across sexes, injury types, psychiatric disorder diagnoses and age groups. We hypothesized that melatonin use is associated with a decreased risk of self-harm.

Methods

Study sample

We linked information from national population-based registers using unique personal identity numbers (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009) assigned to each Swedish resident at birth or immigration to Sweden. Demographic information and emigration data were retrieved from the Total Population Register and Migration Register (Ludvigsson et al., 2016). The Cause of Death Register (Brooke et al., 2017) was used to extract information on date of death. Data on melatonin prescriptions were obtained from the Swedish Prescribed Drug Register (PDR; Wettermark et al., 2007), which was initiated on July 1st 2005 and contains information on all dispensed medicines classified according to the Anatomical Therapeutic Chemical (ATC) system. Data on clinical diagnoses were collected from the National Patient Register (NPR), which has nationwide coverage for inpatient care since 1987 and outpatient care since 2001, coded according to the International Classification of Diseases (ICD) 9th and 10th editions (Rück et al., 2015).

We identified all individuals born between 1989 and 2008, alive and living in Sweden on January 1st 2006 or at age 5, whichever occurred last, and who received a melatonin prescription between ages 6 and 18 years (inclusive). Participants were followed from 1 year preceding melatonin-treatment initiation through the year after that date. Censoring occurred on December 31st 2013, at emigration or death, or on the day individuals turned 19 years, whichever occurred first. We excluded patients with less than 1 month of follow-up after melatonin-treatment initiation and patients who collected a melatonin prescription during the first year and a half of PDR initiation (wash-out period between July 1st 2005 and December 31st 2006), resulting in a study population of 25,575 individuals. This study was approved, necessitating no informed consent (Ludvigsson et al., 2015), by the Regional Ethical Review Board in Stockholm, Sweden (2013/862-31/5).

Melatonin medication

For the period under consideration in this study, melatonin was available in Sweden only as a prescription medicine (i.e. not available over the counter); therefore, we were able to capture all melatonin use within the country. A person was considered exposed to melatonin medication (ATC code: N05CH01) if a prescription was dispensed from January 1st 2007 and between ages 6 and 18 (inclusive). Since the most commonly recommended melatonin administration time is around bedtime, treatment initiation was defined as the day following the first recorded dispensation of a melatonin prescription. Thus, if an outcome was recorded on the same day as melatonin dispensation, the patient was not considered exposed to melatonin on that day. Two dispensations falling within 30 days apart of each other were considered to belong to the same treatment period. If a new melatonin dispensation date fell within the previous treatment period, the extra pills from the previous prescription were counted and added to extend the same treatment period (i.e., medication stockpiling). Since the PDR does not contain structured information for daily dosage, individuals were assumed to take one melatonin pill per day. However, details on the number of pills per day are available as an unstructured free-text variable, which refers to directions that prescribing clinicians can provide to patients. In a sensitivity analysis, we estimated daily dosage using an existing algorithm (Zhang et al., 2021) to predict the number of pills per day from this free-text variable (Methods S1).

Injuries

The outcome event was an inpatient or outpatient contact for injuries during the follow-up and between ages 5 and 18 (inclusive). Diagnoses of injury were identified and grouped according to the ICD-9 and ICD-10 systems. We examined any type of injury as well as specific injuries (i.e. body injuries, falls, intentional self-harm – i.e., purposely self-inflicted poisoning or injury –, poisoning – i.e., poisoning without specification on the intention –, and transport accidents), including the first recorded diagnosis within each group of injury, irrespective of other injury diagnoses. ICD codes used are reported in Table S1.

Psychiatric comorbidities

The NPR was used to identify inpatient and outpatient diagnoses of psychiatric disorders received between birth and age 18 (ICD codes in Table S2). For the most prevalent psychiatric disorders (i.e. attention-deficit hyperactivity disorders [ADHD], autism spectrum disorder [ASD], depression, and anxiety disorders) we explored whether these comorbidities influence the rate of injuries before and after melatonin use.

Statistical analysis

Poisson regression was used to estimate between-individual incidence rates (IRs) and 95% CIs in each of the 12 months prior to melatonin-treatment initiation and in up to 12 months after this date (depending on censoring). Furthermore, we assessed IRs of injuries during on- and off-treatment periods in the year following the first recorded prescription dispensation. That is, for each month of follow-up after medication initiation, we computed the IR during the "on-treatment time" and the IR during the "off-treatment time", irrespective of the patients' treatment status in previous months.

Conditional Poisson regression was used to assess within-individual incidence rate ratios (IRRs) and 95% CIs in the months following melatonin-treatment initiation (up to 12 months, depending on censoring), using the month preceding melatonin initiation (month -1) as the reference category. A sensitivity analysis using month -12 as the reference category was also conducted. First, we estimated IRRs irrespective of whether individuals were on or off melatonin medication during the months following treatment initiation; then the same model was used to compute IRRs during on- and off-treatment periods for each month of follow-up after medication initiation.

When estimating IRRs, the comparisons between time periods preceding and following treatment initiation were made within individuals (i.e. modeling each individual as a separate stratum); in this way, each individual acts as her/his own control, enabling adjustment for unmeasured confounders that are constant in an individual during the follow-up including, but not limited to, sex, age at treatment initiation, early life risk factors, disorder severity and genetic liability for sleep problems, psychiatric disorders and injuries (Mullins et al., 2021).

We performed all analyses stratified by sex, psychiatric disorders and age at first melatonin-treatment initiation. The age groupings were 6–10-year-olds, 11–14-year-olds and 15–18-year-olds.

Finally, in a sensitivity analysis, we excluded individuals who were prescribed antidepressants (ATC: N06A) in the year preceding and/or 3 months following melatonin-treatment initiation; this was performed in an attempt to limit the effect of concurrent use of such medications, which could have influenced the risks of the outcomes of interest, especially in the case of self-harm.

Throughout all analyses, 1 month was considered to consist of 30 days. All tests of statistical hypotheses were 2-sided and used a significance threshold of .05. Data management was performed using SAS version 9.4.6 (SAS Institute, Irvine, CA, USA); analyses were performed using R software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Details of the study cohort are shown in Table 1. We included 25,575 children and adolescents (58.2% male) who initiated a melatonin treatment between ages 6 and 18. The follow-up time started 1 year prior to medication initiation, and, if no censoring occurred, it ended 1 year after treatment initiation (mean follow-up time was 680 days). The median [IQR] age at first recorded melatonin dispensation was 13 [9, 16] years for males and 15 [13, 17] years for females. Melatonin treatment was initiated most commonly during the month of November, while July and August were the months with the fewest new melatonin users (Figure S1). Mean length of first melatonin-treatment was 6.4 months (median [IQR] treatment duration: 2.3 [0.7, 6.6] months).

Among melatonin users, a total of 22,299 individuals (87.2%; 58.5% male) received at least one psychiatric diagnosis by age 18 (Figure S2 and Table S3), with ADHD being the most prevalent diagnosis, particularly in males (53.9%; 66.5% male). A total of 5,205 individuals (20.4%; 52.9% male) had at least one recorded injury during follow-up (see Table S4 for details on total number of injuries before and after melatonin-treatment initiation). The most common outcomes in the study cohort were injuries of different body regions, for example, injuries to the head, shoulder, wrist, etc. (17.2%; 57.5% male). Sex differences were observed for self-harm and poisoning, with females displaying approximately five and four times higher prevalence than males, respectively. There was extensive diagnostic overlap of self-harm and poisoning, with 50.7% of self-harm diagnoses overlapping with poisoning diagnoses (i.e. individuals received both self-harm and poising diagnoses on the same date), and 75.3% poisoning diagnoses overlapping with self-harm diagnoses. This overlap reflects the fact that most patient are likely to receive two separate diagnoses when treated for poisoning: one for poisoning (with no intention specified), and another one for intentional self-harm (once the intention behind the poisoning event has been established). The main methods of self-harm were poisoning (57.7%) and by using a cutting or piercing instrument (34.1%).

Absolute risks

Injury rates in the year preceding and following medication initiation are presented in Figure 1 and in Table S5. When analyzing self-harm and poisoning, IRs were found to progressively increase during the last two to three unmedicated months, especially among females, peaking in the month immediately prior to medication initiation (self-harm IRs per 100 person-years [95% CIs] were 18.2 [15.6–21.3] in females and 2.9 [2.1–4.1] in males), followed by an IR drop in the month following melatonin prescription (11.1 [9.1–13.5] in females and 1.4 [0.9–2.2] in males). In contrast, the patterns of rates of body injuries, falls and transport accidents did not seem to vary systematically around the treatment initiation date.

When comparing on- and off-treatment periods in the months following medication initiation (Figure S3), estimates were overall comparable although being on medication was associated with decreased IRs during the first 3 months after treatment initiation.

Results from the analyses stratified by psychiatric disorders and age groups are presented in the Figures S4–S6. Overall, the highest IRs preceding

Table 1 Study cohort characteristics

	Entire cohort		Males		Females	
	n	%	*n*	%	*n*	%
Study cohort	25,575	–	14,889	–	10,686	–
6–10 years at first melatonin prescription	6,840	26.7	5,021	33.7	1,819	17.0
11–14 years at first melatonin prescription	7,327	28.7	4,674	31.4	2,653	24.8
15–18 years at first melatonin prescription	11,408	44.6	5,194	34.9	6,214	58.2
≥1 psychiatric disorder between ages 0–18	22,299	87.2	13,037	87.6	9,262	86.7
≥1 injury during follow-up	5,205	20.4	2,756	18.5	2,449	22.9
Body injuries	4,402	17.2	2,529	17.0	1,873	17.5
Falls	2,141	8.4	1,252	8.4	889	8.3
Intentional self-harm[a]	1,053	4.1	212	1.4	841	7.9
Poisoning[b]	938	3.7	219	1.5	719	6.7
Transport accidents	749	2.9	427	2.9	322	3.0

	Median	IQR	Median	IQR	Median	IQR
Age at first melatonin prescription, y	14	[10–16]	13	[9–16]	15	[13–17]
Age at first diagnosis of ADHD, y	11	[8–15]	10	[8–14]	14	[10–16]
Age at first diagnosis of ASD, y	11	[8–15]	11	[7–14]	13	[9–16]
Age at first diagnosis of depression, y	15	[14–17]	15	[13–17]	15	[14–17]
Age at first diagnosis of anxiety disorders, y	15	[13–17]	14	[12–16]	15	[14–17]

Diagnoses of injury were identified and grouped according to the ICD-9 and ICD-10 systems. ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; y, years.
[a]"Intentional self-harm" includes purposely self-inflicted poisoning or injury.
[b]"Poisoning" refers to poisoning diagnoses without specification on the intention.

melatonin-treatment initiation were found for adolescent females (age group 15–18 years) for self-harm, particularly among those patients who, by age 18, received a diagnosis of depression (IR, 36.1; [28.9–45.2]) or anxiety disorders (IR, 42.3; [34.4–52.1]). Although males presented low IRs for all outcomes and across all strata, those aged 15–18 years displayed similar patterns of IRs for self-harm and poising observed in females, with the highest absolute rates found in the month immediately prior medication for self-harm among patients who, by age 18, were diagnosed with depression (IR, 18.4; [11.8–28.9]) and anxiety disorders (IR, 20.0; [12.4–32.1]).

Relative risks

Figure 2 shows the within-individual IRRs for different types of injuries and in each of the 12 months following medication initiation, using the last unmedicated month (month -1) as the reference category. While no statistically significant changes in risks were observed for body injuries, falls and transport accidents, the risks for self-harm and poisoning were statistically significantly lower during the months following melatonin-treatment initiation (the IRR [95% CIs] in the month following melatonin-treatment initiation was 0.58 [0.46–0.73] for self-harm and 0.59 [0.45–0.78] for poisoning). Sex-specific IRRs are available in Table S6.

In Figure 3, relative risks for on- and off-melatonin periods within each follow-up month are reported. Estimates were overall comparable, although slightly decreased risks of self-harm and poisoning were observed during the on-treatment periods over the first months following medication initiation. Results from the analyses stratified by psychiatric disorders and age groups are shown in the Figures S7–S9.

Sensitivity analyses

Melatonin daily dosage was predicted from free-text information to be one pill in 75.2% of the prescriptions (median [IQR] treatment duration: 2.1 [0.7, 5.7] months). When using the predicted daily dosage, absolute and relative risks remain consistent with the ones from the main analyses (Figure S10).

We estimated IRRs of injuries using month -12 (rather than month -1) as the reference category. In these analyses, the risk of self-harm was higher throughout the year following melatonin-use initiation (Figure S11).

Finally, we identified 5,630 individuals (22.0%; 60.3% female) who were prescribed an antidepressant in the 1 year preceding and/or 3 months following melatonin-treatment initiation. When excluding these participants from the cohort, all absolute rates decreased but females still displayed similar self-harm IR patterns to the ones from the total female cohort, as well as decreased relative risks (the IRR [95% CIs] for self-harm in the month following melatonin-treatment initiation was 0.46 [0.27–0.76] among adolescent females with psychiatric disorders; Figure S12).

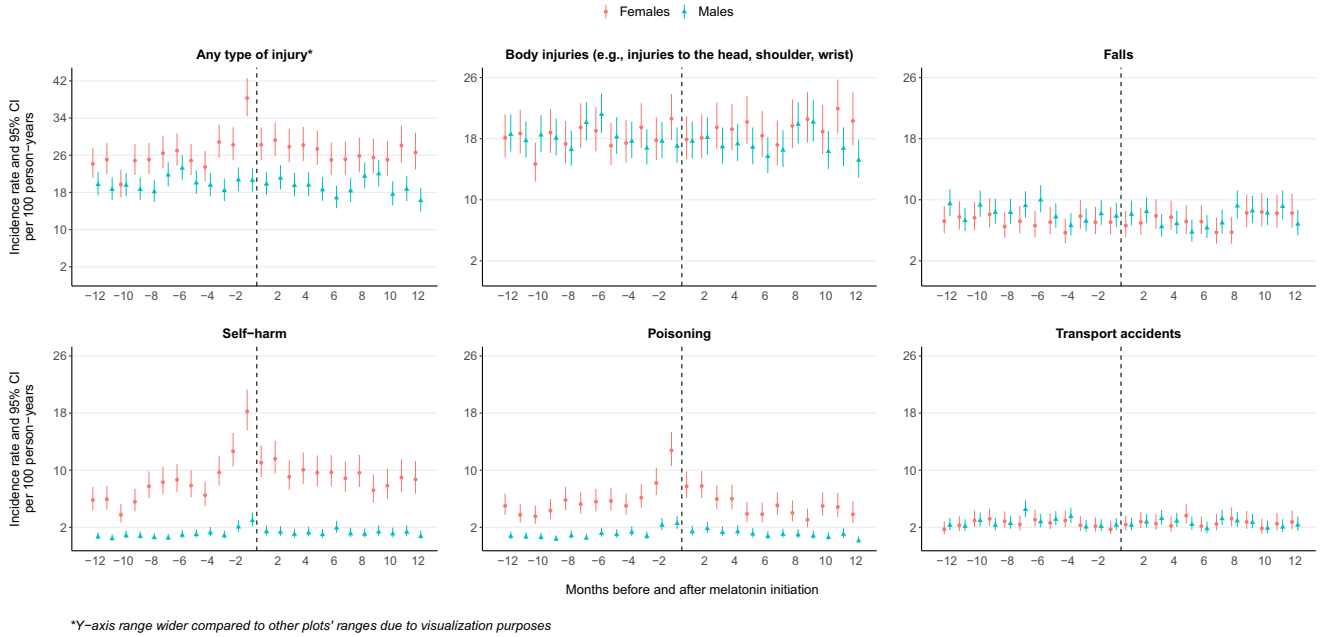

Figure 1 Sex-specific incidence rate of different types of injuries in the year before and after melatonin-treatment initiation. *Y-axis range wider compared to other plots' ranges due to visualization purposes

Discussion

This is the first study assessing the absolute and relative risks of intentional self-harm and unintentional injuries among a pediatric population of new melatonin users. Our findings show that, while the risks of unintentional injuries were comparable in the year before and after melatonin-treatment initiation, the risks of self-harm and poisoning were highest in the month immediately prior to medication initiation, and decreased directly after. Given the extensive overlap between poisoning and self-harm diagnoses, it is not surprising these two types of injuries showed similar risk patterns (Bohnert & Ilgen, 2019).

Psychiatric comorbidity was very common in this study population, with 87.3% of youth treated with melatonin being diagnosed with at least one psychiatric disorder. ADHD was the most common comorbidity (more than 50% of new melatonin users), which was expected given that sleep disturbances are associated with this psychiatric condition and are also frequent side effects of ADHD medications (Konofal, Lecendreux, & Cortese, 2010). Investigation across psychiatric comorbidities, sex, and age revealed that the risk distributions for self-harm and poisoning were largely driven by patients suffering from depression and/or anxiety disorders at some point during youth, particularly female adolescents; this is in accordance with prior research linking depression and suicidal behavior, with female patients displaying the highest risks, especially at younger ages (Leone et al., 2021; Qin, 2011).

When comparing on- and off-melatonin periods following treatment initiations, estimates were overall similar, although melatonin use was associated with lower risks of self-harm and poisoning during the first months after medication initiation.

Several mechanisms could explain our findings. For example, it is possible that melatonin treatment directly reduces the risk of intentional self-harm by treating sleep problems related to psychiatric comorbidities, especially anxiety and depression. Another possibility is that melatonin could play a role in pain modulation (Xie, Fan, He, & Huang, 2020), acting on the decreased pain sensitivity displayed by adolescents who self-harm (Cummins et al., 2021). Alternatively, melatonin prescription could be an indicator of the medical attention that these patients are receiving in the health care system. As a consequence, beyond melatonin treatment, a number of other factors could play a role in treating sleep problems and/or preventing self-harm in these patients, such as clinicians' and care-givers' increased awareness and monitoring, behavioral interventions, psychotherapy, placebo effect and concurrent use of other medications. Interestingly, the self-harm risk pattern in our study was similar to the one observed in a prior study exploring the association between antidepressants and suicide, where the risk of suicidal behavior was highest immediately before medication initiation, and steadily declined thereafter (Lagerberg et al., 2021). Given that in our study many individuals displaying such risk pattern were patients with depression and anxiety, it is possible that our results were driven by the concurrent use of antidepressants. However, when excluding individuals on antidepressants, we observed a similar pattern of intentional self-harm rates and a decrease in self-harm risk following

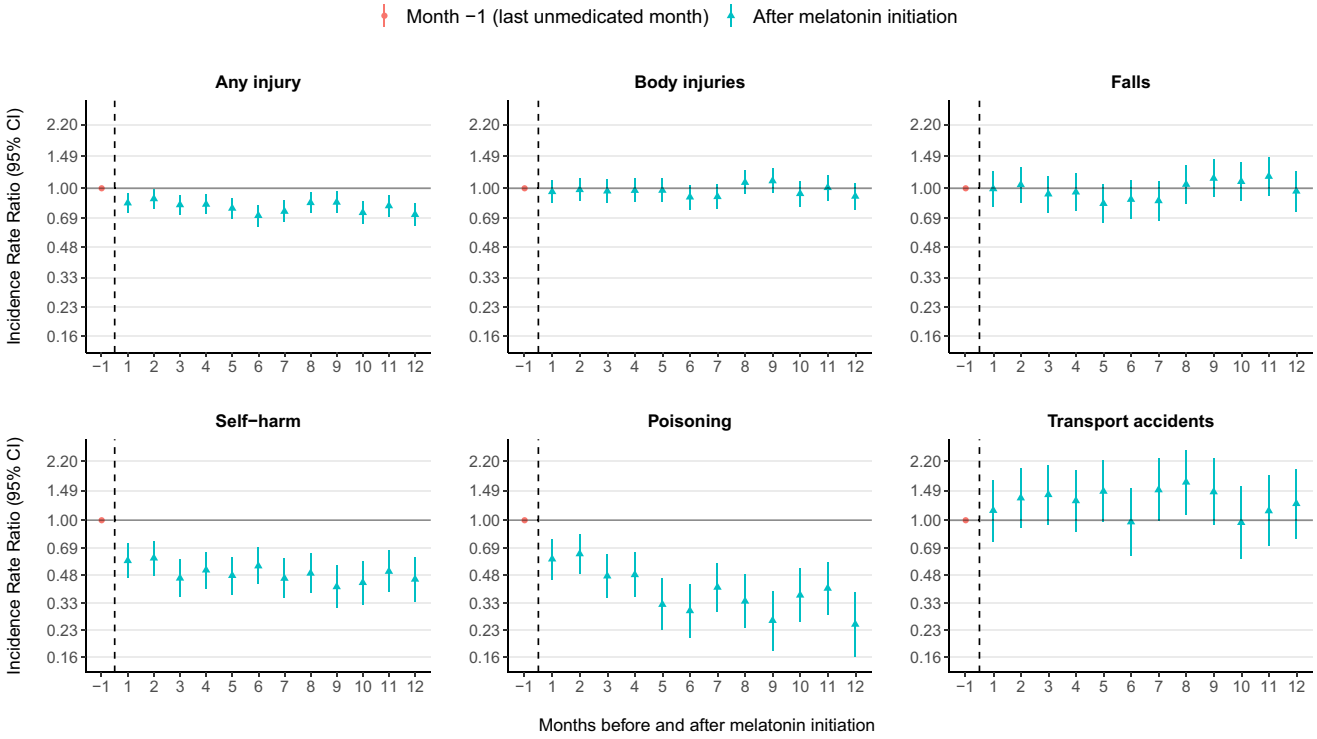

Figure 2 Within-individual incidence rate ratios of injuries in the 12 months after first melatonin initiation

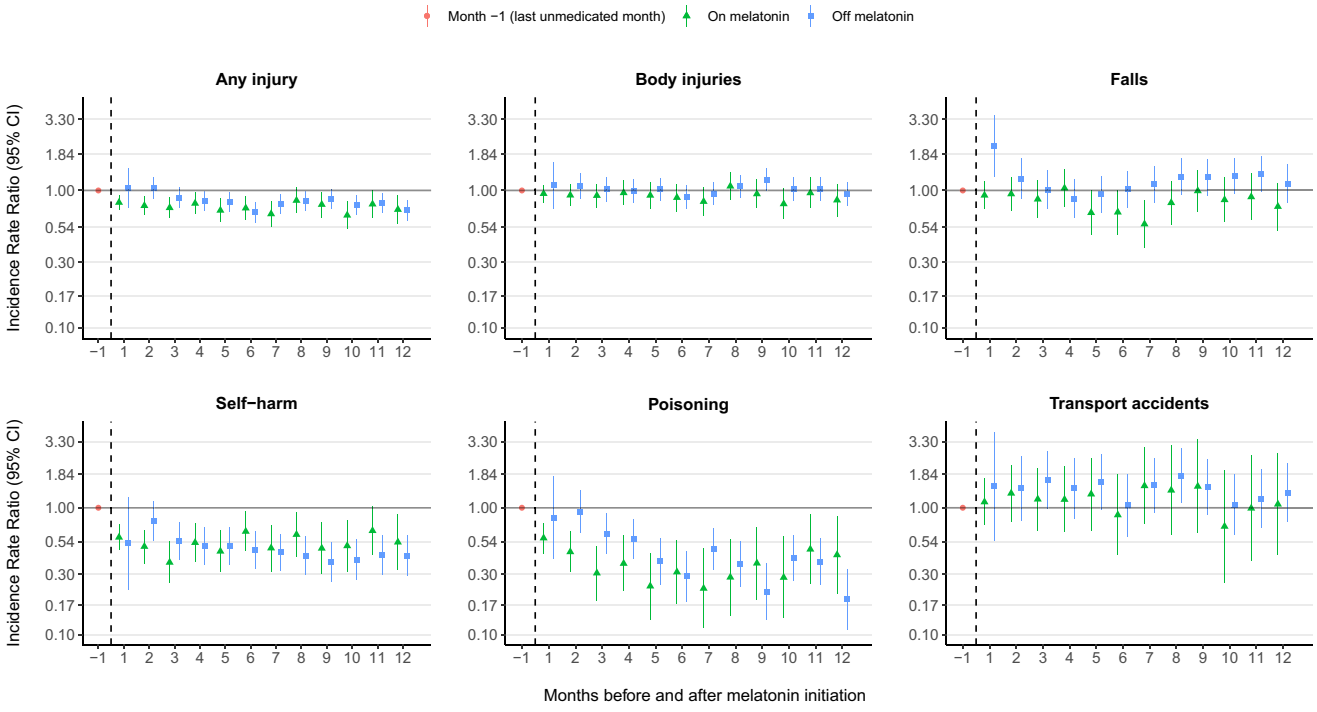

Figure 3 Within-individual incidence rate ratios of injuries in the 12 months after first melatonin initiation, comparing on- and off-melatonin periods

melatonin-use initiation among females, suggesting that antidepressant use did not entirely explain our results.

Furthermore, it is important to note that there could be a selection bias: the likelihood of melatonin prescription may be influenced by the occurrence of an injury event. This could be particularly likely in the case of self-harm. As a consequence, the month immediately prior melatonin-use initiation can be expected to display an elevated outcome rate, and therefore, choosing this as the reference month when estimating the relative risk may lead to an over-estimation of risk reduction. For unintentional injuries, a possible way to overcome this is by using

a different reference period (e.g. month -12, as performed in our sensitivity analysis) (Whitaker & Ghebremichael-Weldeselassie, 2019). However, month -1 may be more informative and relevant as a reference period when exploring intentional self-harm, given that this outcome is associated with sleep problems and its rate is expected to be higher around the time of sleep disorder treatment.

Because self-harm is more common in adolescence than in childhood, the fact that females in our cohort were older than males could partially explain why the relative risk of these diagnoses were higher among females compared to males. A possible reason for sex differences in age at first melatonin prescription could be linked to sex and age differences in ADHD diagnosis, given that this condition and its medications increase the risk of sleep disturbances. In fact, in our cohort there were more males than females with ADHD (61.3% vs. 43.1%), with a median age at first ADHD diagnosis of 10 years for males and 14 years for females. The same sex and age differences in melatonin treatment were previously described in a Swedish study, which reported an increased use of melatonin among boys than girls, with males starting treatment earlier and more often combining this with regular use of ADHD medications (Furster & Hallerbäck, 2015). As the authors of the study concluded, this suggests that females and males partly are prescribed melatonin for different reasons.

Overall, compared to the last unmedicated months, melatonin initiation for sleep problems was associated with decreased risks for self-harm and poisoning among adolescent females with psychiatric disorders, especially depression and anxiety disorders. However, these risks were still elevated compared to the risk observed 12 months prior to melatonin treatment, which could be partially explained by the fact that prior self-harm events increase the risk of further events (Bostwick, Pabbati, Geske, & McKean, 2016), encouraging close monitoring of this vulnerable population.

These findings suggest that treating sleep disturbances associated with depression and anxiety may be an important factor in decreasing the risk of intentional injuries and poisoning in this pediatric population. Further studies are needed to examine the efficacy of melatonin and other sleep-improvement interventions in reducing self-harm.

Limitations

This study has several strengths, including the use of nationally representative data, complete information on all melatonin prescriptions, the inclusion of psychiatric comorbidity information and the use of within-individual analyses to adjust for time-constant confounders. However, there are also some important limitations. First, injuries and psychiatric disorders diagnosed within primary care by general practitioners were not included in this study, possibly limiting the generalizability of the findings to the more severe clinical cases, as well as to treatment-seeking individuals. However, diagnoses given to children and adolescents are well captured in the National Patient Register, since it is standard for the pediatric population to be referred to outpatient specialist care, including general pediatrics and child psychiatry clinics; moreover, self-harm and poisoning are mostly severe outcomes requiring hospitalization or specialist health care, especially among these young patients. Second, there is a possibility that individuals who are considered off-melatonin in our analyses, were prescribed other types of hypnotic drugs (e.g. z-drugs and sedating antihistamines), although medicines other than melatonin are rarely prescribed to the pediatric population due to side effects and risks of overdose (Läkemedelsverket, 2014). Third, the design used in this study requires patients to have survived until melatonin-treatment initiation; therefore, we could not include individuals who died by injury prior to medication initiation. Finally, we did not investigate nonpharmacological interventions (i.e. psychotherapy) or use of psychiatric medications other than antidepressants, which could have influenced the risks of the outcomes of interest.

Conclusions

Our findings suggest that melatonin use is associated with a decreased risk of intentional self-harm among adolescent females with psychiatric disorders. Although nonpharmacological treatments were not investigated and causality of the findings cannot be claimed, this study supports the hypothesis that improving youth's sleep hygiene may be an important intervention to reduce self-harm in this pediatric population.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Methods S1. Prediction of treatment dosage from free-text prescriptions.
Table S1. Diagnostic classification of injuries considered in this study.
Table S2. Diagnostic classification of psychiatric disorders considered in this study.
Table S3. Psychiatric disorders diagnosed between birth and age 18 years among new melatonin users.
Table S4. Number of injury events in the year preceding and following melatonin-treatment initiation.
Table S5. Sex-specific incidence rate (IR) per 100 person-years of different types of injuries in the year before and after melatonin-treatment initiation.
Figure S1. Distribution of melatonin-treatment initiation by month.

Figure S2. Psychiatric disorders diagnosed between birth and age 18 years among new melatonin users.
Figure S3. Incidence rate of any type of injury in the year before and after melatonin-treatment initiation.
Figure S4. Incidence rates of any type of injury in the year before and after melatonin-treatment initiation, across specific psychiatric comorbidities.
Figure S5. Age- and sex-specific incidence rates of any type of injury in the year before and after melatonin-treatment initiation.
Figure S6. Incidence rate of self-harm in the one year before and after first melatonin initiation among adolescents (age group 15–18 years) with depression and anxiety.
Figure S7. Incidence rate ratios of any type of injury in the 12 months after melatonin-treatment initiation, across specific psychiatric comorbidities.
Figure S8. Age- and se-specific incidence rate ratios of any type of injury in the 12 months after melatonin-treatment initiation.
Figure S9. Incidence rate ratios of self-harm in the 12 months after first melatonin initiation among adolescents (age group 15-18 years) with depression and anxiety.
Figure S10. Absolute and relative risks of injury using predicted daily dosage.
Figure S11. Within-individual incidence rate ratios of injuries in the 12 months after first melatonin initiation, using month –12 as the reference category.
Figure S12. Absolute and relative risks of self-harm among adolescents (age group 15-18 years) with depression and anxiety, excluding patients on antidepressants in the one year before and 3 months after melatonin use.

Acknowledgements

This study was funded by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no. 721567. A.B. was supported by Stiftelsen Söderström - Königska sjukhemmet, the Swedish Research Council (No 201700788) and through the regional agreement on clinical research between Stockholm Region and Karolinska Institutet (No 20180718) while working on this project. B.M.D. was funded by the American Foundation for Suicide Prevention (DIG-1-037-19). Z.C. was supported by the Swedish Research Council (2018-02213). The funding organization had no part in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

The corresponding author confirms that she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors are not permitted to share the data used in this study. However, researchers can access the data through application to the Swedish National Board of Health and Welfare (Socialstyrelsen) and to Statistics Sweden (Statistiska centralbyrån).

M.L. is an employee of Johnson & Johnson. H.L. reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. A.L. is an employee of and owns stock in Johnson & Johnson. R.K-H., A.B., T.L., B.M.D., Z.C., J.B. and S.E.B. report no financial relationships with commercial interests.

Correspondence

Sarah E. Bergen, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, SE-17177 Stockholm, Sweden;
Email: Sarah.Bergen@ki.se

Key points

- There is an established link between sleep disorders, injuries, and self-harm in youth.
- It may be possible that melatonin treatment could reduce the risk of these negative outcomes among young patients with sleep disturbances through the improvement of sleep problems.
- Compared to the last unmedicated months, decreased risks of intentional self-harm and poisoning were observed following melatonin-treatment initiation among females with depression and anxiety.
- Improving youth's sleep hygiene may be an important intervention to reduce self-harm in this pediatric population.
- Further studies are needed to examine the efficacy of melatonin and other sleep improvement interventions in reducing self-harm.

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Accepted for publication: 6 February 2023