Insomnia Clinical Trials

Insomnia is the most common sleep condition affecting Americans. The National Center for Sleep Disorders Research at the National Institutes of Health estimates that 30-40% of the population has experienced symptoms of insomnia within the last year. The same poll indicated that the most common symptoms that people reported were trouble falling asleep and staying asleep.

The National Sleep Foundation (NSF) has conducted several nationwide polls regarding insomnia and has discovered common trends. Results of their 2002 poll reported that 63% of women, versus 54% of men, suffer from symptoms several nights a week. Other findings displayed variances in insomnia symptoms and age. Adults ages 18 to 29, for example, are more likely to experience insomnia than their older counterparts. Parents also showed to be more susceptible to symptoms of insomnia, 66% versus 54%.

Insomnia is the Latin term for “no sleep”.

Due to the high prevalence of insomnia, pharmaceutical companies have invested millions into the development of drugs aimed to cure the disorder. Like any other drug, clinical trials are a critical component of the development process and require special attention. This document will outline the importance of insomnia clinical trials and shed light on some of today’s common FDA practices.

Insomnia Defined

The term insomnia is comprised of several different variations, including: difficulty falling asleep, difficulty staying asleep, just having non-restorative sleep in general, or any or all of these. The most common type of insomnia is difficulty staying asleep – sleep maintenance, followed by difficulty falling asleep – sleep initiation or onset. These complaints are typically first diagnosed through patient self-reports. Insomnia itself might drive a patient to see a clinician, insomnia might be a perceived consequence of another problem (eg, congestive heart failure or chronic pain), or insomnia might be reported when the individual is asked about it specifically by the clinician. Most insomnia tends to be co-morbid, occurring at the same time as another medical condition – typically with psychiatric conditions such as depression or anxiety. It is hard to determine cause or consequence of insomnia in co-morbid conditions, but it is clear that insomnia, coupled with a co-morbid condition, creates a bidirectional vicious cycle that makes both conditions worse. Consequently, the prevailing thought is to treat both insomnia and a co-morbid condition at the same time.

Insomnia drives a great many individuals to their physicians seeking relief. The on-label class of pharmacologic agents used to manage insomnia is hypnotics, comprised of a variety of compounds with varying mechanisms of action designed to increase sleepiness and/or decrease arousal. Many of these medicines, such as the benzodiazepines (eg, Restoril, Halcion), have been available for years. Ambien (a nonbenzodiazepine that still binds to the benzodiazepine receptor, although only to specific subunits) was introduced in 1992 and quickly became a gold-standard. Since that time, other nonbenzodiazepines have been introduced, including hypnotics that

Insomnia is considered chronic if it occurs at least 3 times per week.

bind to other receptors in the brain, such as melatonin (Rozerem) and histamine (Silenor). Orexin antagonists (suvorexant), the newest members of the hypnotic drug class, have not yet been approved by the FDA. The past 20 years have seen an explosion in hypnotic medication R&D – a quest to create the fastest-acting, easiest-dosing, safest agent for the management of insomnia.

Ambien is the most commonly mis-used sleep drug.

Clinical Trial Study Participants

Any pharmaceutical company hoping to gain FDA approval of a new hypnotic obviously needs to demonstrate its safety and efficacy for insomnia. The challenge in doing so is that insomnia rarely occurs by itself, rather, its most conventional form is as a co-morbidity. So, to ensure that the drug is targeting the right condition, the most important inclusion criterion for subjects in clinical trials is the diagnosis of primary insomnia, ie, insomnia with no co-morbidities. Subjects typically need to meet DSM-5 criteria (see box), with symptoms occurring on at least three nights per week for at least three months, and the insomnia should not be attributable to another disorder. Any co-morbidity typically is considered to be an exclusion criterion (anxiety, depression, neurologic disorders, chronic pain, heart disease, etc). Study participants should be free of any clinically significant abnormal laboratory findings, electrocardiographic abnormalities, or vital sign abnormalities. It also is important to exclude subjects with a significant history of alcohol or drug use, as well as certain behaviors that can impact sleep, such as smoking, shiftwork, and recent travel across multiple time zones.

Most efficacy and safety trials include “adults,” typically individuals 18 to 64 years of age. “Elderly” cohorts also are common, typically enrolling subjects 65 years of age and older. Studying older cohorts is not only usually an FDA requirement, it’s an important consideration in a population that has some complicated treatment challenges and for which dosage adjustments are required. Older patients may not metabolize hypnotics in the same way that younger people do, resulting in higher blood levels that can represent a risk to the patient. Therefore, a lower dose often is tested in elderly subjects. Further, older adults often are frail or disabled (and more prone to falls), the prevalence of dementia is higher, and the likelihood of polypharmacy also is greater, so the need to assess hypnotics for safety is particularly important in this patient population. The importance of a well-defined patient population cannot be overstated, as multiple confounding factors can impact sleep and interfere with the ability to accurately assess the therapeutic value of a drug.

Polysomnography in Clinical Trials

PSG tracings are divided into 30-second periods or “epochs”. Therefore, each 8 hour tracing is divided into 960 30-second epochs.

In clinical practice, the diagnosis of insomnia is based on patient report. Patients describe their symptoms to their doctors, a diagnosis is made, and a treatment plan is developed. Overnight sleep testing, or polysomnography (PSG), is not required to render the diagnosis or develop a treatment plan unless underlying sleep disorders (e.g., sleep apnea, restless legs syndrome) are suspected. However, in clinical trials, the use of patient reports alone has not been considered sufficient to document the efficacy or safety of an investigational drug being developed for insomnia. Objective data from PSG studies have been required for this purpose. PSG involves the collection of multiple physiologic measures during sleep including measures of electroencephalographic (EEG), electrooculographic (EOG), electromyographic (EMG), and electrocardiographic (ECG) activity, as well as measures of airflow, respiratory effort, and blood oxygen level. PSG recordings typically are performed in a controlled, laboratory environment, and are conducted for an eight hour period during the subject’s normal sleep time. These recordings provide a minute-by-minute tracing of the subject’s sleep, allowing us to determine if the subject is awake or asleep at any given time. They also allow us to examine brainwave activity to “score” sleep so that we can provide a detailed analysis of when the subject was asleep versus awake, and the stage of sleep that he or she was in at any given moment.

The endpoints for PSG studies have been established over the course of multiple hypnotic development programs. Common endpoints include latency to persistent sleep (LPS), which is a variable that reflects how quickly one falls asleep after the start of a PSG recording, and Wakefulness After Sleep Onset (WASO), which is a measure of the amount of time spent awake after sleep onset and before the final awakening. Many other endpoints might be assessed in a clinical trial for insomnia, such as total sleep time (TST), sleep efficiency (SE; the ratio of time spent asleep to the amount of time spent in bed), latency to rapid eye movement sleep (REML), number of awakenings (NAW), and the total minutes and/or percentages of stages N1, N2, N3, and REM sleep.

Each epoch is assigned a stage score. The following stages can be identified for each epoch: Wake N1 (light sleep), N2 (moderate depth sleep), and N3 (deep sleep, also called delta or slow-wave sleep).

Abbreviation	Variable Long Name	Definition	Unit
LPS	Latency to Persistent Sleep	Duration of the time measured from lights off to the first epoch of 20 consecutive epochs of non-wake.	Minutes
TST	Total Sleep Time	Duration of total REM and NREM sleep during time in bed.	Minutes
SE	Sleep Efficiency	Total sleep time divided by time in bed, multiplied by 100.	%
WASO	Wake After Sleep Onset	Duration of wakefulness from onset of persistent sleep to lights on.	Minutes
NEW	# of Awakenings After Persistent Sleep	Count of total # of awakenings from onset of persistent sleep until lights on.	Number
ST N1	Stage N1 Duration	Duration of Stage N1 during TIB.	Minutes
ST N2	Stage N2 Duration	Duration of Stage N2 during TIB.	Minutes
ST N3	Stage N3 Duration	Duration of Stage N3 during TIB.	Minutes
ST REM	Stage REM Duration	Duration of REM during TIB.	Minutes
REM Latency	Latency to REM	Duration of time measured from lights off to the first epoch of REM sleep.	Minutes

Despite the importance of PSG in evaluating the efficacy and safety of a hypnotic, self-report data are no less critical. It is necessary to assess each subjects personal experience to determine if an investigational drug helped them fall asleep, stay asleep, reduce the number of awakenings during the sleep period, or allow them to feel refreshed and alert the following morning. Therefore, sleep diaries often are employed as self-report measures in insomnia clinical trials. After all, it would be pointless to market a drug that produced an effect on PSG variables that could not be perceived by the patient!

Insomnia can be hereditary. Studies show that 35% of insomnia sufferers had a family member with similar sleep disturbances.

PSG trials create the foundation for hypnotic approval. Historically, these studies were short-term trials lasting only a couple of weeks in duration. However, in recent years, we have seen study designs that have employed three-month or six-month treatment periods in order to assess efficacy and safety. This has gone hand in hand with a fresh perspective on hypnotic labeling. Recently approved hypnotics have not been approved for the “short-term treatment of insomnia” as their predecessors were, but instead approved for “the treatment

of insomnia" with no specific limit on the appropriate term of medication use. Such labeling has been made possible by the longer-term trials conducted by pharmaceutical companies. Some of these longer-term trials have included periodic PSG assessments in order to document drug effects, while others have employed only self-report measures. Both types of studies are meaningful components of an NDA submission, and the trials that rely on self-report data offer a valuable complement to PSG studies.

Self Report Measures

Self-report measures are valuable in assessing therapeutic effects and drug safety. Instruments may focus on variables specifically related to sleep, such as the time it takes to fall asleep or the time spent awake in bed, but also might address the patient's distress regarding her symptoms, as well as daytime functioning. Some questionnaires, such as the Short Form Health Survey (SF-36), can be used to gain an understanding of the subject's quality of life. Self-report measures may be used as secondary endpoints in PSG trials, or they may provide primary endpoints in outpatient studies. Subjects also are frequently asked to maintain a thorough sleep diary throughout the trial, in which they may be asked to record any stress experienced during the day, number and duration of naps, any medications taken during the day apart from the study drug, etc. Morning experiences also may ask to be recorded.

1 in 4 Americans take some type of medication to help them year.

Self-Report Insomnia Assessment Tools	
PSQI (Pittsburgh Sleep Quality Index)	Assess sleep quality over a 1 month period. Variables assessed include sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of medications, and next-day effects of poor sleep.
ISI (Insomnia Severity Index)	A short survey consisting of 7 questions that assesses standard parameters such as falling asleep, staying asleep, and waking too early, as well as satisfaction with sleep, how others perceive the effects of sleep loss, how distressed the person is about sleep, and the daytime effects of insomnia.
KSS (Karolinska Sleepiness Scale)	A situational assessment of sleepiness at any given time during the day, measuring 10 minute segments of time.
ESS (Epworth Sleepiness Scale)	As assessment measuring the likelihood of sleepiness (or dozing off) during 8 different daytime activities (e.g. stuck in traffic, watching television, etc.)

Special Considerations for Clinical Trials in Insomnia

Clinical trials can be designed in a variety of ways. Drug trials, in particular, are tailored to best evaluate an intervention from the standpoint of safety and efficacy. However, not all interventions for all medical conditions are assessed in exactly the same way; the nature of the disorder or the medication and the target patient population itself contribute to choices made in trial design. What are the common considerations for interventional clinical trials for insomnia?

Trial Design

Proof-of-Concept

An experimental model based on first-night adaptation effects in a sleep laboratory environment has commonly been used to assess hypnotic efficacy. This model takes advantage of the long latency to sleep onset and sleep disruption experienced by healthy subjects during their first night in a sleep laboratory environment. One of the first studies to use this model examined temazepam's hypnotic and sleep stage effects in a parallel group study of 201 healthy, normal subjects with no sleep complaints. Each subject was randomly assigned to receive either placebo, or 7.5 mg to 30 mg of temazepam 30 minutes before bedtime on their first night in the sleep laboratory. Subjects were given an 8-hour sleep opportunity while PSG recordings were obtained. The PSG data revealed that total sleep time and sleep efficiency increased in a linear fashion with increasing doses of temazepam relative to placebo, providing support for the use of the "first night" effect as a model of transient insomnia. This model appears particularly useful in assessing drug effects on sleep latency. One of the key trials in zolpidem's clinical development program examined the effects of zolpidem in a double-blind, parallel-group study of 462 normal volunteers. Zolpidem was tested at doses ranging from 5 mg to 20 mg. Statistical analysis of the 7.5 mg and 10 mg doses showed that zolpidem decreased sleep latency, increased sleep duration, and reduced the number of awakenings relative to placebo, without significant effect on next-day psychomotor performance. Since the original temazepam study was conducted, the model has been employed to assess the hypnotic efficacy of benzodiazepines, nonbenzodiazepines, and other drugs with novel mechanisms of action, such as ramelteon.

Chronic insomnia that is left untreated can result in an increase in alcohol abuse.

Phase-advance models have been used with success in assessing the efficacy of hypnotics in treating transient insomnia. One of the advantages of these models is that they can be used in either crossover or parallel group designs, whereas first-night models, by definition, are limited to parallel group designs only. One of the earliest studies of the phase-advance model used a 180° shift of the sleep/wake cycle in 12 healthy subjects to determine the effects of triazolam, flurazepam, and placebo in a parallel-group design. Subjects who received placebo demonstrated significant sleep loss following the manipulation of their sleep, while the effect was attenuated for those in the active medication groups. One of the interesting aspects of the phase-advance model is that it may be used to assess sleep maintenance by demonstrating separation between active drug and placebo in the later portions of the sleep period. While the magnitude of the phase-shift has been thought to be of importance, several studies have used short phase advances in order to detect meaningful effects. For example, one study has shown that temazepam 7.5 mg and 15 mg administered to subjects in a 2-hour phase-advance paradigm had similar effects on sleep architecture, while statistically significant effects on latency to persistent sleep, total sleep time, and other sleep variables relative to placebo have been found with other drugs such as indiplon, and gaboxadol using this model, occasionally coupled with the first-night model of transient insomnia.

Insomnia can be hereditary. Studies show that 35% of insomnia sufferers had a family member with similar sleep disturbances.

When pregnant, women have an 80% chance of experiencing sleep disturbances.

Late Phase Studies

Most interventional phase 3 insomnia medication trials are placebo-controlled, randomized, and double-blinded, enrolling thousands of subjects. Depending upon the number of subjects enrolled, the trial may have multiple sites. Unless short-term polysomnographic data are collected (ie, requiring an overnight stay), most insomnia drug trials are conducted on an outpatient basis. While trials in the 1990s and early 2000s tended to be short in duration (eg, 7 to 14 days), the more recent hypnotics clinical trials typically last from several weeks to six months or longer (and may even extend beyond that as open-label trials). This shift in trial duration came

about as a consequence of a change in the two-week use limitation in earlier hypnotic labeling, to no limitation in duration of use in the newer hypnotics. Further, a longer-term trial is better for evaluating treatment-emergent adverse events and development of tolerance to the medication. A run-in or washout period may precede the trial by one or two weeks.

There are a variety of noise models that have been used in phase 2 studies of insomnia. While the specific implementations may differ, these models offer a method of assessing drug effects in the presence of experimental stimuli that perturb sleep, thereby demonstrating sleep maintenance effects. This approach is a departure from other models that give rise to healthy subjects to continuous white noise during the sleep period, at levels sufficient to disrupt sleep (eg, 45 dB-75 dB). This design may be able to detect differences between drug conditions when novel methods of data analysis, such as cyclic alternating patterns, are used. Another common noise model involves the use of traffic noise played during sleep, and has been shown to separate immediate-release from modified-release formulations of hypnotics. Problematically, however, the use of the traffic noise model has not shown consistent results when differentiating active drug from placebo.

Required Trial Components

Virtually all clinical trials evaluating pharmacologic interventions for any disorder are required to demonstrate safety and efficacy. While initial trials may evaluate safety and efficacy in adult populations, safety, efficacy, and tolerance may be assessed in subsequent trials in pediatric and aged populations. Teratogenicity is assessed in preclinical research; it would be rare for this to manifest as an adverse event in a clinical trial, as pregnancy is usually an exclusion criterion. No concerns about teratogenicity have arisen in postmarketing surveillance for any of the on-label hypnotics taken at recommended doses.

There are 3 different classification of insomnia: temporary, acute, and chronic.

One of the reasons Ambien became so popular after it was launched was because, due to its highly specific binding to the benzodiazepine receptor (ie, as compared with the nonspecific binding of the older benzodiazepines), both abuse potential and adverse effects were mitigated. However, when reports of “sleep eating” and “sleep driving” and other unusual behaviors associated with taking Ambien began to surface, the FDA, in 2007, required a change in labeling for the entire hypnotics class (including the non-GABA drugs like Rozerem) to include a warning about “sleep-related complex behaviors.” At the same time, the FDA required a warning about anaphylaxis and angioedema. This was not a black box warning, only a required change in labeling.

Given that the hypnotics are psychoactive drugs and labeled as schedule C-IV (ie, controlled substance; Rozerem and Silenor are not C-IV) drugs, the concern for the potential of abuse exists, so abuse potential and habituation are common concerns in clinical trials for hypnotics. The formulations of some of the nonbenzodiazepine hypnotics have also been of concern; buccal and sublingual transmucosal delivery of zolpidem allow for faster onset of drug effects. These – as well as conventional oral delivery – have been a concern for abuse and dependence potential. Adverse event considerations are similar for other psychoactive medications (such as antidepressants, etc), and change in mental status is an important consideration. Suicidality and suicidal ideation are concerns, as they are with the antidepressants (Silenor is low-dose doxepin, which is used at higher doses as an antidepressant). Since risk of suicidal ideation is increased in certain subpopulations (eg, comorbid depression, females, the elderly, etc), it is an important consideration in clinical trial design. Use of the Columbia Suicide Severity Rating Scale (CSSRS) is now a required component in hypnotic clinical trials.

Lack of sleep associated with insomnia can result in additional health problems.

With increased interest in comparative efficacy studies (comparative efficacy research, or CER), the FDA has become more interested in seeing how new submissions for hypnotics compare with the “gold standard” (usually zolpidem) with regard to safety and efficacy, particularly with regard to minimum effective dose. Clinical trials for hypnotics – and sometimes even preclinical trials – have started including these studies.

Recent FDA Activity on Insomnia

In January of 2013, the FDA released a safety announcement regarding next-day impairment (eg, “driving and other activities that require full alertness”) associated with the use of zolpidem (Ambien, Ambien CR, Edluar, Zolpimist, Intermezzo, and generics), stating that the FDA was requiring the manufacturers of zolpidem products (but for Intermezzo, which is a low-dose formulation) to lower the recommended dose. This change is reflected in the most recent package inserts, although dose escalation if the lower dose is not effective is still mentioned as an option.

In July of 2013, Merck announced that they had received a Complete Response Letter from the FDA regarding their first-in-class orexin antagonist suvorexant. The FDA had safety concerns with regard to the higher doses of the drug, and would not approve it unless the recommended dose was 10 mg, instead of the higher recommended doses of 30 mg and 40 mg that were originally submitted with their NDA. Merck says they are “working expeditiously” with the FDA to make the drug available.

Insomnia Studies at Clinilabs