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Review Article

Review on Neuro Degenerative Disorders – with Reference to Ethinomedicinal and Novel Strategies

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ABSTRACT

The whole globe counts about 450 million patients with NDDs by WHO. These are huge socio economic burden for the whole world. Certain neuronal changes occur due to oxidation, inflammation, ubiquitination, etc. leads abnormal changes in behavioral, psychological, mobility characters.

For the treatment of NDDs no much feasible and effective drugs or strategies are developed till date. Some synthetic drugs show some neuro protective characters but in addition shows a lot of ADRs. To counter these ADRs use of phytochemicals are a great choice but the clinical feasibility is still a big question.

Strategies like, stem cell therapy, gene therapy. Immune therapy, neuronal stimulation, Nano formulation, use of IoT and robotics are an emerging field of research because of their incomparable outcomes. Such therapies are only feasible theoretically but all these strategies are still under infancy but some also showed remarkable results.

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INTRODUCTION

According to the WHO reports around 450 million people around the globe suffer from different types of NDDs. Neurodegenerative disorders often referred as NDDs are the mental, psychological and behavioral changes seen in any person due to abnormal conditions occurred in the brain. NDDs include mental disorders like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, Autism, Dementia, Depression. NDDs occur due aggregation of protein and inflammation as well as oxidative stress, abnormal ubiquitination and further damaging the BBB, insufficient or depletion in the amount of neurotransmitter synthesis and more [1].

For the treatment of the NDDs some first line synthetic drugs are used for better results and quick action but also the ADRs of these synthetic drugs ca never be ignored. So as to reduce the use of synthetic drugs and to enhance patient safety along with easy availability of the drugs, the use of natural products has been a choice for many researchers. As in case of most NDDs the proper pathogenesis is still unknown and if known then there is a lack proper therapeutic procedure. Undoubtedly, the natural drugs serve as a very promising method for treatment still they are not much reliable as researches are still under process. So to overcome such issues, use of some smart and innovative therapeutic aids are used for the treatment. Such aids may include the stem cell therapy, gene therapy, Immune therapy, use of artificial intelligence, robotics etc. Technological advances in the field of treatment of NDDs have shed rays of hope as the new therapeutic strategies are more reliable and show least ADRs [3 - 9].

A SHORT DESCRIPTION ABOUT THE DIFFERENT NDDS

1. Alzheimer's disease (AD)

AD is characterized by cognitive decline, neuronal loss, neuronal inflammation, and neuronal death, which is also known as apoptosis and/or necroptosis. Moreover, aggregation of β- amyloid (Aβ) is one of the main features of AD. The formation of hyper phosphorylated Tau (microtubule-associated protein) in the neurons is also linked with AD [1]. The symptoms of AD can be directly correlated with the decreased cholinergic neurotransmission; therefore first and foremost approach is to increase the availability of ACh by inhibiting its degradation by the enzyme AChE.

Based on this intervention, four AChE inhibitors were developed and approved by U.S. FDA. These include donepezil, rivastigmine, tacrine and galanthamine are most commonly used for mild to moderate cases of AD. However, tacrine is no longer

marketed because of its poor tolerability and signs of hepatotoxicity in controlled trials [10]. The second promising approach is the anti-glutamatergic strategy based on which N-methyl D-aspartate (NMDA) receptor antagonist, memantine has been developed. It reduces the glutamate excitotoxicity and has shown beneficial effects in moderate to severe cases of AD [11]. Recently the focus is on disease modifying approaches like antiamyloid, anti-tau, anti-inflammatory, caspase inhibitors and statins etc. which can delay the disease progression.

2. Parkinson's disease (PD)

PD is a movement disorder which is characterized by abnormal aggregation of α-syncline protein in the neurons. PD is arising due to degradation of dopamine carrying neurons in the substansianigra. The neuronal death occurs in PD is due to the damage of free radicals and Lewy's bodies formation [13, 14]. There is degeneration of the dopaminergic neurons resulting in diminished dopamine levels in brain and the most common therapeutic approach is to raise the levels of dopamine in brain, for which levodopa, the dopamine precursor, is most effective symptomatic treatment. However, the chronic use of levodopa is associated with dyskinesia. Monoamine oxidase B (MAO-B) inhibitors, catechol-o-methyl transferase (COMT) inhibitors and dopamine agonists are the other available treatments of PD as these drugs either boost the levels of dopamine in brain or mimic the effects of dopamine [11].

3. Amyotrophic lateral sclerosis (ALS)

The word "Amyotrophic" refers to the muscular atrophy seen in the neurodegenerative diseases, while "lateral sclerosis" refers to the sclerosis observed in the nerve tissues of the lateral spinal cord. As the disease progresses, lower motor neurons (LMNs) and upper motor neurons (UMNs) degrade, and patients experience increasing muscle weakness and wasting, eventually losing the ability to speak, swallow, and breathe. ALS generally occurs in two stages, "limb onset" (disease begins with weakness of limbs) and "bulbar onset" (characterized by difficulty in swallowing, chewing and speech). But the serious adverse effects associated with these drugs led to the development of novel non-dopaminergic treatments like adenosine receptor antagonists, NMDA antagonists, calcium channel blockers, glucagon like peptide-1 agonists, iron chelators, anti-inflammatory agents, anti-oxidants and gene therapy [4, 11].

NATURAL PRODUCTS USED IN THE TREATMENT OF NDDS

For the treatment of NDDs there are several front line synthetic drugs like

Levodopa, Memantine, Tacrine, Velnacrine, etc. These synthetic drugs can be neurotransmitter precursors or may be agonist or antagonist depending upon the nature and method of treatment of the disorder. Undoubtedly these synthetic drugs are very efficient and potent in curing the disorders but the drastic adverse reactions (ADR) can never be ignored. So as to minimize the adverse reactions and to maximize the availability and efficacy the phytochemical has been a great subject of consideration by many researchers [2].

Phytochemicals are the chemical constituents that are present in the nature and are derived from the plant source. The natural herbal ingredients has been on use since the ancient times. As for many traditional drugs, many clinical concerns have arisen regarding the use of Natural Products, mainly focusing on the lack of scientific support or evidence for their efficacy and patient safety. These clinical uncertainties raise critical questions from a bioethical and legal point of view, as considerations relating to patient decisional autonomy, patient safety, and beneficial or non-beneficial care may need to be addressed, meaning that many intriguing points may arise regarding the use of natural products[2]. The use of natural products is more emphasized because of:

- ❖ Dissatisfaction with the results of traditional drugs
- ❖ Claims on the efficacy of the traditional drugs
- ❖ High cost of the traditional drugs
- ❖ Improvements in the quality, efficacy and safety of herbal medicine with development of science and technology
- ❖ A movement towards self-medication.

Many plant based products are extracted and are used for the treatment of various disorders are termed as phytochemicals. Phytochemicals tend to produce less adverse reactions as compared to the synthetic drugs and are safer.

Natural alkaloids used for the treatment of NDDs

Alkaloids are the nitrogen containing organic plant compounds that may be toxic but they too tend to produce therapeutic effects. The sesquiterpene alkaloid, called *huperzine A*, was isolated from the club of the family of *Huperzia.* Natural terpenoids for the treatment of dementia and related diseases. *Ursolic acid* is a pentacyclic triterpenoids and was first isolated and identified in apple epicuticle waxes about 100 years ago. It is present in many plants such as apples, basil, blueberries, cranberries, etc. Triterpenoid peroxides as potential ant dementia therapeutics. Recently, French

scientists from Marseille isolated the norlupane triterpenoid hydroperoxide from sediments of the abiotic degradation of terrestrial vascular plant material in the Canadian Arctic [12].

Pharmacological evaluations of natural extracts from existing literatures:

- ***Raut et al.,*** Studied on *W. somnifera*to evaluate dose related tolerance, safety and activity and suggested that the average tolerance dose concentration was 750– 1250 mg/day. *Withaniasomnifera*inhibited NADPH-d activity which is induced by stress, the mode of action of *W. somnifera*on NADPH-d by inhibiting the release of corticosterone and by activating choline acetyltransferase which boost serotonin in hippocampus [15 - 16]. As we know *Withania somnifera* (Ashwagandha) is an Ayurvedic medicine which has been used for many decades for its anti-inflammatory, anti- oxidant, anti-stress and neuroprotection, immune boosting and memory power enhancing ability.
- ***Nah et al***., studied [17] on *Ginseng* which has the ability to inhibit voltage dependent Ca^{2+} channels by a receptor linked to G protein which is sensitive to toxin. The study revealed that *Ginsenoside*a saponin which is found in trace amount helps in modulating neuronal Ca^{2+} channels. The *Ginsenosides* (Rb1 & Rg3) of *Ginseng* possess neuroprotective effect thereby making them an excellent compound for treating neurodegenerative diseases [18]. The active compound of *P.ginseng,* is proven for its neuroprotective effect on dopaminergic neurons by inhibiting the elevation ofnigral iron level, lowering the expression of DMT1 (divalent metal transporter) and potentially increasing the expression of FP1 (ferroportin) in Parkinson's disease.
- ***Shinomol et al.,*** evaluated on *Baccopa monnieri* otherwise known as Brahmi is well known for its medical properties in Ayurveda. *Baccopa monnieri* is commonly found in India and Australia. It has a potential to rejuvenate nerve cells and also has a great ability in improving memory power. The two saponins of Brahmi are Bacoside A & B which are made up of Sapogenins—Bacogenins A1–A4, Betulic acid and various alkaloids [19]. Among the two main saponins Bacoside A is said to improve the memory power [20]. Apart from memory boosting ability *B. monnieri* is also used as anti-oxidant, anti-stress, anti-inflammatory, anti-microbial and smooth muscle relaxant.

Achyranthes aspera often called as Latjira, belonging to the family *Amarantheceae*.

A.aspera is often found as a weed all over India. A. aspera has a number of disease curing properties but the curing of NDDs are still very less known. Most researchers did not find any anti-depressant properties through open field test and forced swimming test. The methanolic extract of *A. aspera* showed anxiolytic effect due to the presence of phytoconstituents like alkaloids, steroids and triterpines. It could be used for management of anxiety disorder as it is an economical product.

Table 1: Plants showing different biochemical properties along with their active constituents are presented in the table below:

Plants	Active constituents	Properties
Pavetta crassipes	quercetin	Antioxidant [21]
Piper nigrum	piperine	Antioxidant [22]
Buddleja salviifolia	Phenols, flavonoids	Antioxidant and anticholinesterases[23]
Corydalis ternate	protopine	Antioxidant and anticholinesterace[24]
Piper nigrum	piperine	Antioxidant and anticholinesterace
Salvia plebeian	Essential oil	Antioxidant[25]

Table 2: Plants and their active constituents used in NDDs are represented in the table below:

Plant	Active Compounds	Disorder
Adhatoda vasica	Vasicine, vasicol, vasicinol, arachidic, cerotic, linoleic, and oleic acids	AD, PD [26]
Ginkgo biloba	Amentoflavone	PD [27]
Mandukparni (Centella asiatica)	Asiaticoside	Schizophrenia [28]
Panax ginseng	Ginsenoside	PD [29]
Rauvolfia serpentine	Reserpine	Schizophrenia [30]

DRUG REPURPOSING – A NOVEL STRATEGY AGAINST NDDS

Drug repurposing is a very significant and effective method for treatment of a no. of NDDs. It involves the investigation of existing drugs for new therapeutic purposes. Anti-cancer drugs can be repurposed for the treatment of AD. This can be possible because cancer and NDDs share signaling pathways such as mitochondrial dysfunction, oxidative stress, compromised cell metabolism and

development of misfolded proteins. It has been seen that patients suffering from breast cancer and are treated with chemotherapy show lower risk of developing AD [7, 31].

Drugs that are repurposed for AD treatment -

- Carmustine is a Nitrosourea, used as an alkylating agent in treating brain cancer. Due small molecular size, lyophilic it easy penetrates the BBB. Carmustine showed a strong reduction in amyloid- β production, at a non- toxic dose [32].
- Bexarotene, a retinoid X receptor antagonist, used to treat cutaneous T-cell lymphomas, has proven to be capable of reversing neurodegeneration [33].
- Paclitaxel, an antimitotic agent approved for ovarian and breast cancer, and non-small cell lung cancer, among others, has also been studied as a potential treatment for AD [34, 35].
- Even anti-biotics like azithromycin and erythromycin, macrolide antibiotics, have shown inhibition of the amyloid precursor protein, resulting in the decrease of cerebral levels of amyloid-β [36].
- The antiepileptic drug valporic acid has been suggested as a neuroprotective agent for AD, as it has shown reduced formation of amyloid-β plaques and improvement in memory deficits in transgenic mice [37, 38, 39, and 40].
- Antidiabetics likeLivoglutide have also been repurposed for AD, since type 2 diabetes has identified as a risk factor for AD. Insulin can also induce neuronal stem cell activation and cell growth and repair, and treatment with insulin has shown neuroprotection and a regulation on the levels of phosphorylated tau protein, as well as an improvement in memory and cognition. [41, 42, 43].

Also in case of patients suffered from PD, drug repurposing worked in minimizing the disease symptoms which are due to loss of dopaminergic neurons within substantia nigra. Although PD is not curable but the current therapeutic strategies are efficient in managing the disease symptoms [7].

Drugs repurposed for PD treatment-

1. Amantadin was first discovered for the treatment of influenza but later it was repurposed and is used as an antiparkinsonian drug. It showed significant results in increasing dopamine and blocking its reuptake [44].
2. The antibiotic doxycycline, a potential anti-AD and anti-PD candidate. In fact, changes in the concentration of doxycycline can select between antimicrobial and anti-inflammatory activity [45].
3. Exenatide is glucagon-like peptide-1

used for the treatment of type 2 diabetes, like liraglutide, discussed previously. It has been studied as a treatment for PD, and has shown neuroprotection and beneficial neuroplastic change that can delay or prevent disease progression [46].

Table 3: Summary of the repurposed drugs

DRUGS	USED FOR / AS	REPURPOSED FOR
Carmustine	Alkylating agent in brain cancer	reduction of amyloid-β production
Bexarotene	Cutaneous T-cell lymphomas	reversing neurodegeneration
Paclitaxel	Antimitotic agent in ovarian and breast cancer	AD treatment
Azithromycin and Erythromycin	Antibiotics	Inhibition of a0myloid-β
Amantadin	Anti-influenza drug	PD treatment
Doxycycline	Antibiotic	AD and PD treatment
Valporic acid	Anti-epileptic	Neuroprotective agent
Exenatide	Anti-diabetic (type 2 diabetes)	PD treatment

STEM CELLS THERAPY IN NDDS

- Stem cells act as immune modulatory and neuro-protectors. Stem cell therapy is key to treatment of a no. of disorders including the NDDs. Stem cell therapy came into highlights when PD patients from Mexico was treated with this therapy [47]. Today stem cell therapy offers a promising hope for treatment of almost all NDDs.
- Stem cell therapy challenges the fundamental mechanisms of neuronal degeneration and enables the neural tissue regeneration [48].

There are the various types of stem cell therapies

1. Embryonic stem cells (ESCs)

This kind of stem cell therapy is still under trial and is waiting for approvals [49, 50]. The first clinical application of ESCs derived tissue in the CNS was oligodendrocytes in treatment of spinal cord injury. Translating ESCs into novel therapies in neurodegenerative diseases needs careful consideration as it is associated with the risk of tumor formation [51, 52].

2. Induced Pluripotent stem cells (IPSCS)

Reprogramming of adult somatic cells to acquire similar characteristics as ESCs. These cells are referred to as IPSCs. Such reprogrammed cells now offer the promising avenue to generate autologous dopaminergic neurons for transplantation in PD patients. The IPSCs platform has a distinct advantage over ESCs in the sense that IPSCs are autologous and therefore the

transplantation does not require immunosuppressive agents. However, similar to ESCs, an important risk of IPSCs is tumor formation. The differentiation of IPSCs into mature neurons is more difficult than ESCs. Hence, the clinical application of IPSC in neurodegenerative diseases is still not feasible [53 - 56].

3. Mesenchymal stem cells (MSCS)

This type of therapy is still under clinical trials and the mechanisms underlying MSC proliferation and differentiation still remains unknown. In preclinical trials, when MSCs were delivered via intracerebral or intrathecal injection then neuronal growth, anti-inflammatory properties were seen along with decreased apoptosis [57, 58].

4. Neural stem cells (NSCS)

NSCs can be produced from foetal or adult central nervous tissues via the dissection of specific brain regions. NSCs have the capacity to differentiate into oligodendrocytes, neurons, and astrocytes [59]. NSCs can synthesize d-serine. D-Serine, the co-agonist of N-methyl-D-aspartate receptors, has been recognized as an important gliotransmitter in the central nervous system [60]. D-serine has been shown to regulate neurogenesis by promoting NSC differentiation into neurons. Low oxygen conditions and hypoxia-inducible factor 1 alpha were identified to be critical for NSC development [61 - 65]. The fundamental mechanism for the observed improvements after stem cell therapy in the central nervous system is believed to be neuroprotection. Neuroprotection is achieved through the secretion of growth factors *i.e*. brain-derived neurotrophic factor, glial cell line- derived neurotrophic factor, and nerve growth factor. Genetically engineered stem cells in recent studies have the tendency to over express growth factors which in turn enhance their neuroprotective capacity [66]. The outcome of stem cell therapy can be improved through the combination with other adjunct therapies. For example, stem cell therapy with erythropoietin demonstrated synergistic effects on neurogenesis [66].

IMMUNOTHERAPY AGAINST NDDS

The immune system or its derivative components could be harnessed to fight the misfolded and aggregated proteins that accumulate in several neurodegenerative diseases [9]. Immunotherapy can be done through different methods like –

- ❖ Targeting inflammatory mediators
  - Inhibition of soluble TNFα
  - GM-CSF and cytokine dysregulated
  - GLP-1 and PPAR-γ
- ❖ Targeting the interaction between PRRs and DAMPs
- ❖ Vaccine therapy
- ❖ Amyloid β targeting therapies

- ❖ Tau targeting therapies – use of anti-phosphorylated tau antibodies.

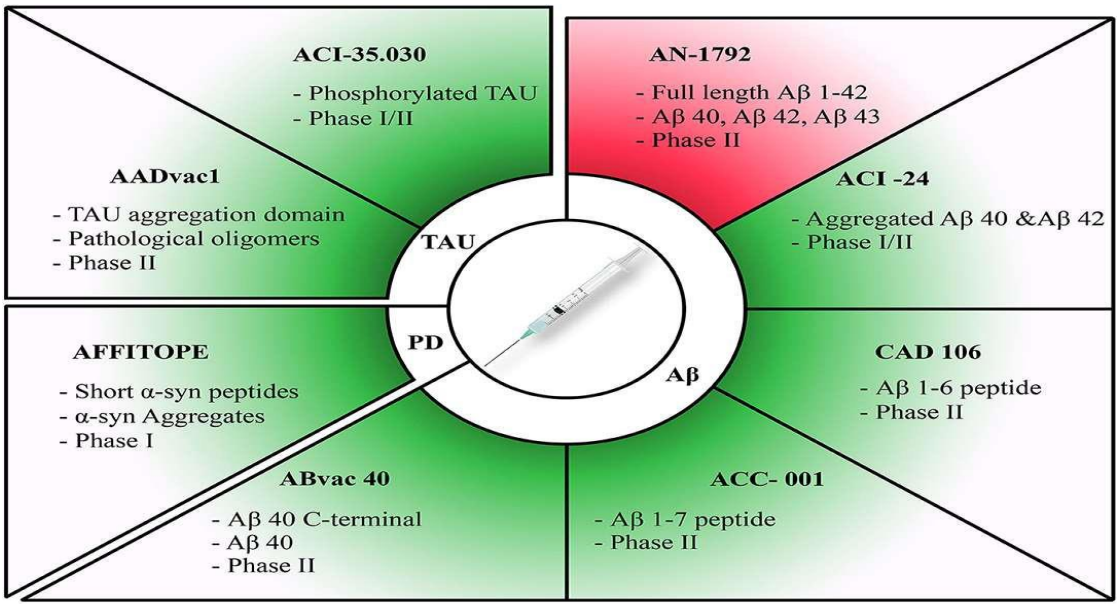


Figure 1: Chart above shows a summary of active immunization therapies assessed in clinical trials for different diseases. Discontinued trials highlighted in red and ongoing trials highlighted in green. Therapies have been categorized according to each pathology they target. The targets of each therapy along with its current clinical trial phase have been stated for each therapy.[9]

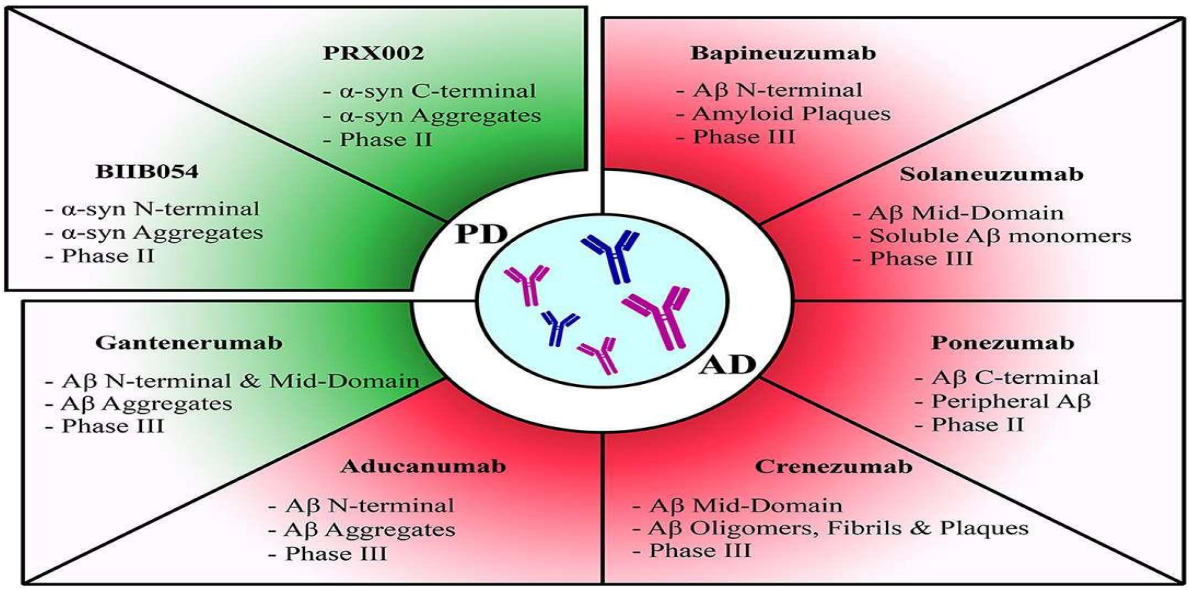


Figure 2: Chart above shows a Summary of passive immunization therapies assessed in clinical trials for different diseases. Discontinued trials highlighted in red and ongoing trials highlighted in green. Therapies have been categorized according to each pathology they target. The targets of each therapy along with its current clinical trial phase have been stated for each therapy.

USE OF PARA MAGNETIC MOLECULES – TO UNDERSTAND AND FIGHT NDDS:

This method targets to cure the misfolded proteins. Here the paramagnetic molecules are used to diagnose and monitor the disease conditions [8].

Understanding Protein Misfolding

When proteins lose their native structure either by mutation or environmental effects, they are typically identified and cleared by the cell. However, elevated levels of misfolded proteins — accumulating either by increased production or decreased clearance — can lead to disease. In the disease pathway, oxidative stress and associated inflammation in response to aggregates of misfolded proteins act as critical mediators of cell death [8].

Novel Approach to Treating AD

Electron Paramagnetic Resonance (EPR) spectroscopy designed by US Davis Prof. John Voss and his team. It introduces "spin probes" (researched and designed by John Voss in collaboration with US Davis Prof. Lee Way Jin) — unique paramagnetic molecules with unpaired electrons — that can bind to these misfolded proteins and report on their dynamics and degree of aggregation. These spin probes carry some unique properties. For example, they can deliver potent antioxidant activity in a catalytic manner [8].

Another key property of the innovation results from the ability of the agents to generate contrast in magnetic resonance imaging (MRI), which then can be used as a diagnostic tool and understand the course of treatment [8]. A series of proprietary spin-labeled agents that preferentially bind to aggregates of misfolded proteins and provide neuronal protection from toxic effects of amyloid-beta. These molecules have been termed paramagnetic amyloid ligands (PALs) as they are not only neuroprotective but also can be visualized in the brain with MRI [8].

NANO-FORMULATION TECHNIQUES – AN EFFICIENT BUT LESS KNOWN TECHNIQUE

The greatest advantages of Nano drug delivery is to increase in the bioavailability and thereby maximizing the therapeutic index of the drug by specifically targeting particular cells or tissues. This helps to reduce the overall side effect of the drug [67]. The size range of the nanoparticles helps it to cross various biological barriers within the body especially the blood brain barrier which is a very challenging question [68, 69, and 70].

1. Electrospinning

Electrospinning is a process in which high voltage is applied to a polymer solution which in turn produces electrostatic force at the tip of the needle thereby forming a Taylor cone which elongates into a fluid

jet, this charged fluid jet is collected on a grounded collecting device. Electrospinning is able to produce nanofibers with diverse forms, such as core–shell fibers, hollow fibers applications for more than a decade, and it has gained a lot of interest in neural tissue engineering [71, 72, and 73].

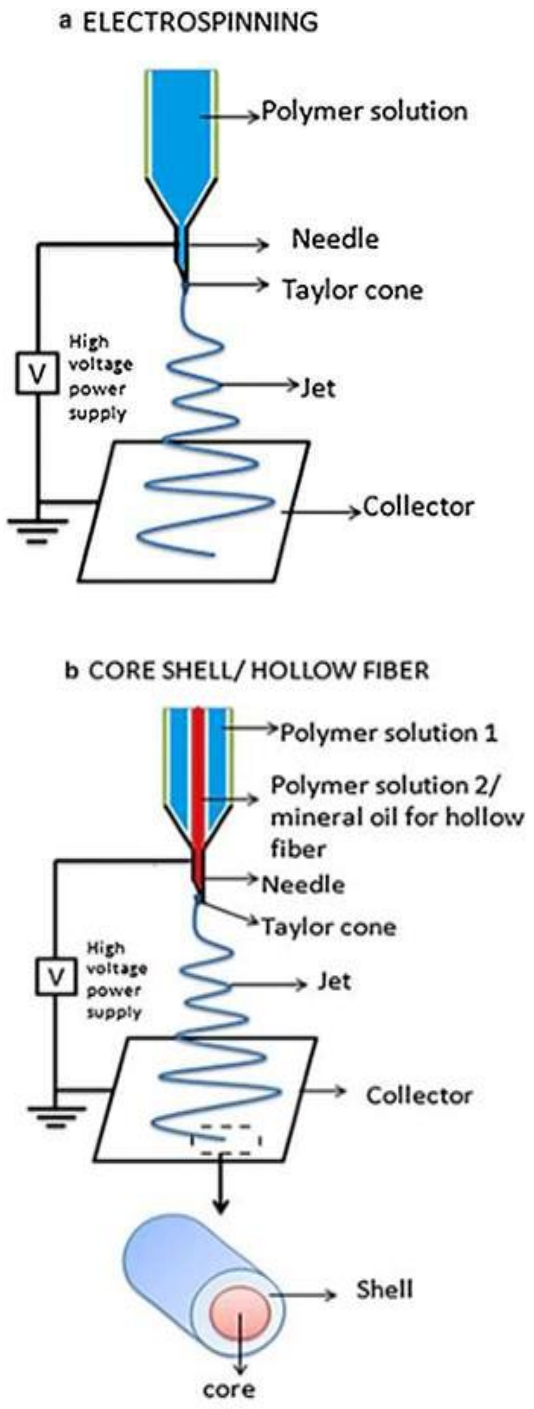


Figure 3: Process of Electrospinning [74]

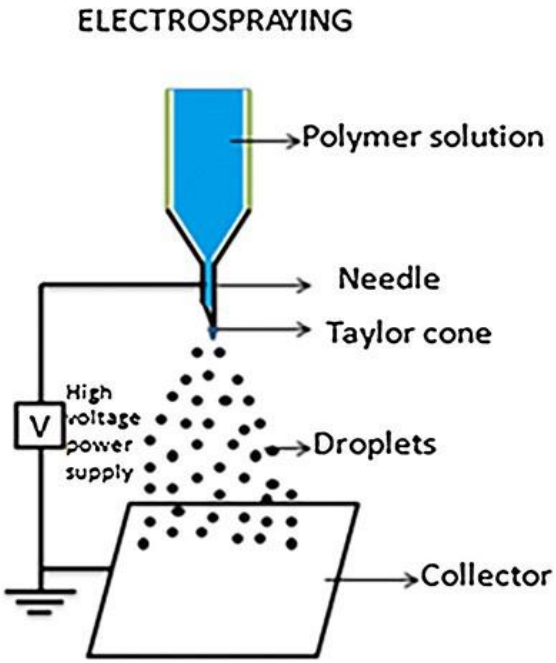


Figure 4: Process of Electrospraying [74]

2. Electro spraying

Another promising technique in the field of Nano drug delivery is electro spraying. Electro spraying is otherwise known as electro hydrodynamic technique following the same principle as that of electrospinning. The experimental setup is made up syringe pump containing polymer solution which is connected to high voltage and a stationary collector. The jet form the Taylor cone is broken down into droplets producing micro and nanoparticles which are accomplished by altering various properties such as voltage,

flow rate etc. [75]. Some of the greatest advantages of electro spraying are size distribution, increase in loading efficiency and the one step process of particle synthesis. The method helps in the direct incorporation of drug into the polymer when compared to other methods of nanoparticle preparation. Electro spraying technique enhances the biocompatibility and efficacy of biomaterials [117, 145].

ALS AND ADVANCEMENTS IN ITS TREATMENT

As there are no potent cures for ALS and there are no therapies so far known except the use of Riluzole and Edarvone that too they can only suppress the symptoms and increase the life up to several months [78, 79]. Hence in such a scenario there is urgent need of development of advanced technologies so as to monitor, diagnose and treat the symptoms of ALS.

Repurposing of Masitinib is a tyrosine kinase inhibitor used to treat cancer in dogs. It has been proven that mastinib inhibit the glial cell activation and increases survival in appropriate rat models [80]. Similarly drugs like Triumeq (for anti – HIV therapy), Retigabine (anti-epileptic), Tamoxifen (antioestrogen) are repurposed for the ALS treatment [81 - 84]. With technological advances in fields such as next-generation sequencing and -omics profiling, the genetic underpinnings of ALS have become clearer in recent years [11].

The gene *SOD1* in particular has received significant research attention, as this was the first gene found to be associated with ALS. *SOD1* has been targeted with antisense oligonucleotides (currently in phase III clinical trial) [11].

Some advance engineered therapies are used widely for the treatment of ALS- Internet of things (IoT), wearable devices, augmentative and assistive communication with brain-computer interfaces (BCI) and eye tracking (ET) support, and robotic rehabilitation can fill this gap. Such technologies could allow a specialist team to care for patients throughout their disease regardless of patients' ability to travel to the multidisciplinary canters [85, 86, 87]. Such platform comprised three main components:

(1) The commercially available Mega Faron 180 accelerometer and 2-lead ECG sensor, attached to the chest;

(2) A Life-Insight Hub, that received data from the sensor via a secure Bluetooth wire-less signal every 2 min, and which in turn automatically uploaded data in real time to secure cloud servers;

(3) A digital speech capture system comprising a high-fidelity microphone

connected to a computer, with bespoke software that instructed the patients to say a series of vowels, words, and paragraphs, which were then recorded and immediately automatically transferred to a secure server via mobile connectivity [89].

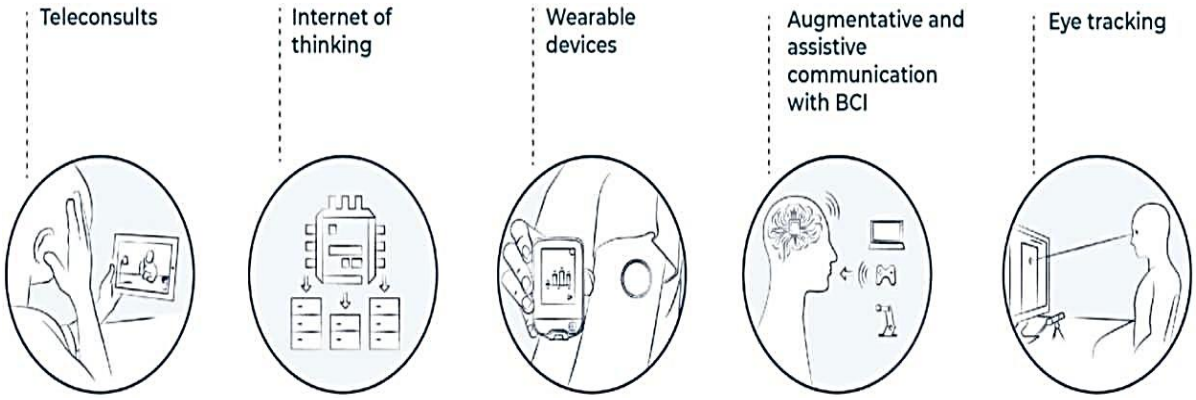


Figure 5: Telemedicine [4]

Telemedicine is a general term, first introduced in the1970s, to indicate the use of telecommunications technology to provide healthcare services to persons who are at some distance from the healthcare professional provider. Telemedicine must not replace traditional health services but rather to integrate them to improve effectiveness [88].

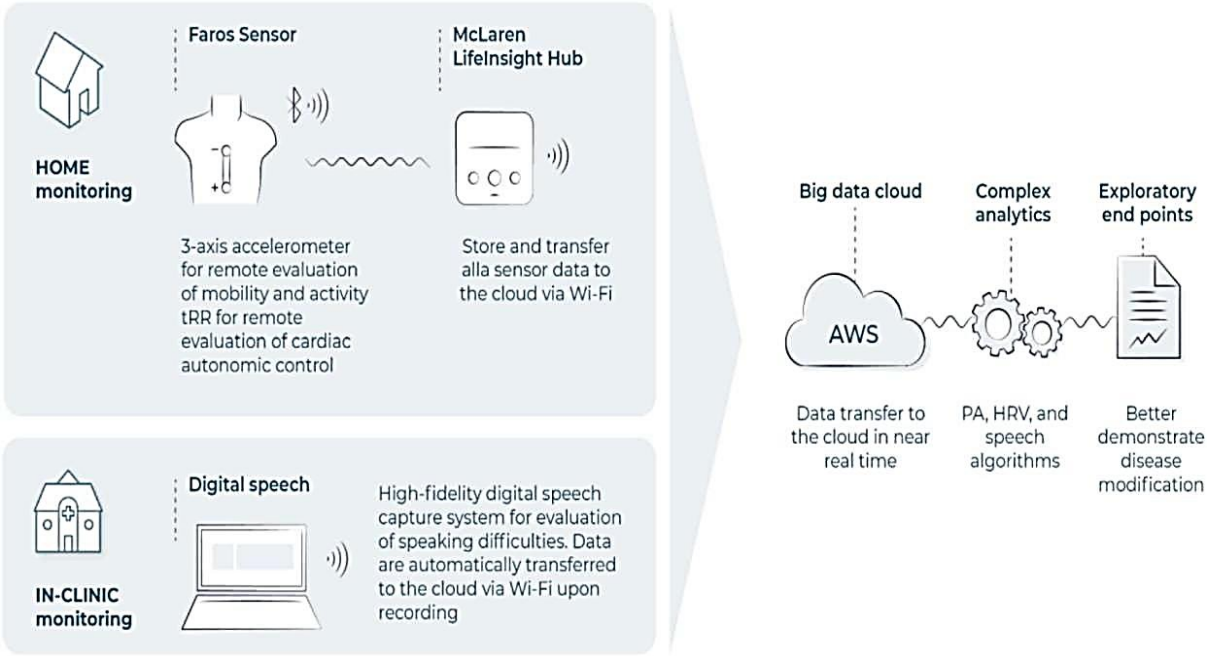


Figure 6: Telemedicine layout [4]

Advantages, disadvantages and improvements needed in telemedicine method:

High-tech augmentative and alternative communication (HT-AAC) technologies- aims to help and improve communication abilities of individuals with difficulties in using common channels of communication, especially verbal and written. Such technologies are defined augmentative because they extend or replace means of communication for physically impaired people, but at the same time, they are defined alternative as they use multimodal method so f communication, which are different from the traditional ones, giving to patients the opportunity to maintain their communicative function by producing write nor spoken messages. Brain-computer interface (BCI) that enables the generation of a control signal from brain responses such as sensory motor rhythms and evoked potentials, thus conveying messages directly to a computer, which performs the desired action. Brain activity can be monitored by several methods as: electroencephalography (EEG), magnet often- cephalography (MEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS). How- ever, these latter two are expensive [90 - 95].

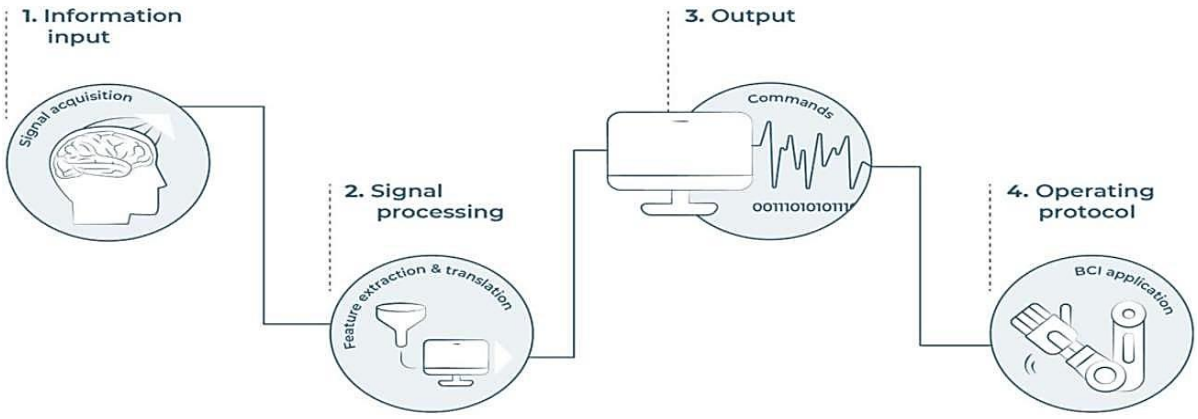
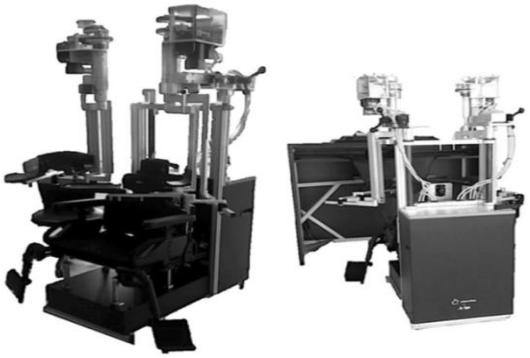


Figure 7: brain-computer interfaces

Neuro – rehabilitation in ALS using robotics. **[96, 97, 98]**

- Robotic rehabilitation is another Emerging technology that is giving its first steps in ALS, and represents a promising tool that can be used not only to assist patients but also for their assessment and training throughout the course of the disease, as it is increasingly clear that either progressive motor weakness and cognitive decline play a significant role in ALS disability [4].



(a)

(b)

Figure 8: a. Robotiv exoskeleton b. Armeo Power

CONCLUSION AND FUTURE PROSPECTUS:

NDDs are a major setback for the entire globe. Day by day the older population around globe is rising and as a result the no. of NDD patients is also rising. So as need of the hour more and more research works are needed to be conducted and some technically advanced and reliable therapeutic methods should be adopted. Let it be Nano-formulation or gene therapy or immunization or stem cell therapy these all methods are still in stage of infancy. There is lack of proper medications for complete cure of NDDs. The synthetic drugs administer do not promise to provide complete recovery. In such a case when natural drugs are thought to be used, their methods are also under infancy. Hence in the near future there are chances of advancement in robotics, IoT, and other reliable and less ADR showing therapies.

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