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Primary Insomnia: Treatment Options, New and Old

Learning Objectives

1. Describe the health consequences associated with insomnia.
2. Describe the normal sleep cycle.
3. Define primary insomnia.
4. Denote side effects associated with specific hypnotics.
5. Identify drugs that have been shown to be safe and effective in the treatment of primary insomnia.

Introduction

In January 1965, Randy Gardner, an 18-year-old high school student, broke the Guinness Book of World Records for longest continuous time awake by staying awake for 264 hours, or 11 straight days.¹ Unlike Randy Gardner, who was intentionally trying to stay awake, a significant number of people have problems each night going to sleep, staying asleep, or feeling rested with they arise. Approximately 20% of Americans have intermittent or chronic insomnia.² Studies in China, Japan, Finland, Mexico, Canada, Sweden, Norway, France, Great Britain, Italy, Germany and South Korea all have shown a similar prevalence of insomnia.³ In the US direct insomnia-related costs are estimated to be \$14 billion and indirect costs are estimated to be to \$28 billion.² Individuals suffering from insomnia experience fatigue, mood disturbances, cognitive and memory impairments which lead to an overall decreased quality of life and social functioning.^{4,5} Frequent use of medical services, chronic health problems, increased drug use, and perceived poor health are typical of persons with insomnia.² Insomnia has also been associated with heart disease, hypertension, anxiety, depression, and musculoskeletal problems.²

About the Author:

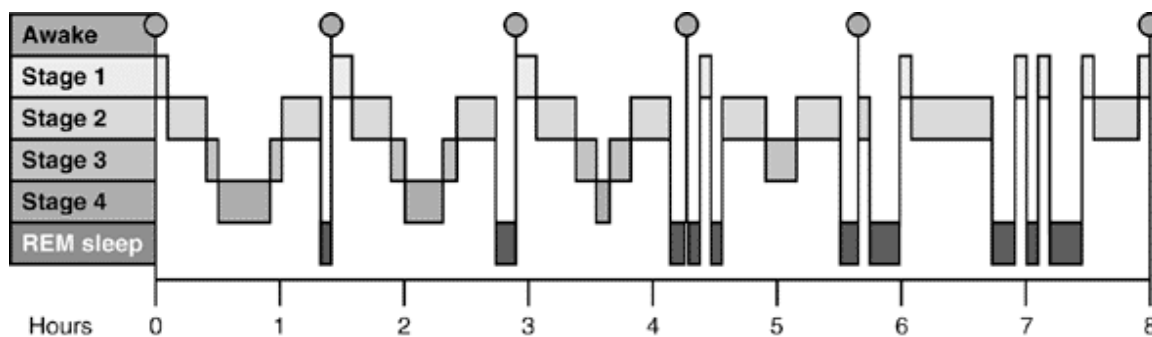


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Sleep

For most people, a good night's rest occurs when they cycle through the five distinct stages of sleep four to six times a night. The five distinct stages of sleep are: rapid eye movement (REM) sleep and stages 1, 2, 3, and 4 of non-rapid eye movement (NREM) sleep.⁶ Normal sleep is a cyclic phenomenon consisting of 90-minute cycles of REM and NREM sleep patterns of varying lengths of time throughout the night (Fig. 1).^{7,8} When a person begins falling asleep, transitioning from wakefulness to sleep, they enter stage 1 NREM sleep. Generally, after one to seven minutes in stage 1 NREM sleep a person enters stage 2 NREM sleep for 10 to 30 minutes.^{8,9} Slow-wave sleep, seen in stages 3 and 4 NREM sleep lasts for 30-45 minutes, is the deepest level of sleep and makes up about 10-20% of total sleep time. Most "deep sleep," stage 3 and 4 NREM sleep, occurs in the first half of the night with the deepest sleep occurring in the first several hours.¹⁰ When a person becomes deprived of sleep, the body tries to make up for the deprivation by increasing the amount of time spent in stage 3 and 4 NREM sleep.⁸ REM sleep, also known as dream sleep, follows stage 4 NREM sleep although there may be a brief return to stage 2 NREM sleep before REM sleep begins. The first REM cycle lasts just four to eight minutes and often ends with a brief body movement and the beginning of a new sleep cycle.⁹ REM sleep becomes longer and more intense toward the morning wake hours whereas stages 3

Figure 1. From *The Merck Manual of Diagnosis and Therapy*, Edition 17, Section 14. Neurologic Disorders, Chapter 173. Sleep Disorders, (<http://www.merck.com/mrkshared/mmanual/figures/173fig1.jsp>) edited by Mark H. Beers and Robert Berkow. Copyright 1999 by Merck & Co., Inc., Whitehouse Station, NJ.



and 4 NREM sleep become shorter^{9,11} Dreaming occurs mainly in REM sleep with 85% of subjects reporting dreaming when awoken from REM sleep.⁸ The function of REM sleep is not known but it is speculated that it may play a part in consolidation of memories and brain development.⁸ The proportion of REM sleep remains constant throughout life whereas the deep, restorative NREM stages 3 and 4 sleep diminish with age and stage 4, the deepest sleep, is virtually non-existent in the elderly.⁸

Insomnia

Surprisingly, researchers have not been able to discover or agree upon why we sleep or the function of sleep.^{8,9} Anyone who has experienced a night or two of insomnia, however, knows the importance of sleep to personal well being. Primary insomnia, is defined as difficulty initiating or maintaining sleep or non-restorative sleep, lasting for a least 1 month and causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.⁶ For a diagnosis of primary insomnia these disturbances cannot be due to another sleep disorder (e.g. sleep apnea or restless leg syndrome), mental disorder (e.g. depression), medical condition (e.g. chronic obstructive pulmonary disease), or due to direct physiological effects of a substance (e.g. alcohol or other medications). Psychophysiologic or conditioned insomnia, idiopathic or childhood-onset insomnia, sleep state misperception insomnia, poor sleep hygiene insomnia, fatal familial insomnia, and insomnia due to other extrinsic factors are all types of primary insomnia.^{12,13} Treating primary insomnia before it becomes a chronic problem is important because the direct and indirect costs of insomnia to society are great and it is a major risk factor for the development of depression, anxiety disorder, and substance abuse.^{2,4-6,12}

Treatment of Insomnia

Insomnia is the second most common complaint heard in the primary care setting.¹² Consequently, primary care providers must select and provide treatment options for patients suffering from insomnia. Cognitive-behavioral and pharmacological therapy are both recommended treatments for primary insomnia.^{10,14,15} Within both categories, there are a number of treatment options.

Cognitive-Behavioral Therapy

Sleep hygiene education, stimulus control therapy, sleep restriction therapy, relaxation training and cognitive therapy are the most commonly used cognitive-behavioral treatments for primary insomnia (Fig. 2).¹⁵ Often, a combination of these techniques is utilized. A meta-analysis comparing stimulus control and sleep restriction therapies to pharmacological therapy in treating persistent primary insomnia found little difference between the two treatments.¹⁶ In fact, cognitive behavioral therapies showed a slight advantage in decreasing

ing latency to sleep onset (LSO), the time it takes to fall asleep. Likewise, an evidence based review on chronic insomnia and its management by the Agency for Health Care Research and Quality concluded that cognitive-behavior therapy significantly increased sleep quality and efficiency and significantly decreased wakefulness after sleep onset.²

Fig. 2 Sleep Hygiene Instructions

1. Sleep only as much as you need to feel refreshed during the following day.
2. Get up at the same time each day, 7 days a week.
3. Exercise regularly.
4. Make sure your bedroom is comfortable and free from light and noise.
5. Make sure that your bedroom is at a comfortable temperature during the night
6. Eat regular meals and do not go to bed hungry.
7. Avoid excessive liquids in the evening.
8. Cut down on all caffeine products.
9. Avoid alcohol, especially in the evening.
10. Smoking may disturb sleep..
11. Do not take your problems to bed. Plan some time earlier in the evening for working on your problems.
12. Train yourself to use the bedroom only for sleeping and sexual activity.
13. Do not try to fall asleep.
14. Put the clock under the bed or turn it so that you cannot see it.
15. Avoid naps.

Pharmacological Therapy

Over-the-Counter Products

Alcohol, antihistamines, L-tryptophan, melatonin and valerian are often used for self-medication. While alcohol has been shown to decrease the latency to sleep onset, as the blood alcohol level falls, it causes sleep fragmentation. It is also known to worsen snoring and sleep apnea and can lead to alcohol dependence; therefore, alcohol is not a recommended solution for insomnia.^{4,17}

Over-the-counter antihistamines are the most widely used, recommended, and prescribed medications for insomnia.¹⁴ There is little or no evidence, however, documenting the safety and effectiveness of antihistamines in treating insomnia.^{14,18} Antihistamines are not a recommended treatment of insomnia because of lack of proven efficacy and significant side effect profile that includes cognitive impairment, urinary retention, and tolerance.^{12,18}

An evidence-based review by the Agency for Healthcare Research and Quality (AHRQ) concluded that there was insufficient evidence to evaluate the safety and efficacy of L-tryptophan and valerian in treating chronic insomnia.² The same evidence based review concluded that there is some evidence that melatonin is effective in some subsets of chronic insomniacs.² Similar to antidepressants, in 8 studies, melatonin showed a small but statistically significant difference of 8 minutes in sleep onset latency compared to placebo. Study estimates ranged from roughly 20 minutes improvement in sleep onset latency to 10 minutes detriment. Unlike antidepressants and benzodiazepines, however, melatonin was not associated with significant adverse reactions.

Prescription Drugs

Antidepressants

Antidepressants have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia; however, trazodone, amitriptyline and trimipramine are frequently prescribed for this purpose.¹⁴ One evidence-based review, however, concluded that there is some evidence for the effectiveness of treating chronic insomnia with antidepressants, more studies are needed.² Currently, antidepressants are not recommended by many experts for treatment of primary insomnia because of lingering daytime sedation, anticholinergic side effects, and the possibility of aggravating restless leg syndrome by tricyclic antidepressants.¹⁴

Benzodiazepines

Estazolam, flurazepam, nitrazepam, quazepam, temazepam, and triazolam have been approved by the FDA for the short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.¹⁹ The onset of action, half-life, and type of insomnia are relevant factors in determining the appropriate benzodiazepine for an individual. Temazepam (Restoril®, Mallinckrodt) and estazolam (ProSom®, Abbott) are recommended for persons who have problems staying asleep or going back to sleep after being awoken.²⁰ Triazolam, because of its short half-life, is best for persons who have more problems initially falling asleep than staying asleep. Lorazepam (Ativan®, Wyeth-US) is indicated for insomnia due to anxiety or transient situational stress.¹⁹ In one evidence-based review, benzodiazepines were determined to be safe and effective in the treatment of chronic insomnia even though they were associated with a significantly greater number of adverse events compared to placebo.² In this review, the most commonly reported adverse events were somnolence, headache, dizziness, nausea, and fatigue, but there were no reports of falls, injury or death.² Other side effects of concern are possible daytime residual effects related to sedation, rebound insomnia, withdrawal symptoms, and tolerance.^{2,21} The risk of these adverse effects occurring in an individual are related to dose, elimination half-life, and age, as these effects can be more pronounced in the elderly.²¹ There is also a potential for abuse, especially in patients with a history of drug or alcohol abuse.²¹ Reduction of slow-wave sleep, the deepest and most restorative sleep, is also a side effect of all benzodiazepines.²

Benzodiazepine Receptor Agonists (Non-benzodiazepines)

Zaleplon (Sonata®, Wyeth Laboratories), zolpidem (Ambien®, Searle-US) and eszopiclone (Lunesta™, Sepracor) are hypnotics that are structurally unrelated to benzodiazepines yet similar in the proposed mechanism of action. The exact mechanism of action of eszopiclone is not known, but it is believed the sedative properties are due to its binding to GABA-receptor complexes at binding domains located close to, or allosterically coupled to, benzodiazepine recep-

tors.²² Zaleplon and zolpidem are thought to bind to the GABA_A subunit alpha-1 complex interacting preferentially with the omega-1 receptors.^{23,24} The Agency for Health Care Research and Quality has stated that based on indirect comparisons, non-benzodiazepine hypnotics appear to be safer than benzodiazepines in treating chronic insomnia.²

Eszopiclone

Racemic (RS)-zopiclone has been available in the United Kingdom since 1989²⁵ and is available in over 80 countries worldwide for the treatment of insomnia.²⁶ Although zopiclone has never been approved for use in the US, eszopiclone was approved by the FDA on December 15, 2004. Eszopiclone or (S)-zopiclone, is the active isomer of racemic zopiclone. Six randomized-controlled trials, 5 in patients with chronic insomnia and 1 in a transient insomnia model, were submitted to the FDA to support eszopiclone's approval request.²⁷ These trials showed significant between-treatment differences for the 2 mg and 3 mg doses in non-elderly adults, and for the 1 mg and 2 mg doses in the elderly.²⁷ The 3 mg dose was shown to have the best results for treating both sleep latency and sleep maintenance in non-elderly adults. Unpleasant taste was the most frequently reported side effect (26%) and appeared to be dose related.²⁷ Dry mouth, dizziness, infection, hallucinations, and decreased libido were also noted to be possibly dose related.

Initially, the neurobiological review team for the FDA Center for Drug Evaluation and Research (CDER) did not want to grant eszopiclone an approvable status based on carcinogenicity concerns seen in animals, and a disproportionate number of malignancies seen in one of the pivotal trials (16-24 cases/593 in the eszopiclone group versus 0/195 in the placebo group).²⁷ After more explanation from the drug sponsor on the malignancies seen in the pivotal trial, the neurobiological review team concluded that in the controlled clinical trials, the data did not suggest a signal for the occurrence of malignancies, and recommended approval by the FDA.²⁷

Eszopiclone is rapidly absorbed, with peak plasma concentrations within 1 hour of oral administration and a terminal half life of 6 hours.²² The inactive primary plasma metabolites are (S)-zopiclone-N-oxide and (S)-N-desmethyl zopiclone.^{22,26} A randomized study to determine the effect of food on the pharmacokinetics of a single 3 mg dose of eszopiclone found that a high fat content meal decreased the C_{max} by 22-22% and the t_{max} by 1 hour. The terminal half-life was not affected.^{26,28} The sleep onset of eszopiclone may thus be delayed by taking eszopiclone with or after a meal. Pharmacokinetic studies in elderly patients showed C_{max} was increased up to 45%, t_{max} was increased from 35-62% and AUC was doubled compared to normal subjects.^{22,26} Consequently, the recommended starting dose for elderly patients is 1 mg.²²

Zaleplon and Zolpidem

Zolpidem and zaleplon have been available in the U.S. much longer than eszopiclone. Zaleplon was approved for the short term treatment of sleep onset insomnia on August 13, 1999.^{29,30} During clinical trials it was shown to decrease the time to sleep onset, but it was not shown to increase the total amount of sleep time or decrease the number of awakenings during the night.³¹ Zolpidem was approved by the U.S. FDA on December 16, 1992, for the short term treatment of insomnia.²⁴ Recently, zolpidem has been in the news with reported cases of sleep-walking, driving and eating.³² In the zolpidem new drug application review of the clinical trials submitted to the FDA, reviewers requested that the drug sponsor submit more detailed information on the neurologic and psychiatric adverse effects seen during the clinical trials of zolpidem.³³ There were 30 reports of amnesia/memory loss, 29 euphoria, 14 depression, 10 hallucinations and 30 'other'. In the studies submitted with the new

drug application, the incidence of psychiatric/neurologic effects was 8.7% (93/1058). The doses ranged from 5 to 60 mg. The medical officer who reviewed the cases determined that most of the cases of hallucination, amnesia/memory loss, and depression that occurred at the recommended dose could be explained by the patient's life situation rather than an effect of zolpidem, and approval of zolpidem was recommended. A number of cases of sleep-walking and sleep-eating have been reported in the medical literature.^{34,35,35-37} Of particular interest, in 5 of the reported cases, the patients were also receiving a serotonin-reuptake-inhibitor.³⁶⁻³⁹ In all cases, the sleep-walking abated when the zolpidem was discontinued.

Indiplon

Indiplon is a GABA-A potentiator with high affinity for the alpha-1 subunit.⁴⁰ Phase III studies have been completed and submitted to the FDA with the initial hope for a May 2006 approval date.⁴⁰ However a May 15 action from the FDA to determine that the 5 mg and 10 mg capsules were approvable, but the 15 mg XR tablets were not, indicates a delay in the process. Abstracts have been published of two posters that reported the results from 4 different double-blind placebo-controlled indiplon trials in treating women with primary insomnia.^{41,42} These posters were presented by representatives of Neurocrine Biosciences, the developer of this drug. There is insufficient detail in the published abstracts to judge the clinical significance of the results of these studies. The doses used in the studies ranged from 5mg to 20 mg nightly, and the duration of treatment ranged from two weeks to three months. The sample size for the studies ranged from 156 to 408 subjects. Women in two of the studies ranged in age from 21 to 64 years, and in the other two studies were 65 years of age or older. Two of the studies were designed to primarily evaluate the effects of the drug on latency to sleep onset and two used total sleep time as the primary outcome measure. All of the measures were based on patient reported times. Although the authors claimed these studies show that indiplon was effective at reducing the time to sleep onset, and increasing total sleep time, the details are not sufficient in the published abstracts to judge the clinical value of these effects. No details were reported on any adverse effects in these studies. The marketing status of this drug remained unclear at the time this article was completed.

Melatonin Receptor Agonists

Ramelteon

Ramelteon (Rozerem[®], Takeda Pharmaceuticals America, Inc.), approved by the FDA on July 22, 2005, for the treatment of sleep onset insomnia, is a melatonin agonist that acts by binding to the melatonin M1 and M2 receptors with little or no affinity for the GABA receptor complex.^{43,44} Seven studies were evaluated in the new drug application clinical review of ramelteon.⁴⁵ Two studies were done in transient insomnia patients and 5 were done in patients with chronic insomnia. Doses ranged from 4 mg to 32 mg at bedtime. The primary efficacy variable in most of the studies was latency to persistent sleep (time to fall asleep) as measured objectively by polysomnography. In a few of the studies the primary efficacy variable was the latency to persistent sleep as measured subjectively by patient questionnaires and diaries. This was also used as a secondary measure in some of the studies. The medical officer who reviewed the data concluded that the studies objectively showed that ramelteon decreased the latency to persistent sleep time (based on polysomnography study) but that the subjective evidence (patient questionnaires) was inconsistent. While 8-19 minute decreases in latency to sleep onset may have been statistically significant, patients did not perceive the decreases to be of any significance. In treating insomnia, how a person perceives a drug to be working may be more pertinent than any objective laboratory measurements.

The most often reported side effects were headache, nausea, dizziness and next day somnolence. Three studies were also done to measure the effect of ramelteon on the endocrine system. In one of the studies, a small but statistically significant increase (> 40 mcg/L) in prolactin levels was observed in several patients receiving ramelteon. Because of the short duration of the study, causality of ramelteon could be neither proved nor disproved. Even mild prolonged hyperprolactinemia can lead to dysregulation of the reproductive axis and result in hypogonadism in men and women, and amenorrhea in women. Therefore, the medical officer recommended that as a Phase IV commitment, the drug sponsor do a further study to identify the extent and persistence of elevated prolactin levels in patients receiving ramelteon. It was also recommended that the drug sponsor set up a pregnancy registry and monitor the rate of neoplasms in chronic users of ramelteon. In pre-clinical data, there was a positive finding in an in-vitro chromosome aberration genetic toxicology study, and dose dependent development of hepatic tumors was seen in mice. The director of the division overseeing the approval did not believe that the recommendations to set up a pregnancy registry or to do a further study to evaluate hyperprolactinemia and tumor incidence in chronic ramelteon users were necessary but did think it was important to watch for signals of more significant morbidity in the post-marketing period and that both the division and the drug sponsor should monitor the post-marketing reports for these abnormalities for 5 years after the approval date.

Conclusion

Prescription sleep-aids are big business, and the business is likely to get bigger and more competitive. Five new drugs for the treatment of insomnia: gaboxadol (MK0928), eplivanserin (SR46349B), LY2422347, GW679769, are currently in Phase III and Phase II trials.⁴⁶ The New York Times reported that about 42 million sleeping pill prescriptions were filled in 2005, an increase of 60% from 2000.⁴⁷ This may be a reflection of the aging population or it may be an effect of the nearly \$300 million spent by pharmaceutical companies in advertising prescription sleep-aids in 2005 and people's willingness to take a pill to solve a problem.⁴⁷ There are times, when a sleep-aid may be helpful, but like all medications, there are costs and adverse effects as well as benefits associated with them. When treating primary insomnia, healthcare providers should not forget that cognitive-behavioral therapies have been shown to be effective as well. Many different treatment options are available for treating insomnia with varying degrees of proven safety and efficacy. Because of this fact, pharmacists knowledgeable in the treatment of primary insomnia can be of great help in guiding patients towards the best possible care.

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PRIMARY INSOMNIA: TREATMENT OPTIONS, NEW AND OLD

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Signature/Date

(circle the correct answer)

1. What percent of the population has been estimated to suffer from intermittent or chronic insomnia?
 - a. 5%
 - b. 10%
 - c. 15%
 - d. 20%
2. The deepest level of sleep is experienced during _____.
 - a. slow wave sleep
 - b. stage 1 NREM sleep
 - c. REM sleep
 - d. stage 2 NREM sleep
3. A small increase in prolactin levels was seen in one trial for which of the following drugs?
 - a. eszopiclone
 - b. gaboxadol
 - c. eplivanserin
 - d. ramelteon
4. Alcohol has been shown to increase the amount of deep sleep but has also been shown to cause _____.
 - a. sleep fragmentation
 - b. sleep cycles absent of REM sleep
 - c. increased drooling
 - d. sleep cycles absent of NREM sleep
5. One evidence-based review found that _____.
 - a. sedating antidepressants were more effective and better tolerated than benzodiazepines in treating primary insomnia
 - b. melatonin showed no efficacy in any treatment group in treating insomnia
 - c. benzodiazepines are safe and effective for the treatment of chronic insomnia
 - d. antihistamines are safe and effective for the treatment of chronic insomnia
6. In a study treating patients for insomnia, unpleasant taste was a side effect observed in 25% of patients taking which of the following drugs?
 - a. eszopiclone
 - b. ramelteon
 - c. sertraline
 - d. trazodone

7. All of the following have been shown to be safe and effective in treating insomnia EXCEPT:
 - a. cognitive-behavioral therapy
 - b. temazepam
 - c. antihistamines
 - d. eszopiclone
8. Which of the following benzodiazepines is recommended for patients having difficulty falling asleep?
 - a. temazepam
 - b. estazolam
 - c. quazepam
 - d. triazolam
9. The recommended starting dose of eszopiclone for elderly patients is _____.
 - a. 0.5 mg
 - b. 1 mg
 - c. 1.5 mg
 - d. 2 mg
10. Treating primary insomnia is important because it _____.
 - a. is a risk factor for depression
 - b. has been associated with hypertension
 - c. can result in a decreased quality of life
 - d. all of the above

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	Agree			Disagree	
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Generic Name Trade Name (FDA Therapeutic Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Alglucosidase alfa <i>Myozyme</i> (BIOL) (O)	Genzyme (Apr. 28, 2006)	ALGLUCOSIDASE ALFA 44000080 (0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Pompe disease. IV Infusion	GLYCOGENOSIS 271.0
Lubiprostone <i>Amitiza</i> (S)	Sucampo Pharma (Jan. 31, 2006)	LUBIPROSTONE 56120016 (1 citation)	Chronic constipation. Capsule	CONSTIPATION 564.0
Decitabine <i>Dacogen</i> (O)	MGI Pharma Inc. (May 2, 2006)	DECITABINE 10080410 (16 citations)	Myelodysplastic syndromes. Injection	NEOP, NOS-HEMAPOIESIS/ LYMPH 238.7

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P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

O = Orphan drug.

BIOL= Biological.

Selected Bibliography

Decitabine

Wijermans P, Lubbert M, Verhoef G, Bosly A, Ravoet C, et al. Low-dose 5-Aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter Phase II study in elderly patients. *J Clin Oncol.* 2000; 18:956-962. (*IDIS* Article Number 443264)

Investigators conducted a multicenter, Phase II study that consisted of 66 patients (median age 68 years) with myelodysplastic syndrome who received intravenous decitabine doses of 45 mg/m²/day for 3 days every 6 weeks up to a maximum of 6 cycles. Investigators reported a 49% rate of response for a median duration of 31 weeks, and myelosuppression as the most serious side effect.

Lubiprostone

Kelly K. Lubiprostone: a novel chloride channel activator for the treatment of constipation. *Formulary.* 2006; 41:118-129. (*IDIS* Article Number 550410)

This review provides information about lubiprostone's mechanism of action, pharmacokinetics, interactions, dosing and side effects, as well as safety and efficacy information reported in the clinical trials.



Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

Comments on a recent case report of possible low dose steroid associated reversible dementia by Sachs and Shulman¹ and on “steroid psychoses” and steroid dementia syndromes

Perspective from



an *IDIS* Subscriber

Introduction

The recent publication of a case report dealing with a patient's immediate recovery from a dementia syndrome, after discontinuing months of low dose prednisone therapy, should alert us to the real possibility of reversible steroid dementia. The patient had taken the initiative to increase his dose from 10 mg twice daily to 100 mg twice daily for at least three months, presumably to enhance the positive sense of well-being he had experienced when the prednisone was initiated. The patient was originally taking prednisone to treat his polymyalgia rheumatica. Subsequently he developed mania with psychotic features. Returning his prednisone dose to 10 mg twice daily and treatment with risperidone and valproic acid had little effect. He did not return to his previous normal mental state, instead he exhibited features consistent with early dementia. He was admitted to a psychiatric ward and underwent neurological testing and testing for possible infectious or toxic-metabolic causes for the persistent cognitive deficits. He was discharged but became more agitated and was subsequently admitted to a locked Alzheimer facility. The family sought another neurological opinion. The steroids were subsequently tapered and completely stopped with improvement in confusion almost immediately. I believe the most important aspect of the case is the five month long dementia-like syndrome, which persisted after his prednisone dose was reduced to 10 mg twice daily, and then further tapered to 3 mg daily. His dementia finally reversed two weeks after his prednisone was discontinued.

Early case series on mental disturbances with cortisone and ACTH

During the summer and fall of 1950 cortisone from Merck and Company and ACTH from Armour Laboratories first became generally available in the United States.² In 1955, Goodman and Gilman's 2nd edition³ described the recently discovered actions of corticosteroids on the central nervous system as well as a variety of mental status changes in patients with Cushing's disease and in patients who received ACTH or the new 11,17-oxysteroid compound.

Just two years later, Rome and Braceland⁴ published their observations on the psychological response(s) to ACTH, cortisone, hydrocortisone, and other corticosteroid compounds. They described a variety of syndromes ranging from a “mild increase in the sense of well-being, admitted only in response to direct questioning” to frankly psychotic behavior, mood alteration, or thinking disturbances. Sixty percent of the reports were described as Grade 1 or 2, which in their case series related to an increased sense of well being, an invariably elevated mood, increased motor activity and muscle strength and an increased appetite. Twenty to thirty percent of the reports were described as Grade 3, which included “every clinical type of psychiatric reaction to stress, short of overt psychosis.” Patients described as having Grade 3 responses could be profoundly lethargic and indiffer-

ent or exhibit excitement, restlessness or hypomania. The remaining ten percent of reactions were described as Grade 4 responses, which in their case series were limited to grossly psychotic reactions. They described the psychotic reactions to ACTH or steroids as “unexpectedly brief.” In most cases they had subsided within a few weeks of discontinuing steroid treatment. On multiple occasions Rome and Braceland observed the same psychological response in the same patient after repeated courses of ACTH or hydrocortisone.

Clark and colleagues⁵ also described mental disturbances associated with the use of cortisone and ACTH. They noted mental disturbances were not an uncommon complication of therapy with cortisone or ACTH. Their original case series was of 10 patients, all of whom completely recovered after treatment was discontinued. They went on to publish a second series of 13 additional cases, only 16 months later.⁶ Neither the absence of prior psychiatric history or tolerance of a previous course of treatment could assure the absence of a mental disturbance during subsequent treatment with ACTH or cortisone. Spontaneous recovery occurred in all cases, unless death intervened. In two cases “a relatively small amount of hormone was given before mental symptoms appeared.” In both of their reports, there was no relationship between the average dose or total dose and the duration or severity of the mental disturbance.

Case Reports-mental status changes associated with steroid use

Greeves⁷ described a 21-year-old female, with no history of psychological disturbance, who was referred to begin electrolysis for excessive body hair. She received a single dose of 5 mg prednisolone in the evening, a 2.5 mg dose the next morning and another 5 mg dose that evening. After her first dose she described “feeling in a daze,” after the second dose she reported feeling “dazed again and increasingly nervous,” and after the third dose she could not rest and had problems focusing her vision. The next morning she took her fourth dose and described the following event, “she saw a human arm come out of the sea and grab a policeman's leg which he then cut off with gardening shears.” She reported for electrolysis that morning and was described as distressed. Her prednisolone was discontinued. When seen the next day she had returned to normal. This case is considered to be remarkable for the low dose of the steroid and the speed of onset of the delusion.

Hollman and Allen⁹ described an 8-year-old girl treated for asthma with inhaled triamcinolone, three inhalations twice daily, followed by a five day course of prednisone 5 mg three times daily. Over the next few months there was a decline in school performance and exaggerated mood swings. On examination she had both clinical and laboratory features of steroid excess. Her steroid regimen was tapered and four months later her school performance and moodiness had improved.

Sharfstein and colleagues⁹, at the National Institute of Mental Health, describe three adult patients who developed behavioral abnormalities while on long term alternate day prednisone (60 mg/day) regimens. All three experienced mood elevation, lasting all day on the days they took prednisone, consistent with the criteria for a manic episode. On their off days they experienced mood changes consistent with a major depressive disorder. In two of the three patients the abnormalities were diminished when their prednisone dose was lowered to 50 mg despite continuing the alternate-day regimen. One of the patients experienced “difficulty concentrating, accomplishing simple arithmetic tasks and remembering four objects after three minutes”. The authors were most surprised by the wide swing from high to low mood within a narrow time frame and the consistent relationship to the day of prednisone administration. In their experience psychiatric symptoms associated with steroid use usually present between the second and third week of treatment, but on occasion can occur “almost immediately”. They warn that “the specific factor(s) which predispose some persons to the behavioral effects of steroids are not understood”.

Phalen¹⁰ described a 69-year-old man, with no personal or family psychiatric history, who developed a sixty day manic episode following a course of prednisone (tapered from 20 mg daily) for obstructive lung disease. Six months later he developed mania three weeks after beginning beclomethasone dipropionate nasal spray for allergic rhinitis. In addition to mania, he experienced visual and auditory hallucinations, was disoriented, and had poor short and long term memory. The patient’s steroid nasal spray was discontinued, he was treated with haloperidol for six weeks, and was sufficiently improved to be discharged home. At his ninety-day follow up only a few short term memory problems were noted.”

Cushing’s syndrome and neuro-psychiatric disturbances

Wolkowitz and colleagues¹¹ in their review of steroids and memory problems or psychosis in medical illness, include data from Starkman and colleagues reporting a “63% incidence of decreased concentration and an 83% incidence of impaired memory in this disorder (Cushing’s syndrome).” Standard medical texts include neuropsychiatric disturbances as a common manifestation of Cushing’s disease with a prevalence of from 6% to 40% depending on the specific type of disturbance. They describe problems with mood, cognition and less frequently psychosis.¹²

Steroids in healthy volunteers – neuro-psychiatric disturbances

Wolkowitz and colleagues¹³ gave 12 healthy volunteers (free of Axis I diagnoses for at least 2 years) placebo for 5 days, prednisone 80 mg daily for 5 days and placebo again for 7 days. Nine of the 12 subjects experienced behavioral changes including: hypomania, decreased sleep, loss of concentration, mild depression, and depersonalization. EEG changes which correlated with behavioral ratings suggested that biological factors might be responsible for the behavioral changes seen with prednisone. A decade later, Wolkowitz and colleagues¹⁴ again studied the effect of steroids in healthy medication free subjects and in a group of clinically depressed patients. They found a specific pattern of increased errors of commission in verbal memory tasks with no significant change in rates of errors of omissions. Their results suggest the possibility of “steroid specific” cognitive impairments.

Steroid dementia

Varney, Alexander and MacIndoe¹⁵ were the first to describe a “corticosteroid-induced mental disorder distinct from steroid psy-

chosis.” Their series of six patients (on 60 to 100 mg of prednisone daily) were seen at one hospital over a period of three years. Originally steroids were not suspected as causative agents of the mental status changes at the time of patient referral. They had been referred for neuropsychiatric testing because of unexpected improvement after diagnoses of Alzheimer’s disease. The fifth and sixth patients were referred to one of the authors (JM) for neuropsychiatric testing after resolution of a previous episode of steroid psychosis. The patients had substantial disturbances in memory retention, attention, concentration, and occupational performance. Three of the 6 patients had complained of changes in mental status but in the remaining 3 patients, changes in their mental status were clear only after formal mental status testing. None of the 6 patients were manifestly demented, amnesic, or disoriented, or appeared toxic or intoxicated. However each was impaired in relation to normal mental function. They point out that “patients of average intelligence in the early stages of Alzheimer’s disease are also known to be unaware of their mental status changes.” None of their patients had any symptoms of the so called steroid psychoses at the time the decline in their mental status was discovered. In 4 patients there was no prior history of steroid psychosis and in the other 2 the “steroid dementia like syndrome” persisted for a period of nine months in one and twenty-four months in the other patient, after the steroid psychosis had resolved. Their case series is consistent with the possibility of a “reversible steroid associated dementia like syndrome” unrelated to steroid psychosis.

Steroid dementia – possible long term effects after steroid withdrawal

Wolkowitz and colleagues¹¹ included several anecdotal cases of long lasting cognitive impairment following steroid treatment. They acknowledge that litigation related to the impact of mental impairment on disability is pending in some of the cases, which might cloud the issue. In one case an attorney who was prescribed high dose prednisone in error experienced steroid psychosis with mood changes which resolved promptly after steroid taper. However, “cognitive difficulties” kept her from returning to work for at least two years”. She complained of difficulty keeping track of information, e.g., she could not remember the first page of a book by the time she read the second page. Three independent neuropsychologists assessed her cognitive performance as consistent with bilateral hippocampal damage, likely of recent onset. Another case involved a 52-year-old research chemist whose job had required detailed literature reviews with innovative and abstract thinking with focused concentration. After treatment with prednisone for over a month (prednisone dose range 40–130 mg daily) followed by a three month tapering regimen, he developed problems with focus and memory. The memory difficulties have persisted for over two years. The patient now needs to carry a note pad with him to record significant details or events he would otherwise forget. He claims to have no difficulty with long term knowledge based memory. It has been over two years since steroid treatment was discontinued and the patient remains on disability.

Relationship of steroid dementia to “steroid psychosis”

Although steroid dementia has not been described in prospective controlled clinical trials, several case series and scattered anecdotal reports support its existence.^{1,6,15} Early writers suggested that steroid associated mental disturbances (dementia) occurred only in patients with prior psychiatric histories, or in patients with prior or recent steroid psychosis. Recent commentators have concluded that “steroid psychosis and steroid-related cognitive impairment may occur independently.”^{11,15} Ling and colleagues¹⁶ in their review of the psychiatric side effects of corticosteroid therapy, reported that “preexisting psychiatric illness does not seem to increase the likelihood of a reaction

(psychiatric) to corticosteroids. Most patients surveyed by Ling and colleagues¹⁶ had no history of mental disturbance in their past.

Conclusion

Cases of reversible dementia do exist. Cummings and colleagues¹⁷ list seventeen known drug causes of reversible dementia, including steroids, in their review. Cummings and colleagues concur with Lishman's¹⁸ definition of dementia in two contexts: to refer to primary dementing illnesses such as Alzheimer's and Pick's disease, and, in a much more general way, to refer to a clinical syndrome of chronic mental status impairments that may be caused by a large variety of illnesses.

A simple literature search of the last 15 years yielded 16 case reports of possible drug induced dementia from: memantine, carbamazepine, isoniazid, sertraline, thalidomide, methotrexate, lithium, dorzolamide eye drops, phenytoin, or mianserin. Most published cases of drug associated dementia describe resolution of the dementia syndrome when the drug(s) are discontinued.

The minimum dose or duration of therapy of oral or inhaled steroids which can lead to mental disturbances in an individual patient is not known.

The real problem may simply be that most clinicians, patients, and their families, are not aware that drug therapy could be causing such problems. Without the awareness that drug therapy might cause mental disturbances, many if not most patients, will be afraid to inform anyone of such symptoms. The patient may worry about the possibility of being diagnosed or misdiagnosed with a psychiatric disorder, being considered senile or insane and losing their independence. Descriptions of patients from clinical studies and case reports of patients with mental side effects of both steroids and non-steroidal anti-inflammatory drugs are consistent with such unreported experience.^{19, 20}

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