ejpmr, 2021,8(6), 204-210

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

SJIF Impact Factor 6.222

Review Article
ISSN 2394-3211
EJPMR

ELECTROCEUTICALS: AN AUFKOMMENDE TECHNIQUE IN NEUROLOGICAL SCIENCES - A REVIEW

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Article Received on 01/04/2021 **Article Revised on 21/04/2021** **Article Accepted on 11/05/2021**

ABSTRACT
Background: This review is based on the case approach to identify the usefulness of electrical appliances for mankind. Each individual is unique and, therefore, electroceutical devices should also have the patient-specific element for smarter use of the implant. This newly emerging field of electroceuticals needs to be understood keeping in mind the body's electrical grid and the language of nerve impulses to treat various diseases and disorders affecting the mankind. The review pinpointed that electroceuticals is supplements to traditional treatment. Although much usefulness is found toward using electrical impulses to treat the organ, the devices need to be designed with relatively small wires and batteries for easier implantation. **Objective**: The objective of the present study is to understand the use of electricity in treating ailments to mankind where they need not swallow the pills or inject intravenously rather have the device implanted which would monitor the nerve impulses, detect if any problems exist, and then supply electricity to the organs affected to make them function properly. **Conclusion**: Although many usefulness is found toward using electrical impulses to treat the organ, the devices need to be designed with relatively small wires and batteries for easier implantation. Each individual is unique and, therefore, electroceutical devices should also have the patient-specific element for smarter use of the implant.

KEYWORDS: Electroceuticals, Neurological science, patient-specific implantation.

INTRODUCTION
For the past few decades drugs are ruling the roost. Any diseases or disorders that can't be treated by drugs are treated by surgeries or interventions. But in this conventional system of medical therapy, the drugs we use can cause mild to severe side effects. Almost all the drugs act by modifying any of the molecular pathways associated with the disease. They travel throughout the body and cause disruption of tissues beyond that targeted for the treatment, because their action can't be exactly localized to the defective part or organ. And also continuous use of certain drugs may cause serious side effect like drug dependency, and there are cases where the existing drugs fail to provide desired effects. Here comes the need for an alternate to drug based remediation.[1]

We all know that, our body functions are regulated through brain & nervous system; a circuit of neurons communicating through neural impulses. Even the endocrine system is under the control of CNS by a complex array of feedback mechanisms. Then think about a method in which the neural impulses that control the body will be entrained to regain the lost function & re-establish a healthy balance. [2]

DEFINITION
Electroceuticals are a new category of therapeutic agents which act by targeting the neural circuits of organs. The therapy involves mapping of the neural circuitary and delivering the neural impulses to the specific targets. The impulses may be administered via an implantable device positioned accordingly with the location of the target, where the action is required.[1]

WHY NERVOUS SYSTEM
There are two reasons for selecting nervous system as the target for action of electroceuticals; Neural circuits are excellent targets for therapeutic intervention because:

1)They comprise discrete components- interconnected cells-fiber tracts and nerve bundles allowing pin-point intervention.

2)They are controlled by patterns of action potentials which can be altered for treatments.[3]

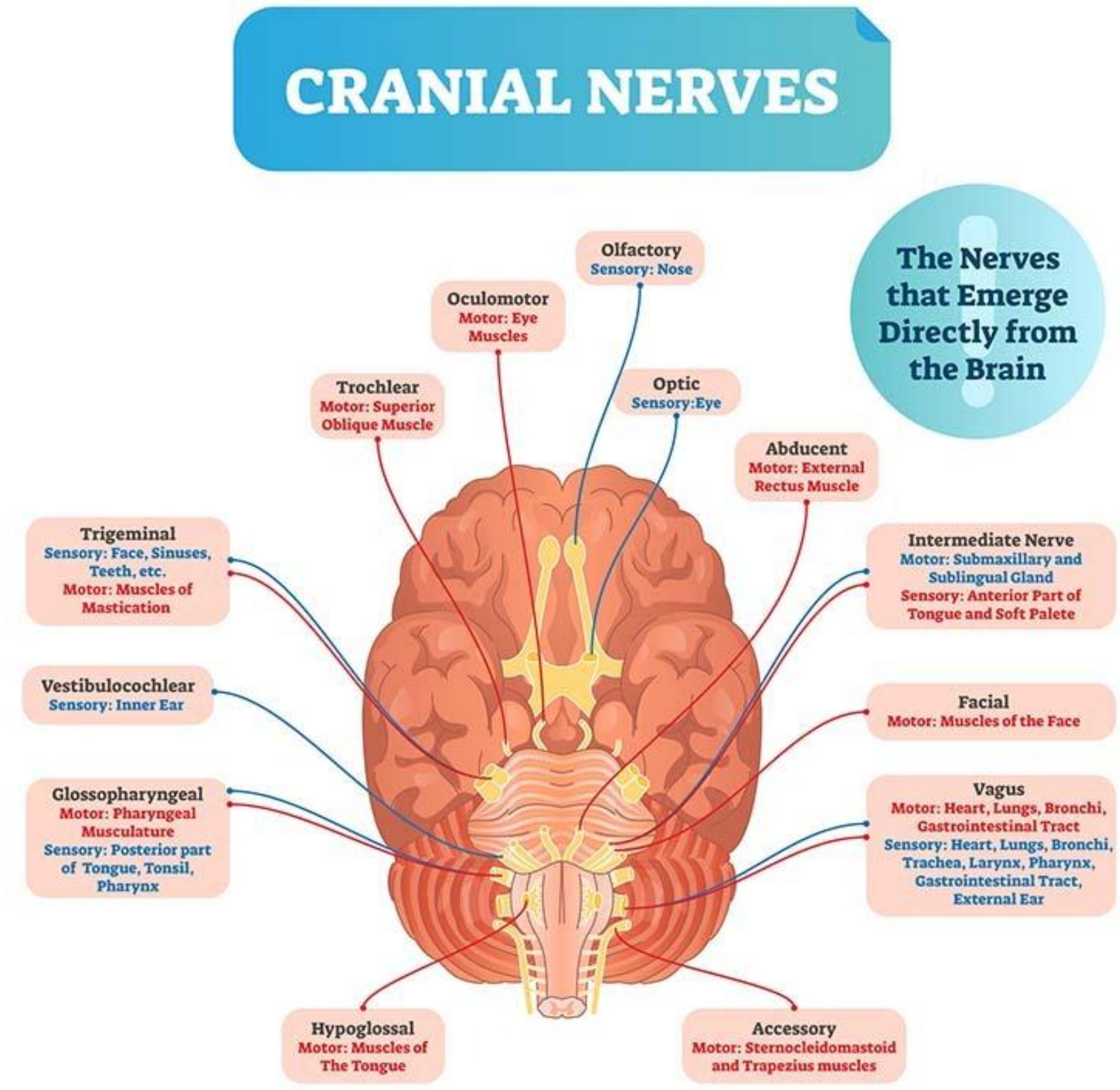

Figure 1: Cranial nerves.

MECHANISM

The mechanism involves the following steps;

1)Mapping the neural circuits associated with disease.

2) Anatomical: Nerves & brain areas associated with diseases are identified to define the anatomic site for intervention.

3) Signalling: Identify exact electrical signal/action potential/patterns associated with health so that these patterns could be replicated.[1]

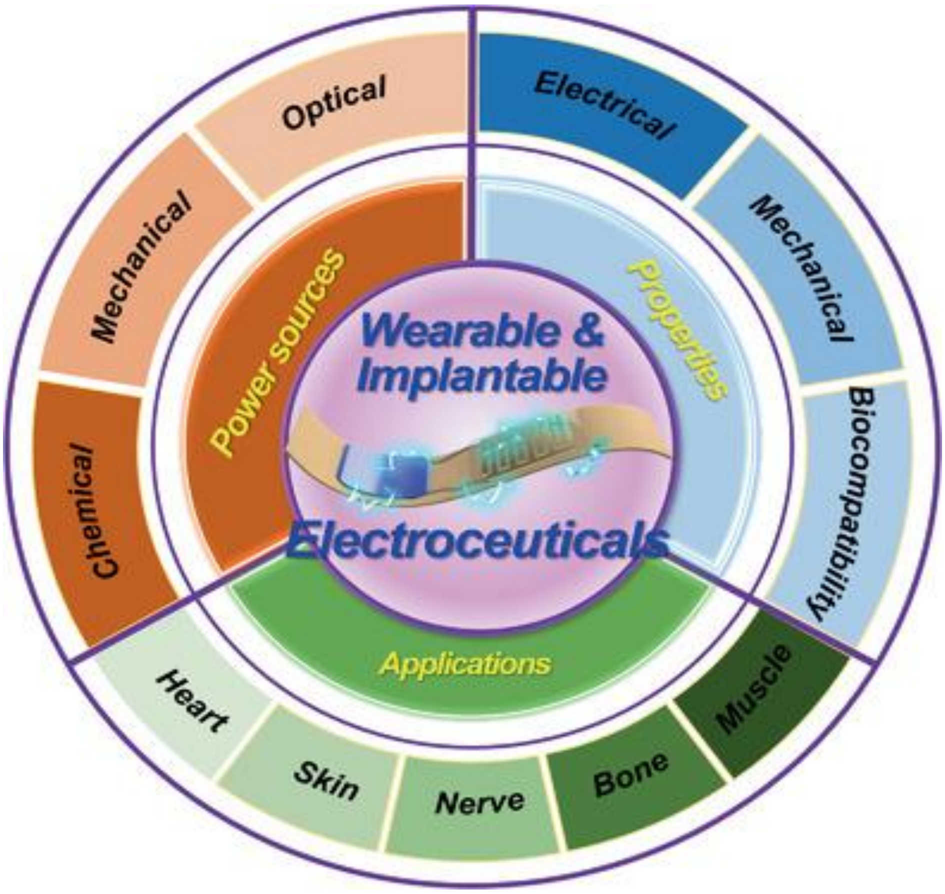

Figure 2: Overview on Electroceuticals.

WORKING

The working of electroceuticals can be said simply in three words i.e, monitoring, detecting and curing. Electroceutical devices are developed in such a way that they can be attached to nerve bundles to alter electrical signals sent to brain or organs. They contain microchip-controlled electrode arrays powered by electromagnetic energy (heat, light, or magnetic), mechanical or chemical energy harvested from body's resources.[1]

HISTORY

For centuries, it is known that living organisms which are made of cells respond quickly to electrical impulses. In 1780, Luigi Galvani, an Italian physician found that when a small electric voltage applied to frogs' leg, muscle made a twitch though the frog was dead. It is a known observation that every organ of our body produce action potential, when electric signals flow to and from along the neural network resulting in some kind of impulse.

In early 1980s, Aim Louis Benabid, a French neurosurgeon, during his experiment, made lesions to occur in the thalamus of brain and electrical frequencies at varied intensities were applied, to the tissue. He discovered that the tremors were suppressed at 100Hz frequency.

The concept of electroceuticals were 1st found in 2002 by neurosurgeon Kevin J. Tracey, President of Feinstein Institute in his experiment with a specific drug to limit the damage caused by swelling of brain in stroke patients, which was a response by body's immune system to injury. He found that the drug's application caused shutting down the immune response of the entire body. They discovered that the drug affected vagus nerve, which is involved in the regulation of body's immune system mediators called cytokines, that were causing the inflammation. Tracey then realized that, instead of drugs being used to stimulate vagus nerve, the nerve itself could be manipulated. .[3]

In 2012, the experiment identified that acute rheumatoid arthritis can be cured in 8 weeks by implanting an electronic nerve stimulator to the vagus nerve. This was a milestone in the history of electroceuticals, later lead to the treatment of many ailing conditions such as asthma, diabetes, hypertension, arthritis, pain and possibly even cancer as well as to control neuropsychiatric ailments, in Parkinson's and seizure disorder.

Bioelectric devices; pacemakers and defibrillators were the 1st such developed and implanted devices in the human body and are electroceutical devices which stimulate nerves and tissues. Later, many other implants in the spine, ear and eyes have been developed. The invent of wireless chips by Ada Poon and John Ho in

2014 from Stanford university is enabled to stimulate the nerves to relieve pain and many other diseases.[2]
First generation of these devices were available in size of a pill or pen, but nowadays they have reached the size of a pin head. However, the future will be of micro or even nanoscale devices. In 2017, FDA approved non-implanted devices that eases opioid withdrawal by sending to branches of the cranial and occipital nerves through skin behind the ear.[4]

USES

- Stimulation of Islets of Langerhans helps to produce more insulin at the time of meal ingestion.
- Stimulation and dilation of airways during episodes of asthmatic attacks.
- Stimulation of sacral nerve to restore bladder control in patients with paraplegia.
- Gastric contractility treatment in patients with diabetic mellites.
- Cochlear implants and eye implants.
- Stimulation of skin nerves to arrest infection.

  In cardiology
- Pacemaker, defibrillation, resynchronization applications.
- Usefulness in heart failure, coronary artery disease and myocarditis.
- Carotid baroreceptor stimulation to treat resistant hypertension.

  Electrophysiology
- Low energy multistage electrotherapy to treat atrial and ventricular tachyarrhythmias.
- Medium voltage electric therapy; to treat pulseless electrical activity.
- Spinal cord stimulation to treat refractory angina.
- Cardiac contractility modulation devices for contractility enhancement.

  Vagus nerve stimulation (VNS)
- To treat psychiatric disorders, addictions, epilepsy and depression.
- Release of a specific neurotransmitter in spleen, quiets immune cells involved in inflammation throughout the body. Spleen is stimulated electroceutically to alter the activity of T cells, impeding the progression and production of inflammatory substances like tumor necrosis factor that accumulates in joints of patients with rheumatoid arthritis.
- Also, in crohns disease (inflammation of intestine) use of electroceuticals are encouraging.
- In cerebrovascular disease, metabolic dysregulation, dementia.
- In autoimmune disorder like lupus (were vagus nerve itself become underactive).
- In prevention of immune rejection of transplanted tissues.
- To correct balances in smooth muscle tone to treat hypertension and pulmonary diseases.[4]

ADVANTAGES

- There is no need of drug administration or any kind of complex procedure as in surgeries.
- These can't only cure the diseases but also regulate body activities like food intake, cardiac activity, pancreas, liver, kidney and spleen functions.
- These give more precise, specific and quicker responses.
- Efficient and localized action.
- More patient specific.
- We can optimize and personalize the use of these devices.
- It has fewer side effects compared to drug-based treatment.
- Small size, easier to tolerate because it acts on specific nerve.[4]

DISADVANTAGES

- The neural structure is too complex to be mapped completely.
- It is a challenge to address the enormous number of neurons durably, reliably and non-disruptively.
- There is a possibility that the impulse targeted to a specific nerve group may also stimulate surrounding neurons and affect them undesirably.
- Cost of implants are high.[4]

APPLICATIONS – MARKETED DEVICES [8]

Electroceuticals for Treating Headaches

One of the most active areas of treatment in electroceuticals is chronic headaches. A company out of New Jersey called electroCore (ECOR) had raised about $127 million in funding before going public last year on the NASDAQ. It had a value of about $426 million at the time of the IPO, but has dropped to a current market value around $245 million in just nine months, despite receiving FDA clearance last November for gammaCore, its non-invasive vagus nerve stimulator therapy to help prevent cluster headaches in adults. Cluster headaches, which may or may not be caused by clusterfcuks, are a series of short but intensely painful headaches that can occur daily for weeks or months at a time.

Figure 3: Electroceutical for headache.

Neuromodulation for Treating Epilepsy

While cannabis has emerged as an effective treatment for some types of epilepsy, the disorder affects about 65 million people worldwide, requiring different kinds of therapies. London-based LivaNova (LIVN) is known for its implantable SenTiva VNS (Vagus Nerve Stimulation) Therapy. The FDA has approved VNS Therapy as an add-on therapy for those 4 years and older to treat focal or partial seizures that do not respond to seizure medications. A device is implanted under the skin in the left chest area. An attached wire is wound around the vagus nerve in the neck. The whole package is then programmed to deliver pulses at regular intervals. Studies have shown that the therapy improves over time, from reducing seizures by 36% after six months to about 75% after 10 years.

Electroceuticals for Treating Chronic Back Pain

Back pain is the single leading cause of disability around the world, with estimates that it costs the U.S. economy alone more than $100 billion in healthcare bills, lost wages, and productivity. Not surprisingly, then, we found quite a few companies offering nutraceutical solutions for back pain.

For instance, Nevro (NVRO) out of Silicon Valley went public less than five years ago and sits on a market cap of about $1.8 billion after an initial IPO valuation of nearly $425 million. It offers an FDA-approved spinal cord stimulation technology it calls HF10, which involves inserting thin, insulated wires in the back near the spinal cord that are connected to a small battery-powered pulse generator, which is implanted just under the skin. The mild electrical pulses help calm the nerves.

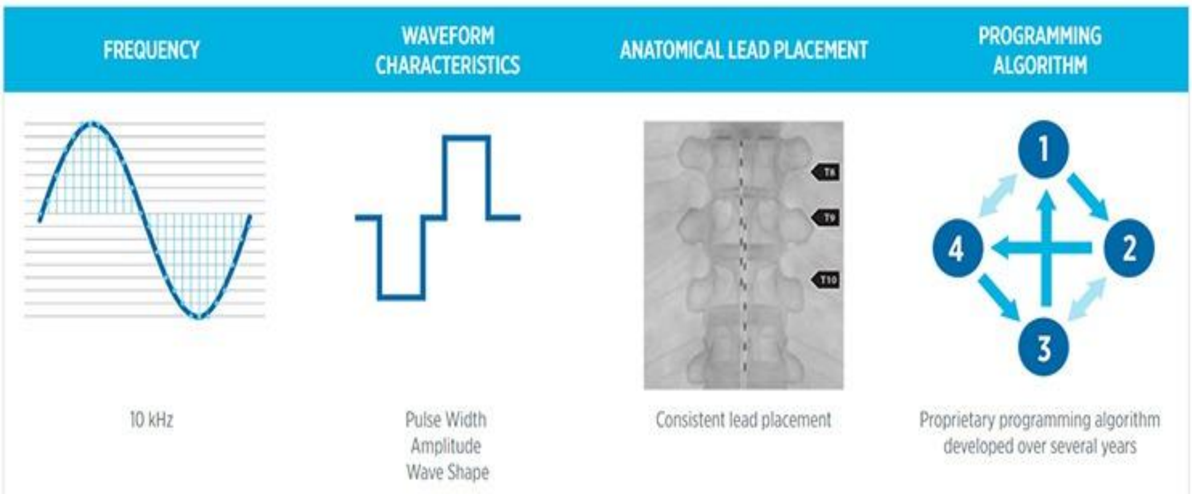

Figure 4: The Nevro platform. Credit: Nevro.

Sacral Neuromodulation for Urinary and Faecal Dysfunction

This next topic isn't for the squeamish: Urinary and faecal dysfunction. At least 33 million Americans suffer from an overactive bladder, while it's estimated that one in three people deal with these problems. One possible treatment is through sacral neuromodulation, which involves sending mild electrical pulses to stimulate the sacral nerves located in the pelvis area to modify the messages between the muscles there and the brain. Axonics Modulation Technologies (AXNX) out of the Los Angeles area already has approval for its sacral neuromodulation system in Europe. A lead with four electrodes is inserted in the sacrum and connected to an implantable pulse generator that sits under the skin in the upper buttock area.

Figure 5: Credit: Axonics Modulation Technologies.

Electroceutical for Treatment of ADHD

While exact numbers are hard to come by, as much as 11% of children and even 4.5% of adults have been diagnosed with **A**ttention **D**eficit **H**yperactivity **D**isorder (**ADHD**). Most treat the condition with medication. But a Los Angeles company called NeuroSigma, which has raised **$13.4 million** in financing since it was founded in 2008, has an alternative to drug stimulants for millions of kids and adults. Its Monarch eTNS System is a non-invasive electroceutical device for stimulating the trigeminal nerve, the largest of the cranial nerves that is responsible for sensations in the face and motor functions such as biting and chewing. It also projects directly or indirectly to areas of the brain involved in ADHD, epilepsy, and depression, among other conditions.

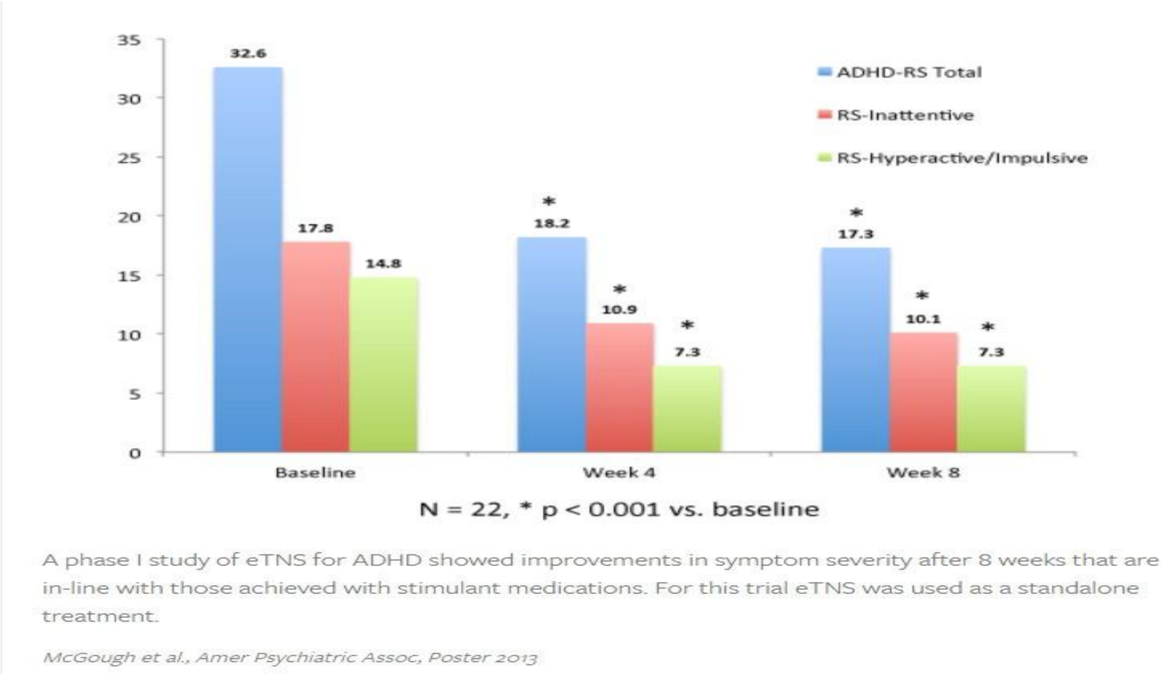

Figure 6: A phase I study of eTNS for ADHD.

Bioelectronic Treatment for Sinus Pain

To prove there's no chronic condition too niche for bioelectronics, Tivic Health out of Silicon Valley has raised $1.8 million for a handheld device to treat sinus pain due to allergic rhinitis or hay fever. There's certainly a huge market potential: About 8% of U.S. adults were diagnosed with hay fever in 2016 alone. In January, Tivic received FDA clearance to sell Clear UP as an over-the-counter device for sinus pain. It works by gliding along the outside of the nasal passages to deliver low-current electrical waveforms that stimulate the nerves under the skin to help relieve sinus pain. No drugs or sprays required.[6,7,8]

NEWER DESIGNS

- **Biodegradable implants**

John Rogers, Northwestern university, Evanston III, developed biodegradable implants which continuously deliver electrical pulses to nerves and breaks down when its use is over. It is only wide as small coin and thick as sheet of paper and it is flexible enough to wrap around an injured nerve. It is powers and controlled wirelessly by a transmitter outside the body. It can electrically stimulate a nerve for about 2 weeks before the body absorbs it.[5]

- **Electric bandage**

Xudong Wang, material scientist, University of Wisconsin, Madison, has developed a bandage that converts mechanical energy emitted by our body motions into electricity. It relies on the phenomenon known as triboelectricity, the most common cause of static electricity. When 2 substances repeatedly touch and then separates, the surface of one material can steal electrons from the other. It consists of a Teflon strip that slides back and forth over a copper-coated plastic layer. Compared to the older electrotherapy devices, which administered intense shocks, these bandage's gentler pulses reduced the production of reactive oxygen species (chemicals that could potentially harm cells) by nearly a factor of 5.[5]

CONCLUSION

The electroceuticals industry is rapidly ramping up amid big investments. As more studies and trials examine the mechanisms and effects of electroceuticals; they may be able to cure a wide range of chronic disorders, reducing the need to take medicines for millions of patients. Open innovations and flexibility in dealing with the intellectual property will be important in this procedure. Together we can bring about the era of electroceuticals, where they will be the mainstay of medical treatment.

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