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Melatonin Use in Pediatrics: Evaluating the Discrepancy in Evidence Based on Country and Regulations Regarding Production

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Melatonin manufacturers in the United States have begun producing melatonin products specifically targeted for use in the pediatric population. This paper aims to critically evaluate the evidence available regarding the use of melatonin in children based on where the clinical trials are performed and the regulations regarding the production of melatonin in that country.

Melatonin is regulated differently around the world with the least amount of regulation placed on OTC supplements in the United States. The majority of studies evaluating melatonin use in the pediatric population are conducted with children who have comorbidities, such as autism spectrum disorder or attention-deficit/hyperactivity disorder. Evidence supporting the use of US formulations of melatonin in the otherwise healthy pediatric population is non-existent. Based on the lack of safety regulations in place in the United States and the lack of evidence regarding US melatonin products, they should be used sparingly in the otherwise healthy pediatric population, if they are used at all.

ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBT, cognitive-behavioral therapy; CNS, central nervous system; CR, controlled release; CSOI, chronic sleep onset insomnia; DLMO, dim light melatonin onset; DSPS, delayed sleep phase syndrome; EHR, electronic health record; EMA, European Medicines Agency; ER, extended release; EU, European Union; FDA, US Food and Drug Administration; FR, fast release; IQ, intelligence quotient; IR, immediate release; NICE, National Institute for Health and Care Excellence; OTC, over the counter; PR, prolonged release; SR, sustained release; TFDA, Taiwan Food and Drug Administration

KEYWORDS child; maintenance disorders; melatonin; non-prescription; pediatrics; pharmaceutical regulation; sleep initiation

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Introduction

Melatonin is commonly used as a remedy for various sleep disorders; however, there is conflicting evidence about the efficacy and safety of melatonin for these indications.[1,2] Many factors must be considered when evaluating this evidence, including where the study was completed, whether melatonin is considered a prescription or dietary supplement in the country performing the research, type of sleep disorder, length of therapy, age of the study participants, and comorbid disease considerations.[1,2]

Melatonin is a hormone produced by the pineal gland. It is involved with the human body's circadian rhythm, otherwise known as the sleep-wake cycle.[1–3] The retina of the eye senses darkness and sends a trigger to the hypothalamus, stimulating melatonin secretion from the pineal gland.[4] Melatonin is also involved in growth hormone secretion and sexual maturation.[4–7] Young adults typically secrete 5 to 25 mg of melatonin every evening.[7] Information about the role of melatonin on pubertal development is limited, and further research is needed to address the use of melatonin as a sleep aid in younger populations, and how it may affect pubertal development.[8]

It is important to recognize that although melatonin is an endogenous hormone in the body, the melatonin available for purchase is a synthetically made compound. Researchers outline the concern of serotonin contamination as serotonin overdoses can occur with relatively low levels of serotonin.[9] Studies evaluating purity of melatonin products determined contaminants such as tryptophan-related compounds as well as significant quantities of serotonin.[9,10] Detection of tryptophan in these supplements is concerning. Eosinophilia-myalgia syndrome, a disease that occurred in an epidemic outbreak, was linked to L-tryptophan containing dietary supplements.[11] This outbreak resulted in 1500 cases and 30 deaths.[11]

In the United States, melatonin is regulated as a dietary supplement. Many dietary supplements marketed in the United States have been discovered by the FDA to be tainted with compounds that do not appear on the

Table 1. Definitions of CSOI as Defined by Various Authors

Reference	Definition
Janjua[19]	Difficulties sleeping deemed by child or parent occurring at least 4 days a week for at least a year. In children >6 yr, those who are unable to sleep by 8:30 pm with an allocated 15-min interval additional per year for older children and sleep latency at least ≥30 min.
Vriend[20]	In children ≥6 yr, CSOI is defined as falling asleep after 8:30 pm. Every 1 yr thereafter an additional 15 min is allocated until 10 pm (up to age 12). Additionally, the child must experience the time from lights off to falling asleep for at least 30 min.
Van Geijlswijk[21]	International classification of sleep disorders classifies CSOI as at least a 20-min sleep latency occurring for 3 months with more than 3 nights a week being affected.

CSOI, chronic sleep onset insomnia

product label.[12–17] These compounds include medications that have been both banned and approved by the FDA, some of which have modified chemical structures with similar pharmacological activity.[12–17] Despite dietary supplements lacking safety and regulation, production of melatonin products claiming to provide sleep benefits for the pediatric population continues to increase.

Most children who experience difficulty sleeping are diagnosed with a variety of sleep disorders including, but not limited to, idiopathic chronic sleep onset insomnia (CSOI), delayed sleep phase syndrome (DSPS), or behavioral insomnia of childhood.[18,19] CSOI is defined as the chronic inability to fall asleep with slight variation in the definition based on the author. Table 1 provides the variety of definitions for CSOI. CSOI can develop alone or in combination with dim light melatonin onset.[22,23] Dim light melatonin onset is how the circadian pathway regulates itself to secrete melatonin at night, and some children experience a delayed secretion of melatonin, which may account for the inability to fall asleep.[22,23] DSPS is a circadian sleep disorder that entails an individual waking up later than usual due to a timing imbalance.[20] DSPS is likely derived from an underlying delayed sleep pattern, but does not affect sleep quality or duration.[24] Behavioral insomnia of childhood is defined by the inability to stay asleep or with difficulties falling asleep.[20] These sleep disorders have often prompted the use of melatonin; however, melatonin is becoming increasingly popular in the absence of the diagnosis of a sleep disorder.

Melatonin manufacturers have begun producing melatonin products specifically targeted for use in the pediatric population. This paper aims to critically evaluate the evidence available for the use of melatonin in children, taking into consideration where the clinical trials are performed, and the regulations regarding the production of melatonin in that country.

Table 2. Regulations of Melatonin per Country

Country	Regulations	Prescription/Non-prescription (Melatonin)	Comments
United States	Considers all supplements safe until proven unsafe. Not regulated prior to market availability.	Non-prescription dietary supplement	FDA not required to test new ingredients/supplements in clinical trials.
Canada	Medications fall under the Food and Drug Regulations issued by the Canadian Government[25]	Non-prescription health product	Must contain Natural Product Number.
European Union	Medications are regulated through the European Regulatory Network, which consists of 50 regulatory authorities from across Europe[26]	Prescription for sustained release; less than 2 mg immediate release has variable status based on country	European Medicines Agency has set specific guidelines for use. Some countries, such as Poland, consider melatonin non-prescription
Non-European Union Countries in Europe (Norway)	Medications are regulated by the Norwegian Medicines Agency[27]	Prescription[27]	
United Kingdom	Follows the European Union Guidelines	Prescription	
Taiwan	Medications are regulated under the Pharmaceutical Affairs Act	Controlled-substance	

Table 3. Melatonin Products Indicated for Children's Use in the United States

Brand	Active Ingredients per Serving	Directions	Comments
Zarbee's Naturals Sleep Tablets[45]	Melatonin: 1 mg	3–5 yr: Consult a physician for serving, not to exceed 1 tablet 6–12 yr: 2 tablets ≥12 yr: 3 tablets Give 30–60 min before bedtime	Not recommended for children <3 yr or who weigh <31 lb Contact physician if using for more than 14 consecutive days
Zarbee's Naturals Sleep Liquid[46,47]	Melatonin: 1 mg	3–5 yr: Consult a physician for serving, not to exceed 1-mL dose 6–12 yr: 2-mL dose ≥12 yr: 3-mL dose Give 30–60 min before bedtime	Not recommended for children <3 yr or <31 lb. Slight warming sensation post administration is normal. A similar product by Zarbee's also contains melatonin and dark honey for cough
Zarbee's Naturals Chewable[48]	Melatonin: 1 mg Honey: amount unknown	3–5 yr: Consult a physician for serving, not to exceed 1 tablet 6–12 yr: 2 tablets ≥12 yr: 3 tablets Give 30–60 min before bedtime	Made in Canada Contact primary care provider if using for more than 14 consecutive days
OLLY Kids Sleep Gummies[49]	Melatonin: 0.5 mg; Chamomile: 2.5 mg; Passion Flower: 2.5 mg; Lemon Balm 2.5 mg; L-Theanine: 15 mg	≥4 yr: Start with 1 gummy and give up to 2 gummies Give 30 min before bedtime	Discuss with health care provider prior to use. Do not use for more than 2 wk
Vicks Pure Zzzs Gummies[50]	Melatonin: 1 mg Chamomile and Lavender: 30 mg	Child: start with 1 gummy and give up to 2 gummies as needed Given 30 min before bedtime	They advertise low dose (0.5 mg) 1 serving size = 2 gummies Consult health care professional before use. Do not use for more than 14 days
JoySpring Liquid Sleep Berry[51]	Melatonin: 3 mg; Vitamin D3: 12.5 mcg; Formula (blend) 200 mg: Elderberry ([sambucus Nigra]), l-theanine	1–2 servings Give 15 min before bedtime Shake well	Consult provider if <18 yr
Spring Valley Kids Gummies[52]	Melatonin: 1 mg	≥2 yr: chew 1 tablet under adult supervision Give 30 min before bedtime	Consult a physician before adding melatonin to your child's diet. Do not use if your child has an endocrine/autoimmune condition
Good Day Chocolate Sleep Milk Chocolate Vitamin for Kids[53]	Melatonin: 1 mg	≥3 yr: 1 piece Give 30–60 min before bedtime	Made with fair-trade milk chocolate. Consult physician if using for more than 14 days
Natrol Kids Melatonin Tablets and Gummies[54]	Melatonin: 1 mg	≥4 yr: 1 tablet Give 30 min before bedtime	Consult a physician before using

Methods

Search Strategy. PubMed was used with the following search terms: MeSH; Child + Melatonin (filter: selection of clinical trials), MeSH; Child, Preschool + Melatonin (filter: selection of clinical trials) and lastly the MeSH terms; Pediatrics + Melatonin (filter: selection of clinical trials). Inclusion criteria included the following terms: autism, attention-deficit/hyperactivity disorder (ADHD), atopic dermatitis, insomnias, neurodevelopmental disorders, and generally healthy individuals. Exclusion terms included the following: critically ill, surgical, migraine prophylaxis, anxiety/pain, Dravet/epilepsy, cancer, bipolar disorder, cystic fibrosis, Angelman syndrome, tuberous sclerosis complex alone, Smith-Magenis syndrome alone, Rett syndrome, and visually impaired. The exclusion criteria were created because the aim of this research is to evaluate the evidence for the generally healthy pediatric patient population that may be using OTC melatonin products. Critically ill patients and other exclusion conditions are patient populations that melatonin may be used for in an acute care setting or under the supervision of health care provider(s), which are outside the scope of this paper.

Search Criteria. Regulation of melatonin was dependent upon the country of origin. The US regulations were found using the PubMed search terms: Dietary Supplement + Pharmaceutical Preparations + United States Food and Drug Administration (filter: 5 years) with supplemental information found at the US FDA website. Canadian regulations were extracted from the government's website under the Departments and Agencies Health Canada subsection. The safety review of melatonin guides the use of melatonin in the Canadian territory, and supplemental information pertaining to drug monographs was also obtained from the Health Canada website. Regulations for use of melatonin in the European Union (EU) were located in the European Medicines Agency (EMA) governmental website. Specific guidelines pertinent to each country were found utilizing each country's government website. The United Kingdom falls congruent with the European guidelines, with supplemental information from the National Institute for Health and Care Excellence (NICE) guidelines. Regulations for Taiwan were found under the Taiwan Food and Drug Administration (TFDA) governmental website.

Results

Regulation. Medication regulations and specific guidelines are dictated by the regulating authority of the country of origin. Melatonin, as seen in Table 2, falls under different regulations dependent on which country is using the medication. Melatonin is classified as non-prescription in both the United States and Canada; however, it is regulated differently between the 2 countries. Melatonin is a prescription in most European countries, with the exception of a few countries, such as Poland.

United States. Melatonin is regulated as a dietary supplement in the United States. This differs dramatically from non-prescription and prescription medications. Dietary supplements are considered safe until proven unsafe and thus are permitted to market prior to any efficacy or safety analysis.[15,28] Thus, all melatonin products marketed in the United States, which are available as dietary supplements, have not been evaluated for safety or efficacy in a clinical trial. Guidelines are currently limited for OTC products; however, the American Academy of Sleep Medicine has a weak recommendation to not use melatonin to treat sleep onset or sleep maintenance insomnia in adults with no current recommendations for children.[29]

Canada. Melatonin in Canada is licensed to be sold as an OTC medication with use beginning in 2005. For OTC medications to be sold legally in Canada, each OTC natural product must contain a natural product number or a drug identification number-homeopathic medicine number.[30,31] Identification numbers indicate that each individual product has met specific requirements and is reviewed under Health Canada. These requirements include evaluating the safety, efficacy, and quality of all medications available prior to and after introduction to the market. Evidenced-based claims must include data analyzed via a risk-based approach to support the efficacy and safety of each individual product.[32] Both prescription and non-prescription medications are reviewed by experts in the Health Products and Food Branch of Health Canada.[33,34] The Health Products and Food Branch is the governmental agency that focuses on ensuring all medications, including that of natural health products, are safe and follow nutritional standards. It is the major contributor to the investigation of safety issues.[25]

Vitamins and supplements with therapeutic claims are further regulated under the Natural Health Products Regulations.[31,34] For natural health products to be brought to market, these supplements must have safety and efficacy evidence and are only allowed to be used under good manufacturing practices. Use of melatonin in the adult population is not recommended for more than a 4-week course and is not authorized to be used in children ages 11 and younger.[25] Due to the results of international reports of conflicting evidence of neurological side effects, Health Canada requests parents of children and adolescents consult a health care provider prior to using melatonin.[25]

European Union. Melatonin in the EU is available as a prescription. Melatonin prescription products in the EU are Circadin (Neurim Pharmaceuticals, Tel Aviv-Yafo, Israel) and Slenyto (Neurim Pharmaceuticals). Circadin is indicated for individuals aged 55 years and older for the short-term treatment (13 weeks) of primary sleep disorders.[35] Circadin is available in 2 mg prolonged-

Table 4. Melatonin Studies in Children in the United States

Reference	Sample Size (age range, yr)	Melatonin Dosage, Product	Duration	Summary and Comments
Autism				
Gringras[55]	119 (2–17.5)	Starting dose of 2 mg (ER). If no improvement after 3 wk, increased to 5 mg nightly. During open-label period, dose could be increased to a maximum of 10 mg. Give 30–60 min before bedtime. Circadin produced by Neurim Pharmaceuticals.	13-wk then 91 wk of open-labeled tx.	Individuals in the United States and across 10 EU sites diagnosed with ASD ± ADHD, received ER melatonin or placebo. At 13 wk, sleep was longer with melatonin (57.5 min) than placebo (9.14 min) ($p = 0.034$). SE were somnolence, fatigue, upper respiratory infection, mood swings, vomiting, agitation, headache, cough, and dyspnea. Somnolence occurred more frequently with 28.3% of melatonin (28.3%) vs placebo (10.8%). One seizure occurred with placebo group.
Wirojanan[56]	12 (2–15)	3 mg Melatonin supplied by Twinlab Corporation.	5 wk (1 baseline wk, 2 wk of treatment, followed by cross-over to 2 wk of alternative txs).	Individuals with autism, confirmed fragile x syndrome, or both were randomly assigned to melatonin or placebo. Sleep onset, total duration, onset latency time, and number of night awakenings were recorded via an Actiwatch. Caregivers/parents completed a daily sleep diary. Sleep onset was the only variable that achieved a statistical difference from placebo ($p = 0.017$). No SEs were reported.
Andersen[57]	107 (2–18)	<6 yr old started with 0.75–1 mg and increase 1 mg every 2 wk as needed to maximum of 3 mg. ≥6 yr started on 1.5 mg. Increased to 3 mg after 2 wk and to 6 mg after 4 wk, as needed. Give 30 min to 1 hr before bedtime.	On average for 1.8 yr.	One hundred eight children with autism and sleep concerns noted in their EHR were included in an open-label study, which evaluated response to melatonin based on parental reports focusing on sleep onset, sleep-maintenance, or both: 27 (25%) noted sleep was no longer a concern; 64 (60%) noted improved sleep but continue parental concern; 14 (13%) noted sleep continued as a major concern; and 1 reported worsening sleep; 3 children had SE that included daytime somnolence and increased enuresis.
Malow[58]	24 (3–10)	Initially 1 mg (4 mL) for 3 wk. If no response after 3 wk, increase to 3 mg; if no response after 3 wk, increase to 6 mg; if no response after 3 wk, increase to 9 mg. Give 30 min before bedtime. Melatonin provided from Natrol.	17 wk (1 wk of baseline, 2 wk of accumulation period and 14 wk of tx.	Twenty-two individuals with ASD and a sleep delay of >30 min for ≥3 nights/wk were randomly assigned to melatonin or placebo. Actigraphy showed a decrease in sleep latency ($p = 0.0001$), improved sleep duration ($p = 0.011$), sleep efficacy ($p = 0.026$), and wake time after sleep onset ($p = 0.022$) on melatonin. Response was not associated with age or weight. The only SE was loose stools in 1 child.
Neurodevelopmental disorders				
Dodge[59]	20 (1–12)	5 mg Melatonin was from Regis Technologies, which provided chromatography-confirmed pure melatonin.	6 wk (tx for 2 wk, washout period for a wk before and between alternative tx).	Children with autism, global developmental delay with mental retardation (IQ ≤ 50), or spastic quadriparesis were randomly assigned to melatonin or placebo, followed by cross-over. Results were obtained via a sleep log. Melatonin decreased time to fall asleep ($p < 0.05$) and an increased sleep duration ($p < 0.007$) when compared with baseline. No significant SEs were noted.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ER, extended release; EU, European Union; IQ, intelligence quotient; SE, side effect; tx, treated/treatment

Table 5. Melatonin Studies in Children in Canada

Reference	N (Age range, yr)	Melatonin Dosage	Duration	Summary/Comments
ADHD				
Weiss[60]	19 (6–14)	5 mg Give 20 min before bedtime. Melatonin was manufactured by Circa Dia BV.	30-day cross over (10-day tx periods) with 3-mo post open-label study)	Nineteen children with ADHD and comorbid insomnia, who did not respond to sleep hygiene, were randomly assigned to receive melatonin vs placebo. Sleep onset latency was measured via actigraphy and somnolog (sleep diary). Actigraphy indicated superiority of melatonin by 16 min of decreased sleep latency ($p < 0.01$). Somnolog results noted a change from baseline (mean of 91.7 min) to a mean of 62.1 min on placebo ($p < 0.05$) and 46.4 min on melatonin ($p < 0.01$). SEs were similar (20% with melatonin, 23% with placebo). Except for migraine, all SEs were mild.
Insomnia				
Carr[61]	44 (2–18)	5, 10, and 15 mg depending on response. Melatonin was obtained from Circa Dia BV.	Up to 9.6 yr, mean 4.3 yr	Open-label study obtained from 41 caregivers regarding long-term efficacy and safety of melatonin in children with neurodevelopmental disorders and refractory circadian rhythm sleep disorders. Mean age at enrollment was 6 yr. Mean duration and dose of melatonin was 4.3 yr and 10 mg, respectively. For part of the study, 5 mg SR melatonin was given (1 mg FR and 4 mg SR). At an unspecified time, the company manufactured a new 5-mg FR formulation. For the CR product: 19 children began 5 mg; 21 began 10 mg, and 4 began 15 mg. Efficacy with the FR formulation was less; hence, the dose was increased for the majority of the participants. All caregivers reported benefits on sleep difficulties and positive effects on overall health. Negative feedback related to the change in perceived effectiveness when CR formulation was changed to FR (9/41 caregivers, 22%). Although excessive morning sedation, nausea, diarrhea, irritability, nasal allergy, and rash were the most reported, they were mild. Limitations: Open-label with efficacy/safety determined by caregiver reports.
Neurodevelopmental disorders				
Wasdell[62]	50 and 47 (2–18)	A range from 5 to 15 mg of CR melatonin. Given 20–30 min before bedtime. Melatonin was provided by Circa Dia BV, a 5-mg formulation (1 mg FR melatonin and 4 mg CR melatonin).	10 days of tx; 3–5 days washout period; 10 days of alternative tx; then 3 mo open-labeled study	A randomized, placebo-controlled trial of melatonin for delayed sleep phase syndrome and impaired sleep maintenance in 50 children with neurodevelopmental disorders. Forty-seven children then participated in a 3-mo open-label trial. A significant correlation was noted between the actigraphy and somnologs results for total night-time sleep and sleep latency. For actigraphy, night-time sleep ($p < 0.01$) and sleep latency ($p < 0.01$) improved. SEs reported were cold/flu/infection (20%), seizures (16%), and gastrointestinal illness (50%). Authors report similar SEs in the placebo group, but the quantity and frequency were not provided.
Jan[63]	42 (0.5–21)	A range from 2 to 25 mg of melatonin FR. FR was from Sigma Company (St Louis, MO) and CR was from Neurim Pharmaceuticals. In the subsequent study, FR and CR were obtained from Twin Laboratories (Ronkonkoma, NY).	Average duration of FR and CR was 2.2 and 2.8 yr, respectively.	Clinical trials of CR melatonin in 16 children with sleep-wake cycle disorders who were previously tx with FR melatonin. Patients could begin with CR melatonin and transition to FR, or vice versa. The final average doses for FR and CR melatonin was 7 mg and 5 mg, respectively. Younger children were started at smaller doses in the beginning of the trial but ended on larger doses than older patients, suggesting that dose and dose response is not directly proportional to age. CR tx resulted in ~50% reduction in dose from FR. Children had very complex neurodevelopmental disorders, which made determining SEs difficult. Some patients required a change in the doses of seizure medication following melatonin.

ADHD, attention-deficit/hyperactivity disorder; CR, controlled release; FR, fast release; SE, side effect; SR, sustained release; tx, treatment

release form.[35] Slenyto is available in 1 and 5 mg melatonin prolonged-release form, and is authorized for the treatment of insomnia in patients aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome.[36] Smith-Magenis syndrome is a disease that affects many parts of the body with features that include sleep disturbances and mild to moderate intellectual disability.

Prescriptions undergo regulation by the European medicines regulatory network, a network consisting of the European Commission, the European Economic Area, and the EMA.[26] Inside of this network, experts are allocated to provide scientific guidance for the use of medications in allocated member states. Medications can be marketed for use in all member states, known as the centralized procedure, or for use in only a specific country, known as the decentralized procedure.[26] Regardless of the procedure, medications are subject to the same rules and regulations. A requirement for approval or refusal for marketing medications is that each medication must have a European Public Assessment Report.[26] The European Public Assessment Report must be published on the EMA website.[26] Although there is an overarching regulation on melatonin on behalf of the EU, there remains variations of what is permitted per country within the EU. For example, in 2011, melatonin become available as a supplement product in France at doses less than 2 mg. Doses at or exceeding 2 mg remain prescription.[37] The supplement products are still regulated in France by the General Directorate for Consumer Affairs, Competitions Policy and Fraud Control. This regulatory agency examines the composition of the dietary supplements and ensures products are labeled accurately.[38]

Other countries within the EU such as Denmark, Czech Republic, Slovenia, and Switzerland do not permit melatonin at any dose to be available as a "food supplement" and are only available as a prescription.[37]

United Kingdom. Medications in the United Kingdom are regulated by the Medicines and Healthcare Regulatory Agency, which requires medicine products to meet specific requirements for safety, efficacy, and quality.[39] The United Kingdom has only 1 licensed product of melatonin, Circadin. It is the same licensed product approved for the EU. Use of melatonin in other forms or for those who are younger than 18 years of age is considered unlicensed and off-labeled use, respectively.[39] Guidelines and recommendations for the use of medications fall under NICE.[40] The NICE guidelines follow the EU regulations with the recommendation that melatonin can be used in individuals over the age of 55 for the short-term treatment of primary insomnia. The NICE guidelines also support the use of unlicensed or off-label use of melatonin when clinically applicable and if the use of a licensed medication is not appropriate.[40]

Taiwan. The regulating authority for medications in Taiwan falls under the Ministry of Health and Welfare.[41] Under the Ministry of Health and Welfare, the TFDA focuses on regulating medications based on the safety and quality of medications and food, which must comply with the Pharmaceutical Affairs Act.[41] Under the TFDA, the use of melatonin is not mentioned. Although current information on melatonin use is lacking, the medication appears to be considered a controlled substance since 1996 with consequences linked to the production or dispensing of this medication.[41,42] Patients who carry controlled medications into or out of the Republic of China must get a permit to do so.[41]

Melatonin Use in the Pediatric Population.

United States. In the United States, melatonin has become increasingly popular as an OTC dietary supplement. A National Health Interview Study was conducted between 2007 and 2012 in the United States evaluating complementary health approaches in children between the ages of 4 and 17 years of age.[43] Melatonin use in children increased from 0.1% in 2007 to 0.7% in 2012, and is considered 1 of the top 3 most used supplements by this population.[43,44] The number of melatonin products sold in the United States and indicated specifically for children are also increasing, with common products depicted in Table 3.

Melatonin products targeting use in the pediatric population in the United States contain directions recommending doses ranging from 0.5 to 6 mg per dose. Directions for use and age recommendations vary between each supplement. JoySpring melatonin products do not give a specific age to begin use, however, do recommend consulting a physician in patients younger than the age of 18. Other products give dosing recommendations beginning at 2, 3, and 4 years of age. Some similarities between the products exist in that most products recommend consulting a physician before use, and a few products recommend not using for more than 14 days. Only 1 product recommends avoiding in children with an endocrine or autoimmune condition. Directions for the timing of the supplement administration range between unspecific times before bed to 60 minutes before bed.

Other Country of Study. Current studies evaluating melatonin use in the pediatric population are detailed in Tables 4 through 8 and are arranged by country of origin and comorbidities of the patients in the studies. Five studies have been completed in the United States. Four of these studies were conducted in children with autism, and 1 in children with neurodevelopmental disorders. In Canada, 1 study has been conducted with children with ADHD, 1 with insomnia, and 2 studies with neurodevelopmental disorders.

Many of the studies included in this review used actigraphy as the primary method to determine sleep outcome with sleep logs/diaries being the alternative process. Actigraphy is measured through wrist bands that are worn overnight to record movements via specialized software.[82] A few studies used both processes to assess sleep outcomes.

Table 6. Melatonin Studies in Children in the European Union (Countries Include Netherlands)

Study	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
ADHD				
Tjon[64]	24 (unknown)	3 mg	52 wk	A preliminary open-label study to evaluate the efficacy and safety of melatonin in individuals with ADHD taking methylphenidate. Twenty-four individuals were included, although long-term results (following 3 months of therapy vs 4 weeks) were only available for 13 individuals. Short-term melatonin improved time to falling asleep (n = 24; range: 15–240 min). Following 3 mo of melatonin (n = 13), to falling asleep ranged from 15 to 64 min, and was determined to provide a statistically significant change in onset of sleep ($p < 0.01$). There was no difference in long-term safety compared with 1 wk of treatment. Limitation: no baseline characteristics were provided.
Van Der Heijden[65]	105 (6–12)	Weight less than 40 kg = 3 mg. If more than 40 mg, then 6 mg at 1900. Melatonin was provided by Pharma Nord.	5 wk (1-wk baseline 4 wk of tx)	Effect of melatonin on sleep, behavior, and cognition in ADHD and CSOI were evaluated in patients aged 6 to 12 years not taking any medication for ADHD and chronic insomnia were randomly assigned to receive melatonin or placebo. Sleep results were obtained via actigraphy and sleep diaries. When compared with placebo, the melatonin group experienced improved sleep onset (26.9 ± 47.8 when compared with placebo group (10.5 ± 37.4, $p < 0.0001$). An advance in DLMO 44.4 ± 67.9 min vs a delay in placebo 12.8 ± 60 min, $p < 0.001$. Total sleep also increased in the melatonin group 19.8 ± 61.9 min compared with placebo, −13.6 ± 50.6, $p = 0.01$. SEs reported in the melatonin group included headache (5.7%), hyperactivity (5.7%), dizziness (3.8%), abdominal pain (3.8%), and diarrhea (1.9%). No SEs were reported in the placebo group.
Autism				
Cortesi[66]	134 (4–10)	3 mg (1-mg FR, 2-mg CR) at 2100. Titrations were not allowed. Melatonin provided by Armonia Retard 3 mg (Nathura, Montecchio Emilia, Italy)	12 wk	A randomized placebo-controlled trial evaluating the efficacy of melatonin (n = 34), melatonin + CBT (n = 35), CBT (n = 33), or placebo (n = 32) in 134 patients. Sleep latency, total sleep time, wake after sleep onset, and number of awakenings measured by actigraphy, sleep questionnaire, and sleep diary submissions were assessed. Mean total sleep mean time improved on melatonin (17%), melatonin + CBT (22.01%), and CBT (9.31%), but no improvement was noted in the placebo group. All active groups achieve statistical significance in time effect ($p < 0.001$). Mean sleep onset latency decreased in the melatonin (44.3%), melatonin + CBT (60.75%), and CBT (22.5%) groups, but there was no decrease with placebo. Statistical significance was determined for the time effect ($p < 0.001$) and time × group effect ($p < 0.001$). No SEs were reported.
Paavonen[67]	15 (5–17)	3 mg daily	14 days of active tx	Effectiveness of melatonin for tx of sleep disturbances in 15 children with Asperger disorder. Evaluations were conducted prior, during, and 3 weeks post tx, and results were evaluated via actigraphy and questionnaires. Sleep latency measured by actigraphy decreased from 40.2 ± 24.09 to 21.82 ± 9.64 ($p = 0.002$), but sleep duration was unchanged. Behavioral measures significantly improved ($p = 0.001$), and mild tiredness (n = 2), dizziness (n = 1), and diarrhea (n = 1) were reported.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBT, cognitive-behavioral therapy; CR, controlled release; CSOI, chronic sleep onset insomnia; DLMO, dim light melatonin onset; FR, fast release; IR, immediate release; PR, prolonged release; SE, side effect; tx, treatment

Table 6. Melatonin Studies in Children in the European Union (Countries Include Netherlands) (*cont.*)

Study	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
Insomnia				
Van Maanen[68]	84 (7–12)	3 mg (IR) of melatonin at 1900 Melatonin was provided by Pharma Nord.	3–4 wk	A randomized controlled study of the effects of melatonin (n = 26), DLMO (n = 30), and placebo (n = 27) in children with CSOI. Some in the melatonin group had underlying disorders (ADHD [5] and ASD [2]). Similar values were noted in the other 2 groups. Other participants were generally healthy children experiencing insomnia. DLMO melatonin levels were measured from saliva. Outcomes were measured via actigraphy, sleep diaries completed daily via the internet by parents, and sleep reduction questionnaires taken prior to and following the study. Sleep latency improved with melatonin compared with placebo ($\beta = -0.33$, $p < 0.01$). Sleep onset time advanced for both the melatonin ($\beta = -0.65$, $p < 0.01$) and DLMO ($\beta = -0.23$, $p = 0.02$). Melatonin provided the best results in total sleep time. Although there was an increase in sleep onset, the reduction of about 15 min on sleep latency ensured an overall improved sleep outcome. One child left the melatonin group due to various complaints (joint pain, headache). No other SEs were reported.
Van Geijlswijk[21]	59 (6–12)	0.3–10 mg	≥6 mo	A follow-up study evaluating sleep and safety of long-term melatonin in children with idiopathic CSOI. Duration of melatonin use was 3.1 yr with an average dose of 2.7 mg. Multiple SEs were noted (e.g., nausea [n= 1], apathy with weight gain [n = 1], and headaches). Twenty-one (38%) reported experiencing headaches regularly, 11 (20%) once a month, and 23 (42%) reported never experiencing headaches. There was no change in puberty onset. Limitation: Subjective data.
Van Geijlswijk[69]	120 (6–12)	0.05, 0.1, and 0.15 mg/kg given between 1730 and 1930	1 wk	In order to determine if there is a dose-response of melatonin for reducing sleep onset latency and advancing DLMO, patients were randomly assigned into a group with different weight-based dose of melatonin or placebo. Melatonin/advance sleep onset by approximately 1 hr ($p < 0.001$) and decrease sleep onset latency by about 35 min ($p = 0.007$ for 0.05 mg/kg, $p = 0.001$ for 0.1 mg/kg, and $p < 0.001$ for 0.15 mg/kg). DLMO was advanced by 50–90 min in the melatonin groups, which was statistically different from placebo ($p < 0.001$) in the 0.1 and 0.15 mg/kg groups. It did not achieve statistical significance in the 0.5 mg/kg group. Authors propose only 1 wk of data are difficult to ascertain dose-response. Common SEs were red cheeks (n = 15), red eyes (n = 15), yawning (n = 15), pale complexion (n = 8), dizziness (n = 8), feeling cold (n = 8), headache (n = 2), nausea and stomach pain (n = 1), and dizziness and nausea (n = 1).
Van Der Heijden[70]	110 (6–12)	5 mg given at 1800 or 1900	4 wk	The purpose of this study was to determine if DLMO could predict the time of treatment for melatonin. Results were measured via saliva hourly from 1900 to 2300 and via actigraphy. Melatonin advanced DLMO with positive 1:12 hr ($p < 0.001$), sleep onset with positive 0:42 hr ($p = 0.004$), and sleep latency decreased by approximately 25 min ($p = 0.019$). Total sleep duration was not statistical different from placebo.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBT, cognitive-behavioral therapy; CR, controlled release; CSOI, chronic sleep onset insomnia; DLMO, dim light melatonin onset; FR, fast release; IR, immediate release; PR, prolonged release; SE, side effect; tx, treatment

Table 6. Melatonin Studies in Children in the European Union (Countries Include Netherlands) (*cont.*)

Study	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
Insomnia				
Smits[71]	33 (6–12)	5 mg at 1800, adjusted to results. Melatonin was provided from Helsinn Chemicals.	5 wk (1-wk baseline, 4 wk tx)	Children were randomly assigned to receive either melatonin or placebo for 4 wk but could continue post study. Actigraphy and sleep diaries\determine sleep onset and DLMO was measured via saliva. Lights off time improved by about 40 min based on diary responses in the melatonin group (p = 0.035) but did not change in the placebo group. Sleep onset evaluated via actigraphy also changed significantly with an approximate 1 hr of improvement from baseline in the melatonin group (p = 0.005) and a worsening of onset in the placebo group. DLMO and sleep onset, using diary reports and actigraphy, did not correlate. Transient headache at initiation of melatonin (n = 2) and new onset epilepsy (n = 1) were reported.
Braam[72]	58 (1–58)	5 mg at 1900 for those ≥6, 2.5 mg at 1800 for those <6 yr. Melatonin was supplied by Duchefa Farma BV.	5 wk (1-wk baseline, and 4 wk tx)	Participants were randomly assigned melatonin or placebo after 1 wk of baseline. The melatonin group experienced significantly shorter sleep onset time (~34 min, p = 0.005), decreased sleep latency (~30 min, p = 0.002), increased sleep time (~48 min, p = 0.032), and less time awake during the night (42% improvement, p = 0.012). SEs in the melatonin group were included restlessness (n = 5), daytime crying (n = 5), decreased appetite (n = 5), and restless legs (n = 1).
Neurodevelopmental disorders				
Braam[73]	49 (4–78)	<6 yr received 2.5 mg at 1800, >6 yr received 5 mg at 1900 Melatonin was supplied by Duchefa Farma BV.	4 wk tx with a 1-wk washout period	Includes adults and children with intellectual disabilities experiencing chronic insomnia. About 33% were over 20 yr. Outcome measures were Maladaptive Behavior Scale for the Mentally Retarded (SGZ) scores (components: SGZ-A, aggressive maladaptive behavior; SGZ-V, verbal aggressive behavior; SGZ-Z, mixed maladaptive behavior; SGZ-T scores from SGZ-A, SGZ-V, and SGZ-M that reflects the overall severity of challenging behavior), time lights went out, sleep latency, total sleep time, and number and duration of night wakes. Statistical significance in change/improvement was determined for SGZ-M (p = 0.003), SGZ-T (p = 0.005), sleep latency (−34 minutes, p < 0.001), decrease in wake time (0.66, p = 0.002), and total sleep time (increased by ~34 minutes, p = 0.043). Limitation: inclusion of adults may not be clinically applicable to children.
De Leersnyder[74]	88 (6–12)	4 mg of PR if body weight < 40 kg. If > 40 kg then 6 mg Circadin produced by Neurim Pharmaceuticals.	6–72 mo	Questionnaire results used to determine sleep quality, mood, and onset. PR melatonin increased sleep duration (10.1%, p < 0.001), improved quality of sleep (75%, p < 0.001), decreased sleep latency (44.0%, p < 0.001), and the number of awakenings (75%, p < 0.001). Daytime somnolence was reported (n = 2). Other SEs were mild, but specifics not provided. Limitation: no placebo group.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBT, cognitive-behavioral therapy; CR, controlled release; CSOI, chronic sleep onset insomnia; DLMO, dim light melatonin onset; FR, fast release; IR, immediate release; PR, prolonged release; SE, side effect; tx, treatment

Table 7. Melatonin Studies in Children in the United Kingdom

Reference	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
Autism				
Wright[75]	17 (3–16)	Starting dose: 2 mg; 30–40 min prior to sleep, titrations allowed, and maximum dose was 10 mg Melatonin and placebo supplied by DHP Pharma.	3 mo with tx and crossover with 3 mo of alternative tx	Cross-over trial with melatonin and placebo in individuals with ASD who were referred by a pediatrician or specialist for sleep problems. This study assessed sleep latency, complete sleep time, and numerical quantity of awake periods throughout the night via questionnaires. Sleep latency proved to be significantly shorter with melatonin (by ~ 47 min, p = 0.004) and showed longer total sleep time (~52 min, p = 0.002); however, the difference from placebo for the number of nighttime awakenings was not significantly different. SEs were similar between groups, but the authors did note the following were reported as "never present" more often in the placebo group: daytime drowsiness (melatonin 35%, placebo 69%); reduced appetite (melatonin 35%, placebo 50%); reduced alertness (melatonin 59%, placebo 81%); and diarrhea (melatonin 71%, placebo 88%).
Garstang[76]	7 (4–16)	5 mg Melatonin and placebo were produced by Penn Pharmaceutical; however, these were recalled during the time of the study for empty capsules.	4 wk, followed by 1-wk washout period then 4 wk of alternative tx	Seven children were randomly assigned to receive placebo or melatonin. This was followed by a washout period then alternative tx. Outcomes were based on sleep charts recorded by parents/caregivers. Overall sleep time increased with placebo (8.05 hr baseline to 8.75 hr [95% CI, 8.56–8.98]) and with melatonin (9.84 hr [95% CI, 9.68–9.99]). Nighttime awakenings also decreased statistically from baseline, with placebo (0.35 baseline to 0.26 [95% CI, 0.20–0.34]) and melatonin (0.08 [95% CI, 0.04–0.12]). Study limitations: small sample size.
Insomnia				
Hancock[77]	21 (5–15)	5 mg of melatonin	2 days	Twenty-one healthy children and 7 with tuberous sclerosis. This study evaluated melatonin in generally healthy patients (n = 21) and those with tuberous sclerosis complex (n = 7) and endogenous melatonin secretion. Urine samples were collected in 24- and 48-hr periods to determine extraction of the melatonin metabolite. After the first 24 hr of tx, metabolites ranged between 11.1 and 40.1 mcg, and total course metabolites ranged from 11.1 to 40.2 mcg. Melatonin resulted in a mean improvement in total sleep time, 0.55 hr, p < 0.05. Circadian patterns of children in this study were similar to adults.

ASD, autism spectrum disorder; IR, immediate release; SE, side effect; tx, treatment

Table 7. Melatonin Studies in Children in the United Kingdom (*cont.*)

Reference	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
Neurodevelopmental disorders				
Gringras[78]	146 (3–15)	Doses began at 0.5 mg and were increased every 4 wk to 2, 6, and 12 mg dependent on response; Given 45 min before bedtime	12 wk	Objectively and subjectively, the authors measured sleep time and sleep onset latency. Children fell asleep faster (measured by sleep diaries: approximately −37.5 min and actigraphy approximately −45.3 min). Although melatonin increased total sleep time by 22.4 min, the change was not statistically significant. SEs were similar between both groups, but cough and mood swings were reported more in the placebo group.
Appleton[79]	110 (3–16)	Doses began with 0.5 mg and could increase based on response to a maximum dose of 12 mg during the first 4 wk. Melatonin was supplied by Alliance Pharma.	12 wk	This trial evaluated total-time sleep time in 146 individuals randomly assigned to receive IR melatonin or placebo. Results were determined via sleep diary and actigraphy. Total sleep time reported via sleep diaries increased from 22.43 to 44.34 min ($p = 0.04$). A reduction in sleep latency by ~45 min (actigraphy [95% CI, −68.75 to −21.93]; $p = 0.0003$), and approximately 38 min (sleep diaries [95% CI, −55.27 to −19.71 min]; $p < 0.0001$). There were no significant differences between groups in SEs. Prior to randomization, 16 children had a diagnosis of seizures of which 13 experienced a seizure during the study with a total of 411 seizures reported. SEs were similar between the 2 groups.
Ross[80]	46 (1–13)	Children < 5 yr were started on 2.5 and children > 5 yr on 5 mg. Could increase by 2.5 mg to a maximum of 7.5 (<2 yr) or 10 mg (> 2 yr). If children later awoke up to 5mg was permitted as a 2nd dose. Melatonin was supplied by Penn Pharmaceutical.	1 wk of pre-tx, followed by 1 wk of tx with melatonin	Twenty-eight children with a variety of disorders that affects CNS and impacts sleep from an outpatient neurology clinic were included in this study. Observations were made via sleep diaries. An interesting component of this study was organization of sleep problem type and corresponding response to melatonin. For fragmented sleep, 3 participants found melatonin beneficial and 2 did not. For "difficulty settling," 12 found melatonin beneficial and 2 did not. For "low requirement," 7 determined benefit, 1 did not. For "awaking" sleep problems, 11 found benefit, 4 did not. For delayed-sleep phase, 2 found melatonin beneficial, 9 did not. Median sleep time premelatonin and postmelatonin was 54 hr and 65.5 hr ($p < 0.005$). There was a significant difference ($p < 0.005$) in nighttime sleep premelatonin (53 hr) and postmelatonin (64 hr).

ASD, autism spectrum disorder; IR, immediate release; SE, side effect; tx, treatment

Table 8. Melatonin Studies in Children With Atopic Dermatitis in Taiwan

Reference	N (age range, yr)	Melatonin Dosage	Duration	Summary/Comments
Chang[81]	48 (1–18)	3 mg/day	4 wk of tx followed by 2 wk washout period and alternative tx for 4 wk	Postrandomization individuals diagnosed with atopic dermatitis received either placebo or melatonin. Individuals on melatonin had a lower SCORing Atopic Dermatitis (SCORAD) index by 9.1 as compared with placebo (95% CI, −13.7 to −4;6; $p < 0.001$). Sleep onset occurred 21.4 min sooner with melatonin (95% CI, −38.6 to −4.2; $p = 0.02$). No SEs were noted.

Discussion

Melatonin is regulated differently around the world with the least amount of regulation placed on OTC dietary supplements in the United States. A study conducted on US melatonin products discovered a variation of 0.3 to 5 mg/unit difference from the label content.[10] One supplement had 15% less melatonin than the labeled amount. Varied amounts of melatonin in products sold in Canada have also been found, even under stronger regulations of OTC supplements.[9] In a study conducted in Canada, the authors quantified the amount of melatonin in 30 commercial products with −83% to +478% of what was depicted on the label, not meeting a 10% margin of error.[9] As evidenced by these studies, melatonin content in OTC dietary supplements can vary widely from what is listed on the bottle.

Current clinical trials do not commit to using a specific brand or generic melatonin product, increasing the variability of products across all nations completing studies on pediatric melatonin use. For example, as seen in Table 4, the United States completed 6 clinical trials with the inclusion criteria mentioned earlier, but only 3 trials disclosed the melatonin product that was used in the study. Two of the manufacturers, Natrol (Chatsworth, CA) and Twinlab (Boca Raton, FL), produce only vitamins and supplements, whereas Regis Technologies (Morton Grover, IL) is a chemical supplier and manufacturer of active pharmaceutical ingredients.[83]

In clinical trials conducted in Canada per Table 5, all 4 studies disclosed where the melatonin was obtained. All melatonin products were obtained abroad from a variety of different manufacturers and did not include the generic OTC melatonin that is available for use in Canada. One study used the EU product, Circadin, and the other 3 studies used Circa Dia BV (Amsterdam, Netherlands) that is based in the Netherlands.

Five of 12 clinical trials conducted in the EU, as seen in Table 6, used the following manufacturers: Neurim Pharmaceuticals, Pharma Nord (Vejle, Denmark), Duchefa Farma BV (Haarlem, Netherlands), and Helsinn Chemicals (Pazzallo, Switzerland). All of these manufacturers produce prescription regulated melatonin products. Melatonin use in the EU is approved for the medication Circadin, which, at this moment, is produced from a manufacturer with headquarters out of Israel, and a branch located in Switzerland. Pharma Nord falls under Danish pharmaceutical control, a member state of the EU. Duchefa Farma BV is also based in the Netherlands.

In the United Kingdom, 4 of 6 studies conducted in Table 7 disclosed the manufacturer of melatonin. The manufacturers include Penn Pharmaceutical (Tafarnaubach, United Kingdom), Alliance Pharma (Chippenham, United Kingdom), and DHP Pharma (Kent, United Kingdom). It is important to mention that although the status of melatonin use in Taiwan is unknown, melatonin is still studied in both the adult and pediatric populations, as seen in Table 8.

Melatonin supplements sold OTC are generally targeting overall healthy individuals, including some children who are having issues sleeping. Table 9 depicts the number of studies conducted in each location. As seen by the table, the studies with otherwise healthy individuals were mostly conducted in the EU, and no studies were conducted in the United States for children without other comorbidities such as autism and neurodevelopmental disorders. It is important to mention that products sold in the United States likely base their claims off studies conducted in other countries that have different regulations for the production of melatonin. This brings up the concern of the inappropriate extrapolation from studies conducted in other countries with different standards on the use of melatonin than here in the United States. Table 9 provides an overview of studies evaluating melatonin in pediatric populations respective to the country of origin and comorbidities, if applicable.

Conclusion

The majority of studies evaluating melatonin use in the pediatric population are conducted with children who have other comorbidities. The data supporting the use of melatonin in the otherwise healthy pediatric population are limited and/or non-existent (in the United States). There is growing evidence for the use of melatonin in patients with certain comorbidities including ADHD, autism, and neurodevelopmental disorders, but these data are extrapolated from variable settings based on the country and regulations in place for the

Table 9. Overview of Studies

Study Location	Insomnia/Otherwise Healthy Individuals	Autism	Atopic Dermatitis	ADHD	Neurodevelopmental Disorders
United States	0	4*	0	0	1
Canada	1	0	0	1	2
European Union	6	2*	0	2	2
Non-European Union (such as Norway)	1	0	0	0	0
United Kingdom	1	2	0	0	3
Taiwan	0	0	1	0	0

ADHD, attention-deficit/hyperactivity disorder
* One study consisted of United States and 10 European Union sites.

production and use of melatonin. Based on the lack of efficacy and safety regulations in place in the United States, pediatricians, pharmacists, and caregivers/parents should consider the following when using melatonin in pediatric patients: 1) Document the initiation of product, and share with all providers and caregivers, including the product name, dose, and administration schedule (frequency); 2) Evaluate response to therapy, starting at the lowest dose and titrating based on response. Document any changes to therapy, including if dosing changes occur, or change of product; 3) Document any side effects/adverse effects and report adverse events associated with the melatonin product to the Safety Reporting Portal available at: https://www.safetyreporting.hhs.gov/fpsr/WorkflowLoginIO; 4) The Safety Reporting Portal is the only mechanism in place to ensure the safety of OTC dietary supplements in the United States. Share this portal information with caregivers and all providers of the pediatric patient to help support this ongoing effort to evaluate the supplement products in the United States; and 5) Studies evaluating the safety and efficacy of the specific OTC supplements available in the United States targeting pediatric patients is needed. As of now, safety and efficacy cannot be ensured by utilizing the products available in the United States for the pediatric population.

Article Information

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