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Sinaptica Therapeutics

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The annual listing of 10 companies that are at the forefront of providing Neurology solutions and impacting the marketplace

Sinaptica Therapeutics

MedTech Upstart Takes on Alzheimer's with Radical New Approach


Ken Mariash, CEO

Precision Neuromodulation of the Default Mode Network slows disease progression by an unprecedented 80%+ in landmark Phase 2 clinical study

Researchers have spent decades and billions trying to develop an effective treatment for Alzheimer's disease, the most feared disease, ahead of cancer, stroke, and heart disease combined—according to a survey by the Milken Institute. Pharmaceutical approaches have targeted two key proteins, amyloid and tau, both of which are linked to disease progression, but neither have been proven to be causative of Alzheimer's. The efficacy of the latest anti-amyloid antibody drugs is so marginal that experts debate their clinical meaningfulness, plus they carry significant side effects.

An exciting new MedTech approach to treating Alzheimer's is focused on the neurodegenerative aspects of the disease, leveraging an evolving understanding that Alzheimer's is as much an electrical disorder as it is a biochemical one. As a pioneer in this emerging field, Sinaptica Therapeutics is targeting this electrical component of the disease, significantly slowing disease progression by using personalized neuromodulation to strengthen synaptic connections within a key brain network involved in memory.

In many areas of medicine, neuromodulation devices have become established tools for treating a range of important diseases—in some cases displacing drugs. As our scientific understanding of neural circuitry and biomedical engineering have advanced exponentially, these treatments have become more sophisticated, targeted, and now personalized.

Next-gen neuromodulation is used to treat pain with spinal cord stimulation, Parkinson's with deep brain stimulation, epilepsy and rheumatoid arthritis with vagus nerve stimulation… the list goes on. Most traditional neuromodulation therapies involve targeting a specific nerve to achieve a specific therapeutic result—but Sinaptica is going beyond this linear approach.

Sinaptica has created a new, drug-free, noninvasive way to treat Alzheimer's disease using precision network neuromodulation.

There are three critical elements that make Sinaptica's therapy different:

1) Targets the entire distributed brain network associated with Alzheimer's—the Default Mode Network

2) Applies sophisticated algorithms to patients' imaging and EEG data to personalize the treatment, recalibrating in a closed-loop manner periodically

3) Delivers ongoing neurostimulation using neuronavigation for precise, reproducible, safe targetry

"This new approach is based on a fundamentally new way of understanding the brain and the disease of Alzheimer's. When we combine the proprietary elements of our personalized neuromodulation therapy, the results so far are stunning," said Ken Mariash, CEO of Sinaptica Therapeutics.

1) Targeting the DMN, the network where Alzheimer's emerges

Unlike traditional neuromodulation approaches that target one specific nerve, Sinaptica's Alzheimer's therapy targets the entire brain network. The brain is organized into multiple large-scale functional networks. The Default Mode Network (DMN) manages episodic memory and introspection. One could think of it as where we form our internal narrative—our sense of self (see publication in Neuron). There has been a significant amount of recent research identifying the DMN and its dysfunction as playing a central role in Alzheimer's pathology and progression. In fact, it's one of the earliest harbingers of Alzheimer's.

'Network modulation,' as the company refers to it, is more complex than simple nerve stimulation, and Sinaptica's therapy involves new tools of increasing complexity, requiring visualization, ultraprecise targeting, complex signal processing, and dynamic adjustments over time.

This precision-targeted stimulation strengthens the Default Mode Network by inducing neuroplasticity, facilitating the brain's ability to forge new connections and fortify existing ones.

2) Precision medicine: personalized for each patient – The MAINTAIN™ algorithm

Every patient's brain responds differently to stimulation, so Sinaptica uses a proprietary calibration process to customize its therapy, which the company calls the MAINTAIN™ algorithm. In the calibration process, the device delivers single pulses to different locations within the Default Mode Network and records the propagation of each signal throughout the network using 64-channel EEG. The data is uploaded to Sinaptica's proprietary cloud-based personalization software, which analyzes the data in spatiotemporal domains, and returns a specific "prescription" for that patient that determines where to stimulate, and how to stimulate, in order to achieve the optimal resonance of the DMN. The MAINTAIN™ algorithm was created based on a decade of research on proprietary data sets.

3) Weekly nDMN therapy

After the MAINTAIN™ calibration is performed, the patient comes back for weekly 25-minute sessions while comfortably reclined. Neuronavigation ensures that the optimal spot is reproducibly stimulated in the same way, every week. To target the Default Mode Network, Sinaptica's therapy is delivered through magnetically induced neurostimulation through the precuneus, the central hub of the DMN, located in the posterior cortices. This neuromodulation of the DMN (nDMN) has no serious side effects, and the minor side effects that do occur, like headache, have all spontaneously resolved without incident in trials to date.

Unprecedented Phase 2 data

Using nDMN—combining the personalized approach, targeting the Default Mode Network, and precision closed-loop neuromodulation—Sinaptica's scientific co-founders achieved unprecedented positive Phase 2 results in mild-to-moderate Alzheimer's patients, achieving over 80% disease slowing on all four gold-standard cognitive and functional endpoints—definitive proof of concept.

On CDR sum of boxes, the gold-standard primary endpoint in Alzheimer's drug trials, nDMN showed a 1.17 points difference from active to placebo, representing an 82% reduction in the rate of decline. And on ADAS-COG and MMSE, two other secondary cognitive endpoints, the study also achieved statistical significance at the same magnitude (3.5 points and 1.5 points difference respectively), reflecting >80% slowing in the rate of decline. On the functional endpoint ADCS-ADL, the study achieved an 8-point spread between active and placebo—in fact the active arm actually improved slightly on Activities of Daily Living (ADLs), whereas the placebo group dropped markedly, as expected.

Not only did nDMN achieve highly statistically significant outcomes on clinical, cognitive and functional endpoints, the study also revealed remarkable changes in the electrophysiology and imaging of the brain, revealing strengthened connections in the Default Mode Network, increasing gamma band activity, preserved evoked potentials, and reducing the rate of grey matter atrophy.

These results provide validation that the treatment creates profound changes in the brain that are strongly indicative of disease modification. The scientific community has taken notice of this groundbreaking work. The Phase 2 data were published in the Oxford University Press peer-reviewed journal, Brain, and Sinaptica's approach earned FDA Breakthrough Designation. The data were also presented from the podium at the Alzheimer's Association International Conference in July 2023.

Renowned scientific team

Sinaptica's scientific co-founders are leaders in the use of novel diagnostic and therapeutic approaches to treating Alzheimer's using noninvasive neurostimulation techniques. They have spent over a decade deciphering the intricate dynamics of brain networks and have completed multiple drug and device clinical trials over the past 10 years.

"Over the past decade or so, we developed noninvasive tools that allow us to peer into the brain by using perturbation-based biomarkers—probing the brain in order to elucidate insights around disease processes, monitor effects of treatment, and personalize therapy. Our Phase 2 study is the culmination of that work," said Sinaptica scientific co-founder Emiliano Santarnecchi.

Giacomo Koch, MD, PhD is Professor of Physiology at the University of Ferrara and Director of the Brain Stimulation Laboratory at Santa Lucia Foundation in Rome, and Emiliano Santarnecchi, PhD, PhD, is Associate Professor at Harvard MGH, Director of the Precision Neuroscience & Neuromodulation Program, and faculty at Harvard. Through meticulous analysis of extensive datasets, these experts have achieved a profound understanding of the brain's responses to stimulation. This research led to their landmark Phase 2 study in Alzheimer's and the founding of Sinaptica.

Changing the trajectory of Alzheimer's

As we look forward, MedTech devices and related breakthrough technologies will be playing a larger and more important role in treating serious, life-altering or life-threatening diseases such as Alzheimer's. It's time to look beyond the narrow scope of drugs and open up to new approaches that can make a difference in many diseases, with Alzheimer's being one of the most exciting and impactful.

Sinaptica continues to push the boundaries of brain science and is preparing for a pivotal Phase 3 clinical study in 2024, building on more than a decade of research on innovative brain targeting methods, biophysical modeling, and noninvasive treatment protocols leveraging machine learning to change the way Alzheimer's is treated and to bring hope to patients and caregivers.