



**Ockham Technical Synopsis** is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

## INSOMNIA

### OVERVIEW

Insomnia is a symptom rather than a disease, characterized by an inadequate quantity or quality of sleep. Affected patients complain of difficulty initiating or maintaining sleep, resulting in non-restorative sleep and impairment of daytime functioning.

The classification, epidemiology, and causes of insomnia must be taken into account when selecting a population for the development of sleep medications. A number of different classification schemes have been proposed for patients with insomnia:

- A 1984 National Institute of Mental Health (NIMH) Consensus Conference divided insomnia into three types: transient (shorter than one week), short-term (one to three weeks), or chronic (longer than three weeks)
- The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, fourth edition, includes four major categories of insomnia, whereas the International Classification of Sleep Disorders (ICSD) includes approximately 40 categories that may have insomnia as a prominent complaint. In the ICSD, insomnia is included within the category of dyssomnia and can occur with extrinsic, intrinsic, and circadian rhythm sleep disorders.

Insomnia is experienced at some time by approximately one-third of the adult population in the United States and is a persistent problem in approximately 10 percent. As an example, the NIMH Epidemiologic Catchment Area Study reported that 10 percent of 7954 adult respondents surveyed between 1981 and 1986 had difficulties sleeping unrelated to neurologic or psychiatric conditions for two weeks or more during the preceding six months.

The prevalence of insomnia increases with age, and symptoms are more common in women than in men. There is also a higher prevalence of insomnia among persons of lower socioeconomic status, in divorced, widowed, or separated individuals, and in those with recent stress, depression, and drug or alcohol abuse.

The symptoms of insomnia frequently interfere with interpersonal relationships or job performance. The following complaints or findings may be noted:

- Difficulty initiating sleep
- Frequent awakenings (including early morning awakening)

- A subjective feeling of insufficient sleep characterized by daytime fatigue or sleepiness, inability to concentrate, irritability, anxiety, depression, or forgetfulness
- A preoccupation with psychosomatic symptoms such as aches and pains in conjunction with sleep complaints.

Multiple Sleep Latency Test (MSLT) results in patients with insomnia generally indicate that, despite reported fatigue, many insomniacs are less sleepy than controls. This suggests that insomniacs suffer from an impairment of the arousal system which results in a hyperaroused state and makes sleep more difficult. Alternatively, these findings may result from an impaired perception of sleep. Over 70 percent of patients with chronic insomnia versus 30 percent of normals report subjective awakeness following awakening from stage-2 sleep, and insomniacs tend to overestimate sleep latency after nocturnal awakenings. One study involved awakening 16 self-described "good" and 16 "poor" sleepers ten minutes after their first sleep spindle on EEG and found that six poor sleepers but only one good sleeper reported that they had never fallen asleep.

Insomnia is a heterogeneous condition. It can result from a wide variety of factors; multiple causes may be contributing in a given individual, and different causes may be responsible for the different types of insomnia (transient, short-term, and chronic).

In the process of drug development, studies are conducted in populations with both primary insomnia and with transient insomnia; primary efficacy outcomes may include measurements of subjective sleep latency, sleep maintenance, and sleep efficiency as measured in the sleep lab.

### TRANSIENT AND SHORT-TERM INSOMNIA

Factors that can result in transient or short-term insomnia are similar, but the disturbances generally must be of greater magnitude to produce short-term insomnia.

These factors include:

- A change of sleeping environments (the most common cause of transient insomnia)
- Jet lag
- Changes in work shift
- Excessive noise
- Unpleasant room temperature
- Stressful life events (e.g., loss of a loved one, divorce, loss of employment, preparing to take an examination)
- Acute medical or surgical illnesses (including intensive care unit syndrome)
- Stimulant medications (e.g., theophylline, beta blockers, corticosteroids, thyroxine, bronchodilators), or withdrawal of alcohol or other central nervous system depressant medications.

## CHRONIC INSOMNIA

Chronic insomnia can be caused by the chronic use of drugs or alcohol, by a number of medical, neurologic, or psychiatric disorders, or by a variety of primary sleep disorders.

Psychiatric and psychological disorders are thought to be the most common causes of chronic insomnia. Insomnia can result directly from a medical illness or indirectly from the medications required for treatment. For example, untreated congestive cardiac failure can cause sleep disruption due to paroxysmal nocturnal dyspnea, while treatment with diuretics may disturb sleep via nocturia. Analogous situations occur with nocturnal angina, chronic obstructive pulmonary disease, and asthma. Specific examples of psychiatric conditions that may be associated with insomnia include depression, anxiety disorders, and schizophrenia.

Chronic insomnia in the absence of a causative medical, neurologic, or psychiatric disorder is common. These patients have either idiopathic insomnia or insomnia as a symptom of another primary sleep disorder.

## PRIMARY INSOMNIA

Primary insomnia is defined by DSM IV as a complaint of difficulty initiating or maintaining sleep or of non-restorative sleep that lasts for at least one month and causes clinically significant distress or impairment in social, occupational, or other important functional areas. The disturbance in sleep does not occur exclusively during the course of another sleep or mental disorder and is not due to the direct physiological effects of a substance or a medical condition. This condition can only be diagnosed after concomitant medical, neurologic, and psychiatric problems have been excluded.

Primary insomnia includes psychophysiologic insomnia, resulting from learned, sleep-preventing associations and increased tension or agitation; it is the underlying problem in approximately 15 percent of all insomniacs attending sleep disorders centers. Affected individuals are overconcerned and overfocused on the problem of sleep, but do not suffer from generalized anxiety, phobic, or other psychiatric disorders. The characteristic feature of psychophysiologic insomnia is the development of conditioned responses that are incompatible with sleep. The disorder begins in some patients during an initial period of stressful events, but the insomnia persists even after the inciting stressors have resolved. The combination of excessive worry, fear, and frustration about being unable to initiate and maintain sleep and the identification of the bedroom as a signal for arousal contribute to negative conditioning and sleeplessness.

Other complaints of insomnia relate to sleep state misperception and inadequate "sleep hygiene" – a term referring to habits that promote sleep. These include avoidance of caffeinated beverages, alcohol, and tobacco in the evening, avoidance of intense mental activities and vigorous exercise close to bedtime, adherence to a regular sleep-wake schedule, and avoidance of daytime naps and excessive time spent in bed.

Patients with sleep-state misperception complain of insomnia and sleeplessness but do not have objective evidence of a sleep disorder. Despite complaints of poor sleep over many years, actigraphic (a technique that measures patient activity and permits an objective assessment of sleep time) or polysomnographic recordings document a normal sleep pattern. The condition may be described as "sleep hypochondriasis," and subjects may subsequently develop anxiety and depression.

## GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

There would not be acceptance of a hypnotic that was associated with significant adverse effects. The sought-after effects are decreased sleep latency and improved sleep maintenance. The clinician's expectation is that a patient will attempt to sleep immediately upon taking a sleeping pill, but unfortunately often patients will delay their attempts to sleep after taking a sleeping pill, resulting in an opportunity for acute, non-desirable effects to emerge (e.g., memory impairment, psychomotor impairment, hallucinations). Such potential problems have to be studied carefully.

Other special groups of adverse events include next-day residual effects (memory, sedation, depression and suicidality), psychomotor and tolerance phenomena, and dependence and withdrawal phenomena (anxiety, insomnia, rebound insomnia, benzodiazepine-like withdrawal symptoms).

Finally, abuse potential has to be assessed.

These studies tend to enroll fast. A big challenge is to make sure sites are well-trained and monitored early on so as to avoid large numbers of mistakes.

These patients can have a number of subtle comorbidities that will affect safety and efficacy assessments: sites can do a lot of pre-screening if trained properly. The protocol must be very specific on exclusion criteria; questionnaires to rule out psychiatric problems can be helpful. Excluded medications must be spelled out clearly as well, as many will affect sleep.

Body-Mass Index (BMI) exclusion needs to be clear, as many obese people have sleep disorders secondary to their obesity, such as sleep apnea.

It is important to provide consistent event terms for adverse events (not everyone understands "sleepy", "drowsy", "sedated", etc., the same way). This can be done via the Investigator Meeting or through separate instructions.

If sleep studies are part of the protocol, it is important to be clear about sleep parameters for inclusion (how much delay in sleep onset, how much awake time after sleep onset, etc.), and to establish clearly whether a central reader or the Principal Investigator will determine who is enrolled.

Because ultimately these drugs are used along with many others, drug-drug interactions are of particular interest.

**COMPETING STUDIES**

<i>Phase</i>	<i>Treatment</i>	<i>Number of Studies</i>	<i>Number of Patients</i>	<i>Number of Sites</i>
II	GW679769	2	441	96
	Gaboxadol	2	570	16
	Escitalopram Oxalate	1	58	1
	Xyrem	1	10	1
	LY2422347	1	400	21
	Rozerem	1	260	72
III	Eplivanserin	3	2648	120
	Ramelteon	2	476	49
	Eszopiclone	1	70	4
	Indiplon	1	380	19
	MK0928	4	2787	121
	Gaboxadol	2	50	1
	VEC-162	1	400	19
	Zolpidem tartrate	2	490	17
IV	Atomoxetine	1	36	2
	Escitalopram Oxalate	1	96	1
	Zolpidem tartrate	2	144	6