Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Cephalon made a strong case for expanded labeling for Provigil to treat Shift Work Sleep Disorder. ♦ TAK-375 may be the least effective hypnotic, and the data is positive mostly for objective, not subjective, measures, but it is unlikely to have the limitations of the benzodiazepines. ♦ Efficacy data for Sepracor's Estorra was impressive, but questions remain about safety. Menstrual cycles and estradiol levels were monitored in one trial, but officials said the completed toxicology studies are clean. ♦ Neurocrine Bioscience's Indiplon-IR induces sleep well, and the company is hoping the MR formulation will maintain sleep. ♦ Use of Orphan Medical's Xyrem in narcolepsy is growing, and it may be useful in fibromyalgia.

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Takeda's insomnia drug, TAK-375, and Cephalon's Provigil (modafinil) for excessive sleepiness dominated this meeting, but there was new data on Sepracor's Estorra (eszopiclone), and Neurocrine Biosciences had a booth and several posters and talks on its Indiplon (NBI-34060). However, the presentations raised almost as many questions as they answered.

About 50 million Americans suffer from insomnia. Symptoms include difficulty falling asleep, awakening frequently during the night, awakening too early in the morning, or awakening feeling unrefreshed. Insomnia can be caused by depression, anxiety, pain, medical conditions, and even environmental factors such as jet lag or shift work. Chronic insomnia typically lasts three weeks or longer, but it can be a shorter period that recurs frequently over months or years. Nearly half of insomniacs suffer from chronic insomnia, and many are elderly.

Sleep specialists generally like hypnotics to treat insomnia. A speaker stated flatly, "The evidence is fairly overwhelming that these (hypnotic) drugs work…My rough calculation is that at least 90% of people experience a therapeutic benefit." Interestingly, most sleeping pill prescriptions are written by primary care doctors, not sleep specialists, and most (60%-80%) go to the chronic user. More than half (50%-60%) of the patients taking hypnotics reportedly are elderly.

However, an NIH-funded study reportedly concluded that chronic use of sleep medications is therapeutically inert – a waste -- for some patients. In addition, another speaker presented "The Dark Side" of hypnotics. He said, "I think the risks outweigh the benefits." He warned that hypnotics are associated with:

- **Long-term mortality risks.** He compared use of hypnotics to the cancer risk with cigarettes, "We accept that cigarettes cause cancer even though the molecular mechanics are still a bit uncertain…On the other hand, the molecular mechanisms by which hypnotics cause death – through apnea – are well understood…Ten studies show increased mortality with sleeping pills…Two studies show no difference, and I'm not aware of any studies suggesting less mortality (with hypnotics)…The newer 'Z' drugs (Ambien, Sonata, Estorra, Indiplon) might be safer than the older benzodiazepines, but I don't know of any strong evidence of that…I'm not sure."

- **Increased insomnia.** He said, "Epidemiological studies show that chronic use of hypnotics is associated with increased insomnia…There are some studies which show that after people stop taking hypnotics they actually sleep better, and this suggests that the long-term use of sleeping pills might make insomnia worse…Drug withdrawal studies (also) indicate that it is possible that chronic hypnotic use causes insomnia."

- **Worse physical functioning,** bodily pain, vitality, social functioning and general mental health. He said, "The implication is that long-term use of sleeping pills actually makes people worse."
- **Falls and accidents,** especially among the elderly. He said, "This is more due to the long-acting agents than the short-acting agents."
- **Impaired next day performance** or, at best, no improvement in next day performance. He said, "If your patients are hoping that by taking a sleeping pill they will do a better job the next day, they are likely to be disappointed. This is true for zolpidem and zaleplon as well as for the older compounds…And there is some evidence that zopiclone impairs driving performance…but the impairment does appear to be greater with the long-acting compounds than the shorter acting compounds."

The two major indications for use of hypnotics:

- Transient/short-term insomnia from acute stress, illness or jet lag.
- Chronic insomnia:
  - Primary or psychophysiological
  - Secondary, refractory to treatment of medical/ psychiatric disorder (e.g., treated depression where insomnia doesn't remit)

There are at least three subsets of chronic hypnotics:

1. Persistent insomnia that exacerbates at withdrawal
2. Persistent insomnia that does not exacerbate at withdrawal. A speaker said chronic use of sleep medications is therapeutically inert for this subset of patients.
3. No persistent insomnia

The Ideal Insomnia Medication

Property	Ideal agent	Benzodiazepines
Rapid sleep onset	+++	+++
Maintain sleep	+++	+ to +++
Produce physiologic sleep	+++	+ to ++
Amnesia/ataxia	–	+ to +++
Drug interactions	–	+ to ++
Residual effects	–	– to +++
Tolerance	–	---
Discontinuation effects	–	– to +
Abuse liability	–	+
Scheduling	–	+++

A speaker attempted to dispel some myths about hypnotics:

Myth 3: *That hypnotics are used predominantly in long-term situations.* A speaker said about 70% of patients use a hypnotic for less than two weeks and only about 10% use one nearly nightly.

Myth 2: *That hypnotics are being overused.*

Myth 3: *That hypnotics are being used more frequently today than in the past.* A speaker said the trend actually has been to slightly lower use of hypnotics, estimating that about 2.5% of Americans used a hypnotic during the past year, down from 2.6% in 1990, "There is a tendency for insomnia to be treated less with medications." According to one estimate, of the 18-45 year olds using a substance to aid sleep in the past year, about 10% used an over-the-counter agent and about 7% used a prescription medication.

Among the key issues relating to new hypnotics are:

Tolerance. Experts insisted that tolerance does not develop with the newer hypnotics, but not every doctor in the audience was convinced. The speaker said, "Many people have written that tolerance (the need to increase the dose to achieve a similar effect) builds with use of these medications for five weeks…I think I can convince you that is not true." He cited studies showing that Sonata and Ambien are not associated with tolerance, whether taken for five weeks or 52 weeks."

Doctor in the audience: "This is interesting and wonderful data…but many patients come in telling me that their sleep aid stopped working and many more are saying they don't like it or it is difficult to get them off. I'm curious about the discrepancy between this experience in the trenches and what the data is showing in the studies."

Speaker response: "Certainly, clinical experience will be different from lab data, but it is my belief that a lot of people who start on the medications and two weeks later say they don't work, didn't get an effective dose. Dose titration is important. Also patient problems don't remain static. Two weeks later the stress in that person's life might be dramatically different. That is a clinical dilemma, but it is not necessarily directly related to efficacy vs. tolerance."

Residual effects. The newer agents claim to cause less residual effects, but none have done next-day driving tests.

Withdrawal (rebound). A speaker said, "It is clear we can get people off (hypnotics) with no problem."

Long-term efficacy. With the exception of a 52-week Sonata study, most insomnia studies have been short-term, but a speaker insisted that the benzodiazepines remain effective for at least six months. Asked whether the s-zopiclone data is strong enough for the FDA to grant a long-term use indication, an expert said, "I don't know of anything that would change the FDA philosophy at this time...and any drug for insomnia at this time will have class labeling on duration of use." Another speaker said, "I don't think we have adequate long-term data…The zopiclone data is only subjective data...We have no

objective data out to one, two or three years, which is the duration so many people are taking these drugs. We find the long-term users are five- to 10-year users, and if people are going to take these drugs for years, then we need to know if they are safe. Look what just happened with HRT for menopause…It might be when a controlled trial is done that we will find that hypnotics do more harm than good."

Sleep Scales

Several speakers at the meeting addressed the issue of the usefulness and validity of various sleep scales, but no one really talked about DSST and its value. One expert commented, "Psychometric scales provide relative (not absolute) measures, which makes them useful for tracking sleepiness over time but problematic for comparing between subjects…I like subjective sleep scales, and I use them, but you need to be aware of the inaccuracies…Sleepiness scales may or may not show the same direction or magnitude of effects as those seen on performance and psychological outcomes. Sleepiness scales completed immediately after performance demands can often show elevated sleepiness… Subjects tend to use a scale consistently but in their own idiosyncratic way...and few use the extreme ends of scales…Subjective sleepiness ratings…provide only limited functional interpretation. Behavioral tests have much better functional validity." Another expert said, "All current measures of sleepiness (self-reporting, cognitive performance, etc., can be influenced by environmental and psychosocial factors…Self-report measures may be the (scales) most affected by other factors."

The most popular sleep scales, the ones a speaker said are the most useful in the lab or in the field, are:

- Stanford Sleepiness Scale
- Karolin's Sleepiness Scale

The sleep field needs better tools, an expert said. He explained, "It is really critical that the field establish a common set of tools, including research diagnostic criteria. It is important that everyone uses the same ones. We need a consistent way to ascertain whether a person has insomnia, and we need severity rating instruments that include a variety of symptoms, distress, and impairment. We also need to confirm or refute whether there are distinct phenotypes (in insomnia)…If subjective sleepiness reports were reliably valid, I don't think we would have spent so much time trying to measure sleepiness."

Subject performance on sleep scales can be affected by:

- Awareness, beliefs and memory of the individual.
- Demographic factors (sex, age, culture, etc). A speaker said males report differently than women, and answers are affected by what the respondent believes is an "appropriate" answer.
- Influence of the activity immediately prior to the scale or an activity anticipated after the scale.
- Implications of the scale response options. That is, the extent to which the scale implies dysfunction, personal weakness, failure or lack of professionalism, victimization or heroic behavior.
- Acuteness vs. chronicity of the assessment context, which is a problem of response bias.

Seven drugs currently are approved in the U.S. to treat insomnia:

- Roche's Dalmane (flurazepam)
- Schering's Doral (quazepam)
- Abbott's ProSom (estrazolam)
- Novartis's Restoril (temazepam)
- Pfizer's Halcion (triazolam)
- Wyeth/Elan's Sonata (zaleplon). There was little or no data at this meeting on any other formulations of Sonata. However, a 52-week study of 5 mg and 10 mg Sonata given at bedtime found no rebound insomnia upon discontinuation. In addition, The following measures were all maintained or improved over the second half of the year: mean sleep time, mean time to sleep onset, and mean number of awakenings. A speaker said, "This is primarily a sleep initiation compound…The efficacy is retained over five weeks."
- Pfizer's Ambien (zolpidem). A speaker said there was no tolerance was shown with eight and 12 week use. Another speaker said a 1994 study found that "Zolpidem, in the recommended dose was ***not*** significantly better than placebo in the fifth week of use." He also cited a study from 2000 that found zolpidem use produced no significant increase in total sleep over four to eight weeks of ***intermittent*** use because of worse sleep on withdrawal nights.

Several new agents are on the near horizon. Sleep specialists appear the most interested in Takeda's TAK-375 – because it works through a different mechanism. Asked how doctors will choose among these agents if all were available, an expert said, "Most doctors will pick one or two they are most comfortable with. It will be like the SSRIs."

PFIZER'S Ambien XR (zolpidem extended release)

A Phase III trial is in progress, with a 2005 lunch expected.

SEPRACOR'S Estorra (eszopiclone)

Estorra is a single isomer of Aventis' Imovane (zopiclone), which has been sold in Europe – but not the U.S. – for more than a decade. Estorra also has been referred to variously as es-zopiclone, S-zopiclone, and esopiclone. In February 2003, Sepracor submitted an NDA for Estorra to treat transient and chronic insomnia, and the PDUFA date is November 30, 2003. The NDA includes data from six placebo-controlled, Phase III trials in more than 2,700 patients.

A Sepracor official said the company does not expect to have FDA approval on the PDUFA date. He suggested there is likely to be additional back and forth for a few months before full approval is granted. The issue does not appear to be efficacy; sources generally agree the efficacy data on Estorra is impressive. Rather, the question appears to be safety. Sepracor officials appear to be banking on the FDA being influenced by the long safety record of use in Europe and the Prescription Event Monitoring (PEM) studies in the U.K. (which looked at the 5 mg and 7.5 mg dose in the elderly), and the safety in PEMs reportedly was very good.

APSS sources were not very concerned about the safety of either zopiclone of eszopiclone. Every expert questioned was aware that there had been a carcinogenicity issue in the zopiclone animal (rat) toxicity studies, but they feel reassured because it was approved in Europe and has been on the market for many years. One researcher said, "RPR (Rhone Poulenc Rhorer) didn't bring zopiclone to the U.S. because its American partner, American Home Products, wasn't excited about it and pulled the NDA. There isn't any real safety issue, but the FDA wanted two-year animal toxicity studies on Estorra."

However, at the NCDEU meeting in late May 2003, a Pfizer researcher said, "The FDA warned us against developing any drugs in this class. We thought this was very unusual. We looked at the zopiclone label in Europe and decided against both pagoclone (now an Indevus drug) and Estorra." He insisted this was the primary reason Pfizer terminated its agreement on pagoclone with Indevus in mid-2002, and Pfizer subsequently signed a co-promotion deal with Neurocrine Biosciences for Indiplon.

The French label for zopiclone lists breast cancer as a risk in female rats and describes the mechanism as an increase in the serum concentration of 17 beta-estradiol, the same active ingredient in many hormone replacement therapies. An increase in thyroid cancer was also noted in dogs due to increased TSH, although this has not been observed in humans.

A Sepracor official said his company was trying to prove mechanistically that Estorra doesn't cause cancer. He said zopiclone is dosed higher than Estorra, "We have significantly refined the dose with the S-isomer…We now have our own preclinical toxicity studies, and the isomer is different, and it is mechanistically different, from zopiclone." Sepracor officials insisted that Estorra is "substantially" different from zopiclone, and that they haven't seen any concerning toxicity issues. The animal toxicity trials are completed, and the data will be given to the FDA this month (June 2003), though Sepracor does not plan to make any of this data public.

If Estorra gets FDA approval, Sepracor intends to sell the drug itself. An official said, "We don't need a partner. We want to sell it ourselves."

Sources all agreed that there is little chance that Estorra will get a label for long-term use, and they doubted that Estorra will get a label that says it doesn't have (or has less) residual sedation. One expert explained, "They would need an active comparator that does produce sedation to compare Estorra to. I can't imagine the FDA saying it is safe for people to drive the morning after taking Estorra." Another said, "DSST is not a functional test. A functional test has to have a positive control. The FDA will want a trial with a positive control."

There will be more data on Estorra in elderly patients at the International Psychogeriatric Association meeting in Chicago August 17-22, 2003.

Besides chronic and transient insomnia, Sepracor is looking at doing studies of Estorra in other sleep disorders such as depression, insomnia related to menopause, pain and rheumatoid arthritis. A Sepracor official said the advantages of Estorra over other hypnotics are:

- Longer half life
- Ability to influence sleep.
- Ability to influence sleep maintenance.
- No gender differences (which does occur with Ambien).
- Some evidence of an increase in quality of life and ability to function.

Long-term Trial: Study 190-049 in Chronic Insomnia

Results were presented from a six-month, randomized, double-blind, placebo-controlled study of 788 adults with chronic primary insomnia at 70 centers. All patients in this trial were crossed over to Estorra (3 mg/day) at the end of this period and followed for another six months. Patients called in once a week using an interactive voice recording system to file a report. All patients were supposed to call in at a specified unique time, but a researcher said some called in as much as four hours late and the reports were still accepted. A researcher said six different analyses of the results from this study all say the same thing: that Estorra is effective. He explained, "No matter how you analyze it (last observation carried forward, intent-to-treat, completors, etc.), the results are exactly the same…This is a strong argument for continued efficacy over 12 months."

The discontinuation rate was fairly high (~40%) in both arms of the trial, but a researcher said this was not due to problems with Estorra. He said, "Those who discontinued due to lack of efficacy was a very small minority." He also said the metallic taste that occurs the next day was not a major reason for discontinuations – and has not been a big deal in Europe with zopiclone.

Among the interesting points the principal investigator made about this trial:

- Throughout the trial and the extension, patients ***self-reported data weekly*** on the same day and at the same time via interactive voice recorder; patients then recapped the entire week. Generally, they rated themselves more alert and said they had a better ability to function on Estorra than on placebo (about a one step improvement on a 1-10 scale).
- All endpoints were subjective.
- A researcher suggested the dropouts were probably gender and age related.
- The infections reported with Estorra included: 2 colds, 1 chest cold, 1 common cold, 1 head cold, 2 upper respiratory infections, 2 tooth infections, 1 skin infection, etc. An investigator participating in an Estorra trial wondered, "Is the drug immunosuppressing people?"
- Patient compliance with dosing was monitored by doing pill counts periodically.
- The principle investigator was not certain if prior malignancy was part of the exclusion criteria.
- In female patients, menstrual cycle lengths were watched and estradiol levels were monitored through blood tests at the start and finish of the trial. A Sepracor official said, "Endocrine changes did not occur in humans."
- Patients did as well or better during the open label phase as they did in the first six months, which an investigator said "could have been a delayed placebo effect."
- There were no DSST measurements in this trial. An investigator said, "This study does not assess residual effects the morning after."
- Patients generally did worse in the last month of the trial, and an investigator said this was due to some patients (20%) going off drug a few days before the last call-in occurred.
- There were no severe side effects when the drug was stopped – including no seizures – but an investigator said he didn't now if patients rebounded when the drug was stopped.
- Estorra is additive to alcohol.
- Asked if he would tell patients they could drive the morning after taking Estorra, an investigator said, "There is no difference from Ambien."
- There is no food interaction with Estorra, and no drug-drug interaction, including no interaction with Paxil (GlaxoSmithKline, paroxetine). It is metabolized by the CYP450 pathway.
- The drug has a 6.5 hour half-life, but it tends to be metabolized more slowly in the elderly. An investigator said, "No doubt it will be studied at a lower dose in the elderly."
- At 3.5 months, Estorra reduced sleep latency about 15 minutes, increased TST about 45 minutes, decreased WASO about 15 minutes, and decreased the number of awakenings by about 50%-75%.
- Asked how PCPs would react to the metallic taste issue, an investigator said, "My sense is they will listen to how patients react to the efficacy."

Results of Estorra Study 190-049

Measurement	Placebo n=195	Estorra n=593
Patients randomized	195	593
Patients completing trial	56.6%	60.5%
Discontinuations	43.4%	39.5%
Patients entering open label phase	111	370
Completion of open label phase	78.5%	82.2%
Any adverse event	70.8%	81.1%
Severe AE	11.3%	12.1%
Serious AE	1.0%	2.9%
Chest pain	0.5%	0.5%
GI disorder	0.5%	0.5%
Deaths	0	0
Headache	19%	19%
Infections	7%	16%*
Metallic taste	0	26%

*p<.05

Median Quality of Sleep Rating with Eszopiclone

Patients	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Estorra	34	19	25	13	9	7
Placebo	22	7	5	6	1	1

Six-Week Results: Study 190-046 in Chronic Insomnia

In this trial, adults were given 3 mg of Estorra for 44 consecutive days and then followed for another week. The patients were given morning questionnaires to capture subjective efficacy and evening questionnaires to capture subjective next day function. PSGs were used to established objective efficacy.

Researchers concluded that Estorra:

- Significantly reduced LPS and significantly increased sleep efficiency at both doses
- Decreased objective WASO
- Improved the subjective measures of sleep
- Had subjective efficacy consistent with objective findings
- Produced a DSST score similar to placebo
- Did not induce tolerance or cause rebound or withdrawal effects at either dose
- Was well-tolerated over 44 days

Results of Estorra Study 190-046

Measurement	Placebo n=99	2 mg Estorra n=104	3 mg Estorra n=105
Completed	94	97 (1 nausea, 1 headache, 1 flu)	101
Adverse events	51.5%	66.3%	70.5%
Serious adverse events	0	0	0
Back pain	7.1%	N./A	3.8%
Headache	12.1%	N/A	16.2%
Pain	8.1	N/A	3.8%
Somnolence	3.0%	N/A	7.6%
Pharyngitis	10.1%	N/A	8.6%
Unpleasant (metallic) taste	3.0%	N/A	34.3%
Discontinuation due to adverse events	18.2%	N/A	15.2%

Members of the audience questioned the presenter:

Q: *What happened between nights 29 and 44?*

A: "Night 29 is the last night of objective PSG data. Between those dates, the subject took the drug at home. So we have subjective data to 44 days and objective data to Night 29. All subjective data were through Day 44 – and withdrawal adverse events were reported on Nights 45-46 through the exit visit at up to Day 53."

Q: *How did Day 29 compare to baseline?*

A: "There was increase in latency to persistent sleep and an increase in WASO as well...so there was some loss of therapeutic effect upon abrupt discontinuation of treatment...but the values did not return to baseline or exceed baseline."

Q: *How does Estorra compare to Ambien? What's novel about Estorra?*

A: "One of the most prominent differences is the half life... Ambien's half-life is significantly shorter than Estorra's, but both bind to the same receptor complex."

Q: *Would the results have been the same if the DSST were done two hours earlier?*

A: "I have no opinion on how DSST impairment would be if the test were administered earlier. I think it is reasonable to say there is a cutoff point where if you move it early enough, you will find impairment as with any hypnotic…but testing was not done then. At this time point, there was no impairment…and dosing at home was at bedtime…so patients were taking it right as they got into bed and we did not see reports of significant adverse events with next day residual sedation."

In an interview, the principle investigator was asked about:

- **DSST**. "DSST is not a functional test for driving or using heavy machinery. It is a test of psychomotor performance, not a functional test, but it is the currently accepted standard to assess next day residual impairment…I don't know of any drug development programs in which driving programs are required for approval…In my opinion, there is no data to suggest next day impairment…In my opinion, there is no reason not to be comfortable with a patient driving to work the next day."

- **Toxicity**. "The adverse events are pretty good. There were only three withdrawals at 300 mg because of adverse events. The retention rate was very high – 93%-96%, and you would expect people to drop out more than that…There was no chest pain in this study."

- **Comparison to zopiclone**. "I think of these as two different drugs. It is important to acknowledge that the drug and the dose is different and take the clinical trial data and accept it just as you would a clinical trial of any new agent…Let the data speak for itself. I don't think you can extrapolate from the racemic to the isomer."

- **Choosing among the new agents.** "I don't know how these medications will be positioned…I guess that is the marketers' job…but there are differences enough in them that they could occupy different niches in the market…but look at duration of action, effects on sleep with a drug like Sonata v. Estorra. The difference in therapeutic value there is obvious -- a very short acting drug vs. a longer-acting drug…Prescriptions will be tailored to the needs of patients…with Estorra we see effects on sleep maintenance...but if a patient needs only sleep onset and not sleep maintenance, then there are other choices available – Sonata, Indiplon or something else…I envision continuing to use more than one of these agents. They will all be used…and I think they will help lead to greater identification of sleep disorders."

Issues that have been raised about Estorra include:

- **Appropriateness of the timing of the DSST test. This** was 9-9.5 hours after dosing. Experts said that 8 hours is standard, but anything in the 8-10 hour range is probably acceptable, so this probably is not a problem for approval.

➢ **Interaction with alcohol.** There is some interaction, but an expert said it is "minimal."

➢ **Lack of big pharma partner and questions about the ability of SEPR to sell this drug itself.** A Sepracor source said the company isn't looking for a partner, that it intends to sell the drug itself.

➢ **Possible concerns at the FDA with the entire cyclo-pyrrolone class.** This suggestion was made but has not been confirmed.

➢ **Repeat of p53 knock-out mice trial.** Sepracor reportedly did this trial twice, but that report was not confirmed. Sources thought it unusual that this test would be done twice unless required to do so.

➢ **Similarities of eszopiclone to zopiclone.** An expert said, "They are virtually identical."

➢ **Size of the six-month study. Were too many healthy patients dosed?** No, these were insomniacs.

➢ **Three study patients in one trial suffered chest pain.** Experts were unconcerned with this reported adverse event, saying it occurs in all trials and with placebo as well.

➢ **Use of median, not mean, values.** In the company's oral presentation median values rather than mean values were used, and that caused some raised eyebrows since everyone else used mean values.

➢ **Sleep maintenance. Is sleep onset maintained over six months, or is there loss of efficacy after Month 4?** The six month trial doesn't appear to show any loss of effect after four months. To the contrary, there appears to be a slight improvement in sleep maintenance after six months when the open label period started. An investigator said this was probably a "delayed placebo effect."

➢ **Mammograms.** There was a report that all women in the six-month study were required to have mammograms, but Sepracor officials and researchers denied this. However, a Sepracor official confirmed that women in the six-month trial had their menstrual cycles and estradiol levels monitored (through blood tests at the beginning and end of the trial).

➢ **Timing of the patient self-reports in the six-month study.** Patients called in once a week to review the entire week. These were self-reports to an interactive telephone voice recording.

NEUROCRINE BIOSCIENCE/PFIZER'S Indiplon (NBI-34060)

An Indiplon researcher said there are two Phase III studies running more than six-months (one with the IR formulation and one with the MR formulation). He also insisted that the toxicology studies of indiplon have been "totally clean." There also is an open label study of more than 12 months in both IR and MR.

Asked what the advantages of indiplon are over other hypnotics on the market or in development, he said," "The half life of indiplon is shorter, and you might infer that this means less next day, residual effect…The IR formulation has great efficacy with minimal net-day residual effect, and the MR formulation will be the first sleep maintenance drug without residual effect." However, he said no functional residual effect studies are currently underway or planned at this time.

Six Phase II trials of indiplon have been completed:

- One IR in elderly insomniacs.
- One IR in adult insomniacs
- Two trials in health patients.
- One MR trial in elderly insomniacs.
- One MR trial in adult insomnias.

Indiplon-Moderate Release (MR)

A researcher presented the results from a randomized, double-blind, placebo-controlled trial of a moderate release formulation of Indiplon (Indiplon-MR) in elderly patients (age 65-75) with sleep maintenance insomnia. The trial tested the safety and tolerability of four doses – 10 mg, 20 mg, 30 mg, and 35 mg. The half-life of Indiplon immediate release (Indiplon-IR) is 1.5 hours, and the MR formulation is designed to extend the duration of action, providing sleep maintenance as well as sleep induction.

Indiplon-MR in Sleep Maintenance Insomnia

Measurement	Placebo	10 mg Indiplon	20 mg Indiplon	30 mg Indiplon	35 mg Indiplon
Awake after sleep onset	103	102	87*	82*	83*
Awake time during sleep	88	82*	67*	68*	65
Number of awakenings after sleep	8.8	7.5	7.1	6.5	6.1
Mean subjective TST	340†	360†	382†	390†	390†
Mean number of awakenings	2.6*	2.2*	1.6*	1.5*	1.3*
Mean subjective sleep latency	50†	25†	18†	20†	N/A
Mean number correct on DSST	55	54	54	53*	50*
Adverse events	7%	8%	7%	17%	17%

* p<.05 † p value unknown

In this trial, 79 patients were enrolled, and 60 completed. Six discontinued for adverse events (none serious), three dropped out for protocol violations, and 10 reportedly were enrolled who did not meet entry criteria and were dropped before the blind was broken. The DSST and other daytime task measures were administered 30 minutes after wakening or about 9 hours post-dose. Researchers concluded that Indiplon-MR promoted sleep onset and sleep maintenance on all key PSG and subjective measures at the 20 mg, 30 mg, and 35 mg doses (but not the 10 mg dose). The drug also was free of residual effects and an increase in adverse events only at the 20 mg dose.

Indiplon and Alcohol

A randomized, placebo-controlled, three-way crossover study in healthy adults found that the co-administration of Indiplon 10 mg and alcohol (to a blood level of 0.07) did not demonstrate any PK or PD interactions. A researcher said, "When the drugs are combined:

- DSST showed a slightly greater but non significant mean change from pre-dose values for the combination than for Indiplon alone at one hour post-dose…We clearly did not see an additive effect of the combination.
- On SCT, there were similar peak effects at one hour post-dose with the combination similar to Indiplon alone; there was no additive effect.
- There was a greater effect of Indiplon alone on sedation vs. alcohol alone, but the combination showed no greater effect than Indiplon alone."

A researcher concluded, "The addition of alcohol to Indiplon produced a non-significant decrease in DSST scores at the expected C_{max} and had no effect on any other psychometric test. It was well-tolerated when administered alone and concomitantly with alcohol in these healthy subjects…(but) I suspect at high enough levels of alcohol this drug could be just as much a date rape drug as anything else.

Indiplon and Alcohol

Measurement	Alcohol	Indiplon	Combination	p-value
DSST number correct	-11.5	-15.2	-20.0	p=.22
SCT number correct	-27.4	-29.7	-34.7	p=.38
VAS (mm)	11.1	25.7	17.1	p=.52
PVT (msec)	20.9	53.7	51.8	p=.89
Adverse events	20%	22%	N/A	N/A

Four Indiplon posters were presented at the meeting, but none are believed to include new data:

1. Indiplon-MR study. A placebo-controlled, double-blind, parallel group trial looked at 40 mg Indiplon-MR in a transient nighttime venipuncture model of 18 healthy young males (age 19-42). There was no statistically significant difference reported in next day DSST, VAS or SCT. The percent of patients reporting good to excellent sleep: 62% with indiplon and 39% with placebo (p=.036). There was no statistically significant effect on the number of awak-enings, and a researcher speculated that this was due to the "severity" of the model and the venipunctures. There was a statis-tically significant increase in LSO, sTST and sleep quality.

2. A sleep initiation study. This study of experimentally-induced transient insomnia in healthy subjects which looked at the drug's effect on sleep initiation at 15 mg and 30 mg. Researchers concluded indiplon causes no residual effects and does not decrease alertness. The most common adverse events were headache (2.6%, asthenia (2.2%) and somnolence (1.3%) and were equivalent across the arms.

Measurement	Placebo n=76	15 mg Indiplon n=76	30 mg Indiplon n=76
Subjective latency to sleep onset	46.9 minutes	25.0 minutes	23.0 minutes
VAS	49.4	51.4	
DSST	53.9 pre 55.7 post	55.5 pre 55.1 post	55.2 pre 55.8 post
SCCT	104.1 pre 104.9 post	106.7 pre 106.4 post	106.0 pre 106.2 post
Adverse Events	11.8%	10.5%	9.2%

3. Safety and Efficacy of Indiplon-IR in elderly patients with primary chronic insomnia. This was a randomized, double-blind, placebo-controlled, four period crossover, dose-response study of 42-patients. There was no statistically significant difference in DSST, VAS or SCT vs. placebo.

Measurement	5 mg Indiplon	10 mg Indiplon	20 mg Indiplon	Placebo
Primary Endpoint: Mean LPS (minutes)	13.8	10.4 *	9.8 *	25.2 *
Mean TST (minutes)	363.7	372.1 **	385.6 *	354.4
Mean Latency to sleep	28.8 **	24.7 *	20.2 *	41.8
Sleep quality	3.3 **	2.9 *	2.7 *	3.7
Subjective TST	340.6	351.3	368.6	314.1
Mean DSST	53.8	52.9	52.0	54.7
SCT	110.2	109.2	112.0	11.04
VAS	28.6	28.5	26.7	29.9
Adverse events	20%	15%q	28%	20%
Somnolence	7%	4%	6%	2%

*p£.001 **p<.05

4. Tolerance study. A randomized, double-blind, parallel group, dose escalation study looked at 3 doses of indiplon given at 8 am in the morning to 30 healthy, young (age 22-41) males. Researchers concluded there was the same pattern with indiplon as with sedative hypnotics. QEEG showed a consistent and dose-related decrease in alpha waves, increase in beta waves and no change in delta/theta waves vs. placebo.

Measurement	10 mg Indiplon n=10	30 mg Indiplon n=10	45 mg Indiplon n=10
T_{max} (hours)	1.31 pre 1.45 post	1.54 pre 1.96 post	1.71 pre 1.79 post
C_{max}	4.33 pre 3.31 post	13.54 pre 15.72 post	15.43 pre 14.28 post

TAKEDA'S TAK-375

This selective melatonin ML-1 receptor agonist is in Phase III trials. TAK-375 is not a racemic but a single enantomer with an "S" configuration. It is 1,000 times more selective than melatonin for ML-1 over the ML-2 receptor. It has a half life of about 1.9 hours. It's major metabolite, M-II, is only one-fiftieth as potent as TAK-375. It is likely that Takeda will seek approval for several doses, probably 8 mg, 16 mg, and 32 mg. A speaker said, "TAK-375 appears to have sleep-promoting effects despite a mechanism distinct from current hypnotics." Another speaker said, "Giving melatonin at bed time lowers core body temperature, and that in and of itself induces sleep."

Takeda may succeed where experts expect Estorra to fail – in avoiding the benzodiazepine class label – because it works by a different mechanism. An expert said, "All (the new agents) but TAK-375 are benzodiazepines. It is too early to tell the relative safety of TAK-375. It will probably be a lot safer, but we need studies to show that. If TAK-375 is no more effective than melatonin, it won't go anywhere. The jury is still out; the studies so far are only small numbers."

Some of the points a researcher made about TAK-375 include:

- **Duration of action.** He commented, "The parent activity ends at four hours. The metabolite keeps working for 12 hours, but it is less potent, so the overall activity is about eight hours.
- **Long-term trials.** A six-month, pivotal Phase III trial began about two months ago, and the data is expected to be presented at APA 2004.
- **Alcohol.** An interaction with alcohol study has been completed, but the data has not been fully analyzed. He doesn't think alcohol interaction will be an issue with TAK-375 or will be clinically important.
- **Food.** Food decreases the absorption time slightly (from one to two hours), so the drug should be taken on a empty meal.

The major critique of TAK-375 is the discrepancy between objective and subjective findings in the trials. So far, Phase II trials appear to show a positive effect from the drug by objective standards but not by subjective standards. A Takeda researcher said, "It is rare to see a lack of observation between objective and subjective responses… Certainly, there were subjective reports that were positive, and at one data point it was positive but the trial was not powered to look at subjective measures. But I would agree that we generally expect to see more subjective perception of promotion of sleep with this degree of effect on objective measures."

Experts generally believe that, at best, TAK-375 will be the least effective of any hypnotic – but without the baggage that attaches to the benzodiazepines. If this proves true, the question will be whether doctors will use TAK-375 only if a patient has side effect problems with another agents, or whether doctors (particularly primary care) will start patients on TAK-375 and only switch to another agent if TAK-375 doesn't work. Sleep experts questioned at the meeting were split on this.

In its trials Takeda is using VAS, DSST and memory recall to measure residual effect. The DSST tests are administered 8-9 hours post-dose. Animal toxicology data so far reportedly has shown no problems. An official said, "The data we have shows TAK-375 works, and the preclinical data indicates it works better than melatonin."

An investigator in the TAK-375 trials said the FDA wants at least two and often three pivotal Phase III trials for hypnotics. He is participating in a six-month Phase III trial measuring DSST, VAS, PSG and monthly PVT. He said he hasn't seen any problems with enrollment, but noted that there is a lot of competition for study patients right now. His impression: "TAK-375 is the least potent but has the fewest side effects of the hypnotics…It would be marketed to people who can in no way have a hangover or who are on other medications."

There were several TAK-375 posters, including:

1. Elderly. A study which showed that the elderly (age 63-79) have a higher systemic exposure to TAK-375 than younger patients (age 18-34). There was an increase in AUC and C_{max}, a longer half life, and a decrease in drug clearance in older patients. Somnolence in the elderly also was slightly greater than for younger patients…There is hardly any hangover effect. This study suggests, a researcher said, that elderly patients should be started on the lowest available dose (which probably will be 8 mg) and then titrated up as needed. He said, "When patients are over 65, you probably should start them on 8 mg and then titrate that up. The most typical dose will be 16 mg."

TAK-375 Monkey Study

Measurement	Melatonin	TAK-375	Ambien
Latency to sleep onset (LSO)	Reduced LSO but not in a dose dependent manner	Reduced LSO in a dose dependent manner	No effect on LSO
Total duration of sleep	No effect	Increased total duration of sleep	No effect
Behavior	No effect	No effect	Highest dose caused sedation
Effect on EEG	None	None	Increased high free components (>14 Hz) in non-REM sleep

2. Monkeys. Takeda researchers presented a study comparing melatonin, TAK-375 (.003 - .03 and .3 mg/kg) and Ambien (1-3-10 and 30 mg/kg) in 22 monkeys.

3. PK. A 60-patient study in healthy adults looked at the PK characteristics of this agent. Researchers found:

a. Mean AUC and C_{mx} increased with dose.
b. Mean half life was 0.83 to 1.90 hours.
c. Mean DSST and VAS were equivalent to placebo.
d. The most common side effects were somnolence and nausea.
e. No evidence of residual effects with any dose.

4. Gender sedation. Another study which found that when TAK-375 is given in the morning, it is equivalent to placebo in terms of DSST, memory, observer and self-rated sedation in men, but that women reported slightly more sedation than with placebo.

TAK-375 in Transient Insomnia

Measurement	Placebo	TAK-375 16 mg	TAK-375 64 mg
PSB latency to persistent sleep	~22 minutes	~11 minutes	~12 minutes
Subjective sleep latency (minutes)	30.3	21.3	24.3
PSG Total sleep time	~412 minutes	~424 minutes	~420 minutes
Subjective TST	407.0	424.0	416.6
Subjective sleep	3.3	3.1*	2.5
DSST ++	57.0	57.7	56.9
Subjective level of alertness +	2.9	2.9*	3.2
Subjective ability to concentrate+	2.8	2.8*	3.0
Adverse events	17.1%	15.9%	17.5%
Drug-related adverse events	8.9%	12.7%	14.3%
Headache	1.6%	7.1%	6.3%
Fatigue	0	2.4%	4.0%
Somnolence	2.4%	4.8%	2.4%
Nausea	0	2.4%	1.6%
Dizziness (ex vertigo)	0.8%	2.4%	0.8%

*** not statistically significant +lower is better ++higher is better**

TAK-375 in Transient Insomnia

This Phase II trial was a first-night effect model, with a parallel group design, of 375 normals, aged 35-60. TAK-375 was given 30 minutes prior to habitual sleep time, and the time in bed was limited to eight hours. TAK-375 cut sleep latency by 40%-50% from placebo. Side effects were similar among the groups, most commonly headache (~10%-11%).

- The 16 mg dose of TAK-375 showed no difference on morning DSST and no difference on a post-sleep questionnaire.
- The 64 mg dose showed no difference on morning DSST, and a small but statistically significant difference vs. placebo on a post-sleep questionnaire: Subjective alertness (p-.020), and ability to concentrate (p=.043).

Compared to placebo, subjective sleep latency was shorter and subjective TST longer in the 16 mg group. There were no differences on these measures between placebo and 64 mg. There was no apparent residual effect observed by DSST, but there was a small but significant reduction in subjective levels of alertness and ability to concentrate in the 64 mg group compared with placebo, though this effect was not observed with the 16 mg dose. Both dose were safe and well-tolerated with no apparent dose-related serious adverse events.

TAK-375 in DSM-IV Primary Insomnia

This was a randomized, double-blind, placebo-controlled, five-period crossover study of 107 patients (age 18-64) with primary insomnia. Residual effects were measured by VAS, DSST, subjective alertness and memory recall test, and there were no differences from placebo with any dose. Adverse events were comparable in all groups, with headache most common at about 6%. A speaker said this trial was not powered to show statistically significant findings on subjective parameters. There also was a relative lack of a dose response curve. In fact, the results were strikingly uniform across the doses.

Researchers found TAK-375:

- Was safe and well tolerated.
- Had no apparent dose-related patterns in adverse events.
- Significantly decreased latency to persistent sleep at all doses.
- Increased total sleep time at all doses, but the increases were not statistically significant.
- Had no residual effects.
- Some "sense of a trend to improvement" on the subjective measure of sleep latency but only at the 16 mg dose.
- Showed no statistically significant effect on the subjective measure of total sleep time.

TAK-375 in Primary Insomnia

Measurement	Placebo	TAK-375 4 mg	TAK-375 8 mg	TAK-375 16 mg	TAK-375 32 mg
Total sleep time (minutes)	~400	~410	~420	~409	~415
DSST	47.4	43.3	64.5	47.7	47.5
VAS	21.0	21.7	19.9	21.8	20.3
Word list memory test	8.0	7.9	7.7	8.0	7.8
Adverse events	19.4%	25.2%	18.3%	19.6%	21.4%
Drug-related adverse events	8.7%	10.7%	9.6%	8.4%	10.7%
Discontinued due to adverse events	0	0	0	0	0
Serious adverse events	1	0	0	0	0
Deaths	0	0	0	0	0
Headache	4.9%	5.8%	4.8%	4.7%	5.8%
Somnolence	1.0%	0	1.9%	3.7%	1.9%
Nausea	1.9%	2.9%	1.0%	0.9%	1.0%
Pharyngo-laryngeal pain	1.0%	3.9%	0	0	3.9%

*** p<.05**

Questions about TAK-375 that were asked and answered at the meeting:

Q: *Does TAK-375 have vasoconstriction properties like melatonin?*

A: "I don't believe so. A lot of those other effects are probably ML-2 receptor-connected, and this is very specific to ML-1."

Q: *Are there drug-drug interactions?*

A: "There are not a lot of pharmacokinetic concerns, but there are pharmacodynamic concerns. Anything that is taken with alcohol, you will have added pharmacodynamic interaction. Whether that happens with TAK-375 is not known at this point."

Q: *Does TAK-375 have a phase response curve, and does the time when it is taken affect the response?*

A: "There is a phase response curve. The full one is not worked out…but there will be data on the phase-shifting capability of TAK-375 in rats."

Q: *What is the effect of TAK-375 on sleep maintenance?*

A: "The increase in total sleep time is literally 100%, a reflection of the sleep latency effect. To date there is very little data to suggest TAK-375 will, in fact, ***maintain*** sleep."

Q: *Are there any studies ongoing of TAK-375 to treat the hot flashes associated with menopause?*

A: Not yet.

CEPHALON'S Provigil (modafinil)

Cephalon flooded this meeting with data on Provigil for a variety of disorders. Provigil is only FDA-approved for narcolepsy and idiopathic hypersomnia, but the emphasis on this meeting was on the use of Provigil for Shift Work Sleep Disorder (SWSD). In addition, studies were presented suggesting it may be useful in treating insomnia, the residual sleepiness in obstructive sleep apnea (OSA), and even cocaine dependence.

Cephalon's sNDA for Provigil seeks approval to treat excessive sleepiness associated with disorders of sleep and wakefulness. In support of this application, Cephalon studied excessive sleepiness associated with:

1. Disorders of sleep-wake cycle regulation with narcolepsy as the representative disease.
2. Sleep disruption, with obstructive sleep apnea as the representative condition.
3. Circadian misalignment, with shift work sleep disorder as the representative condition.

A modafinil researcher said he hopes the FDA approves the drug for all these purposes, but particularly SWSD. He said, "I think this medication offers a unique therapy for people who have problems of sleepiness...and we know this is effective and safe in narcoplespy, but thtere are a lot of other disorders for which this medication might be very beneficial. And if it is approved it will be the only drug approved in this disorder (SWSD)." Another researcher said, "SWSD is not all night workers, but a subset of them who meet certain criteria…I like to think of this disorder as a kind of occupational medicine model."

Shift Work Sleep Disorder (SWSD)

Cephalon sponsored a symposium on shift work and sleepiness. An expert at that session said night shift workers sleep about 100 minutes less in an optimal environment than day workers, "If you work nights, you will have a significant reduction in your sleep….The sleep for night shift workers is shortened and often disrupted."

The prevalence of shift work sleep disorder (SWSD) is estimated to be 2%-5% of Americans. People who have SWSD have the symptoms of insomnia or an excess of sleepiness that occurs as a transient phenomenon in relation to a work schedule.

The symptoms of SWSD are:

- Difficulty falling asleep at available sleep times
- Fatigue or sleepiness during the wakefulness period (working)
- Impairment on the job

Hypnotics as a treatment for SWSD:

- Provide 30-60 more minutes of sleep per night.
- Short-acting benzodiazepines increase total sleep time by 30-60 minutes in simulated situations and probably do better than that in real shift workers.
- May mildly improve alertness during night shift hours.
- May be more helpful in people in their 40s and 50s than in their 20s and 30s.

Countermeasures:

- Napping – but long naps in the evening are not always practical, and short naps during the shift are usually not allowed.
- Hypnotics – but some individuals prefer not to use them.
- Caffeine – but tolerance and side effects (CNS, CV, GI) may occur.
- Melatonin – but the efficacy is not well established, safety has not been studied, and the risk:benefit of an increase in phase shifting is unknown.
- Light exposure – but this is often impractical, and the risk:benefit of increased phase shifting is unknown.

Provigil may not be for every shift worker, but it will help a lot of people, experts predicted. A modafinil researcher said, "I really think this is not for every shift worker. There are some workers who have what's called shift work sleep disorder, which is characterized by a particular constellation of symptoms…What we should tell people is that if you are a shift worker and are having trouble, you first need to attend to those aspects of life that might be problematic…and then people need to talk to doctors and sleep specialists to be evaluated…Most people who have suffered from shift work sleep disorder have simply not come to the attention of a physician. It was a disorder often not diagnosed and probably not treated because there haven't been available treatments. Now the availability of treatment will bring this into the context of primary healthcare, where now a patient can report symptoms to a doctor and have them recognized and treated…With this (SWSD) we are where we might have been with antidepressants 50 years ago…I think this (Provigil) will help a lot of people."

Primary care physicians could prescribe Provigil for SWSD, but sleep experts hope they refer the patients to them for a work-up first. One sleep expert said, "Just as primary care doctors refer sleep apnea patients, I think they will want to refer these patients."

A double-blind, placebo-controlled, parallel group study was conducted over 12 weeks with 200 mg Provigil taken 30-60 minutes before each night shift vs. placebo. Twenty-eight sites participated. Participants, who were age 18-60 and had to work at least 5 night shifts per months with at least three of these consecutive, kept a daily electronic diary at work.

The trial was advertised with a toll-free number for interested people to call, and that generated 4,533 responses. Of these, only 5% (209) were found eligible for the study, but a speaker said this was in line with other trials with similarly complicated inclusions and exclusion criteria. Of these, 90% permanent night shift workers and 10% rotating shifts, with 94% having >10 night shifts per month. The participants came from a variety of professions: 29% worked in healthcare or social assistance, 12% in manufacturing, 11% in transportation/warehousing, 10% in administrative/support services, etc.

Researchers concluded that Provigil significantly improves both subjective and objective measures of wakefulness and sleepiness. Provigil patients also experienced significant improvements in alertness and vigilance, as measured by PVT and patient diaries. The effectiveness of the drug was observed at all dose levels evaluated, including the currently approved dosage of 200 mg/day.

Trial of Modafinil in Shift Work Sleep Disorder

Measurement	Placebo	Modafinil	Explanation
Sleep efficiency	74%	74%	---
Mean Multiple Sleep Latency Test (MSLT) 2-8 am (in min.)	2.1 pre ~2.2 post	2.0 pre ~4.0 post*	0-10 is sleepy, 11-20 is alert
Mean Karilinska scale (12m-8am)	7.1 pre ~6.8 post	7.3 pre ~6.0 post*	6-9 is sleepy, 1-5 is alert
PVT lapses (1-7 am)	22.5 pre ~30.0 post	24.3 pre ~20.0 post*	Lower is better

*p<.05

Among the interesting Provigil posters:

- A U.K. study in sleep-deprived middle-aged volunteers which had a "hint" of improved cognition with Provigil.
- A study that found Provigil increased cognitive functioning chronic pain patients with sedation caused by opioid analgesics.
- Two cardiac studies which found no negative effect of Provigil on: heart rate, blood pressure or QT prolongation. A cardiologist who conducted these studies said, "I'm trying to get Cephalon to study Provigil in the fatigue of heart failure."

Insomnia

The traditional approach to insomnia has been to treat the patient's sleep symptoms so that the patient feels better during the day. However, a researcher did an eight-week study that may change some thinking about insomnia. He found: "There is a hint that modafinil alone might have the capacity to

increase sleep latency…Modafinil alone does not negatively affect sleep continuity in patients with primary insomnia, and in combination with CBT (cognitive behavioral therapy) for insomnia does not significantly alter treatment outcome. Modafinil appears to reduce the daytime sleepiness associated with CBT treatment…I'm not so sure that modafinil alone won't work. We use 100 mg once in the morning. My sense is that is a mistake, and maybe we should split the dose."

Cocaine Dependence

A small, open label study found Provigil improved the symptoms of cocaine withdrawal and improved treatment retention in patients with cocaine dependence. Anecdotal subject reports found that cocaine addicts on Provigil had a sense of well-being, which might have been an anti-craving effect. Provigil also appeared to blunt the cocaine euphoria and reduce craving. A double-blind study is underway at a higher dose (400 mg/day) vs. placebo.

Cephalon's Gabatril (tiagabine)

Cephalon is running two small trials of Gabatril in insomnia – one in non-complaining elderly patients, and one in primary insomniacs. Data is not expected to be available for several months. On the positive side, an expert said there is a suggestion that Gabatril increases total sleep time; but on the negative side, it appears to have a food effect (food delays the onset of action of the drug).

OTHER PRODUCTS

ORPHAN MEDICAL'S Xyrem (sodium oxybate)

Despite having to overcome negative publicity as GBH, the date rape drug, Xyrem is catching on with sleep specialists. It is approved for treatment of cataplexy associated with narcolepsy, but it is being used off-label to treat narcolepsy (with or without cataplexy) and fibromyalgia. The company currently is conducting trials in both narcolepsy and fibromyalgia, and plans to submit an sNDA for excessive sleepiness associated with sleep disorders. A doctor who uses Xyrem said, "Xyrem takes longer to work than Provigil and you have to do more up titration, but the advantage of Xyrem is that, over time, you can ease patients off their stimulant medication to keep the patient awake and to treat the cataplexy. And there are little or no side effects with Xyrem…I try to put all the patients I can on Xyrem, but Xyrem costs $500-$800 a month, and insurance companies generally require patients have both narcolepsy and cataplexy to cover it…I hope Xyrem use grows. It is a ***very*** effective drug…I had an FBI agent on high dose stimulants, and when I gave him Xyrem, he was able to stop all the stimulants; he did great on Xyrem."

An interesting potential use for Xyrem was discussed – fibromyalgia. A researcher reported on a small, open label in which virtually every fibromyalgia patient reported improvement in fatigue and pain scores with Xyrem. He said, "Patients have stayed on the medication for up to 40 months without loss of efficacy."

Researchers also discovered that it is possible to identify which patients have fibromyalgia by studying their alpha waves. An expert said, "Fibromyalgia has been a disease of exclusion...and we believe these data suggest that, with a good history and a good physical, the sleep lab can be used to make a diagnosis using objective criteria (alpha waves)...This need no longer be a diagnosis of exclusions."

A double-blind, placebo-controlled crossover study replicated the results of the open label study, finding that fibromyalgia patients significantly improved clinically with Xyrem. A researcher said, "These studies showed these patients got so well that they stopped going to the chiropractor, herbalist, and acupuncturist, and came out of the healthcare system. They did things they hadn't done in a long time We took them from disability to inconvenience…We have improved the symptoms of patients with fibromyalgia who have alpha intrusion, which may be the vast majority of fibromyalgia patients, and so far that is what our experience suggests."

An investigator said he believes diagnosis and treatment of fibromyalgia will expand the patient base for sleep labs and sleep centers. He explained, "I believe this is very important to the field of sleep medicine…If this is correct and supported by other studies, it will significantly expand the patient base and patient mix of sleep labs and centers…I am not comfortable with Xyrem use in patients without some carefully diagnosed criteria…but we believe the vast majority of fibromyalgia patients will meet this criteria."

PFIZER'S Pregabalin

A double-blind, placebo-controlled, three-way crossover study looked at the sleep effects of pregabalin 150 mg TID (total dose 450 mg) compared to placebo and to Pfizer's Xanax (alprazolam, 1 mg TID) in healthy adults (age 18-50). Use of alcohol, caffeine and nicotine was not allowed during the study. Researchers concluded that pregabalin has a sleep activity profile that is significantly different from the benzodiazepines:

- Pregabalin reduced sleep onset and improved sleep efficiency, but through a different mechanism than alprazolam.
- Alprazolam suppressed Stage 3/4 (slow-wave) sleep while pregabalin enhanced slow-wave sleep.
- Treatment with alprazolam resulted in significantly increased sleep latency compared with pregabalin.
- Daytime sedation was modestly but significantly lower on pregabalin than alprazolam.

- Daytime activity levels as measured by Actigraphy were modestly by significantly higher with pregabalin than alprazolam.
- Pregabalin treatment was similar to placebo and significantly less impairing than alprazolam, in terms of brake reaction time and other psychomotor measures.
- In neuropathic pain, pregabalin would appear to have a therapeutic sleep-activity profile, especially since the patient population tends to be older and frequently is sleep disordered.

Measurement	Placebo	Pregabalin	Alprazolam
Getting to sleep (LSEQ change from baseline)	+3.5	+17.5	+18.8
Quality of sleep (LSEQ change from baseline)	+5.2	+17.4	+19.9
Reduction in number of awakenings >1 minute in duration	-1.1	-3.1	-1.0
Reduction in Total Awake Time (in minutes)	-3.2	-16.4	-7.2
Increased sleep efficiency	0.9%	5.3%	4.2%
Increased total sleep time	0.8%	5.6%	4.6%
Change from baseline in REM latency (in minutes) on Night 4	-10	+12	+58

Methylphenidate

A consultant was approaching poster presenters on behalf of a methylphenidate vendor to see if they wanted to participate in a trial of methylphenidate to treat various conditions, including seasonal affective disorder (SAD). A researcher said, "That is fair game to test. I'm not personally interested in doing that trial. Methylphenidate is not a terribly attractive drug."

MISCELLANEOUS

An interesting study is underway: An eight-week comparison of Ambien, Forest's Lexapro (escitalopram) and placebo to determine the effects on affective disturbance.

There also was an interesting talk on how patients use insomnia medications and Ambien in particular. The researcher found that, in his small sample (23 patients), the average number of pills taken each week was 3.4. He didn't see any evidence of dose escalation, and 61% of patients used the drug intermittently. He said, "Virtually no one is breaking the rules and taking more than 5 pills a week, and almost everyone is breaking up their pill taking schedule…These data should enhance our confidence that within an intermittent dosing scheme, patients do not have pill taking behavior that is consistent with toleration or habituation."

The data suggested that when patients use Ambien intermittently:

- The overall amount of medication used is lower than the maximum allowed (3.5 vs. 5 or more).
- Patients do not escalate the number of doses taken over time.
- The pattern of dosing is conservative and almost always on an interval schedule.
- The pattern of dosing is not significantly different from when patients are receiving placebo.

Researchers from the Army's Walter Reed Research Institute presented three posters looking at the efficacy of melatonin on daytime performance, either alone or in combination with Ambien. In one study of 80 patients, the combination of melatonin and Ambien synergistically increased daytime sleep, but the combination was only slightly more effective than melatonin 5 mg alone, and Ambien impaired performance. Thus, they concluded melatonin alone may be preferable for increasing daytime sleep, at least among people in the armed forces. In another study, melatonin 5 mg did not impair performance at peak concentration (one hour post dose). In the third study, the combination of melatonin 5 mg and Ambien 20 mg caused significantly slower reaction times. There also was some slowing in performance with melatonin 5 mg plus Ambien 10 mg at 1.5 hours but not at six hours.