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Stanford Center for Narcolepsy Research Update 2023-2024

As we approach 2024, we wish to thank our patients for participating in research and clinical trials and our donors, all of whom are advancing our goals to understanding the cause of narcolepsy and hypersomnia, develop new treatments, and eventually prevent and cure this complex disorder.

THE DAWN OF OREXIN AGONISTS

Two years ago, we witnessed the birth of a new class of medications that has the potential to revolutionize the treatment of narcolepsy and hypersomnia: orexin receptor 2 agonists. These medications treat the cause of narcolepsy type 1 (NT1), which is the lack of orexin (a key modulator for sleep/wakefulness cycle). Though two receptors for orexin exist, the medication only replaces activity at the orexin receptor 2, as most studies indicate that the orexin receptor 1 has a more minimal role in regulating sleep/wakefulness. This past year, we've made promising developments with these compounds, fostering a sense of optimism regarding their potential as innovative new therapies for narcolepsy and hypersomnia.

Leading the charge is Takeda Pharmaceuticals, with whom we recently completed phase 2 clinical trials with their third compound in this class, TAK881. Two companies, Jazz Pharmaceuticals and Alkermes, have started human administration trials, and a third company, Centessa, is not far behind. Others will likely follow suit.

In both mice and humans with NT1, two of the orexin receptor 2 agonist drugs made by Takeda (TAK925 and TAK994) were shown to have extraordinary effects on cataplexy and sleepiness. TAK925 was developed to only be administered by infusion, as a “proof of concept” that these drugs were effective. TAK994 was studied orally in over 100 patients and results were impressive. Clinical development was interrupted, however, due to a few patients developing complications unrelated to the drug mode of action.

Together with Takeda, our lab has completed a phase 2 study of TAK881, a longer lasting version of TAK994. Takeda is currently analyzing the data. If the drug is found to be safe and as effective as anticipated, they will move forward with a phase 3 study to confirm its efficacy in another cohort of NT1, narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH) patients, most likely starting this summer.

Phase 3 patients will be randomized into active drug or placebo groups and tests such as the maintenance of wakefulness test (MWT) and other sleep studies will be conducted to assess efficacy. As in phase 1 and 2, all patients completing the placebo-controlled portion (typically 6-8 weeks) will have the option to be placed on the active compound for “an extension study”. These extension studies are performed to assess if the drug is safe long-term. Following completion of phase 3, additional studies with TAK881 in association with other drugs

like oxybate salts or other stimulants will likely be conducted to make sure no rare side effects emerge during long-term therapy or in association with other compounds. Most often, these extension studies continue until drug approval by the FDA, at which time the patients taking the drugs as part of the extension studies are switched to the commercial product.

Most excitingly, these orexin agonist drugs normalized the response to the maintenance of wakefulness test, in which patients are asked to stay awake for 40 minutes without performing any actions to keep themselves awake. In this test, untreated NT1 patients can usually only stay awake for a few minutes, and up to 10 minutes when optimally treated with oxybate salts and other classic narcolepsy drugs, such as stimulants. With the orexin agonist drugs, NT1 patients were able to stay awake for the full 40 minutes. This result is striking, as it would be impossible to reach this effect with stimulants or oxybate salts without producing unwelcome side effects, such as paranoia or the inability to remain still.

We have also observed orexin agonist drugs to be active in NT2 and IH, although a 2–3-time higher dose is needed versus NT1. Side effects were limited to an increased urge to urinate (although this was manageable and disappeared with time), and a modest increased blood pressure, which seemed to subside during long-term therapy and was not vastly different from what is observed with classic amphetamine-like stimulants.

At this juncture, it is clear that orexin agonist drugs are amazingly effective and preferred by many, if not most patients, compared to previously tried therapies. However, more research is needed to optimize the duration of the medications' effect to study whether the beneficial effect will decrease over time. For example, TAK994 was short-acting medication that needed to be administered twice per day and even then, the dosage was not 100% effective for an entire day. At the other end of the spectrum, an orexin agonist dose that lasts too long could disrupt sleep. It is also unclear if these medications will improve disturbed nighttime sleep over time in NT1 patients, who commonly experience this symptom and usually treat it with oxybate salts. Considering that NT1 patients are hypersensitive and require lower doses, some adaptation is likely, and a combination of orexin agonists and sodium oxybate may be ideal for certain individuals.

THE OXYBATE COMPETITION: VARIATION ON A THEME

Although orexin receptor agonists are the most exciting development in narcolepsy and hypersomnia therapy today, these drugs are unlikely to solve all problems for all patients. The introduction of sodium oxybate (Xyrem®) by Jazz Pharmaceuticals a few decades ago led to an incredible improvement in symptoms for NT1 patients when compared to stimulants and antidepressants, the main therapies of the last millennium. More recently, it has become evident that sodium oxybate is also very effective in many patients with NT2 and IH (although it is unclear which patient will respond well or not). Despite this success, sodium oxybate has a high sodium content, raising the specter of increased high blood pressure risk (not unlike a high sodium diet's risk on blood pressure). To mitigate this, Jazz Pharmaceuticals has introduced Xywave®, a low sodium formulation in which sodium has been largely replaced by potassium, calcium, and magnesium. The formulation is likely safer in patients with high blood pressure or fluid retention and has a slightly different pharmacokinetic profile; absorption is slower and peak concentration reached after administration is slightly lower.

In parallel with this, a long-lasting formulation of sodium oxybate (Lumriz®) was also recently introduced by Avadel. It was shown to be as effective as other oxybate salts, but only requires a single nighttime dose instead of two, for Xyrem® and Xywave®. This new formulation will reduce sleep disruption for patients and may be especially useful for children and parents, as currently, parents must wake up to give the second dose to their

child, disrupting sleep for all parties. Interestingly, we wonder if one day Lumriz® and Xywave®/Xyrem® could be co-administered in some patients to optimize therapy individually the same way long and short acting insulin formulations are being used.

BASIC RESEARCH IS STILL CRITICAL

These exciting developments go hand in hand with basic research which will continue to increase our understanding of the cause of these disorders and eventually enable effective personalized treatment. In this direction, our laboratory continues to investigate the autoimmune basis of narcolepsy and its trigger by influenza. Our hope is that this research will lead to a test that could diagnose NT1 with a blood sample, and perhaps one day prevent narcolepsy through a modified flu vaccination. A recent finding suggests that both H1N1 and specific strains of influenza B can trigger narcolepsy.

We are also pioneering cutting-edge artificial intelligence technology to analyze hundreds of thousands of sleep studies to unearth predictors of health, disease, and key biomarkers associated with sleep disorders. Pairing this groundbreaking AI with genetic and proteomic analysis is unraveling the enigmatic realm of sleep and shedding light on the origins of various sleep disorders.

LEARN MORE

Please visit Dr. Mignot's websites which outline his work throughout sleep sciences and narcolepsy. He and his colleagues hope these platforms will attract more like-minded scientists to train and specialize in these areas.

Stanford Center for Narcolepsy
https://med.stanford.edu/narcolepsy.html

Mignot Lab @ Stanford
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Dr. Mignot and his colleagues were the first to discover that narcolepsy is an autoimmune disease caused by loss of hypocretin/orexin, a brain chemical needed for staying awake and controlling dreaming. The Stanford Sleep Medicine clinic treats hundreds of narcolepsy patients each year, many of whom volunteer for research studies. Through his work with these volunteers, Dr. Mignot created a database from the records of thousands of patients from multiple ethnic groups, providing an invaluable resource for the field that has led to many breakthroughs. Dr. Mignot's current research focuses on applications of mobile technology, machine learning, and genetics to the study of sleep and sleep disorders in large population samples. He is the recipient of numerous research grants and honors, including a 2023 Breakthrough Prize in Life Sciences. Dr. Mignot is co-author of more than 200 original scientific publications and is an active member of several professional and governmental organizations, including the National Academy of Sciences and National Academy of Medicine.

OPPORTUNITY TO SUPPORT THIS RESEARCH

Through the generous support of philanthropy, Stanford narcolepsy researchers continue to drive innovative strategies to improve prediction, diagnoses, and treatments. Private funding fuels the advancements that will change the lives of people with narcolepsy.

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CONTACT

If you have questions or if you would like to have a deeper conversation about how you can support this work, please contact:

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