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SCIENTIFIC INVESTIGATIONS

Efficacy and Tolerability of Modified-Release Indiplon in Elderly Patients With Chronic Insomnia: Results of a 2-Week Double-Blind, Placebo-Controlled Trial

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Study Objective: Indiplon is a nonbenzodiazepine GABA potentiator, which exhibits pharmacologic selectivity for $GABA_A$ receptors containing the α1 subunit. The aim of the present study was to evaluate the efficacy and safety of a 15-mg nightly dose of modified-release indiplon tablets in elderly patients with primary insomnia characterized by sleep-maintenance difficulties.

Methods: Two hundred twenty-nine elderly patients, aged 65 to 85 years, who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for primary insomnia were randomly assigned to 2 weeks of nightly treatment with either indiplon, 15 mg, or placebo in a double-blind, parallel-group design. Daily sleep diaries were completed to collect patient reports of subjective total sleep time, wake time after sleep onset, number of awakenings after sleep-onset, latency to sleep onset, and sleep quality. Patient global impression ratings of various parameters of sleep were assessed on a weekly basis.

Results: The least square mean total sleep time was significantly improved with indiplon versus placebo at week 1 (377 ± 4 min vs 328 ± 4 min; $p < .0001$) and week 2 (373 ± 5 min vs 337 ± 5 min; $p < .0001$). Indiplon also significantly improved subjective wake after sleep onset, subjective number of awakenings after sleep onset, subjective sleep-onset latency, sleep quality, and patient global impression ratings of sleep at both weeks 1 and 2. The number and severity of adverse events and rates of discontinuation due to adverse effects were comparable in the indiplon and placebo groups.

Conclusions: In elderly patients with primary insomnia characterized by sleep-maintenance difficulty, indiplon, 15 mg, was well tolerated and significantly improved all patient-reported measures of sleep during 2 weeks of treatment.

Keywords: Primary insomnia, GABA modulators, hypnotics, geriatrics

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An estimated 30% to 50% of individuals over the age of 65 report symptoms of insomnia.[1] The extent to which the increased prevalence of sleep disturbance in the elderly represents primary insomnia or insomnia secondary to age-related medical and psychiatric conditions has not been established.[2] There is substantial evidence that sleep in the elderly without complaints of insomnia is more fragmented, poorer in quality, and characterized by sleep-architecture changes, including decreased stage 3 and 4 (slow-wave) sleep than in healthy younger individuals.[3-8] On the other hand, the increase in insomnia prevalence in the elderly appears to be statistically related to comorbid conditions, at least in cross-sectional studies.[2,9]

Insomnia in the elderly has been reported to be associated with cognitive impairment,[10] increased risk of falling independent of hypnotic use,[11] and reduced quality of life.[12] Increased healthcare utilization[13-15] and cardiovascular-related illness and mortality[16-18] have also been associated with insomnia, although not specifically studied in older adults. As life expectancy steadily increases in the U.S., the absolute number of older insomniacs is likely to grow. Therefore, safety and efficacy of hypnotic medications should be thoroughly assessed in this population.

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and exerts its action by binding at 3 distinct types of GABA receptors (A, B and C). $GABA_A$ receptors are comprised of 5 protein subunits, which exist in dif-

ferent combinations, or subtypes. Different ligands have varying affinity for different $GABA_A$ receptor subtypes, which mediate the diverse clinical effects associated with $GABA_A$ receptor activation (e.g., muscle relaxation, amnesia, anxiolysis, sedation, anticonvulsant).[19,20] Benzodiazepines enhance GABA effects at several $GABA_A$ receptor subtypes. Due to their relative lack of receptor selectivity, their range of clinical effects is broader than more selective ligands, perhaps representing an increased risk of unwanted clinical effects (e.g., impaired coordination).

Indiplon is a nonbenzodiazepine, benzodiazepine-receptor agonist, which selectively binds to the $GABA_A$ receptor subtype containing the α1 subunit. The sedative-hypnotic mechanism of action of indiplon is similar to that of other benzodiazepine-receptor agonists (zolpidem, zopiclone, eszopiclone). Some preclinical data suggest that indiplon may have a higher affinity for the α1 $GABA_A$ subunit than does zolpidem or zopiclone,[21] although it is unclear whether the clinical effects of indiplon will differ from those of other benzodiazepine-receptor agonists.

The selectivity ratio of indiplon ranges from approximately 10-fold (for the α1 vs the α2 subtype) to 350-fold (for α1 subtype relative to the α4 and α6 subtypes). Indiplon has a time to peak plasma concentration of about 1 hour and an elimination half-life of 1.5 to 2 hours. A modified-release tablet formulation of indiplon was designed to provide rapid initial bioavailability, followed by a sequential release of drug to maintain therapeutic plasma concentrations for a longer period of the night. Indiplon exhibits linear pharmacokinetics, thus providing dose-proportional maximal plasma concentrations and total area under the curve. It is metabolized by the hepatic microsomal CYP3A4 pathway to form a demethylated metabolite and by carboxyesterase to desacetyl indiplon, neither of which are pharmacologically active.

The goals of this study were to assess the efficacy, tolerability, and safety of modified-release 15-mg indiplon tablets in elderly individuals (ages 65-85 years) meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for primary insomnia characterized by sleep-maintenance difficulties.

METHODS

Study Design

This was a double-blind, placebo-controlled, parallel-group 2-week study of indiplon 15-mg tablets in elderly patients with primary insomnia characterized by moderate to severe sleep-maintenance difficulties. The study was conducted at 42 U.S. sites in accordance with the Declaration of Helsinki using a common protocol, which was approved by an Institutional Review Board for each study location. Patients were recruited principally by advertisements in local media. Written informed consent was obtained.

Eligible patients completed a 2-week, single-blind placebo screening period. Those who continued to meet study entry criteria were randomly assigned to 2 weeks of double-blind treatment with 15 mg indiplon tablets or placebo. At the end of 2 weeks of double-blind treatment, all patients received single-blind treatment with placebo for an additional week to observe the effects of abrupt discontinuation of study medication. Throughout the study, patients were instructed to take the study medication at bedtime and to complete the morning sleep diary within 30 minutes of awakening and the evening diary immediately prior to bedtime.

Subjects

The sample consisted of men and women ages 65 to 85 years who met DSM-IV criteria[21] for primary insomnia of at least 3 months' duration. Patients were required to have a stable bedtime between 9:00 PM and midnight, normal rise time between 6:00 AM and 9:00 AM, and total time spent in bed varying by 2 hours or less on at least 5 nights per week. Insomnia characteristics required for randomization included patient reports of more than 10 minutes to fall asleep (subjective sleep-onset latency), subjective total sleep time (TST) of less than 6.5 hours, and subjective wake time after sleep onset of at least 45 minutes, all on at least 4 nights per week by history and on at least 3 of 7 consecutive nights during the single-blind placebo screening period in sleep diary reports.

Subjects with a clinically significant or unstable medical disorder in the past 30 days; history of epilepsy or significant prior head trauma; clinically significant findings on physical examination, electrocardiogram or laboratory testing (including detection of illicit drugs or hypnotics in urine); and known sensitivity to benzodiazepines or other GABAergic agents were excluded. Subjects who met DSM-IV criteria for alcohol or substance dependence or abuse in the past year or consumed 5 or more alcoholic beverages per day or 14 or more alcoholic beverages per week were ineligible. While no structured interview was employed, assessment for clinically significant depression and anxiety was included in the initial history. Subjects with current psychiatric disorders, which were judged by the investigator as potentially causing or contributing to insomnia symptoms, were excluded. Use of any anxiolytics, anticonvulsants, histamine-1 receptor antagonists (except loratadine and fexofenadine), narcotic analgesics, or potent CYP450 3A4 inhibitors and inducers (case-by-case decision for the latter) was prohibited. Any chronic medication maintenance therapy, including selective serotonin reuptake inhibitors, or medical treatments such as theophylline or systemic corticosteroids that were not judged by the investigator or the study medical monitor to potentially interfere with the assessment of a hypnotic were maintained throughout the study.

Finally, investigators reviewed sleep history carefully with study candidates to rule out causes for sleep disturbance other than primary insomnia. Subjects who napped 6 or more times per week or for longer than 1 hour daily, planned travel across 4 or more time zones during the study period, or worked night or rotating shifts were excluded, as were those who reported pain or nocturia 4 or more nights per week. Subjects who met DSM-IV criteria for any sleep disorder other than primary insomnia, including restless leg syndrome and sleep apnea, as determined by the clinical interview, were ineligible.

Efficacy Measures

Daily sleep diaries were used to collect patient estimates of subjective TST, sleep-onset latency, subjective wake after sleep onset, subjective number of awakenings after sleep onset, and sleep quality (1 = extremely good, 2 = very good, 3 = good, 4 = fair, 5 = poor, 6 = very poor, and 7 = extremely poor). Patient global impression scales, which rated 4 items (helpfulness of drug, effect on length of sleep, effect on time to fall asleep, and effect on sleep quality) on a 3-point scale (1 = positive effect, 2 = neutral effect, 3 = negative effect), were completed weekly.

During study visits at baseline, week 1, and week 2, investi-

gators performed Clinical Global Impression of Severity ratings for the overall severity of insomnia on a scale ranging from 1 (normal, not at all ill) to 7 (extremely severe). At weeks 1 and 2, they also rated overall change of insomnia during the study on the Clinical Global Impression-Improvement scale, which rated global improvement of insomnia on a scale ranging from 1 (very much improved) to 7 (very much worse).[23] Clinical responders were defined by a Clinical Global Impression-Improvement score of 2 or less ("much" or "very much" improved).

Safety

Safety evaluations prior to and after treatment included physical and neurologic examinations, vital signs, routine laboratory tests (hematology, serum chemistry, and urinalysis), and 12-lead electrocardiogram. Prior to the study, patients were screened for hepatitis B and C and underwent a urine drug screen as noted above. At each study visit, blood pressure, heart rate, respiratory rate, and oral temperature were measured; weight was measured prior to and at the end of the study. All reported or observed adverse events were recorded and rated for severity.

Patient ratings of daytime functioning and drowsiness were performed in the evening and recorded in study diaries. Ability to function during the day was rated on an ordinal scale as 1 = extremely poor, 2 = very poor, 3 = poor, 4 = good, 5 = very good, and 6 = excellent. Daytime drowsiness was rated on a separate scale as 1 = extremely drowsy, 2 = very drowsy, 3 = drowsy, 4 = alert, 5 = very alert, and 6 = extremely alert.

All patients completed the Benzodiazepine Withdrawal Symptom Questionnaire.[24] This validated 20-item questionnaire is used to assess discontinuation-emergent symptoms following treatment with benzodiazepines or other GABAergic agonists. Symptoms were rated on a 3-point scale as "absent," "moderate," or "severe." The Benzodiazepine Withdrawal Symptom Questionnaire was administered at the beginning of single-blind placebo screening/ baseline period, at the end of weeks 1 and 2 of double-blind treatment, on days 1 and 2 of the single-blind discontinuation week and at the end of the single-blind discontinuation week (or at study exit in those with early termination).

To assess for rebound insomnia, the sleep-onset latency and subjective TST on each of the first 2 nights of the single-blind discontinuation week were compared to the average values observed on baseline nights.

Statistical Methods

Statistical summaries and statistical tests were generated using SAS software version 8.2 or higher (SAS Institute, Inc., Cary, NC). For the primary dependent measure, mean subjective TST, a sample size of 110 patients per group was estimated to provide an 84% likelihood for detecting a mean difference of 25 minutes between indiplon and placebo. The estimate assumed a 2-sided test at an α level of.05 and an estimated standard deviation of 62 minutes.

In all statistical analyses of efficacy, indiplon was compared with placebo using a 2-tailed test at a level of significance of .05 in each analysis, unless otherwise specified.

Efficacy analyses were performed on the total sample of randomized patients who took at least 1 dose of double-blind study medication; for patients who discontinued prematurely, the last observation was carried forward. Daily sleep-diary data was averaged to obtain the weekly values. Compliance with diary completion was very good, with a diary completion average of 13.1 among patients receiving placebo and 13.2 among patients receiving indiplon during the 14 days of double-blind treatment (a 94% completion rate).

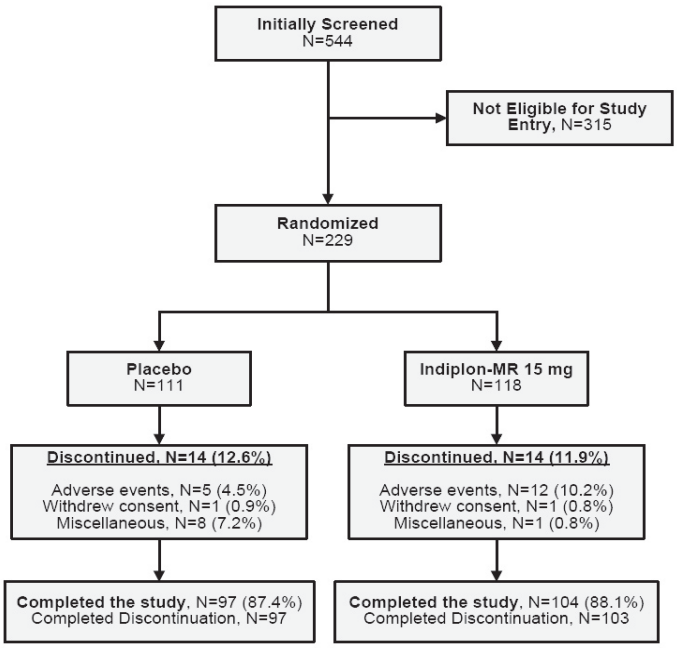

Figure 1—Flow diagram.

All continuous efficacy variables were analyzed via a parametric analysis of covariance model that included main effects for treatment and site and used respective baseline values as covariate. Categorical variables were analyzed using the generalized Cochran-Mantel-Haenszel test with site as a stratum.[25] Demographic and baseline comparisons were made with analysis of variance for continuous measures and Cochran-Mantel-Haenszel test for categorical variables.

Because there were 2 time points of interest (week 1 and week 2), a closed testing procedure was applied, which required establishing significance relative to p values at week 1 before making inference at week 2. This procedure was applied separately for the analysis of subjective TST and sleep-onset latency. The procedure was intended to maintain the type I error rate at < .05. Clinical response was defined, a priori, as the percentage of patients achieving a Clinical Global Impression-Improvement score of 2 or less (much or very much improved).

RESULTS

A total of 229 patients of the 544 screened met all study entry criteria at the baseline visit and were randomly assigned to 2 weeks of study treatment (Figure 1). A similar proportion of patients on indiplon and placebo (87%-88%) completed study treatment.

There were no statistically significant differences between the treatment groups in baseline demographic characteristics and sleep measures (Table 1). At study entry, 93% of patients reported insomnia duration to be at least 2 years. As expected in a sample of elderly patients, medical comorbidity was frequent, with hypertension, hypercholesterolemia, gastroesophageal reflex, and osteoarthritis being the most common medical illnesses. The mean number ± SD of concomitant medications taken during the

Table 1—Baseline Clinical and Demographic Characteristics of Patient Sample

	Placebo (n = 111)	Indiplon-MR, 15 mg (n = 118)
Women, %	64.9	55.1
Age, y	71.5 ± 4.6	71.1 ± 4.8
Race, %		
White	89.2	91.5
Other	11.8	8.5
Body mass index, kg/m^2	27.1 ± 4.4	26.8 ± 4.5
Time since primary diagnosis of insomnia, y	14.5 ± 15.4	11.0 ± 10.9
Sleep characteristics at screen		
Total sleep time		
Minutes	321.1 ± 66.4	323.5 ± 76.4
≤ 300 minutes, %	34	37
Latency to sleep onset		
Minutes	57.0 ± 44.8	55.6 ± 48.5
> 60 minutes, %	37	32
Wake after sleep onset		
Minutes	92.5 ± 50.1	96.2 ± 49.3
≥ 60 minutes, %	72	78
Awakenings after sleep onset		
No.	2.1 ± 1.1	2.0 ± 0.9
≥ 2, %	47	43
Sleep quality[a]		
Subjective rating	4.1 ± 0.8	4.0 ± 0.9
Rated poor to extremely poor, %	29	30

Data are presented as mean ± SD, unless indicated as percentage.
[a]Sleep quality: 1 = stremely good to 7 = extremely poor.

course of the study was 5.5 ± 3.9 for indiplon and 4.7 ± 3.8 for placebo.

Efficacy

Treatment with indiplon resulted in significant ($p < .0001$) improvement compare with placebo in all diary-based sleep measures at both study weeks (Table 3). Mean subjective TST was approximately 35 to 50 minutes greater, and subjective wake after sleep onset 25 to 30 minutes less, with indiplon treatment than with placebo. The proportion of patients taking indiplon who had an increase in subjective TST (at week 2) of more than 1 hour was significantly higher (43%), compared with placebo (22%; $p = .001$). Similarly, the proportion of patients taking indiplon who had a reduced subjective amount of wake time after sleep onset of more than 45 minutes was significantly higher (40%), compared with placebo (23%; $p = .006$). Figure 2 shows that the percentage of patients rating sleep quality as good to extremely good was higher in the indiplon group than in the placebo group during both study weeks ($p < .0001$ and $p < .002$ at weeks 1 and 2, respectively).

The mean group baseline Clinical Global Impression of Severity scores were similar for both indiplon (4.3 ± 0.1) and placebo (4.5 ± 0.1). Mean Clinical Global Impression of Severity scores were significantly lower in indiplon recipients relative to placebo at week 1 (3.4 ± 0.1 vs 4.1 ± 0.1; $p < .0001$) and week 2 (3.2 ± 0.1 vs 3.9 ± 0.1; $p < .0001$). Clinical Global Impression-Improvement responder rates, defined as a Clinical Global Impression-Improvement score of 2 or less ("much" or "very much" improved) were significantly higher on indiplon, compared with placebo, at both week 1 (49% vs 15%) and week 2 (55% vs 28%; $p < .0001$ for both weeks; Figure 3).

Table 2—Comorbid Medical Disorders in Treatment Samples

	Placebo (n =111)		Indiplon-MR, 15 mg (n = 118)	
	No.	%	No.	%
Arthritic disease[a]	49	44	67	57
Hypertension	46	41	61	52
Hypercholesterolemia	27	24	25	21
Gastroesophageal reflux	15	14	28	24
Hypothyroidism	17	15	18	15
Seasonal allergies	16	14	17	14
Osteoporosis	11	10	17	14
Dyspepsia	12	11	10	8

[a]All forms of arthritis, including osteoarthritis and rheumatoid arthritis. MR refers to modified release.

Patient global impression ratings (Figure 4) showed that significantly more patients in the indiplon group reported positive effects of the study drug than did patients in the placebo group ($p < .0001$ for each domain for both weeks). On all 4 patient-rated domains, during both weeks, approximately twice as many patients provided positive ratings with indiplon treatment compared with placebo.

Discontinuation Effects

Indiplon and placebo were discontinued after 2 weeks of treatment. Patients receiving indiplon exhibited a decreased mean ± SD subjective TST relative to baseline on discontinuation night 1 (-10.7 ± 106.1 minutes; NS) and increased subjective TST on discontinuation night 2 (+31.8 ± 84.1; $p = .0004$). The mean subjective TST was increased relative to baseline for the placebo group on both discontinuation night 1 (+63.7 ± 71.6 minutes; $p < .0001$) and night 2 (+55.3 ± 78.4; $p < .0001$).

For the indiplon group, the mean (± SD) sleep-onset latency was increased relative to baseline on discontinuation night 1 (+19.8 ± 86.2 minutes; $p = .027$) and on night 2 (+5.1 ± 64.9 minutes; NS). The mean subjective sleep-onset latency was decreased relative to baseline for the placebo group on both discontinuation night 1 (-12.9 ± 50.5 minutes; $p = .019$) and night 2 (-20.5 ± 43.3; $p < .0001$).

For indiplon and placebo, respectively, the mean Benzodiazepine Withdrawal Symptom Questionnaire change score was similar on postdiscontinuation night 1 (+1.3 ± 0.2 vs +0.8 ± 0.3) and postdiscontinuation night 2 (+0.9 ± 0.2 vs +0.8 ± 0.1). Furthermore, the proportion of patients reporting 3 or more discontinuation-emergent symptoms on the Benzodiazepine Withdrawal Symptom Questionnaire was also similar for indiplon (2.9%) relative to placebo (3.1%).

Safety and Tolerability

At baseline, mean ± SEM scores on the daytime functioning scales were similar in both the indiplon group (3.95 ± 0.05) and the placebo group (3.81 ± 0.06). The indiplon-treated group rated their ability to function significantly higher than did the placebo group at week 1 (mean: 4.01 ± 0.03 vs 3.83 ± 0.04; $p = .0006$) but not at week 2 (mean: 3.97 ± 0.04 vs. 3.88 ± 0.04; $p = .13$).

At baseline, mean ± SEM daytime drowsiness scores were

Table 3—Efficacy of Indiplon on Patient-Rated Sleep Measures

	Placebo		Indiplon-MR, 15 mg		p Value
TST, min		N=		N=	
Baseline	321.1 ± 6.8	111	323.5 ± 6.6	118	
Week 1	327.5 ± 4.4	111	376.6 ± 4.2	117	< .0001
Week 2	337.2 ± 5.1	111	373.2 ± 5.0	118	< .0001
SOL, min					
Baseline	35.2 ± 2.3	111	35.9 ± 2.3	118	
Week 1	34.9 ± 1.8	111	22.0 ± 1.1	118	< .0001
Week 2	31.0 ± 1.8	111	21.2 ± 1.2	118	< .0001
WASO, min					
Baseline	92.2 ± 4.7	111	96.5 ± 4.5	117	
Week 1	84.9 ± 3.2	111	55.7 ± 3.1	117	< .0001
Week 2	80.5 ± 3.7	111	56.4 ± 3.6	117	< .0001
NAASO, no.					
Baseline	2.1 ± 0.1	111	2.0 ± 0.1	117	
Week 1	2.0 ± 0.1	111	1.4 ± 0.1	117	< .0001
Week 2	1.9 ± 0.1	111	1.3 ± 0.1	117	< .0001

Data are provided as mean ± SEM, with last observation carried forward; Least-squares means are data from an analysis of covariance model; latency to sleep onset was from an analysis of variance model using log-transformed data. TST refers to subjective total sleep time; WASO, subjective wake after sleep onset; SOL, subjective sleep-onset latency; NAASO, subjective number of awakenings after sleep onset. MR refers to modified release.

similar in both the indiplon group (3.82 ± 0.06) and the placebo group (3.65 ± 0.06). Daytime drowsiness was rated by the indiplon group as being lower than for the placebo group, but the difference was significant only at week 1 (3.85 ± 0.04 vs. 3.70 ± 0.04; p = .0049), not at week 2 (3.86 ± 0.04 vs. 3.76 ± 0.04; p = .10).

Adverse events occurred in 44% of the patients taking indiplon and 28% taking placebo and tended to be mild to moderate in intensity, with fewer than 1% of patients taking indiplon (n = 1) reporting a severe adverse event. The following adverse events occurred with an incidence of at least 3% in patients receiving indiplon or placebo, respectively: dizziness (8% vs 4%), headache (6% vs 3%), and somnolence (4% vs 2%). There were no reports of falls in patients taking indiplon; 1 fall was reported in a patient taking placebo.

Two potentially medically serious adverse events occurred during the course of the study, both in indiplon-treated patients, neither of which was judged by the investigators to be related to study drug. One patient developed small bowel obstruction and another experienced vertigo. Only 2 laboratory abnormalities were reported during double-blind treatment, neither was considered clinically significant. Hematuria occurred in 1 patient taking placebo; in 1 indiplon-treated patient, urinalysis showed a small number (1+) of leukocytes. There were no clinically significant treatment-emergent abnormalities in vital signs, weight, or electrocardiographic findings in either group.

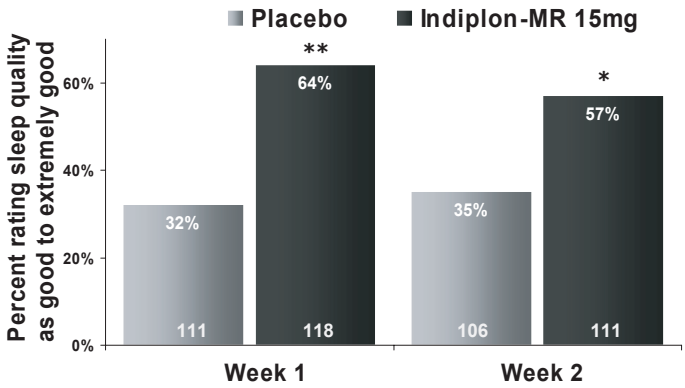

Figure 2—Percentage of patients reporting sleep quality as good to extremely good on indiplon-modified release (MR) vs placebo. Cochran-Mantel-Haenszel significance testing: *p < .002; **p < .0001

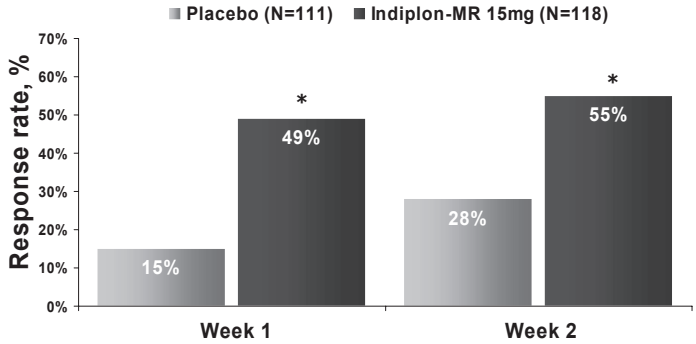

Figure 3—Clinical Global Impression-Improvement (CGI-I)-response at week 1 and week 2: comparison of indiplon-modified release (MR) vs placebo. Responder criteria: CGI-I ≤ 2 (moderate-to-marked improvement). Cochran-Mantel-Haenszel significance testing: *p < .0001

DISCUSSION

The 15-mg dose of indiplon was found to be efficacious in increasing subjective TST and in reducing subjective wake after sleep onset, subjective number of awakenings after sleep onset, and subjective sleep-onset latency in elderly patients with primary insomnia characterized by sleep-maintenance difficulty. The efficacy of indiplon was evident from the first night of treatment and was sustained for the 2-week period of nightly use. Improvement in sleep onset and sleep maintenance with indiplon on sleep-diary estimates were supported by patient global ratings and clinician judgments.

Clinical Global Impression-Improvement responder rates of indiplon-treated patients at week 1 (49%) and week 2 (55%) were 34% and 27% higher, respectively, than rates in patients taking placebo at each respective week.. The definition of global response, and how well it correlates with improvement in sleep-onset and sleep-maintenance variables, is not well-studied. Development of empirically based consensus criteria for a clinically significant treatment response, as well as remission of insomnia, would be a valuable methodologic advance for insomnia-treatment studies.

The ultimate goal of treatment of insomnia is 2 fold. The first is to reduce nighttime insomnia symptoms, and the second is to reduce insomnia-related daytime impairment. Although the current study did not include objective measures of waking function, 6-point patient-rated scales were used to assess perceived daytime effects. There was a small but significant improvement in perceived daytime function and daytime alertness in week 1 but not at week 2. Additional studies are needed to more fully characterize the functional deficits associated with insomnia in the elderly and the extent to which treatment with indiplon or other hypnotics might improve insomnia-related impairment.

Indiplon was well tolerated in this elderly population during 2 weeks of administration. Most adverse events were mild and

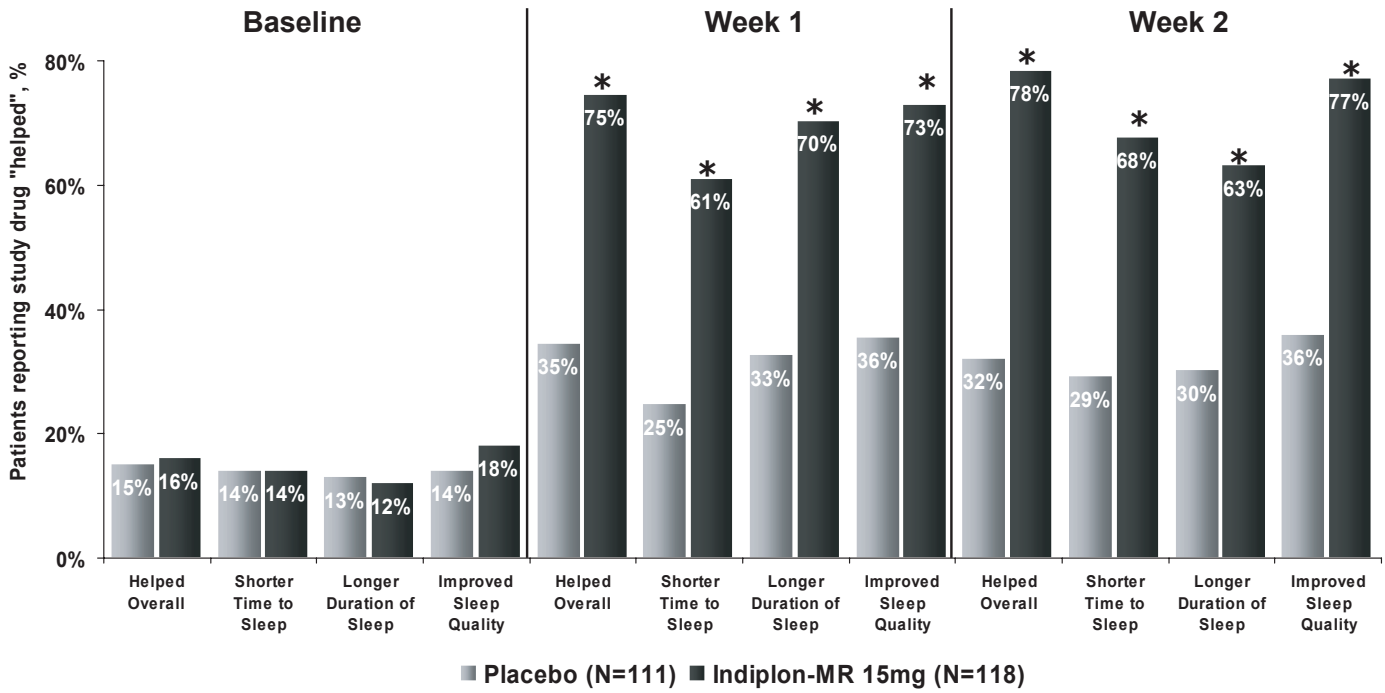

Figure 4—Effect of indiplon-modified release (MR) on patient global impression ratings. Patient Global Impression (PGI) scale: rating 4 clinical outcomes on a 3-point improvement scale: overall helpfulness of drug, effect on length of sleep, effect on time to fall asleep, effect on sleep quality during the placebo run-in and the randomized study. Each assessment time point rates drug effect for the previous week. At the baseline visit, patients in both treatment groups were rating the effect of placebo. Cochran-Mantel-Haenszel significance testing: *p < .0001

transient in duration, and there was no difference in the incidence of any adverse event relative to placebo. No falls were reported in patients receiving indiplon.

Abrupt discontinuation of indiplon was associated with evidence of rebound insomnia on the first discontinuation night. This effect was mild, and, by discontinuation night 2, sleep had returned to baseline levels. Rebound insomnia is commonly observed with short-acting GABAergic hypnotics and typically lasts only 1 night. There was no evidence of any benzodiazepine-like withdrawal symptoms among patients discontinuing indiplon.

Elderly patients with insomnia represent a vulnerable population for which hypnotics with a low risk-benefit ratio are desirable. The data from the study reported here provide strong evidence that indiplon, 15 mg, has a favorable risk- benefit ratio in elderly patients with primary insomnia. In contrast, many widely used treatments for insomnia in the elderly (e.g., benzodiazepine hypnotics, trazodone, and over-the-counter sleep aids containing diphenhydramine) have not been well evaluated as hypnotics, have known undesirable side effects, or both.[26] None of these agents have proven efficacy and safety based on placebo-controlled trials in elderly with insomnia. As a result of the dearth of empirically derived information, physicians often prescribe unproven treatments. Elderly patients often do not communicate the extent of their sleep difficulty.[27,28] Some self-medicate with alcohol, over-the-counter medicines, or both.[29-31] The management of insomnia in this vulnerable population represents a significant public health concern. The thorough evaluation of the efficacy and safety of hypnotics for this population represents an important goal in evidence-based medicine. Since patients with unstable medical or psychiatric illnesses were excluded from this study, it is difficult to extrapolate the current results to elderly individuals with insomnia complicated by significant comorbidity. It could be argued that the requirements for the character and frequency of sleep disturbance and time-in-bed requirements for this study may not be truly representative of the elderly population with primary insomnia. For the purposes of this initial hypothesis-testing study, we believe that some degree of homogeneity of the sleep disturbance was important. Inclusion of a more varied sample of elderly patients with primary insomnia in future studies would clearly provide clinically useful information.

In conclusion, the results from this 2-week treatment study suggest that 15-mg modified-release indiplon is an effective, well-tolerated, and safe hypnotic for the treatment of healthy elderly patients with primary insomnia.

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REFERENCES

1. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97-111.
2. Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG. Incidence and remission of insomnia among elderly adults: an epidemiological study of 6.800 persons over three years. Sleep 1999;22:(Suppl 2):S366-S372.
3. Landolt HP, Dijk DJ, Achermann P, Borbély AA. Effect of age on the sleep EEG:slow-wave activity and spindle frequency activity in young and middle-aged men. Brain Res 1996;738:205-12.
4. Huang YL et al. Age-associated difference in circadian sleep-wake and rest-activity rhythms. Physiol Behav 2002;76:597-603.
5. Ehlers CL, Kupfer DJ. Effects of age on delta and REM sleep parameters. Electroencephalogr Clin Neurophysiol 1989;72:118-25.
6. Bliwise DL. Normal aging. In:Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. Philadelphia: WB Saunders; 2000:26-42.
7. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284:861-8.
8. Vitiello MV, Larsen LH, Moe KE. Age-related sleep change: gender and estrogen effects on the subjective-objective sleep quality relationships of healthy, noncomplaining older men and women. J Psychosom Res 2004;56:503-10.
9. Foley DJ, Monjan A, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiological study of three communities. Sleep 1995;18:425-32.
10. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc 2001;49:1185-9.
11. Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in michigan nursing homes. J Am Geriatr Soc 2005;53:955-62.
12. Byles JE, Mishra GD, Harris MA, Nair K. The problems of sleep for older women:changes in health outcomes. Age Ageing 2003;32:154-63.
13. Hatoum H, Kong S, Kania C, Wong J, Mendelson W. Insomnia, health-related quality of life and healthcare resource consumption: a study of managed-care organization enrollees. Pharmacoeconomics 1998;14:629-37.
14. Kapur VK, Redline S, Nieto FJ, Young TB, Newman AB, Henderson JA. The relationship between chronically disrupted sleep and healthcare use. Sleep 2002;25:289-96.
15. Novak M, Mucsi I, Shapiro CM, Rethelyi J, Kopp MS. Increased utilization of health services by insomniacs—an epidemiological perspective. J Psychosom Res 2004;56:527-36.
16. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. J Intern Med 2002;251:207-16.
17. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 2003;163:205-19.
18. Schwartz S, McDowell Anderson W, Cole SR, Cornoni-Huntley J, Hays JC, Blazer D. Insomnia and heart disease: a review of epidemiologic studies. J Psychosom Res 1999;47:313-33.
19. Nutt, DJ, Glue P, Lawson C, Wilson S. Flumazenil provocation of panic attacks: evidence for altered benzodiazepine receptor sensitivity in panic disorder. Arch Gen Psychiatry 1990;47:917-25.
20. Lydiard RB. The role of GABA in anxiety disorders. J Clin Psychiatry, 2003;64:21-7.
21. Sullivan SK, Petroski RE, Verge G, Gross RS, Foster AC, Grigoriadis DE. Characterization of the interaction of indiplon, a novel pyrazolopyrimidine sedative- hypnotic, with the GABA-A receptor. JPET 2004;311:537-46.
22. Diagnostic and Statistical Manual of Mental Disorders: DSM-IVe, 4th ed. Washington: American Psychiatric Association; 1994.
23. Guy W. ECDEU Assessment Manual for Psychopharmacology. Washington: National Institute of Mental Health-US Dept of Health, Education, and Welfare; 1976. Vol. Publication (ADM) #76-338.
24. Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. J Affect Disord 1990;19:53-61.
25. Berry D, ed. Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker; 1990;464:403-8.
26. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment: prevalence and correlates. Arch Gen Psychiatry 1985;42:225-32.
27. National Sleep Foundation/Gallup Organization. Sleep In America. Princeton; 1995:1-78.
28. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. Sleep 1999;22:S347-53.
29. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411-8.
30. Goldstein, MZ. Practical geriatrics: insomnia in late life. Psychiatr Serv 2001;52:1573-5.
31. Maczaj M. Pharmacological treatment of insomnia. Drugs 1993; 45:44-55.