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Diagnosis and Treatment of Epilepsy using Nanotechnology, Artificial Intelligence and Internet of Things (IoT)#

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ABSTRACT

Over 60 million people worldwide suffer from epilepsy. Despite the high prevalence of the disease, a clinical problem is emerging: The development of resistance to drug therapy. Drug delivery nanosystems, Artificial Intelligence (AI) and the Internet of Things (IoT) appear promising both at the diagnostic and therapeutic levels. This announcement is a review of clinical studies published in authoritative databases. These studies examine the application of drug delivery nanosystems in clinical therapy and diagnosis. At the same time, Artificial Intelligence (AI) and the Internet of Things (IoT) seem to give significant advantages to the treating physician. The application of Artificial Intelligence (AI), the use of Big Data through IoT-based networks, and the utilization of "smart" nanodevices can assist in clinical diagnosis and treatment. Also, drug delivery nanosystems improve biostability, reduce toxicity and control the release of the entrapped drug with better pharmacological effects. A typical example of diagnostic optimization is iron oxide nanoparticles as contrast agents in Magnetic Resonance Imaging (MRI). In addition, in the future, it is sought to design nanosensors that record an epileptic seizure, but have the ability to predict it by informing the patient from his mobile phone.

1. Introduction

Over 60 million people worldwide suffer from epilepsy. Despite the high prevalence of the disease, a clinical problem is emerging: The development of resistance to drug therapy. Thus, seizures become more frequent as the dose is reduced. Up to 40% of patients eventually develop resistance, increasing seizures, the risk of damage to an area of the brain, and mortality rates. Patients experience emotional and behavioral changes, seizures, convulsions, depression and, in some cases, loss of consciousness[1.] Pharmaceutical Nanotechnology has shown that it can contribute to diagnosis using nanoscale biosensors, which record the electrical excitability of the brain. The data can be used to develop algorithms that will be able to predict or characterize epileptic seizures[2]including added socio-economic burden. Unfortunately, only a few suppressive medicines are available, and a complete cure for the disease has not been found yet. Excluding the effectiveness of available therapies, the timely detection and monitoring of epilepsy are of utmost priority for early remediation and prevention. Inability to detect underlying epileptic signatures at early stage causes serious damage to the central nervous system (CNS. The treatment of epilepsy is often complicated by the inability of available antiepileptic drugs (AEDs) to cross the accessory blood-brain barrier (BBB), which could be overcome by appropriate drug delivery systems. The ideal system would provide localized and controlled release of AEDs at targeted sites in the brain to help reduce drug toxicity and enhance their efficacy. Several strategies for effective AED administration have been reported in the scientific literature. Nanotechnology-based systems appear to be a promising and innovative development as several drug delivery nanosystems have recently been reported as effective CNS delivery systems due to their increased biostability, ability to cross the blood-brain barrier (BBB) and their improved selectivity1. Nanotheranostics systems (nano therapeutics & diagnostics) combined with the Internet of Things (IoT) and artificial intelligence (AI) bring new possibilities for the immediate relief of epileptic seizures. Finally, the use of smartphones and portable devices (smart watches and fitness trackers) help to evaluate and monitor the neuronal impulses of the brain[3].

2. Definitions

Nanotechnology-based medicine (nanomedicine) refers to the characterization of surface properties and the design of nanocarriers for various medical strategies. Therapeutic agents are embedded or coated on nano-carriers, small colloidal or solid structural platforms ranging in size from 1 to 1000 nm. These NanoParticles (NPs) readily interact with the cellular environment at the molecular level to produce the desired physiological response. Nanotechnology-based AEDs have recently attracted attention due to their ability to penetrate the BBB, their improved selectivity and the potential for sustained drug release in the brain. Size, molecular weight (MB), copolymer ratio, corrosion mechanism and surface charge are important factors when considering the effectiveness of NPs. For example, the size of NPs is a very important determinant of effective BBB passage. NPs ranging from 35 to 64 nm have easy access to most neural tissues. The synthesis of NPs of specific size could be achieved through different preparation methods. As a result of the reduction in the sizes of NPs, the nanocarrier system exhibits a large surface area that can carry large doses of drugs, effectively reduce the peripheral drug toxicity and provide adequate drug delivery to their targets. The surface charge of NPs is also an important factor in determining their effectiveness in targeting the brain. It has been reported in the literature that neutral and mildly negatively charged NPs are more effective than positively charged NPs. On the other hand, positively charged NPs can make immediate changes in the BBB (albeit for a shorter duration) and are later cleared by the reticuloendothelial system (RES)[1.]

3. Pathophysiology and epidemiology of epilepsy

Epilepsy is a neurological disease characterized by

Table 1. Presentation of the advantages and disadvantages of using nanocarriers from studies performed for CNS diseases[1]. Table 1 is adapted from Reference 1.

Nano-carriers	Drugs used	Advantages	Disadvantages
Liposomes • PEG-Liposomes • Glycolipid conjugated • Immuno liposomes	GABA Phenytoin Thyrotropin	• Biocompatible • Size diversity • Molecular weight and hydrophilicity aids into effective encapsulation and entry to neural tissues skipping body defense machineries	• Susceptibility to RES clearing is more than the other NPs • Prone to phospholipid metabolic degradation leading short stay in the system • In earlier generations, shelf life stability was quite low
• Polymeric nanoparticles • PLGA • Poly(butylcyanoacrylate) • D,L-polyactide • Poly(ε-caprolactone) • Chitosan • Pullulan acetate-PEG • Poly(DL-lactide-co-glycolide) • Poly(glycolic acid)	β-Carotene Probenecid Thyrotropin Phenytoin Ethosuximide Clonazepam Valproate Loperamide Carbamazepine	• Biodegradable and biocompatible • Programmed drug release could be achieved by choosing apt polymer composition, ratio and molecular weight • Preparation easiness and greater stability	• Susceptibility to RES clearing and opsonization
Solid lipid nanoparticles • Chitosan	Diazepam Temozolomide Carbamazepine Riluzole Carvedilol	• Greater physical stability • Less toxicity • Greater surface area • Improve both drug loading and its efficacy • Multiple routes of administration	
Nano emulsion	Amiloride Olanzapine Carbamazepine Clonazepam Levetiracetam	• Stable preparations • Higher rate of absorption • Transmittable in multiple routes with less toxicity and irritation • BBB permeable	
Magnetic nanoparticles • Cobalt (Co) based • Nickel (Ni) based • Iron (Fe) based • Alginate-chitosan	Carbamazepine Alpha-methyl Tryptophan (diagnostic) Ethosuximide	• Precise modular control on transport and delivery to the targets • Minimum toxicity to other tissues	

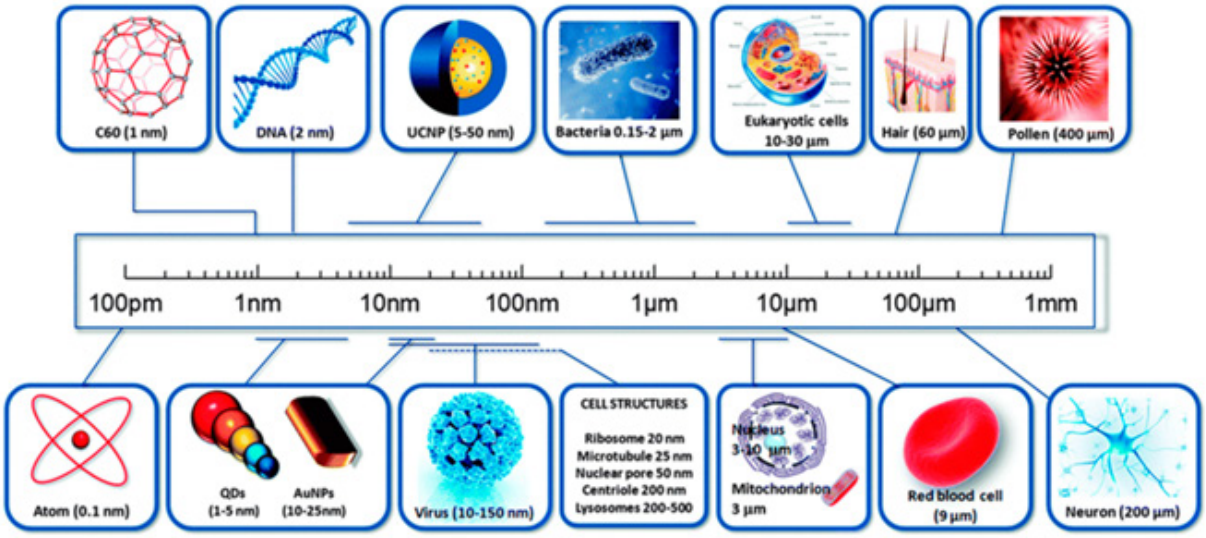

Figure 1. *Comparison of the size of nanosystems with biomolecules and cells. Adapted from ref. 4 (Creative Common CC BY license)[4].*

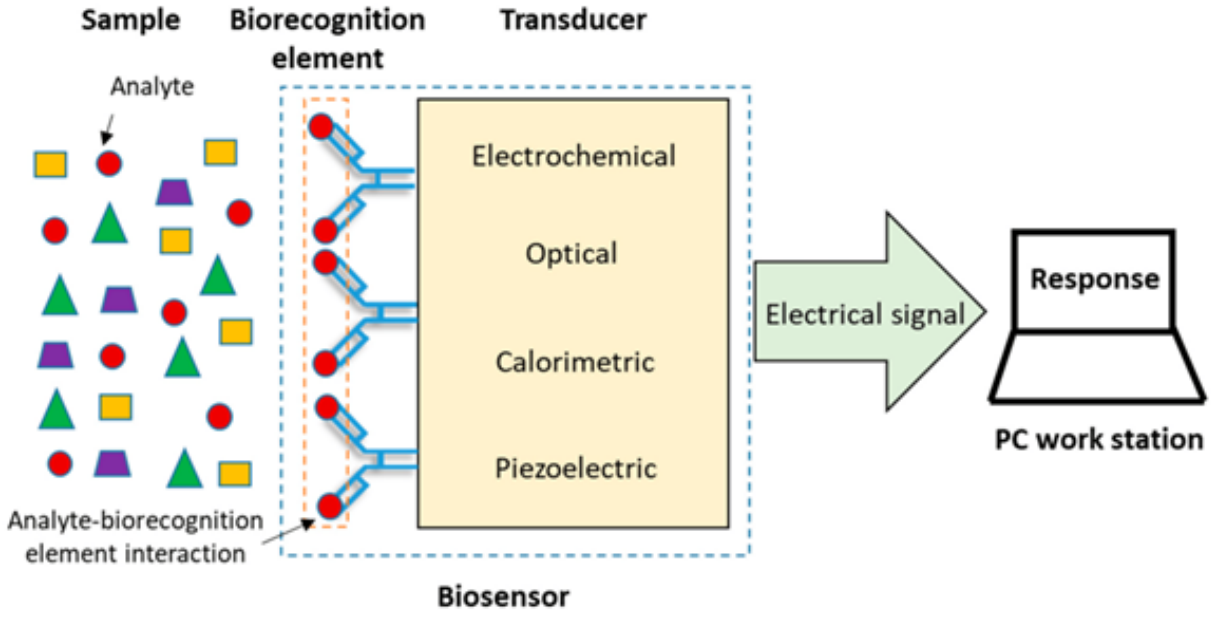

Figure 2. *Presentation of the parts of a biosensor. Adapted from from ref [12] (Creative Common CC BY license).*

abnormal electrical activity that causes seizures in various parts of the brain. This disease has neurological, cognitive, psychological and social effects and affects approximately 50 million people worldwide[5]. Estimates of the global prevalence and incidence of epilepsy vary from country to country. While it is more common in middle-income countries than in high-income countries, there is a significant increase in the number of patients in childhood compared to old age[6]. However, mortality is low. Unintention-

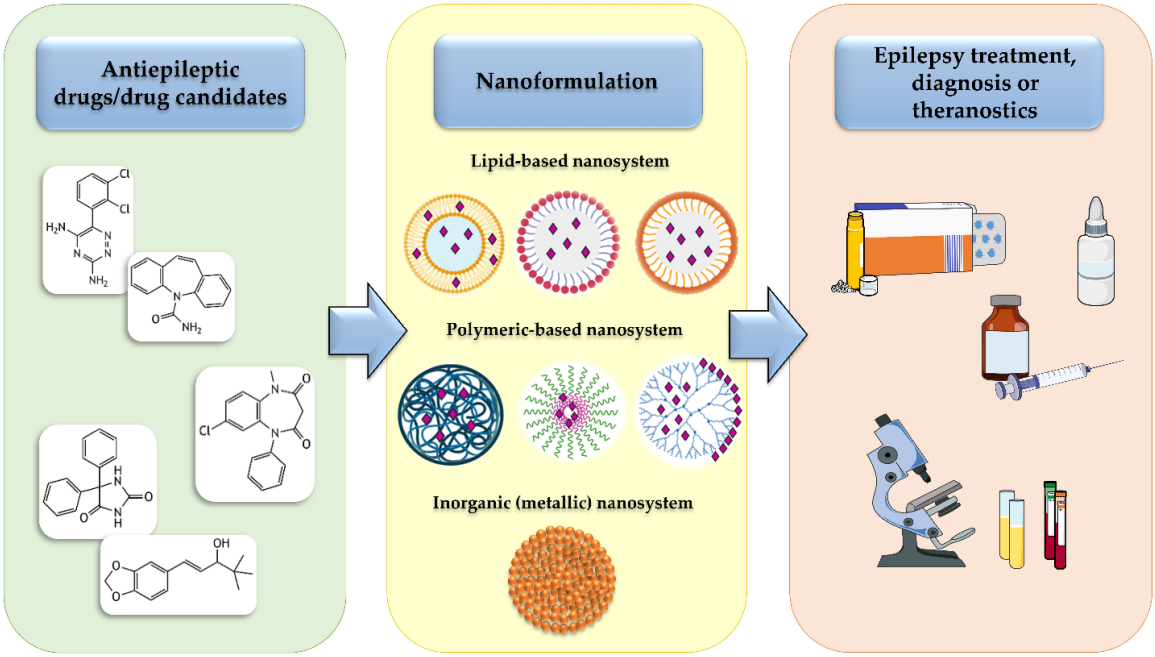

Figure 3. *Presentation of the steps for the formulation of nanomedicines in the treatment of epileptic brains. Adapted from ref. [13] (Creative Common CC BY license).*

al injuries and suicide were found to be among the deaths caused by epilepsy[7]. These results suggest that patients are psychologically affected by the lifelong continuation of the disease[8].

According to the World Health Organization (WHO), seizures are the result of excessive electrical discharges in a group of brain cells. These secretions can appear in many parts of the brain. The frequency of seizures caused by these secretions can range from 1 per year to several per day[8].

4. Diagnosis

Nanotechnology has been used as a diagnostic method in brain disorders. For example, iron oxide (magnetic) nanoparticles (MnPs) are applied as contrast agents in magnetic resonance imaging (MRI) of brain pathologies such as tumors, stroke, multiple sclerosis, acute diffuse encephalomyelitis, and trauma. Attached to non-radioactive drugs such as alpha methyl tryptophan, the magnetic nanoparticles are used for MRI imaging of normal brain functions and changes caused by epileptic activity. Conjugating nanoparticles to specific markers or antibodies can improve diagnostic specificity[9]. Technologies for monitoring neuronal activities are desirable for understanding the mysterious workings of the brain and the underlying mechanisms of neurological disorders such as epilepsy and Alzheimer's disease. In this regard, the potassium ion (K^+), as a key determinant of membrane potential, has been one of the main research targets, because the change in its concentration in the extracellular space directly affects the membrane potential of neurons and alters the intrinsic neuronal excitability and synaptic transmission. Therefore, much effort has been made to develop K+ sensors that have high sensitivity and selectivity. Until recently, K+-selective microelectrodes were considered the gold standard that allow us to measure extracellular K+ concentration ([K^+]o) with high temporal resolution[10].

In the effort to measure the change in potassium

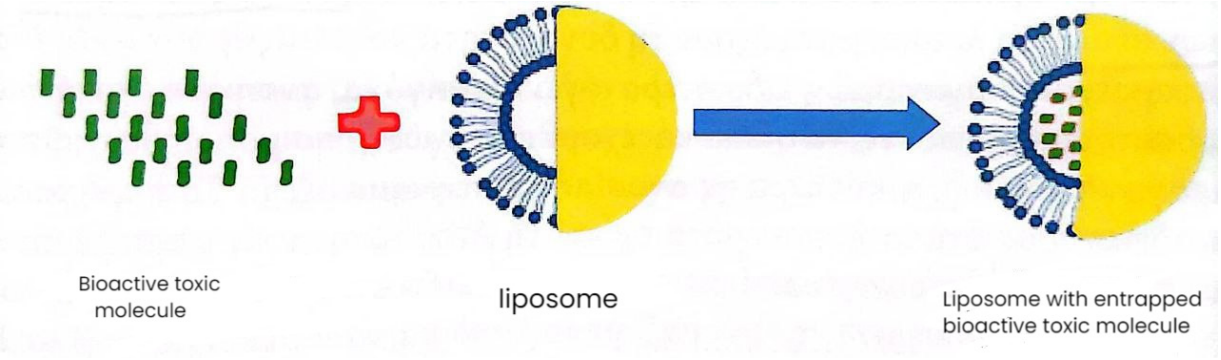

Figure 4. *Bioactive toxic molecule, liposome free of the bioactive molecule and liposome with the toxic bioactive molecule entrapped*[11].

ion concentration in the extracellular space, a nanoscale biosensor was developed by a group led by Zhong Chen and Daishun Ling at Zhejiang University and Taeghwan Hyeon at IBS10. Biosensors are defined as devices used to detect of molecules and which have a biological component (enzyme, antibody, nucleic acid, whole cells or parts of tissues) combined with some physicochemical analytical part. In summary, biosensors give a measurable indication after reacting with the analyzed sample, without requiring the addition of reagents [11].

A biosensor consists of three components:

1. A recognition biomolecule, responsible for the specificity of the sensor to the target molecule (e.g., receptor).

2. A detection element, which acts in some physicochemical way (optically, electrochemically, etc.).

3. A processor-signal converter or electronic processor, to present the results [11].

The experiment's nanodevice consisted of an optical potassium indicator (a dye molecule that fluoresces in the presence of K^+) embedded in mesoporous silica nanoparticles shielded by an ultrathin layer of a potassium-permeable membrane. This membrane is very similar to the potassium channel in brain cells, and the pore size of the nanoparticles prevents other cations (including Na^+) from reaching the marker. This means that the device exclusively captured K^+ ions and could detect their presence at concentrations as low as 1.3 micromoles per liter. Thanks to this high sensitivity, the researchers were able to spatially map sub-milligram changes in extracellular K+ in three different regions of the mouse brain: the hippocampus, the amygdala, and the cortex10. After injecting the nanosensors into various locations in the brain of a test mouse, the team electrically simulated the mouse's hippocampus to induce a seizure and recorded the visual responses of the nanosensors. They then compared these measurements to those obtained from simultaneous measurements made using conventional electroencephalography (EEG). They found that in localized seizures, extracellular K+ concentration increases from the hippocampus to the amygdala and cortex over time, whereas in generalized seizures it increases almost simultaneously in all three brain regions[10].

5. Treatment

Nanotechnology is a rapidly developing field that has given new hope for the treatment of various disorders, including CNS diseases. The ability to cross the BBB and the specificity of targeting appear to be the main obstacles to the success of AEDs in pharmacotherapy. Applications of nano-based drug delivery systems in epilepsy are a promising solution that can overcome these limitations[1].

It is important to note that the treatment of drug-resistant CNS disorders is one of the greatest

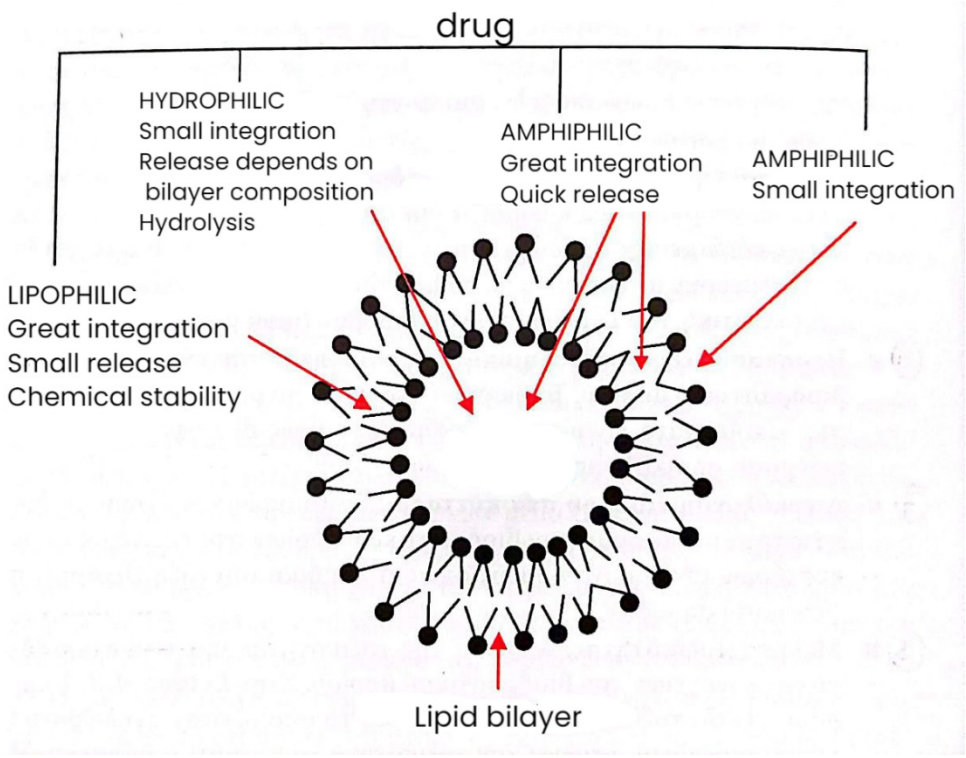

Figure 5. *Placement of the active molecules in the liposome according to their hydrophilicity*[11].

challenges in drug administration. However, there are currently no studies aimed at evaluating the effects of AEDs delivered by drug nanocarriers in experimental models or in patients with drug-resistant epilepsy[9].

Various nanocarriers can easily access targeted brain sites by manipulating the permeability of the BBB. Modification of NPs with surface ligands facilitates BBB crossing by nanocarriers. Due to the presence of transport molecules, such as growth factors, insulin and transferrin, at the BBB, NPs are desirable drug carriers in mapping strategies of epilepsy diagnosis and treatment. The blood-brain barrier acts as a neuroprotective barrier that prevents harmful substances from entering the brain while providing essential nutrients to the tissues. The BBB consists of a network of brain capillaries (microvessels) which are the smallest vessels of the vascular system, with a diameter of 3-7 μm. To ensure an efficient supply of nutrients and oxygen, approximately 100 billion of these microcapillaries are tightly packed and separated by only 40 μm. The transport of compounds into and out of the brain, leukocyte migration, and maintenance of brain microenvironment homeostasis are regulated by the microvascular endothelial cells of the BBB. Neighboring endothelial cells of brain capillaries contain tight junctions with multiple cell-cell protein interactions and some perforations and pinocytic vesicles[1].

6. Liposomes

Liposomes refer to unilamellar or multilamellar phospholipid vesicles that enclose a central aqueous compartment. Liposomes are the most studied AED delivery system due to their biocompatibility, biodegradability, and ability to encapsulate drugs with different lipophilicities and molecular weights. The ease of changing their dimensions, membrane fluidity and surface characteristics make them ideal

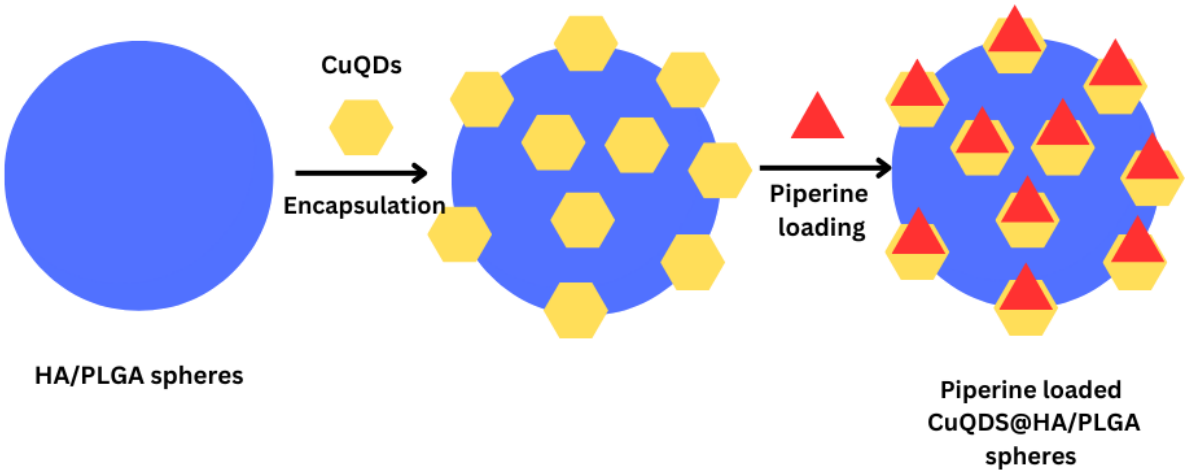

Figure 6. *Schematic presentation of nanocarrier formation and loading of Piperine drug molecules.*

nanocarriers[1].

There have been reports of enhanced bioavailability of drugs across cell membranes and minimization of enzymatic degradation using liposomal carriers. The half-life of liposomes can be improved through reduction of vesicle size, enhanced surface hydrophilicity, or the use of glycolipids and polyethylene glycol. The hydrophilic moieties form a periliposomal layer adjacent to the liposome surface and prevent opsonins from entering the liposome surface, which makes these nanocarriers invisible (Stealth) from direct clearance in the RES[1].

In order to implement stimulus (e.g. pH, temperature) drug release from liposomes, a pH- and temperature-sensitive liposome has been developed, which releases the drug content in response to an acidic environment and elevated temperature (41 °C-42°C) in a specific target tissue. In an early study, Loeb et al. (1982 and 1986) reported that liposome-encapsulated γ-aminobutyric acid (GABA) inhibited penicillin- and isoniazid-induced epileptogenicity in rodents. In another research program, a thyrotropin-encapsulated formulation produced extensive anticonvulsant activity and suppressed seizures in Amygdala-kindling rats (Kindling Amygdala is a type of Temporal Lobe Epilepsy (TLE)[14]. In another study, the same research group reported successful seizure prevention in response to certain threshold concentrations of liposomal GABA in Amygdala-kindling rats. Mori et al. (1995) used liposome-encapsulated phenytoin (PHT-L) to investigate status epilepticus in a rat model. They reported suppression of total seizures and sustained cortical activity in response to PHT-L.[15] Liposome compositions are used in the treatment of many malignant conditions in which secondary epilepsy is a characteristic feature. Brain tumors are often a major cause of seizures. Immunoliposomes are a successful strategy for optimal drug delivery to the brain. They are prepared by conjugating polyethylene glycol (PEG)-stabilized liposomes with monoclonal antibodies to the rat transferrin receptor. Immunoliposomes have been reported to deliver drugs at concentrations four times higher than PEG-liposomes due to targeted action. Some studies of PEGylated immunoliposomes with entrapped antineoplastic drugs have yielded encouraging results relative to the delivery of drugs without them entrapped in immunoliposomes due to targeted therapy. In one study, Yang et al. (2012) reported remission in mouse model glioma in response to guided chemotherapy using[16] PEGylated liposomal[17] doxorubicin combined with repetitive high intensity pulsed focused ultrasound. In another study, Anders et al. (2013) reported the improved of

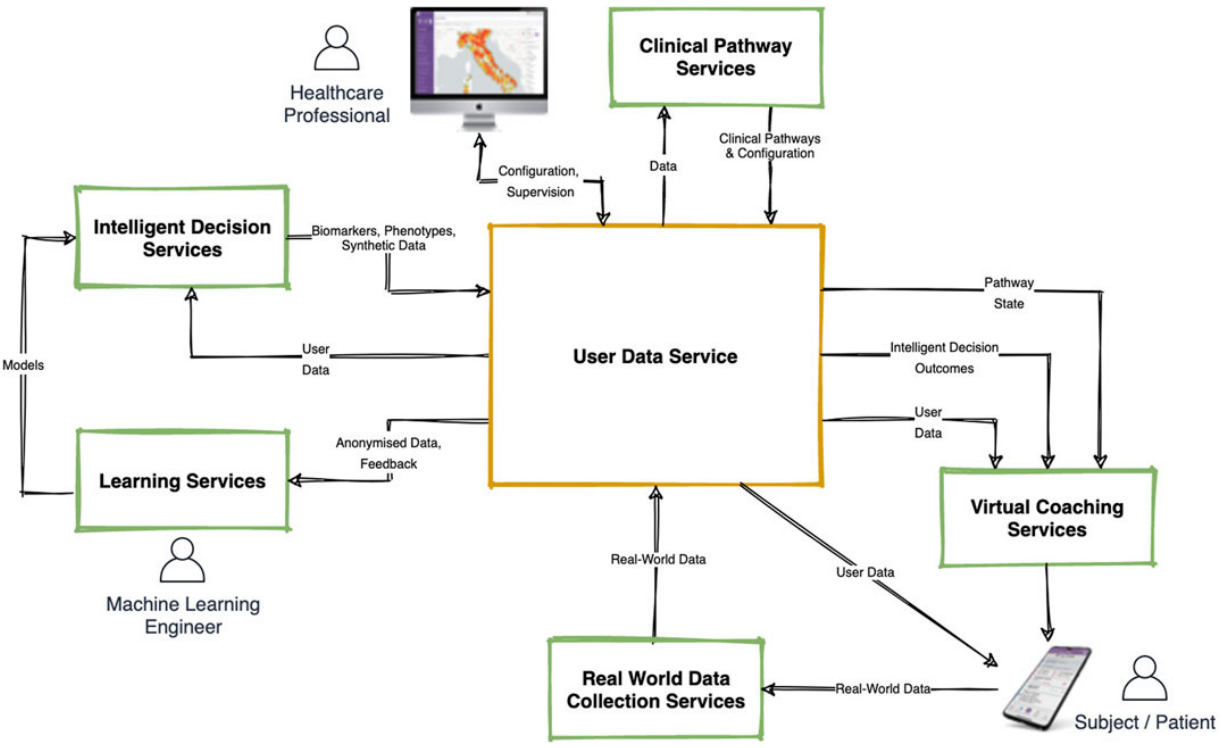

Figure 7. *Schematic representation of data transfer and storage in Healthentia's User Data Service (Cloud). Adapted from ref.[23] (Creative Common CC BY license).*

pharmacokinetics and efficacy[17].

Disadvantages of liposomal nanocarriers

Reported general limitations of liposomal formulations include rapid immune clearance if not surfaced with polyethylene glycol (PEG), from the bloodstream due to destruction by RES cells, low stability after prolonged storage, rapid metabolic degradation of of phospholipids and inability to provide sustained release of the entrapped drugs compared to other nanocarriers. Newer generations of liposomal AED formulations have greatly reduced some of these disadvantages, such as shelf life and stability, compared to previous generations of liposomal AED formulations. In addition, liposomal formulations of several pharmacologically active AEDs in preclinical development, including valproic acid, superoxide dismutase, GABA, and amiloride, are expected to provide new perspectives on drug delivery to the brain1. In addition to liposomes, there are also other nanocarriers, such as dendrimers, micelles, etc. each of which has its advantages and disadvantages in treating brain diseases[1.]

Nano-carriers have two main advantages. First, they have a higher surface-to-volume ratio, so they contribute to a significant reduction in drug concentration. As the dose is reduced, the side effects and toxicity of the drug will decrease. Second, drugs can target a specific tissue. Thus, the effect of the drug is further increased[8,10.]

The pharmacological approach to crossing the BBB is based on the modification, through medicinal chemistry, of a drug molecule to allow permeability of the BBB and render it impervious to drug efflux pumps, such as P-glycoprotein (PgP). One strategy is to develop highly lipophilic and small drugs, allowing them to successfully diffuse through brain endo-

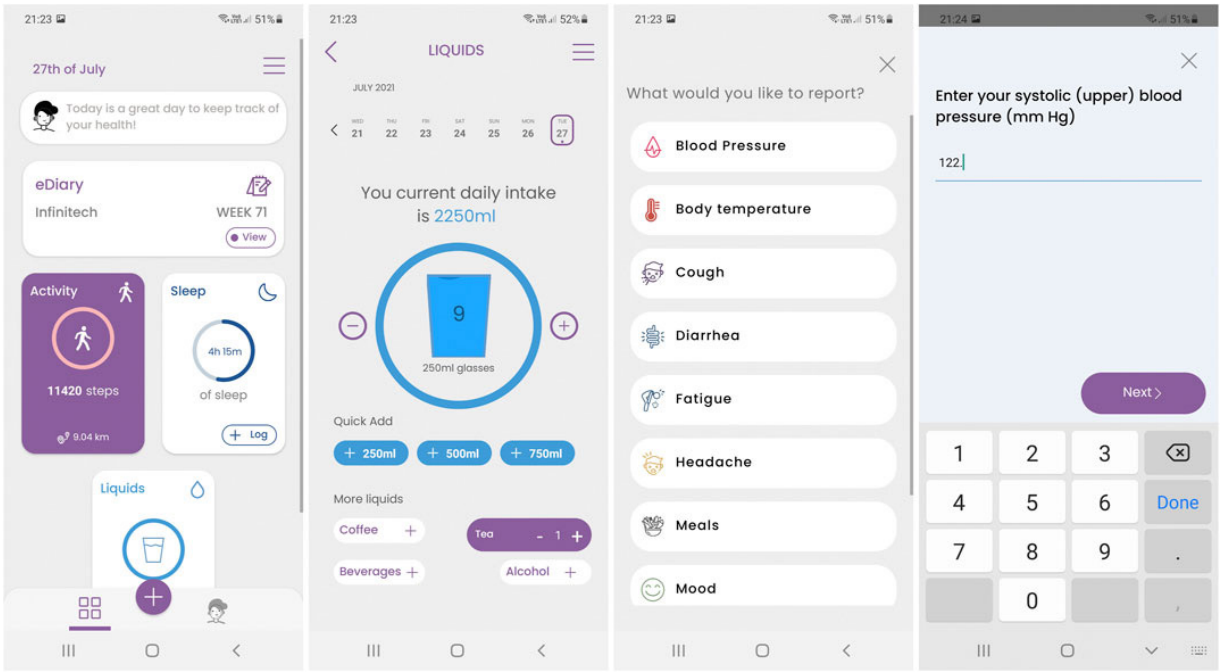

Figure 8. *Collection of Data from the application*[19]*. Adapted from ref.*[23] *(Creative Common CC BY license).*

thelial cells. Unfortunately, this strategy eliminates a huge number of potentially useful polar molecules that could be used to treat CNS disorders. An alternative strategy is to use small water-soluble drugs to facilitate crossing the BBB by the paracellular hydrophilic diffusion pathway, although the majority of these molecules are able to penetrate the mesoendothelial space of the cerebral vasculature up to the tight junctions and not beyond. In addition, it should be mentioned that modifications in the structure of the drug often lead to a loss of the biological activity of the drug[18].

In general, the physiological method shows more advantages, as it takes advantage of the existence of specific transcytotic molecule transport receptors expressed on the surface of the BBB in order for molecules to pass through it.

In recent years, liposomes have been investigated as carriers of drugs, of imaging contrast agents, and genes, particularly for the treatment and/or diagnosis of neurological diseases.

Therefore, it is important to gain a better understanding of the molecular mechanism of the disease and the development of improved diagnostic devices and therapies. Liposomes are promising carriers for CNS delivery[19].

The application of nanoelectronics can solve many problems. An example is the creation of a circuit that allows the normal flow of electricity but prevents the abnormal flow of electricity. This circuit must also be invisible to normal brain activity for the brain to function normally. Simply we need a damping circuit like a filter.

The device when attached to the ECM (Extracellular Matrixes) will eventually change the voltage at that point in the cell when an abnormality occurs[20].

In addition, a study focused on the synthesis of CuQDs@HA/PLGA microspheres for the treatment of epilepsy was carried out. Piperine drug molecules encapsulated with CuQDs@HA/PLGA nanovesicles significantly increased the anticonvulsant efficacy of PTZ-induced kindling in vivo animal models comparable to free piperine molecule treatment. The prepared CuQDs@HA/PLGA nanostructures proved to

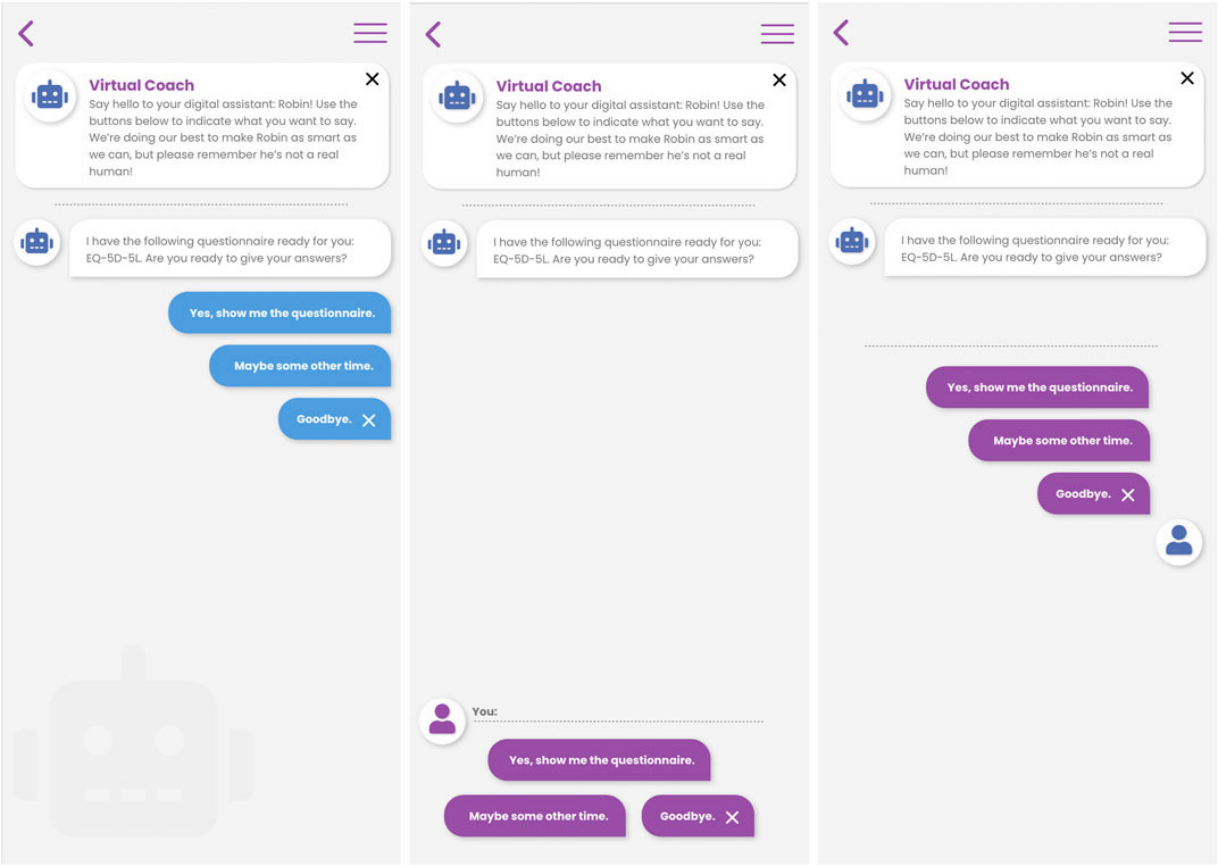

Figure 9. *Three different variations of dialog in chat box are shown[19]. Adapted from From ref [23] (Creative Common CC BY license).*

be a novel platform for antiepileptic drug delivery[21].

Finally, there is increasing interest in intranasal nanotechnology products in the management of epilepsy. The combination of nanotechnology with the nose-to-brain approach helps to increase the effectiveness of the treatment as the medicinal product reaches the target tissue more easily. It also minimizes side effects and patient non-compliance seen with other routes of administration[22].

7. New Technologies

7.1 The role of Nanotheranostics, Internet of Things and Artificial Intelligence in the Diagnosis and Treatment of Epilepsy

Nanotheranostics (nano therapeutics & diagnostics) systems are best proven in terms of targeted and controlled release, an integrated approach that takes into account the anatomy of each individual. Nanotheranostics help in profiling a disease and drugs, as well as understanding the relationship between host and disease. The management of epilepsy in a person is possible through "smart" nanotheranostic systems as they allow the detection and recognition of pathological signs. Nanotheranostics give the advantage of creating a database of information and with further clinical and economic developments may increase its widespread use in epilepsy. Nanotheranostics combined with the Internet of Things (IoT) and artificial intelligence (AI) bring new possibilities to epilepsy. In addition, the use of smartphones and wearable devices can (eg, smart watches and fitness trackers) assess and monitor neu-

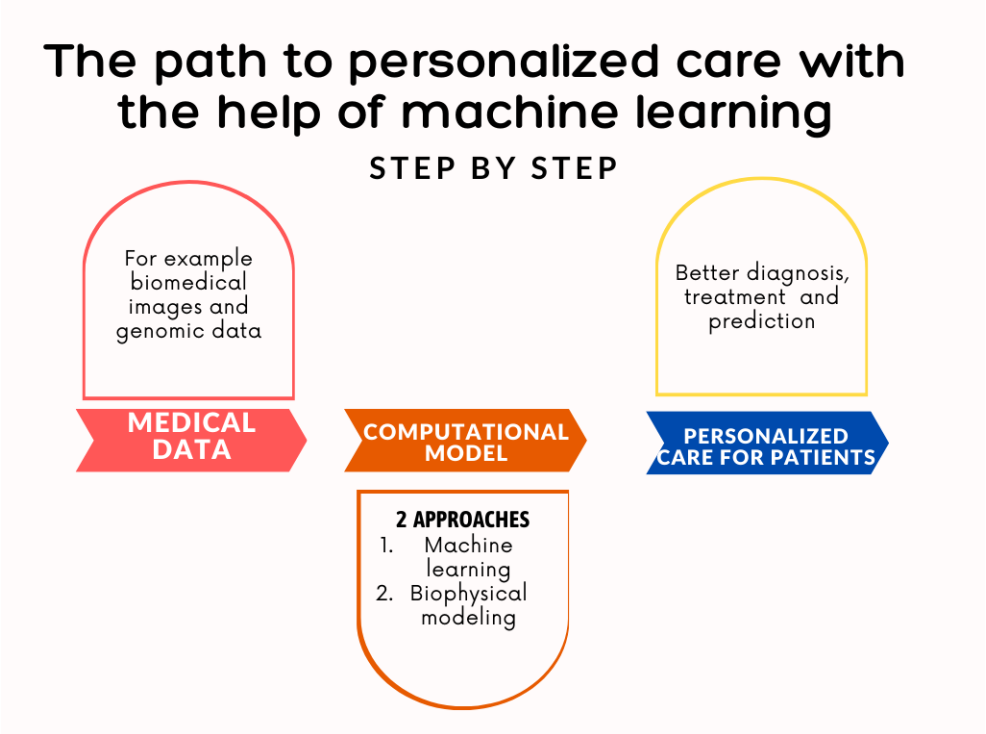

Figure 10. *Illustrating the path to personalized care with the help of machine learning.*

ronal firing or imbalance in the brain[3].

7.2 The application of Digital Therapeutics in Diagnosis and Therapy

More and more people worldwide need to deal with at least two chronic conditions for a significant part of their lives. Specifically, as the OECD (Organization for Economic Cooperation and Development) published in 2019, more than 30% of the population over 15 years old lives with at least 2 chronic diseases and this percentage is expected to increase in the coming years[23].

Thus, traditional health care provision is unable to meet the resulting individual and socioeconomic needs. Digital Therapeutics (DTx) is a form of digital health solutions that "provide evidence-based therapeutic interventions guided by high-quality software programs to prevent, manage or treat a medical disorder or disease". They are used independently or in combination with drugs, devices or other therapies to optimize patient care and health outcomes" (Digital Therapeutics Alliance, 2021). These, therefore, can relieve the health system from the ever-increasing pressure[23].

Healthentia is a CE (Conformité Européenne) Class I Medical Device currently used in more than 20 clinical studies. The Healthentia platform is an e-Clinical solution that captures clinical results from medical and Internet of Things (IoT) devices and offers intelligent services based on Artificial Intelligence (AI). In this way, virtual guidance is sought with no or very little human intervention. The healthcare professional is often available remotely and acts as a safety 'net' to oversee the automated system's decisions. E-coaching can take place in a variety of ways including: Short text messages e.g., website-like content e.g., video tutorials e.g. and realistic three-dimensional (3D) embedded interlocutors[23].

The healthcare professional can securely log into the Healthentia web portal and create interventions. At this point it invites the patient to participate and enables or disables modules such as patient fluid

intake. After the patient accepts the invitation and registers in the application, he fills in some personal information such as age, gender, weight and height. Also, it can connect the app to various apps (eg Fitbit or Garmin Activity Trackers) if they are enabled in the configuration stage to start collecting e.g. daily physical activity and sleep data. The patient receives various health questionnaires (which also include psychological questions) but can also enter data on his own initiative[23].

The real-world data collected is used in a number of ways. First, the patient can view their own information through the mobile app in order to increase awareness of their own behavior (an essential part of the virtual coaching part as described in Coaching: Virtual Coaching in Digital Therapeutics). Second, healthcare professionals (mainly in the case of clinical studies) can view patient data, at an individual level or through various dashboards that provide an overview of patient groups. Communication with the virtual coach is either initiated by the patient or the virtual coach can draw their attention when there is something important to discuss[23].

A new survey was conducted to evaluate the responses that artificial intelligence gives to patients. The researchers used 195 relevant questionnaires posted on Reddit r/AskDocs and answered by certified health professionals. They then posed the same questions to Open AI's GPT-4. A panel of experts who evaluated the results rated the AI responses as "good" and "very good". On the contrary, the answers of the doctors were characterized as "acceptable". It appeared, then, that the experts seemed to prefer the GPT-4 answers by 78.6% compared to the doctors' answers. The conclusion of the study published in JAMA Internal Medicine showed that AI messaging programs can be safely used by healthcare facilities to facilitate patients. It is pointed out, however, that the responses of the system must be under the supervision of doctors[24].

7.3 The application of Machine Learning to Epilepsy

For the seizure detection task, several studies have shown that models were trained through machine learning algorithms using specific features in the time and/or frequency domain based on scalp EEG. In another study, the researchers taught the model to distinguish normal from abnormal electrical activity automatically without requiring any manual process. They also found that seizure detection performance depends on the similarity of the seizure onset pattern between the training data and the test data, i.e., new data with a different onset pattern from that of the trained data could not be detected well. The models were also trained to detect an impending seizure several minutes before onset. In fact, they showed a sensitivity of 80-90%, but we must note that each study had a different prediction time (5'-60' before onset)[25].

In another clinical study the sensitivity of the models to detect seizures reached 65-100% in each patient but when data was obtained for that patient for more than a month. It is worth noting that these models are also particularly useful for the precise definition of the surgical target. Therefore, in addition to facilitating the diagnosis, they essentially help in the treatment as well[25].

Notable is the Multicentre Epilepsy Lesion Detection (MELD) project which used over 1,000 patient MRI scans from 22 global epilepsy centers to develop the algorithm, which provides reports of where abnormalities exist in cases of drug-resistant focal cortical dysplasia (FCD) - the main cause of epilepsy. The researchers then trained the algorithm on examples that had been labeled by expert radiologists as either healthy brains or having FCD – depending on their patterns and characteristics. The researchers found that overall the algorithm was able to detect FCD in 67% of cases (538 participants). Previously, radiologists in 178 of the participants were unable to find the abnormality on MRI but the MELD algorithm was able to identify FCD in 63% of these cases. This is especially important because if doctors can find the abnormality on a brain scan, then surgery to remove it can provide a cure[26].

8. Ethical Artificial Intelligence

Since 2014, private companies, research institutions, and public sector organizations have issued guidelines for ethical artificial intelligence (AI). However, despite the agreement that AI should be "ethical," there is debate over both what constitutes "ethical AI" and what ethical requirements, technical standards, and best practices are needed to implement it. A global convergence was thus found emerging around five ethical principles (transparency, fairness and justice, non-maleficence, responsibility and privacy)[27].

9. Discussion and Conclusions

Antiepileptic drugs are often used in the treatment of epilepsy, but the difficulty with these drugs is the emergence of resistance[8]. One hypothesis to explain pharmacoresistance in epilepsy is the overexpression of multidrug-resistant proteins, such as P-glycoprotein, in the endothelium of the blood-brain barrier[9]. Furthermore, due to AEF only drugs with a molecular mass < 400-500 daltons can cross the BBB. However, before drugs can reach the CNS, macrophages tend to phagocytose them within the RES (reticuloendothelial system) and astrocytes further limit drug accumulation in the brain. Tight barriers in the CNS prevent conventional drugs or chemotherapeutic agents from reaching targeted sites within the brain[1].

Medicines used to treat epilepsy must be administered effectively and safely so that the brain is protected. Therefore, new delivery systems should deliver drugs at concentrations determined to have high therapeutic efficacy in epilepsy without toxicity. Considering this information, there is a need to develop new treatment strategies. With the development of nanotechnology, it has been proven that nanoparticles as a drug delivery system are significantly effective in treating diseases[8].

Nanocarrier systems can fulfill many functions, such as being able to cross the blood-brain barrier (BBB) by passing a specific cell or signaling pathway, respond to endogenous stimulus, support nerve regeneration, and ensure cell survival. Nanotechnology holds the promise of controlling the concentration of drugs and delivering the drug to the target tissue across the BBB[8].

The combination of nanotechnology with Artificial Intelligence and the Internet of Things looks promising. The doctor will be able to monitor the patient's progress through a database as well as be informed of an upcoming seizure. All this combined with the high-quality data provided by Nanotechnology applications (e.g., nanobiosensors) open new avenues for faster and more accurate diagnosis as well as safer treatment.

Various nanoparticle (NP)-based drug delivery systems have been proposed and reported as great AED delivery systems. These when encapsulate antiepileptic drugs (AEDs) seem to be new weapons in the near future for the treatment of epilepsy1. Early and accurate diagnosis of the disease with the help of new technologies (Artificial Intelligence & IoT) as well as treatment using Nanotechnology can significantly improve the patient's quality of life. □

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