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Electroceuticals Industry Landscape

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Overview of Electroceuticals

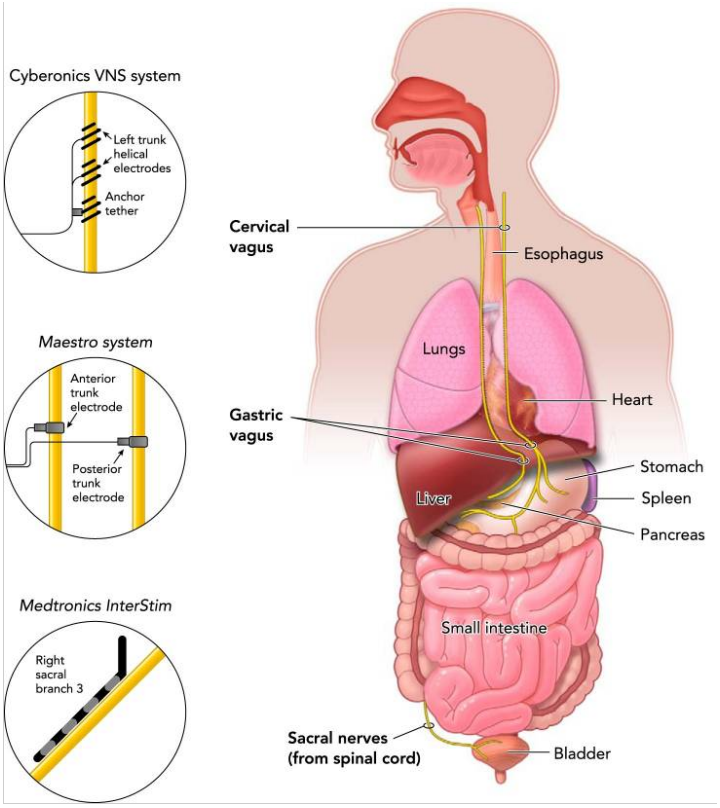
How do Electroceuticals work

Electroceuticals is a term that refers to Electronic Pharmaceuticals. This field is also called Bioelectronic Medicine. The term is used for tiny electronic devices that are programmed to read and modify electrical signals passing along nerves. Their goal is to restore health.

The first and most well known application is the pacemaker invented in 1958. Since then several other Electroceuticals have been FDA approved [1]:

- Cyberonic System - Controlling epileptic seizures (approved 1997)
- Cyberonic System - treat depression (approved 2005)
- Medtronic InterStim System - urinary incontinence (approved 2011)
- Maestro - treat obesity (approved 2015)

The below illustrations (Fig. 1) shows where this devices interact with the Body



Electroceuticals established before 2015 share one major drawback, their selectivity. The Side effects from non-selective stimulation, limits treatment options to only ⅓ of patients (pileptic seizures).

Recently there has been substantial investments made to address these issues. In this report we want to highlight two companies that we feel will have technical relevance in the near future.

Nevro: Managing Chronic Back Pain

Nevro [2] is a California based Company who is a leader in Spinal Cord stimulation to help manage chronic back and leg pain.
It offers an FDA-approved spinal cord stimulation technology (HF10). This 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 and siginficanmlty reduce pain

They were able to provide treatment with substantial pain reduction to 80% of their patients. This is very relevant for two reasons. First Back pain is the number one cause of disability around the world. It costs the U.S. economy over $100 billion yearly[3]. Secondly pharmaceutical treatment options like Opioids have caused a major health crisis in the US.

In general chronic pain is managed by Painkillers. In the past Electroceuticals have only been used in cases where all other treatment options did not produce results. Given the widespread awareness that Painkillers (Opioids) have devastating addictive side effects, Patients might ask Doctors for alternative treatments. On the other hand Doctors are monitored for metrics such as how many patients on opioids they have and their opioids subscriptions that are higher than the guideline [4]. These changes in the Ecosystem might result in the usage of Electroceuticals for chronic pain management rather than long term opioid prescription.

Still the risks of undergoing surgery to implant the device/electrodes is the biggest obstacle. Nevro offers a minimum short term implant that is designed to show if the patient will see beneficial results after the surgery.

Spinal Cord stimulation is an application of Bioelectronics that helps manage the pain of an underlying condition without treating it. In this aspect it is similar to pharmaceutical pain killers.

Setpoint Medical: Chronic Inflammation

The second company we want to highlight is Setpoint Medical [5], a startup based also in California. In contrast to Spinal Cord Stimulation that manages pain Symptoms, Setpoint Medical is working on Electroceuticals that offer a cure for certain autoimmune diseases.

In autoimmune disorders, the body sets off a reaction that destroys normal tissues. With Rheumatoid Arthritis, the body's immune system attacks its own tissue (joints) resulting in pain, diminished function, bone erosion and joint deformity.

A medical breakthrough discovery by Dr. Kevin Tracey [6], discovery, the Inflammatory Reflex, opened up the door for effective treatments by Vagus Nerve stimulation. Setpoint Medical is using this breakthrough on chronic Inflammation Management for rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis and many others.

The device is designed to intersect & manipulate signaling from the Brain through Vagus nerve. The electrical signalling is controlling molecular mechanisms in the body (e.g. TNF) to restore to a normal level. This minimizes the symptoms of the patient.

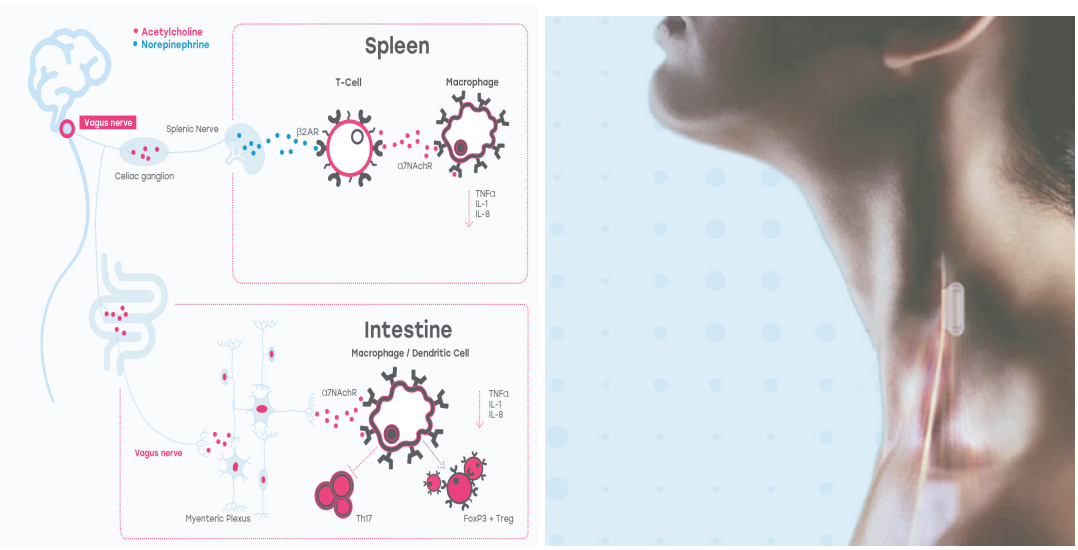


Fig. 2. Setpoint Medical's device for Rheumatoid Arthritis is currently in the clinical pilot trial in the U.S. It is working towards approval in 2025.

Electroceuticals for Autoimmune disorders are gamechangers. One woman with Rheumatoid Arthritis participating in the European trial study reported massive reduction in her Symptoms. She claimed that before the trial she could not hold a pencil, while after the study she was able to go on 20 mile bike rides. Bioelectronic medicine promises to control the body in a much better way than regular drugs.

The future of Electroceuticals

Selectivity:

In the long term Bioelectric medicine will surpass Molecular Medicine in Persission[7]. Molecular medicine can be taken orally, injected or inhaled which creates a systemic exposure of the whole body. Electroceuticals have two advantages. First, Nerves are spatially separated and branch off. So they can be targeted for a single function to restore health. Secondly the electrical signal can be modulated as well over time.
Currently Selectivity of the Nerve stimulus is the biggest challenge for Electroceuticals. Research is ongoing on using more electrode contacts on a single device probe to increase the stimulation parameter space. Each of these electrodes can have unique stimulation (amplitude, pulse duration, duty cycle, frequency) to selective targeting of sub-regions of the nerve.

Closed Loop control:

Current Electroceuticals are open loop controlled (e.g. Nevro HF10). They have to be manually adjusted for each patient for maximum effect at minimal side effects over time. Closed-loop control depends on a dynamic readout from which neuromodulation interventions can be adjusted. The human body shows certain plasticity with time the neuromodulation therapies need to transition to closed-loop control so that they can adapt as well.

Fig. 3 shows two examples currently researched [4]:

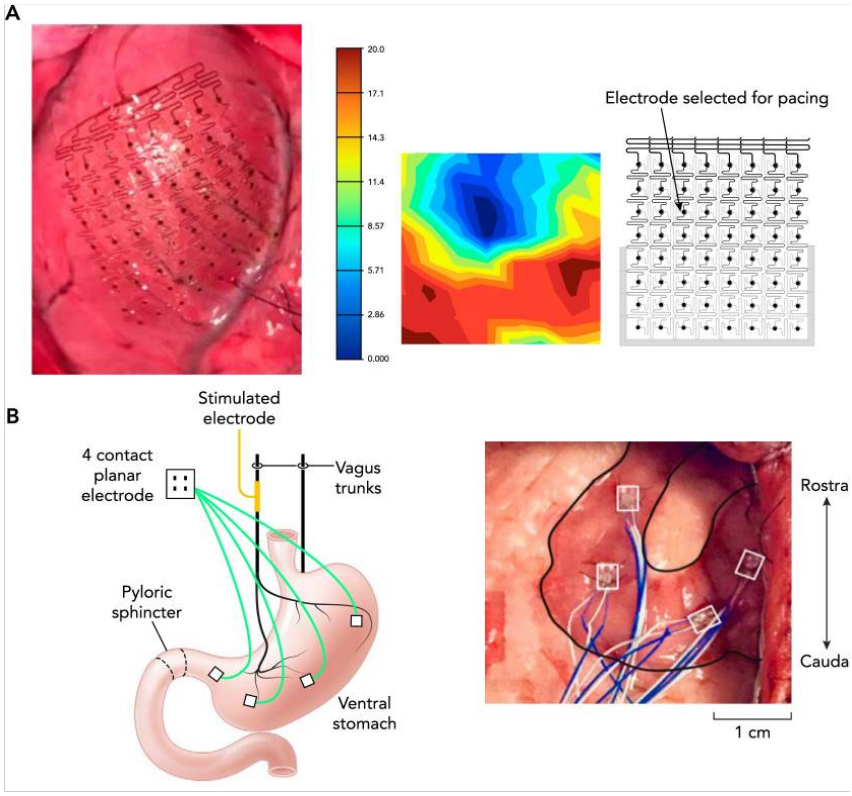


Fig. 3. Examples of Closed Loop control Electroceuticals
A. Sensing of heart. Stretchable thin-film array recording multi-point unipolar electrograms delivering point-specific pacing anywhere within the array surface

B. Stomach organ function. Gastric planar electrodes sensing or for use to compare with other recording sites across the serosal surface of the stomach

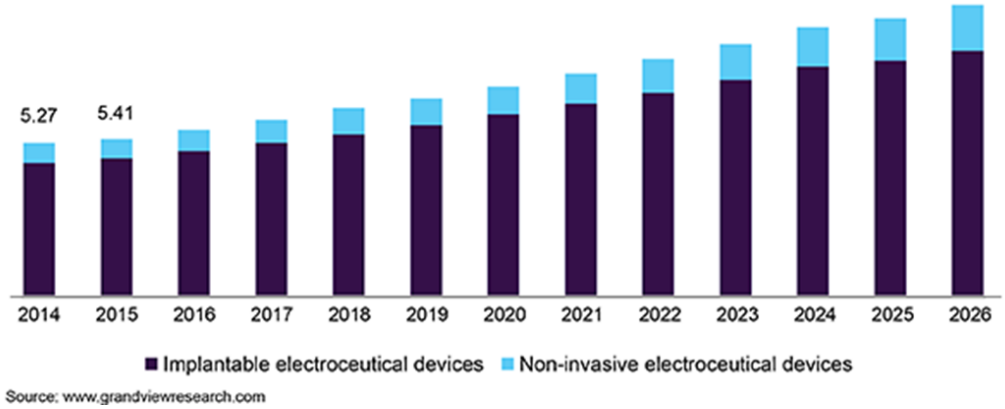
Market Analysis

The global market for pharmaceuticals is huge and is growing at a fast pace. According to PRNewswire in 2019, the market for chronic pain treatment is expected to reach $105.9 billion by 2024 [8]. Similarly, the global market for rheumatoid arthritis drugs is expected to reach $50.5 billion by 2025 [9]. Another big market is expected to be for drugs fighting allergies and this is expected to be $4.8 billion by 2023 [10]. Each one of these markets is a potential market for Electroceuticals, since they have the potential to cure/address the segments serviced by traditional pharmaceuticals more selectively and with less side effects. This is why Electroceuticals as an industry has been making waves in the pharma market.

Market Trend

The explosive growth in Electroceuticals is observed in Fig. 4. According to grandviewresearch [11], the global electroceuticals market is expected to reach $28.5 billion by 2025. It is projected to expand at a CAGR of 7.4% during the forecast period.

According to another report published around the same time in 2019 by BBC publishing [12], the market is expected to reach ~$35billion by 2024.



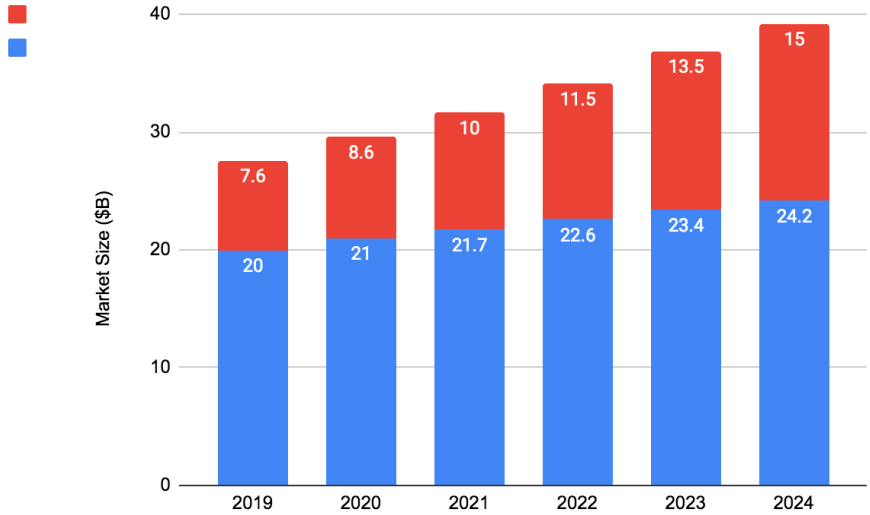


Fig. 4. Global Electroceuticals Market size and growth projections

There are two broad categories within the Electroceuticals market, invasive and minimally invasive. Pacemakers are an example of the first category. This category generally refers to the class of devices where major surgery is needed to place the devices in the human body. The other category is the non/minimally invasive devices, where little to no surgical procedures are needed for the devices to interact with the human body. The invasive category has been around for several decades but continues to grow at a steady pace. The minimally invasive device segment is the more interesting segment as this part has been growing at a higher rate and is expected to explode with the improvement in electronics, data analytics and artificial intelligence.

A Deeper Look at Devices in the Market

Let's take a deeper look at the devices & the companies that make these devices, that are currently available in the market in each segment. First up in the invasive segment is Livanova, which makes devices to address cardiovascular diseases. One example of a device from this company is the aortic valve replacement device. Then there is Medtronic that makes devices addressing several ailments like cardiovascular, smoking related and etc. Finally there is Cochlear which is the leader in devices which help with hearing related issues. Their core device called the nucleus implants are the standard in hearing implant technology. Their newest device is the Cochlear Osia system, which helps hearing using bone conduction and is a good example of a non-invasive electroceutical device. This is a good segway into the minimally or non-invasive market. This segment of the market is where we see the highest growth and interest and several new players with new products are showing up on the horizon. Electrocore has a product called Gammacore, which targets the Vagus nerve and helps prevent migraine and cluster headache. Bioelectronics has several products which also target pain disorders. Similarly Stimwave & Calahealth also have devices in the market targeting pain management.

Mergers and Acquisitions, Joint Venture Trends

A key segment in the Electroceuticals market is expected to be through mergers and acquisitions and joint ventures. One such entity was formed by GlaxoSmithKline and Google's life science spinoff, Verily, in 2016 [13]. The JV is dubbed Galvani Bioelectronics with the goal to treat a wide variety of illnesses through miniature devices that can modify electric signals transmitted by nerves throughout the body. The two companies have pledged $700 million in the venture over the next seven years. GSK will hold a 55% equity interest in the venture. Other heavy hitters have jumped in as well, including the Pentagon (DARPA), which has created an $80million ElectRx initiative and National Institutes of Health, which has dedicated $250 million to SPARC (for Stimulating Peripheral Activity to Relieve Conditions).

Market Segmentation

The Pharmaceuticals market can be divided into two broad categories, reactive (traditional) & preventative (Electroceuticals). We wanted to look at companies and markets in both segments. There is a third segment/group of companies that play in both segments and this segment is becoming more and more important as companies realize that they need to have a portfolio which addresses both segments. Fig. 5 shows the market segmentation of this market prior to 2010. At this time, most of the market was focused on the reactive/traditional type of pharmaceuticals. Big names like Johnson & Johnson, Pfizer, Boston Scientific, Amgen dominated the market. Only one company was working on Electroceuticals, Electrocore. If we look at the same market today, the situation has evolved drastically. Fig. 6 shows the market segmentation for pharmaceuticals in 2020. Not only have a number of new players sprung up in

Electroceuticals, but the market worth of this segment has also drastically increased. Also some of the traditionally focused Pharmaceuticals companies are heavily investing in Electroceuticals, like GSK and Boston Scientific.

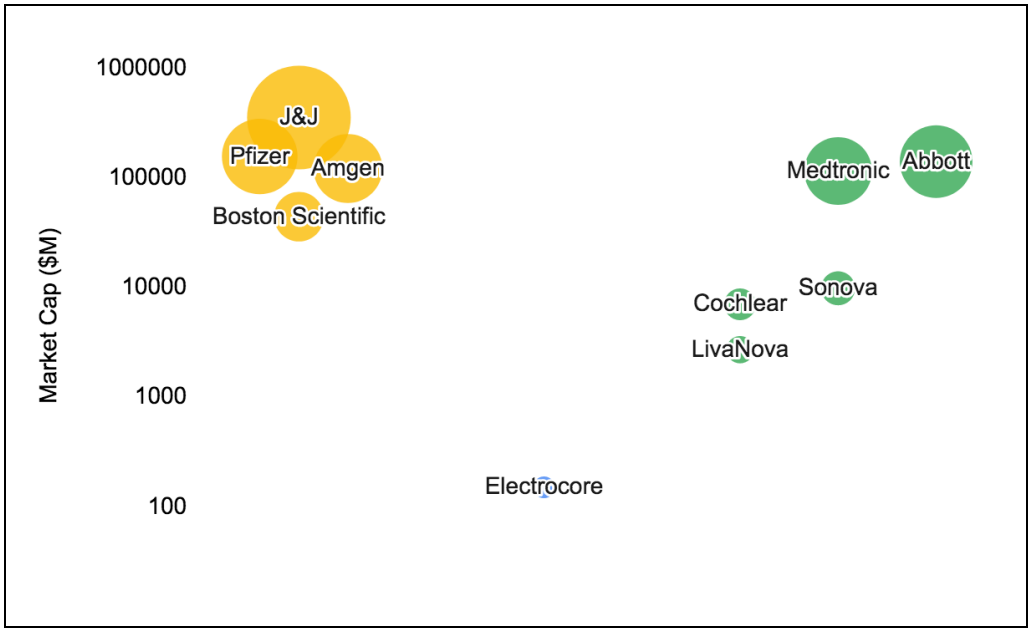


Fig. 5 Market Segmentation of Pharmaceuticals Industry in 2010

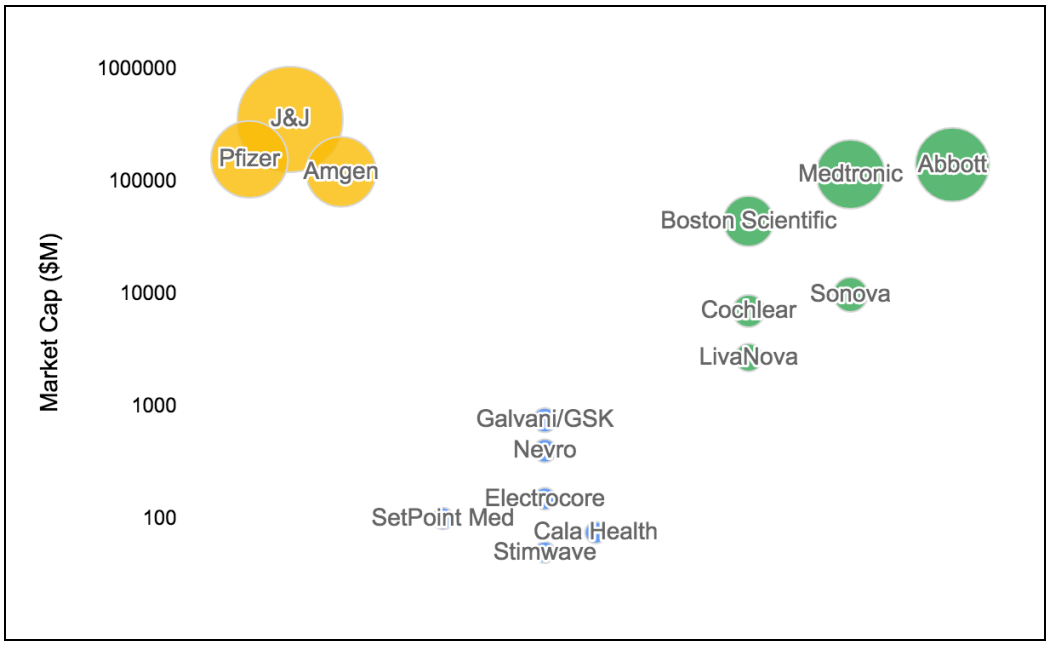


Fig. 6 Market Segmentation of Pharmaceuticals Industry in 2020

Ecosystem

The electroceuticals ecosystem consists of six entities. Devices that connect to the nervous system to deliver electric pulses, patients who are the subjects, doctors who prescribe and monitor the devices, data that is being generated on the patients' body, data analysis that needs to be done on the data to make decisions on next steps and regulatory bodies that regulate the use and types of devices. All of these entities form the ecosystem in a complex and interdependent way. In order for the industry to make progress, advances need to be made in all of these areas. The interdependancy of these areas also lead to a lot of challenges.

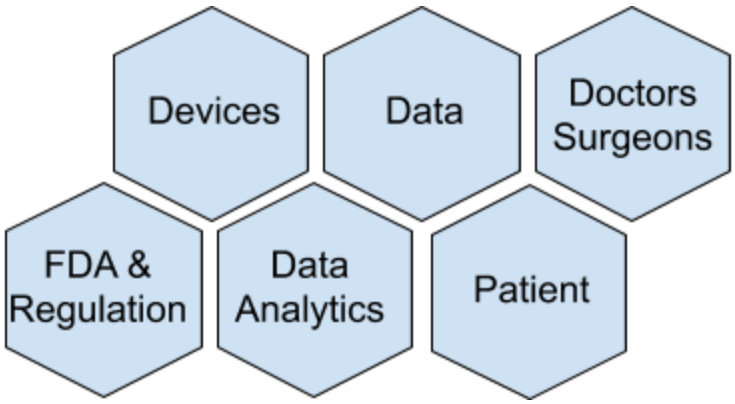


Fig. 7. Electroceuticals Ecosystem

Challenges

Complexity

Electroceuticals have been in practice since the late 1950's when the 1st pacemaker was implanted. Recently neurostimulation therapies such as SCS(Spinal cord stimulation) for failed back surgery syndrome (FBSS), Deep brain stimulation (DBS) for movement disorders such as Parkinson's disease, tremor and dystonia have been developed and advanced. Scientists and Doctors knew more and more about the neural system from how neural reflexes in inflammation, to which peripheral nerves or spinal cord to be stimulated, so a small electrical pulse can suppress the pain[14]. However there are 86 billion neurons and 150 trillion synapses in the human body, we cannot underestimate the complexity of the nervous system and the challenges in reliably, durably and non-disruptively manipulating groups of individual neurons and the sheer volume of neural information flowing through these circuits[15].

Infection

According to the international literature, the incidence of device-associated infection is 1.7% (in six months) for implanted defibrillators and 9.5% (in two years) for

resynchronization devices[16]. It is thus very important to optimize the diagnostic and therapeutic strategies by which such infections can be detected early and treated effectively. Some methods have been developed to achieve the safe and rapid way for implantation such as vein puncture. Other min-invasive devices such as Setpoint and non-invasive ways such as TES(Transcranial electrical stimulation) are also advanced rapidly.

Interference

External sources, either within or outside the hospital environment, may interfere with the appropriate function of Electroceutical devices. The patient and the physician who is responsible for follow-up of the systems may be confronted with some specific problems regarding the various types of electromagnetic interference (EMI). To avoid these unwanted EMI effects one must be aware of this potential problem and need to take some precautions. There are many sources of EMI. Magnetic resonance imaging creates real problems and MRI-safe devices are recommended. Cellular phones might be responsible for EMI when they were held closed to the devices. Anti-theft systems(also called electronic article surveillance or EAS) are not a problem if one walks through it without lingering in or near it[17].

Reliability

Electroceuticals are sophisticated devices that perform life-critical functions. Hence, any risks that may compromise safety should be thoroughly identified and addressed. The advances in functionality of electroceutical devices are accompanied by an in- crease in device complexity, programmability, and connectivity, which often result in a decrease in reliability. The complexity of electroceutical devices, in terms of both hardware and software, is rapidly increasing to enable more sophisticated monitoring, diagnosis, and treatment. It contains various digital/ analog integrated circuits (ICs), including the microcontroller for device control and memory card for data storage, sensors, and actuators. The RF link provides wireless connectivity to other devices, such as a glucose meter or a user remote. It is, essen- tially, a full-featured embedded system. Software has grown significantly in complexity. These sys- tems now have 80k–100k lines of code. Wireless connectivity, which is becom-ing common for remote monitoring, inter-device communication, and postimplant reprogramming, not only provides healthcare professionals with access to the device but also may leave the device open to malicious hacking.

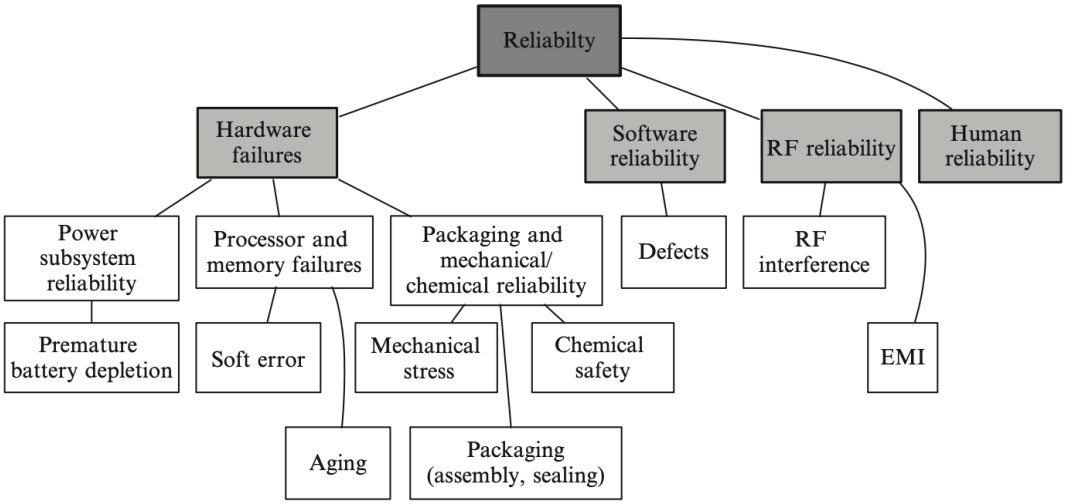


Fig. 8 Reliability issues in Electroceutical Devices

Hardware failures have been the major cause of device malfunctions. An analysis of FDA reports[18] showed that about 80% of pacemaker and ICD malfunctions are caused by hardware failures. These include failures in the battery/capacitor, circuit, connector, and sealing. The software content of devices is increasing at a rapid pace. Pacemakers and other ICDs have 80k–100k lines of code, which is likely to increase further in future versions of these devices. It is, therefore, not surprising that software error is one of the major causes of device malfunctions. It appears that 33.3% of class I recalls, 65.6% of class II recalls, and 75.3% of class III recalls on medical devices were caused by software errors. The life-critical nature of devices demands that the software be reliable and bug-free to ensure safe operation and meet all the requirements and standards. Also RF reliability and Human reliability should not be overlooked while assessing the reliability of critical systems.

Security

Although the risk of hacking represents only a small portion of security vulnerabilities, Several recent works demonstrate security attacks on Electroceutical devices, the security mechanisms in the breached devices were easily broken in these studies[19].

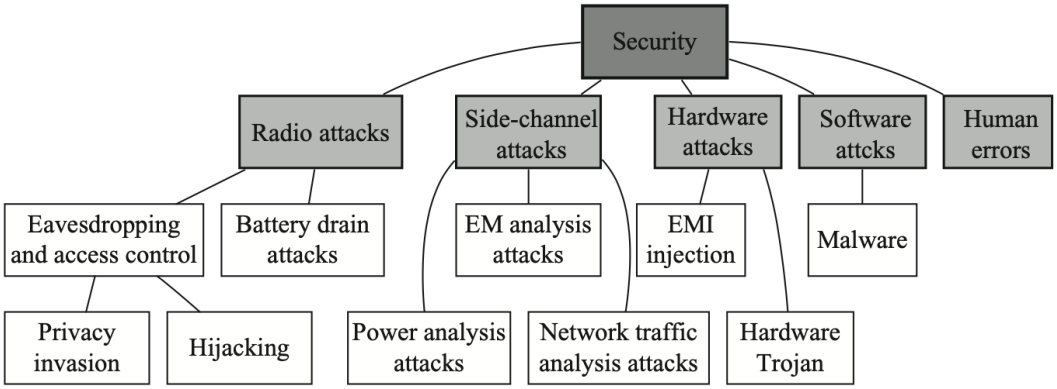


Fig. 9 Security issues in Electroceutical devices

As devices increasingly support wireless connectivity for remote monitoring, treat- ment, and software reprogramming, radio attacks have become one of the major threats to security. And we cannot neglect the side-channel attacks such as EM analysis attacks and software attacks like Malware. Security is a relatively new concern for regulatory agencies, such as the FDA. Manufacturers, being concerned about potential problems or delays associated with regulatory approval, have traditionally had little incentive to add security mecha- nisms to their devices. However, as the regulatory agencies now realize the criticality of security, manufacturers are increasing the amount of attention given to implementing appropriate security mechanisms in their products. Addressing security risks is essential, not only for wide acceptance of Electroceuticals but also for the success of home healthcare.

The three fundamental building blocks of security are confidentiality, integrity, and availability. The implications of these properties are as follows:

- Confidentiality—Only intended parties should be able to access the medical information. Unauthorized parties should not be able to interpret the information.
- Integrity—Accuracy and consistency of medical information must be maintained. The medical information should not be altered by unauthorized parties.
- Availability—The device and its medical information should be available when needed.

Regulations

Due to the safety requirements, many regulations standards have been established from specific materials to multi-phase clinical trials. There are a couple of new areas we want to point out. First we need to treat all patient data safely and reliably. Due to advanced hardware, software, wireless, AI technology, we need to focus more on how to use those

technologies safely, how to provide the identification, aggregation of information and analysis. A central registry is recommended. It will benefit all stakeholders such as patients, investigators, clinicians and regulators. Second several guidelines have been published and attempted to identify and address some established ethics issues such as PD. But for many other areas such as depression, we need more emerging indications. No doubt we will see repaid advances in understanding of the neural system and our brain, it will be crucial that ethical issues surrounding those advances are addressed in parallel[20].

Looking at What's Next

To predict the future of the Electroceuticals industry, we performed SWOT analysis for industry at present. The Electroceuticals industry is at the cusp of a major growth phase with major pharma, technology players forging alliances but also faces significant threats which need to be addressed for realising its growth potential. Currently industry is seeing adoption on few targeted applications like chronic pain management, autoimmune diseases but applicability of electroceuticals scale much beyond.

Table 1 : Summary of Electroceuticals Industry SWOT Analysis

Strengths	Weakness
• Medical breakthroughs & Semiconductor advancements:- Mapping Neural response, Miniaturization, Low power connectivity • Strong VC, Funding interests in Health care	• Long term efficacy, Patient acceptance • Surgical intervention creating barriers • Diverse ecosystem players with conflicting business models
Opportunities	**Threats**
• Ready to take on >100B pharmaceutical industry • Patient compliance, improved quality	• Regulatory Compliance • Security, Privacy concerns • Business model scalability

of care • Big Data/ML:- Improved response, patient care	

Strengths:

The Electroceuticals industry had few medical breakthroughs in recent years with mapping neural systems & brain response. This combined with continued improvement on selectivity using closed loop control increased target applications significantly. Semiconductor advancements on miniaturization, ultra low power connectivity for stimulus control combined with biodegradable components further facilitate continued growth. On financing, healthcare continues to attract huge investments both in the form of VC funding as well as major pharma alliances with Tech leaders.

Weaknesses:

As shown in Fig 7, the Electroceuticals industry has multiple diverse sets of ecosystem players with often conflicting business models which limits growth & scalability significantly. Long term efficacy, safety is yet to be proven limiting patient acceptance to these advanced technologies which create circular dependencies. Surgical intervention for these implants often creates a major barrier for patient acceptance/perception.

Opportunities:

The Pharmaceutical industry is a highly profitable, slow moving industry & presents a huge (>100B) opportunity for electroceuticals as viable long term alternatives. Electroceuticals can improve patient adherence to medication regime which is a major challenge (21) through automation & improved quality of care with faster response time. With increasing scale /adoption of electroceuticals, data analytics using Big Data/ML will constantly improve efficacy & quality of care.

Threats:

As an industry, Regulation challenges remain a major threat for faster adoption of electroceuticals. As industry gains momentum, FDA is stepping up scrutiny across multiple fronts with privacy, security aspects pose threat for acceptance on the patient acceptance front. Business model scalability issues across ecosystem partners combined with pharma industry lobbying power could hold threat to quick adoption of electroceuticals.

Conclusions

We strongly believe electroceuticals will play a major role in healthcare & become mainstay treatment for Chronic pain management, autoimmune diseases. Electroceuticals would also provide solutions for Obesity, diabetics, opioid crisis & have real meaningful benefits to society as a whole. With continued advances in regulations & public policy, Industry is poised for tremendous growth opportunities.

Looking into the future, We see few major trends favoring the electroceuticals industry with technology breakthroughs & huge influx of funding. As industry scales up, growth will accelerate with machine learning / AI based data analytics improving quality of treatment, creating a vicious cycle of faster adoption. Selectivity improvements (Fig 3) will enable more healthcare segments currently served by pharma to move to electroceuticals with less side effects (Pain management/ opioid alternatives).

On the business front, We predict industry players who have strengths in multiple ecosystem components & forge alliances across medical, technology front would achieve business scale quickly to lead the industry. Prime example of such an alliance is “Galvani microelectronics”, a venture formed between google, GSK developing electroceuticals solutions for a wide variety of target applications. As minimally invasive electroceuticals market mature, Google’s investment in AI/ML, Brain map initiatives & GSK’s expertise on the pharma/medicine discovery process could disrupt the pharma industry for many target applications in significant ways. We predict, startup’s targeting large market potential in Chronic Pain management (Nevro) , auto-immune disorders (setpoint) would become acquistion targets for pharma companies (J&J, Pfizer..). Pharma companies who are averse to risk taking & focussed on protecting existing revenue streams will likely find them in tough spots as electroceuticals disrupt the marketplace.

References

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6586833/
[2] https://www.nevro.com/English/us/home/default.aspx
[3]https://www.nanalyze.com/2019/03/electroceuticals-for-6-types-of-medical-conditions/
[4] https://www.youtube.com/watch?v=gMXHAPutGJA&t=97s
[5] https://setpointmedical.com/
[6] https://www.youtube.com/watch?v=AJH9KsMKi5M&t=503s
[7] https://www.youtube.com/watch?v=qXyb8LdkwU4&t=628s
[8] PRNewswire, Feb2019
[9] iHealthCareAnalyst, Nov2019
[10] MarketResearchFuture, Mar2020
[11] Grandviewresearch, 2019
[12] BBC Publishing, 2019
[13] Statenews.com/2019/08/01
[14]https://rupress.org/jem/article/209/6/1057/41310/Neural-reflexes-in-inflammation-and-immunityReflex
[15] https://www.nature.com/articles/496159a
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6071306/
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1564060/
[18] https://jamanetwork.com/journals/jama/fullarticle/202752
[19] https://dl.acm.org/doi/10.1145/2508701
[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397644/
[21] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191684/