Role in therapy of melatonin for the treatment of insomnia in children and adults

Ian R. McGrane, PharmD[1]
Shelby L. Corman, PharmD, MS, BCPS[2]

[1]St. Joseph Medical Center, Polson, MT
[2]Pharmerit International, Bethesda, MD

ABSTRACT

Melatonin is an endogenous indolamine produced by the pineal gland which may have a role in the biological regulation of circadian rhythms, sleep, and mood. Melatonin receptor activation in the hypothalamus likely regulates circadian rhythms. In the United States, melatonin is marketed as a dietary supplement. Clinical trials in children and adults have shown modest clinical benefit in the treatment of insomnia. Adverse events reported in patients receiving melatonin were not significantly different in type or occurrence from those reported in patients receiving placebo. Considering the potential for benefit, lack of significant adverse events, and lack of abuse potential, melatonin may be considered a valid therapeutic option for improving outcomes in certain pediatric and adult patients with insomnia.

KEYWORDS

melatonin, insomnia, adults, children

BACKGROUND

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indolamine produced by the pineal gland which may have a role in the biological regulation of circadian rhythms, sleep, and mood. The production and release of melatonin is closely synchronized with the hours of human sleep. Desynchronization in endogenous melatonin secretion can occur in night-shift workers, airplane passengers, and patients with delayed sleep phase syndrome.[1]

Melatonin activates G protein-coupled melatonin receptors, which results in the inhibition of adenylatecyclase in target cells.[1,2] The Mel1a receptor is the presumed site of circadian actions of melatonin, expressed in the hypophysial pars tuberalis and suprachiasmatic nucleus of the hypothalamus.[1] Melatonin may have intracellular sites of action, directly affecting calcium signaling through interactions with adenylate cyclase, phosphodiesterase, and structural proteins.[3] Melatonin receptors can be found in various tissues throughout the body, though neural receptors in the suprachiasmatic nucleus are more likely to regulate circadian rhythms.[3,4]

Other potential mechanisms of action for melatonin include: the reduction of core body temperature, a measurement linked to the human body subjective sleepiness cycle and inversely related to serum melatonin concentration, and the modification of brain monoamine neurotransmitters, which could initiate events leading to sleep mechanisms.[1]

Secretion of melatonin follows a diurnal rhythm of low daytime concentrations (10-20 pg/mL), followed by increased synthesis and secretion in the evening, reaching peak concentrations (80-150 pg/mL) from midnight to 3 am.[5] The oral bioavailability of melatonin can vary greatly. Low doses of 1 to 5 mg sold over-the-counter at food and drug stores would be expected to result in serum melatonin concentrations 10 to 100 times physiologic concentrations after one hour. Concentrations decline to baseline within roughly four to eight hours post-ingestion.[6] The serum half-life of orally administered melatonin is 30-60 minutes.[7,8] Melatonin is metabolized by hydroxylation in the liver to 6-hydroxymelatonin, which is conjugated with sulfuric or glucuronic acid, and excreted in the urine.[1]

We conducted a semi-systematic review of the literature to describe the safety and efficacy of melatonin for the treatment of insomnia. A MEDLINE search for published clinical trials was conducted for the period of January 1966 to July 2013. Search terms included melatonin and insomnia. Searches were limited to include published English-language articles and studies in humans. The literature search yielded 120 publications for potential inclusion. Case reports, pharmacokinetic studies, trials that enrolled only special patient populations (i.e., ADHD, schizophrenia, cognitive impairment, etc.) with insomnia were not included in this review, nor were studies which primarily evaluated extended-release melatonin. Elimination of these trials yielded a total of 10 clinical trials evaluating the use of melatonin for insomnia in children and adults, which are summarized in Tables 1 and 2, respectively.

Table 1. Efficacy and safety of melatonin in children

Authors	N	Patient Population	Study Design	Treatments	Results
Geijlswijk et al.[9]	72	Children (6-12 years old); chronic idiopathic sleep-onset insomnia	Randomized, double-blind, placebo-controlled, parallel group trial; treatment for 1-week period	Melatonin 0.05 mg/kg (n=14), 0.1 mg/kg (n=16), or 0.15 mg/kg (n= 17) Placebo (n=15) Taken between 5:30 and 7:30 pm nightly	Melatonin treatment advanced sleep onset by approximately 1 h and decreased sleep onset latency by 35 minutes. No dose-response relationship was found between the melatonin ranges studied. Strengths: Study design Intervention and control groups similar Complete follow-up and ITT analysis Limitations: Short duration of treatment Small sample size
Smits et al.[10]	62	Children (6-12 years old);idiopathic chronic sleep-onset insomnia	Randomized, double-blind, placebo-controlled, parallel group trial; treatment for a 4-week period	Melatonin 5 mg (n=27) Placebo (n=35) Taken at 7 pm nightly	Melatonin advanced sleep onset by 57 minutes (p=0.003), sleep offset by 9 minutes (p=0.024), and decreased sleep latency by 17 minutes (p=0.048). Total sleep time did not change in the treatment group compared with placebo. Strengths: Study design Complete follow-up Limitations: 20 children in melatonin group had ADHD, 19 of which used methylphenidate; eight children in placebo group had ADHD, six of which used methylphenidate Sleep was measured with diaries
Smits et al.[11]	38	Children (6-12 years old); idiopathic chronic sleep-onset insomnia	Randomized, double-blind, placebo-controlled, parallel group trial; treatment for a 4-week period	Melatonin 5 mg (n=19) Placebo (n=19) Taken at 6 pm nightly	Melatonin advanced sleep onset per patient diary by 63 minutes (p=0.005), sleep onset advanced per actigraphy by 75 minutes (p=0.005), and total sleep time increased 41minutes (p=0.026). Placebo group did not show any significant changes in these areas. Strengths: Study design Complete follow-up Actigraphy used for sleep measure Limitations: Five children in the melatonin group used methylphenidate for ADHD; six children in placebo group used methylphenidate for ADHD
Eckerberg et al.[12]	21	Children (14-19 years old); sleep-onset difficulties during school week	Randomized, double-blind, placebo-controlled, crossover trial; 5- week duration with one week of placebo, two weeks of melatonin, and two weeks capsule-free	Melatonin 1 mg Placebo Taken between 4:30 and 6:00 pm	Compared to the placebo week, sleep onset was 46 minutes (p<0.05) and 54 minutes (p<0.005) shorter during the first and second weeks of melatonin treatment, respectively. A significant increase in total sleep time vs. placebo was seen only during the second week of melatonin treatment (31 minutes; p<0.05). Strengths: Study design Earlier dosing time compared to other trials Limitations: Actigraphy data was excluded due to software problem Small sample size

Table 2. Efficacy and safety of melatonin in adults

Authors	N	Patient Population	Study Design	Treatments	Results
Ellis et al.[13]	15	Adults (mean 46years old); psychophysiological insomnia	Double-blind, placebo-controlled, crossover trial; 1-week treatment period	Melatonin 5 mg Placebo Taken at 8 pm nightly	Subjective responses in sleep times, sleep-wake ratings, and adverse effects showed no differences between melatonin and placebo ($p>0.05$). Strengths: Crossover design Limitations: Small sample size Patients included had developed tolerance to benzodiazepines or zopiclone Sleep measured with diaries
James et al.[14]	10	Adults(mean 34 years old); disorder in initiating or maintaining sleep	Randomized, double-blind, placebo-controlled, crossover trial; 7 day treatment; no washout period; all patients were evaluated in all treatment arms	Melatonin 1 mg and 5 mg Placebo Taken 15 minutes before bedtime	Subjects showed no changes in the onset, duration, effect on mood or day time alertness the day following treatment. Reported sleep under the melatonin conditions was less than that under placebo conditions, and not statistically significant. There was an increase in REM latency found in the 1 mg melatonin group ($p<0.05$). Patients taking melatonin reported an increase in quality of life, though this data was not presented objectively ($p=0.03$). Strengths: Crossover design Sedative hypnotic medications prohibited for a minimum of four weeks prior to EEG recordings Limitations: Included only patients that reported <4 hours of sleep despite objective findings of >350 minutes and sleep efficacy of >85%-- which may indicate poor insight into sleep habits No washout periods Small sample size
Waldhauser et al.[15]	20	Adults (mean 26.4 years old); healthy volunteers placed under situational insomnia due to nightly tape recorded traffic noises	A 10 night sleep center study; nights 1-2 were center adaption nights, night 3 all subjects received placebo, nights 4-6 randomized placebo or benzodiazepine, nights 7-9 placebo, night 10 half of subjects received melatonin and half received placebo	Melatonin 80 mg Placebo	Sleep initiation and sleep maintenance were affected by melatonin by reducing the time awake before sleep onset by nearly 50%, sleep latency by about 35%, reducing the number of nighttime awakenings by about 35%, decreasing the awakening threshold by more than 20%, and improving sleep efficiency by compared mean values obtained on night 3 of study ($p<0.05$). Melatonin showed trends of improved performance and reaction times compared to placebo following day 10 ($p<0.1$). Strengths: Controlled study conditions Limitations: Situational insomnia population Limited study duration of melatonin treatment Dose of melatonin administered not used in practice

Authors	N	Patient Population	Study Design	Treatments	Results
Baskett et al.[16]	34	Elderly adults (≥65 years old); normal sleepers(n=19) and patients with age related sleep maintenance problems (n=15)	Randomized, double-blind, placebo-controlled, crossover design; 4-week treatment period, 4-week washout	Melatonin 5 mg Placebo Taken before bedtime	Melatonin significantly decreased the number of awakenings in the normal sleepers to 36.4 compared to placebo (40.2). Melatonin did not significantly improve the following sleep parameters in either group: latency, sleep time, sleep efficiency, number of diary awakenings, quality scale, and alertness scale. Strengths: Study design Duration of washout period Actigraphy and sleep diary measurements Complete follow-up Adequate power Comparison against normal sleepers Limitations: Small sample size
Zhdanova et al.[17]	30	Aged adults (>50 years old); normal sleepers (n=15) and actigraphically confirmed patients with decreases in sleep efficiency (n=15)	Randomized, double-blind, placebo-controlled crossover design; 1-week treatment period and 1-week washout; patients were evaluated in all treatment arms	Melatonin 0.1, 0.3, and 3 mg Placebo Taken 30 min before bedtime	The sleep in insomniac subjects was significantly improved with melatonin supplementation. Sleep efficiency was nearly 84%, 87%, and 84% in insomniacs receiving melatonin 0.1 mg, 0.3 mg, and 3.0 mg, respectively, compared to placebo (nearly 78%) ($p<0.05$). No significant increases in sleep efficiency were observed in patients with normal sleep receiving melatonin. Melatonin had no significant effect on behavior or dose related effects on total sleep time, number of awakenings, latency to sleep onset, latency to REM sleep, or percent time spent in any of the sleep stages in both insomniacs and normal sleepers. Strengths: Study design Multiple doses assessed Comparison against normal sleepers Limitations: Included patients with minor psychiatric disorders, though these were not defined Complete follow-up of patients not available

Authors	N	Patient Population	Study Design	Treatments	Results
Haimov et al.[18]	47	Elderly (>65 years old); Independently living insomniacs (n=8); institutional living insomniacs (n=18); patients without a sleep disorder (n=25)	Randomized, double-blind, placebo-controlled, crossover design; 1-week washout period followed by three 7-day treatment periods, separated by at least a 2-week washout period; a continuation period of 2 months was conducted in 17 of 27 patients with insomnia	Crossover period: Melatonin IR 2 mg Melatonin ER 1 and 2 mg Placebo Continuation period: Melatonin ER 1 mg Taken 2 hours before bedtime	Sleep latency was shortened in independently living insomniacs using immediate-release melatonin (32 ±7 min) compared to placebo (54±13 min; p<0.05). Reduction in sleep latency was not found to be statistically significant for extended-release melatonin versus placebo. Changes in sleep efficiency between groups were not clinically significant with immediate-release or extended-release melatonin versus placebo after one week. Sleep efficiency was increased in the continuation period for patients taking melatonin ER (84.3±2.3)compared to placebo values obtained during the crossover period (77.4±1.9)(p=0.008). A decrease in movement activity while sleeping, measured by wrist actigraphy, was found for patients taking melatonin ER (p<0.03). A decrease in movement activity was found for patients who were institutionalized and taking melatonin IR, but not for those who were independently living compared to placebo. Strengths: Study design Duration of washout period Actigraphy used for sleep measure Limitations: Continuation period only with melatonin ER; not placebo-controlled

SAFETY

Reporting of adverse drug reactions in children varied in clinical trials. The most common adverse events were transient and included the following: red eyes and earlobes, yawning, cold feeling, headache, dizziness, and abdominal pain.[9-12] In one trial, seven of 27 children receiving melatonin reported feeling cold, having decrease in appetite, dizziness, and decreased mood after first intake of medication. In the placebo group, three of 35 children were reported to have headache, nausea, dizziness, and increased appetite. No adverse events were reported after three days of therapy initiation.[10] Mild transient headaches during the first two days of melatonin therapy were reported in two of 11 children receiving melatonin in another trial.[11] One child receiving melatonin developed mild generalized epilepsy four months after the initiation of therapy and was continued on melatonin. No adverse events were reported for children receiving placebo.[11]

Adverse events were rarely assessed during clinical trials for adult patients.[13-18] Melatonin was attributed to adverse events in a total of four patients in one trial, which included: slight headache, odd taste in mouth, and feeling of "muzziness".[13] Aging patients who received melatonin 3 mg nightly experienced largely elevated melatonin levels as well as hypothermia; an effect which was not seen at lower doses. Temperatures decreased roughly 0.2°C two to three hours after bedtime compared to melatonin 0.1 and 0.3 mg doses.[17] In a toxicology assessment of 10 mg melatonin for a 28 day period, adverse events were mild and similar to placebo, which included: somnolence, headache, fatigue, and cognitive alteration.[19] No median lethal dose has been determined.[20]

DRUG INTERACTIONS

There have been multiple case reports associating melatonin with minor bleeding and a decrease in prothrombin activity in persons taking anticoagulants such as warfarin.[21] It is believed that there is a moderate increase in bleeds when concomitantly using antiplatelet and non-steroidal anti-inflammatory drugs as well.[21] Melatonin may have an effect on glucose utilization and increasing insulin resistance. Theoretically, melatonin

could decrease efficacy in hypoglycemic drugs such as insulin, glyburide, glipizide, and tolbutamide.[22] Caffeine consumption can decrease endogenous melatonin levels, and theoretically would decrease effectiveness of melatonin.[23] The use of contraceptive medications, fluvoxamine, and verapamil could increase the adverse effects of melatonin.[24-26] Melatonin can decrease the effectiveness of nifedipine; coadministration of melatonin 5 mg at bedtime and nifedipine 30-60 mg daily has been shown to increase systolic blood pressure an average of 6.5 mmHg and diastolic an average of 4.9 mmHg. Heart rate increased by 3.9 bpm.[27]

PLACE IN THERAPY

The American Academy of Pediatrics consensus statement on the pharmacologic management of insomnia in children and adolescents does not provide guidelines for these populations due to lack of large-scale safety and efficacy clinical trials.[28] The American Academy of Child and Adolescent Psychiatry states that in most cases, non-pharmacological, behavioral therapy is first-line treatment in children with insomnia. The guideline states that current safety and efficacy data regarding medication use in the pediatric population is limited to the extent that no recommendations could be made between different sleep agents in this population. It was stated that the pediatric safety and efficacy literature is fairly robust for the use of melatonin, and melatonin may be helpful in reducing sleep-onset latency when taken at bedtime.[29]

Clinical guidelines for the evaluation and management of chronic insomnia in adults recommend the use of short/intermediate acting benzodiazepine receptor agonists (triazolam, zolpidem, eszopiclone, zaleplon, and temazepam) or ramelteon for the treatment of primary insomnia. The use of sedating antidepressants (trazodone, amitriptyline, doxepin, and mirtazapine), sedating anticonvulsants (gabapentin and tiagabine), or antipsychotic medication (quetiapine and olanzapine) may be suitable in some patients, especially when insomnia is secondary to a comorbid disease state which can be treated with these medications. It is recommended to avoid off-label use of antipsychotic medications and antiepileptic medications as evidence is insufficient. It is recommended to avoid the use of FDA approved medications for insomnia including: chloral hydrate, barbiturates, and meprobamate due to adverse effects, tolerance, and low therapeutic index. It is stated that insufficient safety and efficacy data are available for the use of over-the-counter antihistamine products. Melatonin was stated to have shown a small effect on sleep latency and no effect on waking after sleep onset or total sleep time. These guidelines do not recommend melatonin for the chronic treatment of insomnia based on lack of long-term studies.[30]

The American Geriatrics Society recommendations for management of sleep disorders in older persons state that cognitive behavioral therapy is an effective treatment for insomnia (IA). It was stated that the use of non-benzodiazepines and the melatonin receptor agonists are the safest and most efficacious hypnotic drugs currently available (II-IIIB evidence), though melatonin was not specifically mentioned. The use of antihistamines, antidepressants, anticonvulsants, and antipsychotics was cited to be associated with more risks than benefits in the treatment of insomnia (II-IIIB evidence) in geriatric patients.[31]

Based on the available literature, melatonin is associated with modest benefit in both subjective and objective sleep measurements when administered to children and adults in the evening before bedtime. Melatonin is a safe, non-addictive alternative to other sedative/hypnotic medications used in insomnia. The risks for drug-drug interactions and adverse events are low. Melatonin should be considered a reasonable therapeutic option for the management of insomnia in pediatric populations after behavioral therapy has been initiated. This recommendation is based on lack of consensus guidelines for the management of insomnia in children, a minimal side effect profile found in clinical trials, and modest efficacy in clinical trials. Melatonin should be considered a second-line treatment for insomnia in adults, after benzodiazepines and benzodiazepine receptor agonists in patients who are not at risk for abusing controlled medications; or in patients who have a comorbid illness which could receive dual benefit if treated with sedating psychotropic medication such an antidepressant, anticonvulsant, or antipsychotic at bedtime. Melatonin may be particularly useful in adult patients with addictive or abusive behaviors towards controlled substances or alcohol and who would not receive additional benefit from a sedating psychotropic or anticonvulsant medication at bedtime for a non-sleep related indication.

REFERENCES

1. Brzezinski A. Melatonin in humans. N Engl J Med. 1997;336(3):186-95. DOI: 10.1056/NEJM199701163360306. PubMed PMID: 8988899.
2. Ebisawa T, Karne S, Lerner MR, Reppert SM. Expression cloning of a high-affinity melatonin receptor from Xenopus dermal melanophores. Proc Natl Acad Sci U S A. 1994;91(13):6133-7. PubMed PMID: 7517042.
3. Morgan PJ, Barrett P, Howell HE, Helliwell R. Melatonin receptors: localization, molecular pharmacology and physiological significance. Neurochem Int. 1994;24(2):101-46. PubMed PMID: 8161940.

4. Gillette MU, McArthur AJ. Circadian actions of melatonin at the suprachiasmatic nucleus. Behav Brain Res. 1996;73(1-2):135-9. PubMed PMID: 8788491.
5. Dziegiel P, Podhorska-Okolow M, Zabel M. Melatonin: adjuvant therapy of malignant tumors. Med Sci Monit. 2008;14(5):RA64-70. PubMed PMID: 18443563.
6. Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. Proc Natl Acad Sci U S A. 1994;91(5):1824-8. PubMed PMID: 8127888.
7. Avery D, Lenz M, Landis C. Guidelines for prescribing melatonin. Ann Med. 1998;30(1):122- 130. DOI: 10.3109/07853899808999394.
8. Bertino JS, Demuro RL, Blask DE, et al. Absolute bioavailability (F) of oral melatonin (M). Clin Pharmacol Ther. 2000;67:106 (abstract PI-72).
9. van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology. 2010;212(3):379-91. DOI: 10.1007/s00213-010-1962-0. PubMed PMID: 20668840; PubMed Central PMCID: PMC2952772.
10. Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AM, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2003;42(11):1286-93. DOI: 10.1097/01.chi.0000085756.71002.86. PubMed PMID: 14566165.
11. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol. 2001;16(2):86-92. DOI: 10.2310/7010.2001.6942.
12. Eckerberg B, Lowden A, Nagai R, Akerstedt T. Melatonin treatment effects on adolescent student's sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int. 2012;29(9):1239-48.
13. Ellis CM, Lemmens G, Parkes JD. Melatonin and insomnia. J Sleep Res. 1996;5(1):61-5. PubMed PMID: 8795804.
14. James SP, Sack DA, Rosenthal NE, Mendelson WB. Melatonin administration in insomnia. Neuropsychopharmacology.1990;3(1):19-23.
15. Waldhauser F, Saletu B, Trinchard-Lugan I. Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology (Berl). 1990;100(2):222-6. PubMed PMID: 2305009.
16. Baskett JJ, Broad JB, Wood PC, Duncan JR, Pledger MJ, English J, et al. Does melatonin improve sleep in older people? A randomised crossover trial. Age Ageing. 2003;32(2):164-70. PubMed PMID: 12615559.
17. Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab. 2001;86(10):4727-30. DOI: 10.1210/jcem.86.10.7901. PubMed PMID: 11600532.
18. Haimov I, Lavie P, Laudon M, Herer P, Vigder C, Zisapel N. Melatonin replacement therapy of elderly insomniacs. Sleep. 1995;18(7):598-603. PubMed PMID: 8552931.
19. Seabra ML, Bignotto M, Pinto LR Jr, Tufik S. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. J Pineal Res. 2000;29(4):193-200. PubMed PMID: 11068941.
20. "Melatonin" [Date accessed: 2013 Oct. 11] In The Review of Natural Products Database [online database]. St. Louis, MO, Facts and Comparisons, 2013.
21. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev. 2002;(2):CD001520. DOI: 10.1002/14651858.CD001520. PubMed PMID: 12076414.
22. Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, et al. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. Clin Endocrinol (Oxf). 2001;54(3):339- 46. DOI: 10.1046/j.1365-2265.2001.01232.x.
23. Wright KP Jr, Myers BL, Plenzler SC, Drake CL, Badia P. Acute effects of bright light and caffeine on nighttime melatonin and temperature levels in women taking and not taking oral contraceptives. Brain Res. 2000;873(2):310-7. PubMed PMID: 10930561.
24. Härtter S, Grözinger M, Weigmann H, Röschke J, Hiemke C. Increased bioavailability of oral melatonin after fluvoxamine coadministration. Clin Pharmacol Ther. 2000;67(1):1-6. DOI: 10.1067/mcp.2000.104071. PubMed PMID: 10668847.
25. Grözinger M, Härtter S, Wang X, Röschke J, Hiemke C, Rose DM. Fluvoxamine strongly inhibits melatonin metabolism in a patient with low-amplitude melatonin profile. Arch Gen Psychiatry. 2000;57(8):812-3. PubMed PMID: 10920471.
26. Wikner J, Wetterberg L, Röjdmark S.. Does hypercalcaemia or calcium antagonism affect human melatonin secretion or renal excretion? Eur J Clin Invest. 1997;27(5):374-9. DOI: 10.1046/j.1365-2362.1997.1220672.x.
27. Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. Br J Clin Pharmacol. 2000;49(5):423-7. PubMed PMID: 10792199.
28. Mindell JA, Emslie G, Blumer J, Genel M, Glaze D, Ivanenko A, et al. Pharmacologic management of insomnia in children and adolescents: consensus statement. Pediatrics. 2006;117(6):e1223-32. DOI: 10.1542/peds.2005-1693. PubMed PMID: 16740821.
29. Owens JA. Pharmacotherapy of pediatric insomnia. J Am Acad Child Adolesc Psychiatry. 2009;48(2):99-107. DOI: 10.1097/CHI.0b013e3181930639. PubMed PMID: 20040822.
30. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5):487-504. PubMed PMID: 18853708.
31. Bloom HG, Ahmed I, Alessi CA, Ancoli-Israel S, Buysse DJ, Kryger MH, et al. Evidence-based recommendations for the assessment and management of sleep disorders in older persons. J Am Geriatr Soc. 2009;57(5):761-89. PubMed PMID: 19484833.

How to cite this article
McGrane IR, Corman SL. Role in therapy of melatonin for the treatment of insomnia in children and adults. Ment Health Clin [Internet]. 2014;4(2):52-8. Available from: http://dx.doi.org/10.9740/mhc.n190085