Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Pfizer's Ambien and Wyeth's Sonata – along with benzodiazepines and antidepressants - are the most commonly prescribed medications for insomnia, but they are associated with sedation, rebound, abuse potential, dependence, and tolerance, and labeling for short-term use. Several new agents are in development to treat insomnia, including Sepracor's Estorra, Neurocrine Biosciences' Indiplon-IR, Takeda's melatonin agonist, and a sustained-release Ambien. However, none of these is generating much excitement, and experts doubt any agent acting on a benzodiazepine receptor – including Estorra and Indiplon -- will get a non-habituation label from the FDA. Doctors also are reserved on the outlook for Estorra because little data has been available.

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INSOMNIA UPDATE

Insomnia is the most prevalent sleep complaint in the general population. It is frequently a symptom of illness, severe stress, trauma, depression, etc. A one year prevalence study of insomnia in the U.S. found that one-third of people surveyed complained of insomnia. Other surveys of the general population have suggested that up to 49% of adults have brief periods of difficulty sleeping, and about 10% of adults have had insomnia lasting two weeks or longer, and 17% reported the symptoms as serious.

Insomnia is not a disease but a symptom resulting from insufficient sleep or sleep of poor quality. It is divided into two main categories:

- **Sleep onset insomnia** -- the inability to fall asleep naturally.
- **Sleep maintenance insomnia** -- the inability to stay asleep or to resume sleep after waking up in the middle of the sleep cycle.

Insomnia also can be categorized as acute or chronic.

- **Acute insomnia** generally is self-limiting, lasting a few weeks or months.
- **Chronic insomnia** lasts longer than three months and often needs to be treated.

Sometimes lifestyle and behavior changes are sufficient to resolve a person's insomnia, but other patients require over-the-counter or prescription sleep medications. Many of the prescription medications are labeled for short-term use only, so doctors generally prescribe them for no more than three or four weeks.

To check on the outlook for new medications to treat insomnia, nine sleep experts were interviewed. They indicated the four medications most commonly used in the U.S. to treat insomnia today are:

PFIZER'S Ambien (zolpidem). It has a short half life. Side effects include drowsiness, dizziness and a drugged feeling. A sleep expert said, "Ambien came along with the sense that it was going to have less tolerance and less withdrawal side effects – that it was safer in longer term use though it was only tested over four weeks…Ambien has a favorable half-life compared to the benzodiazepines, except Halcion (Pfizer, triazolam) which has a similar half-life." Another expert said, "Two intermittent-dosing studies of Ambien show it looks good and safe – at least on the nights when it is used. Long-term use has been a challenge because it is only approved for four-week use by label." A psychologist said, "The Z-drugs, including zolpidem, have a much better side effect profile than the benzodiazepines and are probably the most appropriate to prescribe." A Florida sleep researcher said, "Zolpidem is really the #1 prescribed agent in the U.S., and that has become a kind of mainstay of treatment for insomnia."

WYETH'S Sonata (zaleplon). Sonata is associated with fewer side effects than Ambien, probably because of its shorter half-life, but most sources described it as less effective. An expert said, "Sonata has a number of unique features. For instance, it has a shorter half life than anything else, so it is the shortest acting agent, which can be good or bad. Sonata is ideal for getting someone to fall asleep, and it can be dosed in the middle of the night if the patient wakes up, provided it is given four hours before (morning) waking, and that has been shown in a study. Sonata also has fewer problems with tolerance and habituation. It may have less motor and memory impairment than other medications. It does have some, but less than benzodiazepines. But its half-life may be too short for some people…Neither Sonata nor Ambien have been tested in long trials, but in open label trials, Sonata looks pretty safe in up to a year of use." Another expert commented, "Some people feel the dose is too low. Some think 20 mg is the right dose, and there is no 20 mg pill…The duration of action is on the short side…People like to use it in the middle of night, but that isn't in the label...and doctors are used to prescribing the drug HS (at the hour of sleep)…This is a drug that can be taken later in the night, but the company can't promote that because it never did middle-of-the-night efficacy studies, only middle-of-the-night safety studies."

Antidepressants, particularly trazodone (Geneva's Desyrel) but also mirtazapine (Organon's Remeron). Antidepressants are not approved by the FDA for treating insomnia, but they are used off-label for that purpose. They have been shown to improve sleep in people who are depressed, and they can be used long-term. A North Carolina sleep expert said, "People moved to antidepressants (from benzodiazepines) because they don't have abuse or withdrawal issues." An Ohio sleep specialist said, "There are a large variety of sedating antidepressants (such as trazodone). In fact, in a recent review…trazodone came up as the most frequently prescribed medication for insomnia even though there are no studies to support its use for insomnia, but there are a lot of studies of trazodone in depression."

Benzodiazepines, such as generic temazepam (also sold as Novartis' Restoril), oxazepam (Faulding's Serax), diazepam (Roche's Valium), alprazolam (Pfizer's Xanax), etc. These are still widely used off-label for insomnia. An expert said, "Temazepam was the top benzodiazepine prescribed, but after you stop it, you still have some residual cognitive problems." An Illinois doctor said, "If anxiety is a component, I may use Klonopin (Roche, clonazepam) – it's a nice, long-acting drug – or Xanax. The benzodiazepines still have a place, more for anxiety-related insomnia." Another expert said, "There is a hassle-factor with using drugs off-label, so I go to sister drugs like Klonopin and Ativan (Wyeth, lorazepam). Generally, people are scared about scheduled drugs, so they go to trazodone, which I don't think is as safe."

Pfizer and Wyeth have tried to distinguish Ambien and Sonata from the benzodiazepines, but sources generally lump them all together. A Pennsylvania sleep expert explained, "I tend to call all them benzodiazepine-receptor agonists because that is what they do…Ambien and Sonata are not technically benzodiazepines, but their action is identical to benzodiazepines. I prescribe whatever the insurance plan pays for. In many cases, my preference is to prescribe Ambien, but for a lot of the managed care organizations, that is not an approved drug or is not first line, so I more commonly prescribe triazolam, and the traditional benzodiazepines."

There are several drawbacks to the existing medications.

- An accredited sleep specialist from Ohio explained, "One problem is dependency, and then after that there is tolerance. If you continue to take a sleep medication for a long time, it does stop working, and once patients have taken it for three months, they become dependent on it to fall asleep. The newer agents claim they don't have as much rebound, but with the benzodiazepines you can get rebound insomnia."
- An Illinois sleep expert said, "For some people they simply don't work very well."
- A Michigan sleep expert said, "There is no data that tolerance or habituation occurs with any of these, but people are reluctant to use them on more than an acute basis. People don't like to use scheduled drugs, and they – Ambien, Sonata and the benzodiazepines – are all scheduled, and there is concern using them on a long-term basis because of the label…There is a fundamental misunderstanding about the treatment of insomnia. There is no published data to show Ambien or Sonata drugs lose their efficacy or cause tolerance. But, instead, they prescribe trazodone, which is not as safe or effective, and they prescribe a lot of benzodiazepines (Klonopin, Ativan, etc.) because you can give them longer."

An expert cited four reasons for physician reluctance to prescribe insomnia medications:

1. A general prejudice against treating insomnia.
2. A prejudice against the benzodiazepine class of drugs.
3. Concern by primary care doctors about use of any scheduled drug.
4. Labels that indicate they can only be used short term.

The key issues with existing medications are:

Side effects. Sleep medications can cause side effects after waking, such as daytime drowsiness or slowed reflexes. Depression of respiration is a problem with benzodiazepines but not with Ambient and Sonata. An expert said, "The most

common side effect with all these drugs is sedation. With some, the effect can last the next day…what is therapeutic at 4 a.m. is a side effect at 10 a.m. In the elderly there is evidence of an increased risk of falls and hip fractures, but there also is some evidence that insomnia itself is associated with falls and fractures."

Rebound. An expert said, "If you look at the Searle (Pfizer) data on Ambien, the data doesn't describe a rebound effect after one month of nightly use. Wyeth did a double-blind study comparing zaleplon (Sonata), zolpidem (Ambien) and placebo and showed that when the experimental medication was rapidly withdrawn (no taper) after one month of nightly use, there was a ***mild*** rebound with people coming off Ambien that lasted maybe 24 hours and then returned to normal. There was no rebound with the Wyeth drug (Sonata)…So there may be rebound with Ambien, but it is probably pretty mild and short-lived." Another expert said, "One thing that can occur is rebound, and it does happen with both short-and long-acting drugs. Usually, it lasts for a couple of days and the person ends up at the pre-treatment baseline, but it is self-limited."

Dependence/habituation/abuse potential. An expert said, "Physiologic dependence is thing a lot of people are concerned about." Another expert said, "One discontinuation phenomenon is withdrawal, which includes new symptoms that did not exist prior to treatment. That is pretty uncommon in people using single doses per day of these medications…The original problem also can come back. That is the real issue. We know insomnia tends to be a chronic or recurrent problem in at least 50%-85% of people who have it, so if you stop taking a short-acting drug, it shouldn't be surprising that people develop symptoms again. Many doctors and patients think that is withdrawal, but it isn't."

Depression of respiration – a problem with benzodiazepines but not with Ambient and Sonata.

Tolerance. An expert said, "Our practical experience says that for many people these drugs just stop working after a while. That's why we try not to use them chronically." A North Carolina sleep expert said, "One of the big concerns is that you lose efficacy over time. Even though some experts, like me, are less convinced the newer pills (Ambien and Sonata) are associated with tolerance and dependence, just the same, the FDA approved them only for short-term use and because they are controlled substances, most doctors are wary of prescribing them long-term – partly for fear of personal liability. If FDA says not to use something, doctors won't, so that puts us in a bind where we don't have any FDA-approved treatments for long-term use." Another source explained, "Insomnia has both initiating and perpetuating factors, which can include poor sleep hygiene or bad attitudes about sleep. Simply giving a sleeping pill may decrease sleep latency, but it isn't a long-term solution. Our approach is usually behavior and pharmacologic at the same time, so whether a drug lasts 30 days or six months really doesn't have that big an impact on long-term treatment for us." A Pennsylvania doctor said, "The evidence for tolerance is based on studies from 20 years ago looking at triazolam mostly, and most of those studies came from one lab. Subsequent studies looking at a wider variety of drugs, including Ambien and Sonata, really don't show tolerance the same way as the earlier studies. Tolerance is one thing that concerns people, but the evidence is not that strong. In some patients it may occur, but it is not an inevitable consequence, though some physicians believe that…There are four- or five-week studies showing continued efficacy over that time, and there are self-report studies using benzodiazepines not available in the U.S. showing 24-weeks of nightly use of mirtazapine and lorazepam, and they continue to show efficacy for 24 weeks…We also know from the anxiety treatment literature that, for anxiety, it is more commonly accepted to treat with the benzodiazepine class over a long period of time, and the general assumption is not that people get tolerant."

Lack of efficacy. An expert said, "Even the Ambien half-life can sometimes be too short. Patients can have trouble staying asleep, and the longer-half life causes next-day sedation."

However, several sleep experts said opinion is changing about the degree to which these side effects occur – especially with Ambien and Sonata.

- A Florida sleep researcher said, "Tolerance and dependence may be issues, but to a lesser degree than with the benzodiazepines. Those problems are a possibility, but they seem to be less of an issue, though they are still an overhang. Rebound is the same situation. It may occur but to a lesser degree than with the benzodiazepines, and there are lot of reports, especially with Ambien, that generally seem to be more positive in that regard."
- A North Carolina sleep expert said, "Habituation and tolerance have been the story for a long time, but a lot of sleep doctors don't buy that any more. There really is no good data that goes beyond about a month of continuous nightly use, but what data there is suggests that, at least for zolpidem (Ambien) and zaleplon (Sonata), neither tolerance nor dependence (indicated by withdrawal) is nearly the issue we thought. Obviously, the best data is placebo-controlled trials, and there are no placebo-controlled trials of nightly use of any sleeping pill that goes beyond about five weeks or so…There are double-blind, randomized trials of Ambien vs. placebo for intermittent use (with patients instructed to take it three or four times a week maximum), and that showed sustained efficacy up to three months or so. So, we are not as certain that the drugs poop out, at least not the new ones."

NEW AGENTS ON THE HORIZON

Ambien and Sonata are not considered a new class of agent, just incremental improvements on the benzodiazepines already available. An expert said, "Companies have mainly been

tweaking the duration of action of medications, and they found molecules that are not benzodiazepines but act on the benzodiazepine receptors, so it's been an evolutionary process." Another said, "There is nothing wrong with what is there already. We just need a clarification of the (usage) guidelines and an understanding of how to use the existing medications. There are very few drugs which doctors use that are as safe as these. In non-abusive personalities, they don't produce abuse…The issue isn't getting better drugs."

Most experts agreed that there is a need for new medications to treat insomnia, but none was particularly excited about any of the agents currently in development. A source commented, "Clearly there is a need for drugs where we don't have to deal with dependence and tolerance issues or rebound at all. Where things have been most lacking is in the sleep maintenance area, and that is where most of the (research) focus is. Sleep maintenance means keeping people asleep once they get to sleep, as opposed to initiating sleep. We want a medication that gets people to sleep quickly, keeps them asleep for the night and when they awaken, there is no residual carryover sedation…There are drugs currently being developed that generally look at the effects on subsets of the benzodiazepine receptor. Those agents generally are trying to improve sleep maintenance." Another expert said, "We need new agents, clearly…I hope these will be better agents. That what we're trying to figure out. I think so, but I'm not sure yet…My general feeling is that the older sleep drugs are okay but not terrific. There is clearly a lot of room for improvement."

What are doctors looking for in a new agent? A Florida doctor said, "If rebound, dependency, and a potential for euphoria, etc., are not issues, and if the drug acts quickly and maintains sleep throughout the night with no residual effects, that would be a big boon." A North Carolina doctor said, "I think that drugs that are similar in type of action probably are going to replace existing drugs. Not until we get something totally different in its mechanism will we look at treating people who are more hesitant themselves or will practitioners use them who are now hesitant about medications. A lot of practitioners right now have a fear of using drugs for sleep, particularly benzodiazepine-related drugs."

A key reason for this lack of enthusiasm about the new agents is lack of information. None of the experts questioned – and many of these were researchers working on one or more of these agents – have seen enough data on any of them to allow them to draw definitive conclusions. An expert said, "Really, the most effective way to get out of the bind is to collect data. We have a lot of conjecture. I think we should carefully look at risk and liabilities of these meds, too."

These experts generally agreed that it is unlikely that any agent acting on a benzodiazepine receptor will get a non-habituation label. Rather, sources predicted that the FDA would label those agents as habituating.

However, several sources said this is an area the FDA is looking at and where the agency's position may soften somewhat. A Michigan doctor said, "The FDA is looking at this whole issue, and they are sensitive to it. They don't want to force doctors to practice off-label. They are now willing to look at chronic data…I think they will put the long-term data in the label. They have agreed in principle to discuss long-term data in the label, but in what context is not sure. They are re-thinking this issue. They are not happy when people are using things not approved for this indication…(But) one fundamental thing won't change: they are scheduled drugs, and that won't change…People have to understand that drug abusers abuse them, not that the drugs cause abuse. The regulations set forth by the government are that anything that has the potential to be abused has to be scheduled." Another expert said, "Investigators and manufacturers have been trying to get the FDA's attention on this. At the NCDEU meeting in 2001, there was a discussion of longer-term approval of hypnotics…NIH won't fund longer-term studies because of the FDA labels, and the FDA says it can't change the label because there are no studies."

Sources also believe FDA labeling will be key to physician use of a new agent and lack of a non-habituation label would be a negative. A Florida doctor said, "There is always that specter that a lot of doctors don't want to get their patients hooked and create a series of other problems. So, sometimes that makes widespread off-label use difficult, and doctors tend to prescribe other agents without those problems -- but which have other sets of problems. Trazodone is widely prescribed and it may have less dependence and tolerance, though it is not 100% clear that is the case, but trazodone has other side effects – such as hypotension. I'm hopeful that the FDA, if the data (on the new agents) is solid, will move off the current labeling. If the companies don't get a good label, it will be harder to market the products. Doctors have become careful."

Among the agents in development are:

SEPRACOR'S Estorra

(referred to variously as es-zopiclone, S-zopiclone, esopiclone, and eszopiclone)

In February 2003, Sepracor submitted an NDA to the FDA for Estorra, a non-benzodiazepine cyclopyrrolone hypnotic, to treat transient and chronic insomnia. The NDA includes data from six placebo-controlled, Phase III trials in more than 2,700 patients. 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. For chronic, daily use, the company has completed a study of 788 patients, with six-month efficacy data and 12-month safety data.

Sources might be more enthusiastic about Estorra if they had seen more data on it, but they frequently commented on the lack of published or presented data on Estorra. Even researchers who participated in the clinical trials have not seen most of the results. Several sources said they expect to see

Estorra abstracts at the June 2003 Associated Professional Sleep Societies meeting in Chicago June 3-8, 2003, with publication likely soon after that. There also may be data on some of this and other new agents at the March 13-15, 2003, meeting of the American Society for Experimental NeuroTherapeutics. A source said, "Nothing has been published, but I think there will be six-month data (on Estorra) at APSS. That is the important thing to look at because it is a placebo-controlled trial. The trial's not perfect, but it will keep the debate open." Another expert said, "The data just hasn't been presented yet. It will be at APSS, and that suggests papers are not far behind." A third expert said, "It seems the company is holding up the data. Sometimes drug companies time data release to tweak the (stock) market. All that is really published on use in insomniacs has been in abstract form, and it was just an abstract; the full-length articles are still to be published." A fourth commented, "What matters is not what hypothetical properties the drug has, but the degree of investment the company has done to prove/disprove the properties. What is critical for Sepracor is showing they have double-blind studies proving no rebound and proving that there is no 'poop out' of the effect after a few weeks, and ideally extending the data beyond four weeks."

Absent this long-term data, sources were cautiously optimistic about Estorra. Among their comments related to:

Unmet need. "I'm enthusiastic, and I expect it will address a significant portion of persons with insomnia who have until this point not been optimally treated with what is available."

No Rebound. "What's interesting about Estorra is that it has been shown to be efficacious and safe in a six-month trial – and it helps people stay asleep…There was no rebound in that study; people did very well. They didn't specifically test withdrawal in that study, but the evidence indicates it doesn't have a withdrawal problem. It is longer-acting than Ambien, so it tends to help people stay asleep, and it has the longest study to date." Another source said, "Rebound has not been directly addressed. There are just very acute studies with a couple of weeks use, but those did substantiate it puts people to sleep okay. The following morning they took measurements of performance on some very simple psychomotor tests and asked patients if they felt sleepy or more alert, and paradoxically they said they felt more alert…The company spin is, of course, that they are more alert because they slept better…but a competing hypothesis is that the patient may still be hung over which the patients are not subjectively aware of. So, it is encouraging that people feel more alert, but that was self-reporting."

Possibly better labeling. "Any product for which the FDA allows the claim of efficacy beyond four weeks – if it were approved as a sleeping pill for use for two or three months -- would be a great. It would release doctors to treat patients for a longer period of time and would give patients potentially more access to these medications which doctors have been afraid to prescribe for longer than the FDA indication…I think it will be useful, but how useful will depend in large measure on things like – class labeling or whether the FDA gets more liberal."

OUS track record. "We have to acknowledge that this drug in its racemic form has been available in Europe and Canada for 15 years or so, and it has a good tack record there, with no major problems, so I expect the S-isomer would perform as well if not better. I think the R-isomer is pretty much inert and neither adds nor detracts, is just dead weight, so removing it just leaves Estorra with the good and none of the dead weight."

Fewer side effects. A Pennsylvania sleep expert said, "Presumably, there are less side effects with S-zopiclone."

Longer half-life. A source explained, "These drugs (Ambien, Sonata and Estorra) have subtle PK differences – for example, a different half-life. Sonata has a very short half life, so if the only problem is a difficulty falling asleep, it may be important. Ambien has a slightly longer half-life, so it is good for awakening. Something even longer would be good for problems all night…S-zopiclone lasts longer than Sonata, but what they (Sonata and Estorra) do in action is fairly similar. Some companies make a big deal of subgroup receptor selectivity, but whether that has practical implications is uncertain."

Sepracor reportedly is hoping to get a non-habituation label from the FDA, but sources were dubious that the company will be successful. A doctor said, "It may get class labeling, no matter how good the data is. Since it is a hypnotic, it may be treated like every other hypnotic -- which means short periods. That would be a pity, but it will be largely up to Sepracor to present overwhelming evidence and really clear-cut evidence – and then the FDA needs to yield a little." Another source said, "I can't see how it would avoid that (label)."

Without a non-habituation label, sources agreed that doctors will be reluctant to use Estorra for long-term as more than they use current medications long-term. A source explained, "Clinicians would get hung up on the labeling because of the liability issue. It would be a shame, I think. I would hope that Estorra gets a (non-habituation) label." Another expert said, "I don't know how the FDA will view it, but the data is there to show it can be used safely every night for six months. And labeling is really not limiting anyone. With (the existing) data, I would be comfortable using it longer (than four weeks)…Even if it didn't get a non-habituation label, I would be comfortable using it longer term. A label is only a few people's opinion; the data is better."

Even if Estorra gets a non-habituation label, some sources were not sure that would move it to the No. 1 position. A doctor said, "The net effect would be to give people more confidence to do something they already are doing in clinical practice anyway – using the existing drugs longer term. The

essential dilemma is that we have short-term treatments for a longer term problem."

NEUROCRINE BIOSCIENCES' Indiplon-IR
(NBI-34060)

This also targets a benzodiazepine receptor subset. In a Phase II trial of 228 patients, it showed a 49% reduction in time-to-sleep onset, and a side effect profile comparable to placebo. A North Carolina sleep expert said, "It has potential in sleep maintenance. There is both a regular and a modified-release version in development, so it may apply to both sleep induction and sleep maintenance. It has some good properties that may make it useful for long-term use – but there is no long-term data yet."

Pfizer recently signed a collaboration agreement with Neurocrine under which the two companies will jointly develop and commercialize Indiplon. Under the agreement, Pfizer will be responsible future development and marketing expenses for Indiplon and will fund a 200 person Neurocrine sales force to detail both Pfizer's antidepressant, Zoloft (sertraline) and Indiplon.

Neurocrine claims to have completed more than 50 clinical trials of Indiplon involving more than 3,800 patients and that "all results to date have been in line and have met expectations." Seven Phase III clinical trials of both an immediate release (IR) and modified release (MR) formulation are underway, with results expected in 2003.

The results of a completed Indiplon Phase III trial of 593 adults with transient insomnia reportedly found the drug safe, well-tolerated, and effective in achieving rapid sleep induction without next day residual effects.

The ongoing Indiplon-IR Phase III trials are focused on demonstrating the long term safety and efficacy in patients suffering from chronic insomnia. This program will include over 1,600 patients in the following four studies:

- A safety and efficacy study of two dose levels in approximately 200 adult patients with Primary (Chronic) Insomnia with the primary endpoint of LPS as measured objectively by polysomnography (PSG).
- A one-year safety study of two dose levels for the long-term treatment of chronic insomnia.
- The RESTFUL trial, a study of safety and efficacy of two dose levels in approximately 600 patients with chronic insomnia.
- A safety and efficacy study of two dose levels in approximately 360 elderly patients with Primary (chronic) insomnia.

The Indiplon-MR program has enrolled more than 600 patients in 14 clinical trials so far. The Indiplon-MR Phase III program is focused on proving efficacy in sleep maintenance. Three Phase III clinical trials have been initiated and will include more than 1,300 adult and elderly patients:

- The SLEEP trial, an ongoing study of long-term efficacy and safety in Primary (chronic) insomnia. This trial will assess two doses vs. placebo in approximately 600 patients with sleep maintenance insomnia (SMO).
- A 35-day inpatient/outpatient study in 300 elderly patients to assess SMO efficacy.
- A trial of 220 patients to assess safety and efficacy in the elderly for SMO.

TAKEDA'S melatonin agonist

This agent binds to the melatonin receptors in the brain to help to induce sleep. A source described it as "Interesting because it is a little different." Another expert said, "It has a different mechanism of action. All the other agents in development are related to the benzodiazepine receptor, though they vary in subtype binding, but this is a new mechanism." A third expert said, "This is very early, but it is interesting because potentially, it won't be scheduled." A fourth commented, "I haven't seen the data on that, but judging by the mechanism, I'm scientifically skeptical about it. What is more likely – what I expect from a melatonin receptor agonist -- is something that decreases alertness, which is not necessarily something that acts as a hypnotic…Actually, the most consistent effects with melatonin have been in healthy young people taking it in the middle of afternoon because that is when their biological clock is winding down."

SANOFI'S Ambien SR

Sanofi is working on a sustained-release form of its currently marketed Ambien. Asked how this compares to regular Ambien, an expert said, "There are no longer-term studies but it would be good for patients where Ambien doesn't act long enough."

NEW USES FOR EXISTING MEDICATIONS

CEPHALON'S Gabitril (tiagabine hydrochloride). This anticonvulsant is approved to treat epilepsy.

ORPHAN MEDICAL'S Xyrem (gamma-hydroxybutyrate). This medication is approved to treat narcolepsy associated with cataplexy and is used as a fibromyalgia sleep medication.

PFIZER'S Neurontin (gabapentin).