

Management of sleep disturbance associated with atopic dermatitis

Kim Kelsay, MD *Denver, Colo*

Atopic dermatitis (AD) is a common childhood skin disease that also affects adults. Sleep problems are frequently associated with AD and negatively affect both patients and their families. Although this problem is well recognized, there are currently limited studies of patients with AD to guide clinical management of sleep disturbances. This targeted review will inform clinicians of the potential therapeutic agents available to manage sleep disturbances and will review literature relevant to improving the sleep of children and adults with AD. On the basis of our clinical experience and the limited data available, we provide a suggested algorithm for clinicians treating sleep problems associated with AD, but clearly more studies are needed to both further characterize the sleep of patients with AD and to test the efficacy and effectiveness of candidate agents in clinical trials. (*J Allergy Clin Immunol* 2006;118:198-201.)

Key words: Atopic dermatitis, eczema, sleep, sedatives, hypnotics, children

Atopic dermatitis (AD) is a chronic skin disease that affects up to 17% of children¹ and 2% to 3% of adults.² AD is associated with dry, easily irritated skin and can range from mild disease to almost total body involvement. Disturbed sleep is commonly reported both by parents of pediatric patients³ and by adult patients.⁴ These subjective reports of disturbed sleep have been corroborated by observational studies demonstrating that children with AD awaken more often and sleep less throughout the night; adults with AD show a similar pattern.⁴ The most obvious explanation for sleep difficulties is that scratching is disrupting sleep. Several groups have examined this through the use of actigraphy and found increased movement during the night in patients with AD^{5,6} compared with control subjects. Benjamin et al⁷ also used infrared video and found that not only were patients with AD scratching, but they were also making other complex movements, such as rubbing, that could potentially damage the skin.

There might be an association between sleep disturbance and the severity of AD.³ More severe disease can lead to more intense itching and, in addition, to increased inflammatory mediators. There is evidence from human and

Abbreviation used

AD: Atopic dermatitis

animal studies suggesting that inflammatory mediators directly affect sleep; for example, several cytokines have been implicated in changes in sleep.⁸ Circadian fluctuations in inflammatory mediators (ie, the increase in inflammation during the night) might also account for the increased sensation of itching at night reported by many patients.

Regardless of the cause, disturbed sleep can have many negative consequences, including impaired motor and cognitive function and changes in mood.⁴ Patients and families also report a lower quality of life that is related to problems with sleep.⁴ In addition, the excoriations and exacerbation of skin disease that can occur during the night are distressing to patients, their families, and the medical team. Given the negative effects of disturbed sleep for patients with AD, providing an effective therapy for sleep disturbances and nocturnal scratching is therefore important.

Despite increasing recognition of the frequency and negative effect of sleep problems in patients with AD, there are few published studies that have examined the efficacy of somnolent therapies for patients with AD. One carefully conducted but small study of 10 patients examined the effects of nitrazepam (a benzodiazepine not available in the United States) on nocturnal scratching.⁹ Although nitrazepam reduced the frequency of scratching episodes, the duration of episodes increased, and therefore the total time scratching was unchanged. In addition, there was no difference between the skin condition of patients taking nitrazepam and placebo. An important observation from this study was that patients taking nitrazepam reported improved sleep and decreased scratching, even though direct observation revealed no change in the total time scratching. Actigraphy or direct observation might therefore be important in future studies and for clinicians when determining the efficacy of an intervention. Although not a direct intervention for sleep, other studies have found that effective anti-inflammatory treatment of AD can improve sleep; for example, children treated with pimecrolimus cream demonstrated skin improvement that correlated with improved sleep.¹⁰

Clinicians wishing to target the disturbed sleep of patients with AD are therefore left to make clinical decisions on the basis of limited evidence. The following reviews the relevant literature regarding sedative-hypnotic medications and supplements, including those with H₁ receptor antagonist activity, benzodiazepines, nonbenzodiazepine hypnotics, chloral hydrate, clonidine, and melatonin.

From the Department of Pediatrics, National Jewish Medical and Research Center, and the Department of Psychiatry, University of Colorado at Denver and Health Sciences Center.

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Reprint requests: Kim Kelsay, MD, National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206. E-mail: kelsayk@njc.org.

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HISTAMINE AND ANTIHISTAMINES

Clinicians consider the first-generation H₁ receptor antagonists, or antihistamines, for treatment of sleep problems associated with AD for several reasons. In addition to antagonizing the inflammatory effects of histamine released from mast cells and basophils, the first-generation H₁ receptor antagonists can cross the blood-brain barrier and affect histamine's role in maintaining central nervous system arousal.¹¹ Diphenhydramine (Benadryl; Pfizer, New York, NY) and hydroxyzine (Atarax and Vistaril; Pfizer) are the most commonly used antihistamines for sedation. Unfortunately, there might be tolerance to the sedating effects, as suggested by studies involving hydroxyzine and diphenhydramine in which subjects reported sedation after an initial dose of medication but no sedation after 1 week or 4 days of therapy.^{12,13} These studies did not examine whether tolerance occurs when the medication is given once a day rather than throughout the day. Another area not examined is the report by patients and clinicians that switching from one first-generation antihistamine to another after the sedating effect has diminished provides temporary improvement in sedation. Of note, the first-generation H₁ antagonists are also muscarinic receptor antagonists and through this can exert anticholinergic side effects, including blurred vision and dry mouth. Hydroxyzine and diphenhydramine are both approved for children and available in liquid form.

Doxepin (Sinequan; Pfizer), a tricyclic antidepressant, is chosen to aid the sleep of patients with AD because it has the highest H₁ receptor antagonist activity among the tricyclic antidepressants and is therefore the most sedating. In addition, doxepin is also chosen because of its anxiolytic and antidepressant effects. However, the dose used to help with sleep is generally lower than the dose necessary for antidepressant effects, and in our experience patients can have difficulty tolerating the side effects of hypotension and daytime sedation with higher doses. If a higher dose is desired, we recommend starting with 10 mg for children and 25 mg in adults and titrating up on the basis of clinical effect. Unfortunately, tolerance also can develop to the sedating effects of antidepressants.¹⁴ Doxepin is available in a liquid form for children, and the approved use is for depression in adolescents and adults.

BENZODIAZEPINES AND NONBENZODIAZEPINE HYPNOTICS

Benzodiazepines act through the gamma-aminobutyric acid-A-benzodiazepine receptor and have been shown to reduce sleep latency and increase total sleep time, but negative effects can include changes in sleep architecture.¹⁵ Clinicians might choose benzodiazepines for patients with AD for their anxiolytic properties in addition to their sedating effects. Negative side effects can include muscle relaxation and memory problems. For patients with asthma, muscle relaxation might place them at increased risk for respiratory compromise during sleep. Benzodiazepines also carry the risks of development of tolerance to the

sedating effects, rebound worsening of sleep problems on discontinuation, and addiction. Several studies have found these risks to be minimal in adults treated for insomnia, but this has not been studied in children.¹⁴ Avoiding the use of shorter-acting benzodiazepines, especially in anxious patients, might minimize the risk of addiction.

At the current time, eszopiclone (Lunesta; Sepracor Inc, Marlborough, Mass), a nonbenzodiazepine hypnotic, theoretically has a better risk-benefit profile than the benzodiazepines. Studies have demonstrated a lack of rebound phenomenon, both over the short and long term.^{16,17} Eszopiclone also has a longer half-life than the other nonbenzodiazepine hypnotics available in the United States, zolpidem (Ambien; Sanofi-Aventis Group, Bridgewater, NJ) and zaleplon (Sonata; King Pharmaceuticals Inc, Bristol, Tenn), although a sustained release form of zolpidem (Ambien CR; Sanofi-Aventis Group) is now available. Eszopiclone is effective not only in reducing sleep latency but also in decreasing wake time and awakenings without changing sleep architecture. Eszopiclone and zolpidem are labeled for use in adults and not available in a liquid form.

CHLORAL HYDRATE

Chloral hydrate also acts through the gamma-aminobutyric acid receptor. High doses can directly open the membrane chloride channel, leading to respiratory suppression and cardiovascular instability. Chloral hydrate therefore has a low therapeutic window, and we suggest 1 night of in-hospital observation with children before using this medication on a brief outpatient basis. Again, tolerance to the sedating effects can develop. Chloral hydrate is approved for use in children.

MELATONIN

Melatonin is secreted by the pineal gland in a circadian rhythm that might be important in regulating sleep phase. There is controversy about the sleep-promoting effects of melatonin (see Scheer and Czeisler¹⁸ for a review of this literature). Two rigorous meta-analyses were recently performed. One combined all studies and found melatonin to have a small but statistically significant effect on sleep onset, duration, and efficiency.¹⁹ In the other study the categorization of study populations led to the conclusion that there is evidence to support the use of melatonin in persons with delayed sleep-phase syndrome.²⁰ In addition, melatonin has also been found to be effective (with minimal adverse effects) in a population of children with sleep-onset insomnia.²¹ It is important to note that the National Sleep Foundation has warned against the use of melatonin in patients with immune problems because of its ability to enhance immune function.²² Patients or parents should be informed that melatonin is not a medication and is not regulated as such through the US Food and Drug Administration.

CLONIDINE

Clonidine (Catapres; Boehringer Ingelheim Pharmaceutical Inc, Ridgefield, Conn) is labeled for children and

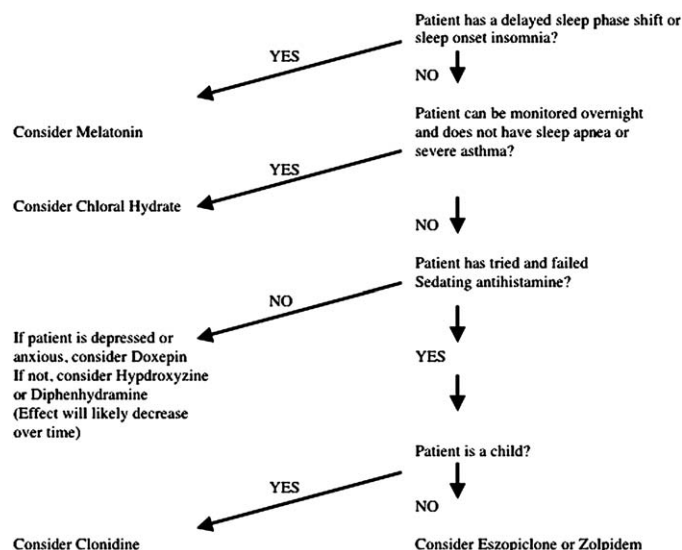


FIG 1. Suggested algorithm for initial choice of medication to improve sleep disturbance of children and adults with AD.

adults as an antihypertensive agent and acts through stimulation of the α_2 -adrenoreceptors in the brain stem. Clonidine also decreases sleep latency, and there is conflicting evidence regarding its effect on sleep architecture, which might be related to differing effects with different doses.^{23,24} Blood pressure should be monitored, and patients should be cautioned that abrupt discontinuation of the dose after regular use might lead to hypertension.

CLINICAL ALGORITHM

On the basis of the above and our clinical experience, we have developed a suggested algorithm (Fig 1) to help make clinical decisions regarding the use of sleep medication. This algorithm is applicable to patients who are experiencing disturbed sleep and scratching during the night in the context of an exacerbation of AD. This algorithm assumes that the above patients are receiving appropriate care for their AD, including skin hydration, control of inflammation, and treatment of superinfections. Given this care, most patients will need only short-term help with their sleep (2-7 days). The algorithm helps clinicians make an initial choice of medication. A partial response might indicate a higher dose is needed, whereas daytime sedation might indicate a lower dose is needed. Patients who receive no benefit from a medication or who experience disinhibition, distress, or both with chloral hydrate or the nonbenzodiazepine hypnotics should switch to another class of medication. Patients should be informed of the risks and benefits of a medication and whether a medication is to be used off label. It is our experience that although medication might be helpful, a goal of 8 hours of uninterrupted and scratch-free sleep might be unrealistic, especially for the first few nights of treatment, during a severe AD exacerbation. A more realistic target is 5 to 6 hours of sleep with decreased scratching. As AD improves, the sleep should improve,

and patients should no longer need a sleep aid. The long-term goal is to provide patients with a medication that they can use briefly during future AD exacerbations. Patients who have a prolonged sleep disturbance not related to worsening of their AD need a complete evaluation of their sleep, behavior, and emotional state.

In deriving this algorithm, we weighed the efficacy and other benefits of using sleep agents over a week or less against the risks for patients with AD. Unfortunately, because there are no studies of agents to target sleep in patients with AD and few studies of sleep agents with children in general, we relied on studies from other populations, mostly adults with insomnia. Eszopiclone and zolpidem have the greatest efficacy with the least side effects in treating adults with insomnia, but other symptoms and problems common to patients with AD might indicate another agent should be considered earlier in the algorithm. For example, agents with H_1 antihistamine properties are considered earlier in the algorithm because clinicians treating patients with AD are often targeting both inflammation and sleep. Other problems reported by many of our patients include symptoms of depression and anxiety. Therefore doxepin is also included earlier in the algorithm than eszopiclone and zolpidem. The high rate of anxiety symptoms reported in the patients with AD in our clinic might increase the risk of addiction in this population. The benzodiazepines are discussed in this article because they are possible choices when treating sleep problems but are not included in the algorithm because of the risk of addiction. Other clinicians might assess this risk differently and choose to include the benzodiazepines among options for treating this population. Many of our patients report a phase shift component to their sleep disturbance. Although controversial, there does appear to be evidence to support the use of melatonin for delayed phase shift in adults and children (see earlier),

and thus melatonin is included in the algorithm. As also mentioned earlier, we are targeting sleep disturbances over several days, until aggressive skin care begins to minimize nocturnal symptoms. Tachyphylaxis is therefore less of a concern than would be the case when treating primary insomnia, and nonaddictive agents, such as chloral hydrate, remain in the algorithm. Finally, chloral hydrate, the antihistamines, doxepin (in adolescents), melatonin, and clonidine, have all been studied in children (although some for other indications besides sleep), thus allowing clinicians to estimate the side effects or risks. Eszopiclone and zolpidem have not been studied in children, and for this reason, our algorithm does not include these agents as first-line choices for children. Clinical failure of several other agents might lead clinicians to reconsider this risk against the potential benefit.

CONCLUSION

The current literature demonstrates a need for effective treatment of sleep problems associated with AD. Sleep problems are common in patients with AD and are associated with scratching. In addition to the damage done to the skin by scratching, poor-quality sleep can have many other negative effects, including diminished quality of life for patients and their families, as well as a negative effect on motor and cognitive function. Despite our knowledge regarding poor sleep, little is known about the sleep architecture of patients with AD. This is currently being investigated (B. Bender, personal communication, May 2006) and will inform therapeutic choices as different medications appear to have different effects on sleep architecture.

With our (limited) current knowledge regarding sleep and AD, the preferred properties of a sedative medication should include decreased sleep latency and a duration of action that approaches 6 to 8 hours and therefore decreases awakenings and increases total sleep time. A minimal risk of addiction, rebound effects, and daytime sedation are also important preferred features of a medication for both children and adults. Patients and families might also have their own priorities with respect to these medications (for an excellent review of pediatric sleep pharmacology, see Pelayo et al²⁵). Given the limitations of self-report for sleep and scratching, clinicians should monitor effectiveness not only on the basis of patient or parent report but also by using objective measures, such as actigraphy.

Studies suggest that sleep improves as the skin improves, but this is another area that needs further investigation and will affect therapeutic choices for sleep problems of patients with AD. Finally, as we gain more knowledge about sleep in patients with AD, we can choose agents to study in randomized, double-blind placebo trials and build an evidence base to inform clinical decisions.

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REFERENCES

1. Boguniewicz M. Atopic dermatitis: beyond the Itch that rashes. *Immunol Allergy Clin North Am* 2005;25:333-51.

2. Leung D, Nicklas R, Li J, Bernstein IL, Blessing-Moore J, Boguniewicz M, et al. Disease management of atopic dermatitis: an updated practice parameter. *Ann Allergy Asthma Immunol* 2004;93(suppl):S1-S7.
3. Chamlin S, Mattson C, Frieden I, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005;159:745-50.
4. Bender B, Leung D. Sleep disorders in patients with asthma, atopic dermatitis, and allergic rhinitis. *J Allergy Clin Immunol* 2005;116:1200-1.
5. Bender B, Leung S, Leung D. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003;111:598-602.
6. Bringhurst C, Waterston K, Schofield O, Benjamin K, Rees J. Measurement of itch using actigraphy in pediatric and adult populations. *Am Acad Dermatol* 2004;51:893-8.
7. Benjamin K, Waterston K, Russell M, Schofield O, Diffey B, Rees J. The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use. *J Am Acad Dermatol* 2004;50:33-40.
8. Kapsimalis F, Richardson G. Cytokines and normal sleep. *Curr Opin Pulm Med* 2005;11:481-4.
9. Ebata T, Izumi H, Aizawa H, Kamide R, Niimura M. Effects of nitrazepam on nocturnal scratching in adults with atopic dermatitis: a double-blind placebo-controlled crossover study. *Br J Dermatol* 1997;138:631-4.
10. Leo H, Bender B, Leung S, Vu Tran Z, Leung D. Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic dermatitis. *J Allergy Clin Immunol* 2004;114:691-3.
11. Timmerman H. Factors involved in the absence of sedative effects by the second-generation antihistamines. *Allergy* 2000;55:5-10.
12. Levander S, Stahl-Backdahl M, Hagermark O. Peripheral antihistamine and central sedative effects of single and continuous oral doses of cetirizine and hydroxyzine. *Eur J Clin Pharmacol* 1991;41:435-9.
13. Richardson G, Roehrs T, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol* 2002;22:511-5.
14. Krystal A. The changing perspective on chronic insomnia management. *J Clin Psychiatry* 2004;65(suppl 8):20-5.
15. Holbrook A, Crowther R, Lotter A, Cheng C, Kink D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000;162:225-33.
16. Rosenberg R, Caron J, Roth T, Amato D. As assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep* 2004;6:15-22.
17. Roth T, Walsh J, Krystal A, Wessel T, Roehrs T. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med* 2005;6:487-95.
18. Scheer A, Czeisler C. Melatonin, sleep, and circadian rhythms. *Sleep* 2005;9:5-9.
19. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep* 2005;9:41-50.
20. Buscemi N, Vandermeer B, Pandya R, Hooton N, Tjosvold L, Hartling L, et al. Melatonin for treatment of sleep disorders. Summary, evidence report/technology assessment No. 108 (prepared by the University of Alberta Evidence-based Practice Center, under Contract No. 290-02-0023). Rockville (MD): Agency for Healthcare Research and Quality; 2004. AHRQ Publication No. 05-#002-1.
21. Smits MG, Van Stel H, Van Der Heijden K, Meijer AM, Conen A, Kerkhof G. 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;42:1286-93.
22. Touitou Y. Human aging and melatonin: clinical relevance. *Exp Gerontol* 2001;36:1083-100.
23. Danchin N, Genton P, Atlas P, Anconina J, Leclerc J, Cherrier F. Comparative effects of atenolol and clonidine on polygraphically recorded sleep in hypertensive men: a randomized, double-blind, crossover study. *Int J Clin Pharmacol Ther* 1995;33:52-5.
24. Miyazaki S, Uchida S, Mukai J, Nishihara K. Clonidine effects on all-night human sleep: opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion. *Special Clin Neurosci* 2004;58:138-44.
25. Pelayo R, Chen W, Monzon S, Guilleminault C. Pediatric sleep pharmacology: you want to give my kid sleeping pills? *Pediatr Clin North Am* 2004;51:117-34.