

Methodological Issues of Measuring Sleep in CNS Trials

- Sleep is essential for healthy life and well-being
- This session will highlight the impact of sleep and wakefulness disorders on the CNS
- Discuss the potential of measures alternative to the “Gold Standard” measurements of sleep and wakefulness
- Consider the methodological hurdles that need to be overcome
- Improve our understanding of the role of objective and subjective endpoints in the development of drugs targeting sleep and wakefulness disorders, whether primary or secondary
- Discuss means to address the equivalence of non-standard measurements to the gold standard, both from a statistical and regulatory viewpoint.

Methodological Issues of Measuring Sleep in CNS Trials

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Agenda

- Introduction
- Consequences of impaired sleep and wakefulness - importance of considering and means to address in trials **Jacobson**
- Objective and subjective measurement of sleep in clinical trials **Savitz**
- Proper validation of measurement tools against the gold standard **Dorffner**
- Measuring sleep quality **Krystal**
- Experience with measuring sleep in circadian-rhythms sleep disorder targeted trials **Moline**
- Regulatory Considerations **Mantua, Reasner, Tome**
- Panel discussion **All and Audience**

CONSEQUENCES OF IMPAIRED SLEEP AND WAKEFULNESS

- Dr William Jacobson
- Senior Director, Harmony Biosciences
- Disclosures:
 - I am a salaried employee of Harmony Biosciences
 - I hold stock in Pfizer, Harmony Biosciences and United Health Group
 - The views expressed in this presentation are the personal views of the speaker and may not be understood nor quoted as being made on behalf of or reflecting the position of Harmony Biosciences LLC .

What are Disorders of Sleep-Wake Instability?

- Problems with quality, timing or amount of sleep
- Sleep and Wakefulness' are two ends of an important spectrum
 - Sleep is a natural, periodically recurring state of inactivity, characterized by the loss of consciousness and reduced responsiveness to external stimuli. In contrast, wakefulness is the absence of sleep and is marked by consciousness, awareness and activity.
 - The neural circuitry underlying the regulation of sleep and wakefulness is discrete for each state yet interdependent; the very arousal systems that are inhibited by sleep-promoting neurons also serve to disrupt these same sleep processes to return the body to a wakeful state¹.
- Disorders of Sleep-Wake Instability are pervasive with medical or mental health disorders such as
 - Depression
 - Anxiety
 - Cognitive Dysfunction
- Are these issues consequences of or contributors to these disorders, i.e. are they primary or secondary – a diagnostic conundrum?
- Linked to many physical or emotional disorders
- What are the consequences of derangements of wake-sleep instability on function?
 - Safety is an important issue. Each of the following disasters have had sleep/wakefulness issues identified that contributed to inappropriate actions with serious consequences
 - Exxon Valdez Oil Spill linked to inadequate sleep.
 - Chernobyl Disaster
 - Challenger Disaster
 - Sleep/wakefulness derangements have also contributed to well known and more common problems:
 - Well known relationship with automobile accidents
 - Need to ensure appropriate degree of wakefulness for occupations such as long-distance truck driving, airline pilots.

¹Saper et al., 2005: Nature 437: 1257-1263

Why are Sleep-Wake Disorders Important in CNS Clinical Research?

- Hypersomnias and Insomnia are pervasive in the population
- Disturbed sleep is a common complaint and a source of distress in many surveys of self-reported health problems¹.
- Sleep-Wake abnormalities can impact or be consequences of multiple phenomena:
 - Cognitive Function
 - Functional Impairment
 - Quality of Life
 - Mood Disorders
 - Fatigue
 - Medical Conditions

Sleep Disorders – 2 Ends of the Spectrum: Hypersomnias and Insomnia

- Disorders of Wakefulness and Sleepiness

- Primary Hypersomnias
 - Narcolepsy type 1 and type 2
 - Idiopathic Hypersomnia
 - Kleine-Levin Syndrome
- Insomnia – Difficulties in initiating or maintaining sleep
 - 3 Components – Predisposing Factors, Precipitating factors, and Perpetuating factors
 - Can be transient, acute or long term
- Restless Leg Syndrome and Periodic Limb Movements During Sleep
- Endocrine Disorders – e.g. Prader-Willi Syndrome,
- Aging

- Parasomnias

- Nightmares and Dream Disturbances – Hypnagogic Hallucinations
- Hypnopompic Hallucinations
- Somnambulism
- Sleep Talking
- Sleep Eating
- Bruxism
- Sleep Related Breathing Disorders
- Myotonic Dystrophy, Cardiovascular Disease, Cancer, Parkinsonism, Chronic Fatigue Syndrome, Fibromyalgia
- Psychiatric Disorders
 - Anxiety Disorders
 - PTSD
 - Depression/Bipolar Disorder
 - Schizophrenia
 - ADHD

Consequences of Impaired Wakefulness

- Incapacitating sleep inertia
- Exhaustion
- Cognitive impairment
- Involuntary somnolence during activities such as driving, eating talking
- Sleep attacks (involuntary, without warning)
- Disorientation
- Potential for falling from cataplexy, if severe
- Possible trouble sleeping at night
- Possible nocturnal compulsive disorders – sleep-related eating disorders, nocturnal smoking, etc.

Consequences of Impaired Sleep

- Cognitive Impairment
 - Multiple domains can be impacted, including:
 - Speed of processing/Psychomotor
 - Memory
 - Attention
 - It is difficult to identify specific domains that are differentially affected by impaired sleep, since multiple cognitive processes are involved in any given performance task each cognitive process being affected by impaired sleep to an unknown extent¹
 - Excessive Sleepiness and impaired wakefulness can both be contributory to cognitive deficits.
 - Many patients complain of “Brain Fog” – a poorly characterized condition involving any or all of difficulties with memory, attention, learning, slowness of thinking, executive function, and other related issues.

Consequences of Impaired Sleep and Wakefulness

- Fatigue
 - Fatigue is a physiological state of reduced mental or physical performance capability resulting from sleep loss or extended wakefulness, circadian phase, or workload (mental and/or physical activity) that can impair a crew members alertness and ability to safely operate an aircraft or perform safety-related duties. - International Civil Aviation Organization, 2011
- Probable Cause: The National Transportation Safety Board determines that the probable cause of the grounding of the EXXON VALDEZ was the failure of the third mate to properly maneuver the vessel because of **fatigue** and excessive workload.
- The Chernobyl disaster and the Challenger disaster have all had fatigue implicated as contributing factors to the events.
- Sleep problems contribute to more than 6,400 deaths annually¹

Fatigue

- Fatigue can be an unrelenting exhaustion, that lasts long, is profound and is not relieved by rest. It's can be a nearly constant state of weariness that develops over time and reduces one's energy, motivation and concentration. Fatigue at this level impacts one's emotional and psychological well-being.
- Fatigue is flexible and can mean both self-rated fatigue such as that which occurs with acute illness, physical fatigue such as which occurs after exercise or demanding labor, or the **fatigue that occurs following disruption to normal sleep wake cycles**. While these are given the same term, they are all different in their consequences and in their biology.
- Fatigue is an integral component or consequence of insomnia as per DSM-V
- It can be difficult to clinically distinguish between fatigue and EDS, but these are distinct entities

Secondary Causes of Impaired Sleep & Wakefulness

- Physical Disorders:
 - DM1
 - PD
 - MS
 - Epilepsy
 - Hypothyroidism
 - Encephalitis
 - Obesity
 - Depression
 - Sleep Deprivation
 - Obstructive Sleep Apnea
 - Sedating Medications -
- Mood Disorders
 - Two of the 9 symptoms, 5 of which must be present for a diagnosis of Major Depressive Disorder, as per DSM-V
 - Fatigue or loss of energy nearly every day
 - Insomnia or Hypersomnia nearly every day
 - Also common in bipolar depression and seasonal affective disorder
 - Sleep problems are frequently associated with the principal diagnostic criteria for many mental disorders. Alterations in the sleep of depressive patients are of high clinical significance because continuous sleep problems raise the chance of relapse, recurrence, or suicide
 - Early research indicates sleep problems may affect psychological and physical wellbeing in older people during the COVID-19 pandemic²

¹ Hutka et al., Int J Mol Sci 2021 22(3) 1333-1349

² Cipriani et al., Int J Environmental Res Public Health 2021 18 1076-1093

Consequences of Impaired Sleep & Wakefulness

- DSM-V defines Hypersomnolence Disorder via a prolonged main sleep period, frequent naps, or difficulty awakening after abrupt awakenings, along with distress or impairment.
- Disordered sleep is often associated with decreased health related quality of life (HRQoL) and may predispose to socioeconomic adversity in many affected subjects¹
- Sleep Issues have been clearly demonstrated to be involved with increased accident rates and have been implicated in some significant disasters
- **Sleep problems are of growing concern in the population so sleep issues, impaired wakefulness, and their impact on daily functioning should be considered in all CNS-focused clinical studies**

We are such stuff as dreams are made on; and our little life is rounded with a sleep.
William Shakespeare

Sleep is the best meditation.” –
Dalai Lama

Sleep is the Swiss army knife of health. When sleep is deficient, there is sickness and disease. And when sleep is abundant, there is vitality and health. –
Matthew Walker

A ruffled mind makes a restless pillow.” – Charlotte
Bronte

How blessed are some people, whose lives have no fears, no dreads; to whom
sleep is a blessing that comes nightly, and brings nothing but sweet dreams.
Bram Stoker

I love sleep. My life has the tendency to fall apart when I’m awake, you know?”
– Ernest Hemingway

There is renewal in rest.” – Lailah
Gifty Akita

“I think sleeping was my problem in school. If school had started at four in the
afternoon, I’d be a college graduate today.” – George Foreman

Sleep is that golden chain that ties health and our bodies together.
Thomas Dekker

Happiness consists of getting enough sleep. Just that,
nothing more.” – Robert A. Heinlein

The amount of sleep required by the average person is five minutes more.” –
Wilson Mizener