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REVIEW ARTICLE

# Nanopsychiatry: Engineering of nanoassisted drug delivery systems to formulate antidepressants

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**Abstract**

Psychiatry involves the study of behavior, mind, personality, emotions, and human thoughts, which helps in the assessment and treatment of various mental health issues. Recently, the complexity of psychiatry has increased among all other medical specialties. Major depression is considered to become the global cause of disability by 2030. Antidepressants are the primary care or treatment given to any patient. Generally, antidepressants work by balancing the neurotransmitters in the brain, which accounts for the change in mood and emotions. The major problem limiting the use and research of antidepressants is blood brain barrier (BBB). They are highly selective for the movement of ions and molecules between blood and the brain. In particular circumstances, BBB hinders the entry of these drugs to the brain, thereby decreasing the efficacy, in turn increasing the side effects. Drug molecules larger than the pore size of BBB cannot pass through them. Nanopsychiatry deals with the application of nanoparticles in designing drugs, treatments, and diagnostic tools for several neurological and psychiatric illnesses. Nanoparticles exhibit a large surface-to-volume ratio which empowers them to remain a primary part of an effective drug delivery system. Nanocarriers made up of biodegradable polymers can overcome the limitations of BBB. Other than polymers, novel surfactant-based nanocarriers are a successful carrier of the drug across the BBB. This review discusses the severity of depression and the need for novel nanoassisted drug delivery systems.

**Keywords:** *Anti-Depressants; Depression; Nanopsychiatry; Psychiatry; Psychotherapy.*

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## INTRODUCTION

Psychiatry is one of the departments among the medical disciplines which involve the study of behavior, mind, personality, emotions, and human thoughts, helping in the assessment and treatment of various mental health issues. In 1808, a German physician, Johann Christian Riel coined the name 'Psychiatry' [1]. There are two dominant theories on the working of the brain, namely, structuralism and functionalism, which were pioneered by Wilhelm Wundt and William James, respectively. Psychoanalysis is usually performed to attain the three major goals of psychology, i.e., to describe, explain, and predict the changes in mind and behavior. Psychologists conduct psychological assessments to better understand the structure, function, and properties of the brain. With the help of these analyses, novel diagnostic and treatment methods can be developed to treat the illness better [2]. The causes of mental issues can be due to several reasons such as stress, social pressure, environmental factors, genetic reasons, and other biological influences. Certain mental disorders are considered critical to be treated, and those who suffer from these are found to have less life expectancy. It is critical to provide a precise definition for mental disorders. The increased complexity of psychiatry and a large list of mental illnesses are the main reasons. Among

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these, major depression will be considered to become the global cause of disability by 2030 [3]. Patients with depression have a high probability of suffering from functional disability than patients with other chronic health issues. The root cause of this disorder remains undefined since there are multiple reasons around us to get depression. It is reported that family history, genetic modifications, day-to-day stress, persistent exposure to toxicants, chemical or hormone imbalance, improper diet are some of the reasons for depression. Hence, designing an appropriate treatment for this disorder is burdensome. Before treating the patients, the medical information like family history of the disease, frequency of depressed feeling, social behavior, etc, has to be examined. Other factors like gender, age, medical histories are also to be considered. At times, the reasons for depression are quite surprising. The cure rate is less due to the efficacy of treatments available [4, 5]. After the diagnosis, antidepressants are the first-line treatment. However, medication with antidepressants can lead to various adverse effects and other metabolic dysfunctions since it deals with the brain and nervous system. Hence, a novel technique has to be developed to suppress the adverse activities caused by conventional antidepressants [6, 7]. This article is written by collecting recent references in the field of nanopsychiatry. The aim of this review is to provide a detailed insight about depression, their diagnosis and conventional treatments. Issues related to the existing treatment and how nanotechnology helps to resolve this is also briefly explained.

## DEPRESSION

Depression is one of the highly heterogeneous clinical illnesses with complicated diagnostics that includes serious lifespan prevalence and produces major disability. The loss of interest in delight, self-reproach, dispirited, sleep deprivation, restlessness, lack of concentration, and suicidal thoughts affect about 16% of the population. The "Monoamine theory of depression" explains the neurological modifications in depression, such as deficiency of serotonergic or dopaminergic functions are the part of depression [8]. The research analysis proved that the pathogenesis of depression is correlated with stress. However, the major cause of depression is still unknown. Factors like genetic, biological, environmental, and psychological play a vital role in depression. It is most prevalent in patients with disorders like diabetes, cancer, heart disease, and other chronic illness. There are several episodes of depression, whereas many go unrecognized (Table 1) [9].

### *Biology of Depression*

Depression is usually caused due to the imbalance of the chemicals in the brain, otherwise called neurotransmitters. The three major neurotransmitters involved are Dopamine, Serotonin, and Norepinephrine. An abnormality in brain regions involved in the generation and regulation of emotions leads to depression. Amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and striatum are the regions where emotions are generated. The lateral prefrontal cortex is where all the emotions are controlled and regulated. There is enough evidence that suggests that these are the regions that have a potential role in the control of monoaminergic activity. These are explained by several hypotheses.

### *Psychoanalytical Theory*

Psychoanalytic theory was first laid out by **Sigmund Freud**, an Austrian neurologist and the founder of psychoanalysis during late 19$^{th}$ century [10]. This theory explains the personality organization and dynamics of personality development which guides psychoanalysis. Psychoanalysis is a clinical

Table 1. Levels of Depression.

| S.No | RANGE OF DEPRESSION SPECTRUM | CORE SYMPTOMS |
|---|---|---|
| 1. | Lower or Mild | Lack of concentration<br>Physically inactive<br>Loss of interest or pleasure in activities |
| 2. | Moderate | Poor or loss of appetite<br>Insomnia<br>Less active with surrounding or Social isolation |
| 3. | Severe | Loss in personal hygienic<br>Agitation or anxiety<br>Suicidal thoughts |

method in the treatment of psychopathology. Since his work, this theory has undergone many refinements. The characteristics of the theory are framed with the results obtained during the study on genetic and developmental aspects. This theory majorly explains the three states of mind, 1) The Conscious Mind, 2) The Preconscious Mind, and 3) The Unconscious mind. This is demonstrated in the form of an iceberg. Hence Freud's theory is also known as the **"Iceberg theory of psychoanalysis"**. Freud's psychoanalytic theory is one of the reason which leads to psychodynamic approach. Freud's theory is the first evidence that states that depression was mostly due to biological factors. This theory laid to the development of several hypotheses which explains the origin and causes of depression [11].

## TREATMENTS

Treatment for depression can either be therapy or medication. The severity, age factor, and other medical condition decide one among these [12].

### *Psychotherapy*

Psychotherapy is otherwise called 'Talk Therapy' performed either by a psychotherapist or a variety of professionals, including psychiatrists, social workers with licenses, medical counselors, trained therapists, and psychiatric nurses. Psychotherapy is a way of treating psychological illness with a combination of verbal and psychological techniques. It generally involves a conversation between the professional and the patient to employ relief from mental illness, resolve personal problems, identify and tackle negative behavioral patterns. Psychotherapy can be used for all mental illnesses but is mostly prescribed for anxiety and depression. There are several types of psychotherapy prescribed based on an individual's medical history, range of severity, age, etc [12, 13]. Psychodynamic therapy, behavioral therapy (BT), cognitive therapy (CT), cognitive behavior therapy (CBT), and interpersonal therapy (IPT) are the major types of psychotherapy.

### *Pharmacotherapy*

Pharmacotherapy involves a drug moiety that is approved in the treatment of depression (Table 2). All antidepressants designed are equally effective, but the medication is prescribed to the patient based on the side effect profile of the drug and the tolerance range of the patient. Activating SSRI (Selective Serotonin Reuptake Inhibitor) is chosen for patients who suffer tiredness as a primary complaint, whereas; sedating drugs work best if the primary complaint of the patient is anxiety. Adverse effects like altered eye, sightedness, xerostomia, constipation, or urinary tract infections are normal when treated with high doses of drugs. However, these can become major issues with elderly people. Therefore, the proper dosage has to be determined carefully [14]. Antidepressants are categorized into three major types, namely, SSRIS, cyclic drugs (tricycles and teracycles), and monoamine oxidize inhibitors (MAOIs). SSRI is considered as the first line of treatment for all types of depressed patients. Tricyclics are preferred best for primary care treatment. MAOIs are not prescribed for primary care treatment and are only advised in the worst conditions due to their severe side effects. They cannot be taken as a combinational drug with others [15].

Table 2. FDA approved Antidepressants.

| Types of Anti Depressants | Drugs | Dosage forms | Half-life |
|---|---|---|---|
| SSRI | Sertraline | Scored Tablets | 1-4 days |
| | Fluoxetine | Liquid | 2-9 days |
| | Paroxetine | Scored Tablets | 10-24 day |
| | Citalopram | Scored Tablets | 35 hours |
| TRICYCLICS | Amoxapine | Scored Tablets | 8 hours |
| | Doxepin | Capsules or Solution | 8-24 hours |
| | Imipramine | Coated Tablets | 11-25 hours |
| | Trimipramine | Capsules | 7-30 hours |
| | Nortriptyline | Capsules or Solution | 18-44 hours |
| TETRACYCLICS | Malprotiline | Scored Tablets | 21-25 hours |
| | Mirtazapine | Scored Tablets | 20-40 hours |
| MAOIs | Selegiline | Coated Tablets | 2-4 hours |
| | Pamate | Coated Tablets | 2-4 hours |
| | Tranylcypromine | Coated Tablets | 2.4-4.8 hours |

## ISSUES RELATED TO TREATMENT

Anti-Depressants are often associated with side effects (Table 3). Physicians also arise a problem with determining the dosage of the drug. The age factor and medical condition are certain factors to be considered before designing the treatment for the patient. Hence, adverse effects linger with the drug and become unavoidable [16, 17]. The list of antidepressants and the related side effects are tabulated in Table-3.

The delivery routes that the delivery vehicles can utilize were clearly explained by Radaic et al. [18]. The Transcytosis pathway, passive diffusion, and carrier-mediated transportation are the three major routes through which drugs enter the brain. The route of entry is decided by the characteristics of the administered particles. Water-soluble particles usually enter via transcytosis or carrier-mediated transport, while particles with high lipophilicity usually choose passive diffusion to acquire the entry. Generally, antidepressants work by balancing the neurotransmitters in the brain, which accounts for the change in mood and emotions. Neurotransmitters endeavor to transmit the signal across neurons. Neurons usually communicate with each other by neurotransmitters-driven signal transfer. Along with this, neurotransmitters are essential to regulate other body functions like heart rate, breathing, appetite, muscle movement, digestion, sleep cycle, concentrations, and more. Depending on the mechanism of action, they can be divided into three major types, inhibitory, excitatory, and modulatory neurotransmitters. Majorly, serotonin and epinephrine account for depression and they belong to inhibitory and excitatory neurotransmitters, respectively [19, 20].

Dopamine can be classified under both inhibitory and excitatory types. Hence, a reduced amount of any one of these three might lead to depression. Therefore, antidepressants are designed to inhibit the reuptake of neurotransmitters in the brain. However, the usual issues related to antidepressants are their entry into the brain. Blood vessels are inadequate to supply blood to the Central Nervous System (CNS). The blood vessels leading to CNS exhibits exceptional features due to the presence of the blood-brain barrier (BBB) [21]. They are selectively permeable, and most of the antidepressive drugs fail to cross this barrier, causing critically low bioavailability of the drug. In the meantime, the expected therapeutic effect is also not achieved. Therefore, to accomplish the targeted therapeutic effect, the dosage is increased. However, these increasing dosages might lead to severe side effects on the metabolism. To tackle this issue, a new formulation can be crafted, in which a lesser dosage will be adequate to provide a better therapeutic effect within a limited time than expected [22, 23].

## NANOTECHNOLOGY-BASED THERAPY

Nanotechnology is the scientific branch that encompasses understanding the fundamentals of basic science, including physics, chemistry, biology, and technologies related to nanosized particles [24]. It is also defined as the construction, manipulation, and utilization of nanometer-scale objects of controlled structure and composition. Nanotechnology has evolved much from being a hypothesis to a general-purpose technology. Nanomedicine is the area where theories and concepts of nanotechnology are applied in the medical field for improving the health and well-being of humans [25]. Nanotechnology is applied in medicine for both diagnostics and treatments in various forms like designing a new drug, improving the efficiency of the existing drug, crafting a new diagnostic approach, or improving the existing method. Researchers are so sharply on

Table 3. Antidepressants and their side effects.

| Sl. No | Drug | Anti-cholingergia | Sedation | Insomnia | Arrhythmia | Nausea |
|---|---|---|---|---|---|---|
| 1. | Amoxapine | Mild | Mild | Mild | Moderate | Nil |
| 2. | Bupropion | Nil | Nil | Mild | Minimal | Minimal |
| 3. | Doxepin | Moderate | Strong | Nil | Mild | Mild |
| 4. | Imipramine | Moderate | Moderate | Minimal | Moderate | Minimal |
| 5. | Protriptyline | Mild | Minimal | Mild | Mild | Nil |
| 6. | Sertaline | Nil | Nil | Moderate | Nil | Moderate |
| 7. | Trimipramine | Minimal | Strong | Nil | Mild | Nil |
| 8. | Trazodone | Nil | Strong | Nil | Minimal | Minimal |
| 9. | Venalafaxine | Nil | Nil | Mild | Nil | Mild |

learning about nanotechnology is the reason the statistics conducted by 'Statnano' revealed that nanomedical research has become widespread in the last decade, resulting in more than 1,00,000 nanotechnology-related articles being published every year [26, 27].

A nanoparticle or an ultrafine particle ranges about 1 to 100 nm in size, possessing significantly excellent physical and chemical properties compared to its larger material. As the shape and size of a particle define its properties, the nanoparticles are of large interest, due to which these two factors can be tailored and controlled as per the need. Nanoparticles can be engineered in extremely diverse shapes like nanoflowers, nanostars, nanoboxes, nanospheres, nanochains, nanorods, etc [28, 29]. Apart from nanoparticles, nanotechnology is also applied in the development of nanodevices and nanorobots. Nanodevices are nothing but nanoparticles designed to interact with the cells and tissues in the bloodstream [30]. It is majorly developed for monitoring the activities and efficiency of the drug load and used as an imaging tool. Various detection instruments, including scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), X-Ray Diffraction, etc., are involved in tracking the nanodevices. Unlike nanodevices, nanorobotics, which involves designing, manufacturing, programming, and controlling nanorobots, remain as a hypothetical concept due to the discussion on the risk and potential regulation, which has not been concluded yet [31]. However, the extensive research on nanobots in the biomedical field has gained rapid development in the last decade. Three major nanorobots, namely, helices, nanorods, and DNA nanorobots, are currently in research for biomedical applications to deliver the payload at the targeted site under laboratory conditions [32]. The field of nanotechnology is a major concern in several fields such as pharmacology, oncology, tissue engineering, biosensing, etc. It also opens new avenues in modeling some complex systems like the central nervous system (CNS). There are numerous advantages of using nanoparticles in CNS, such as crossing biological obstacles like BBB due to its ultrasmall size, improving the specificity of the drug by delivering and accumulating the cargo at the desired site of the body, and reducing the adverse effects by decreasing the dosage. Therefore, nanotechnology has now become an unavoidable concept regarding the diagnosis and treatment of psychiatric illnesses [33, 34].

## NANOPSYCHIATRY

Nanopsychiatry is one of the fields in nanomedicine involving the application of nanoparticles in designing drugs, treatments, and diagnostic tools for several neurological and psychiatric illnesses. Nanoparticles approximately sized between 1 to 100 nanometers can pass through many biological barriers like, BBB which makes them the best suitable potential markers of brain tissue and as drug carriers [35]. Due to the small size of nanoparticles, they exhibit a large surface-to-volume ratio which empowers them to remain as a primary part of an effective drug delivery system. Several psychiatric diseases are being treated with antipsychotic or anti-depressive drugs [36].

In particular circumstances, certain biological obstacles like BBB hinder the entry of these drugs to the brain, thereby decreasing the efficacy, in turn, increasing the side effects. Drug molecules larger than the pore size of BBB cannot pass through them. Due to the ultrasmall particle size, the nanoparticles carrying the drug payload escape the BBB and thus became an indispensable part of psychiatry [37]. The word 'Nano' is often combined with 'Psychiatry' to intensify the importance of nanotechnology in psychiatry. Nanomaterials have become an integral part of experimental neurophysiology for evaluating and monitoring some of the physiological mechanisms of a normal brain [38]. Similarly, newer therapeutic strategies are being designed in clinical research with medication-loaded nanoparticles. This combination of drug-loaded nanoparticles acts either as an agonist or an antagonist and provides access to detect and monitor the physiological signaling pathways of various parts of the brain [39]. The pioneer review was done by Sobarzo-Sánchez et al. emphasized the importance of nanopsychiatry in various fields like diagnosis, treatment, and modulation [40].

### *Pharmacology*

The entry of drug molecules into the targeted site lingers as the major hurdle in pharmacology. The size, rigidity, and shape of the drug molecule is the major limiting factor in drug delivery. Besides these, other physiological processes such as endocytosis, phagocytosis, macropinocytosis are

some of the factors responsible for cell function, which also limits drug entry [29, 41]. All these factors impact the biodistribution of the drug. Any drug designed has to resolve all concerns to achieve the desired therapeutic level. Size, shape, molecular weight, and surface charge are some factors that have to be very particular while designing an antipsychotic drug to escape BBB [42]. As discussed by Fond et al., the size of the particle is very important as it should be around 100 nm [43]. The other properties of the particles, such as their shape, surface charge, contact angle, and rigidity, are also some of the limiting factors in their successful entry into the brain. The surface charge of the particle is crucially essential as it decides the type of endocytosis that the particle should undergo. The angle of contact between the particle and the cell membrane should be 45º or less. Nanoparticles can abundantly increase the bioavailability and pharmacokinetics of a drug. Niosome, liposomes, polymeric nanoparticles, and virosomes are the widely used nanoparticles to encapsulate the drug [44-46]. The major issues for which the nanoassisted drug delivery is designed are the safety and efficacy of antipsychotic drugs. Ultrafine lipophilic molecules are the ideal molecules that can easily cross the BBB. If the drug molecule cannot cross the BBB, it usually circulates throughout the bloodstream causing many undesired effects. In the meantime, the drug has to pass the barrier quickly, or else it might expose itself to enzymatic degradation by opsonization leading to zero therapeutic effect. There are two basic paradigms proposed regarding drugs reaching their site in the brain [47]. **First paradigm:** This paradigm explains designing an inactive drug that can only be activated by certain enzymes in the brain. Hence, this will happen only if it crosses the BBB. They will directly undergo enzymatic degradation in the bloodstream and get digested if it fails to cross the barrier. This is one way of getting rid of adverse effects. The major drawback of this concept is the no of active candidates. Only a limited no of candidates will be sent. Therefore, the therapeutic effect will not be satisfied even if it escapes the barrier. The frequency of the dosage also should be multiplied more than normal [48, 49]. **Second paradigm:** The second paradigm involves nanocarriers or vehicles which can easily cross the BBB. This could solve the above problem. The delivery of the drug is achieved in a sequence of steps such as (i) encapsulation of the drug molecules into the carrier, (ii) tagging of a specific ligand on the surface of the vehicle to target the desired cell, and (iii) direct delivery inside the cell by Ligand-Receptor mechanism [48, 50].

*The Inspection of Living Organisms*

Nanotechnology provides a greater advantage *in vivo* imaging and metabolome analysis. Nanoparticles act as a technical assistant in imaging [51]. Nanoparticles are used as contrast agents in MRI to target the site better with the help of the ligands tagged onto their surface. Among other nanoparticles, fullerenes are proved to serve as a good candidate for contrast agents and as biotracers. This technique is currently in development for Alzheimer's disease. Biomarkers of nanoparticles can be used as early markers to diagnose psychiatric diseases or to track psychotropic drugs [51, 52].

*Metabolome Analysis*

The metabolome is the one that is examined during finer analysis. Metabolites are any molecules of low molecular weight. They act as vehicles or carriers, substrates, or products that are involved in all physiological cascades. A metabolome is a group of metabolites that belong to a particular biological system. Nuclear Magnetic Resonance spectroscopy (NMR) is the most widely used instrument for profiling the metabolome by detecting the mechanism of the metabolites in different biological complexes [53].

*Modeling of Central Nervous System*

The cortex and neural networks of the brain have a complex organization. A complete understanding of the brain circuits eases the issues. However, the study research has not found a complete conclusion about the working of the human brain. Nanotechnology made a breakthrough recently at the synaptic level. The importance of nanodevices in modulating the neurophysiological condition of depression and their contribution to correcting the abnormalities contributing to depression at the genetic level was well explained by Kakkar *et al.* [54]. Furthermore, the dose of antidepressants can also be guided by nanorobots. Metal oxides and chalcogenide materials are used to make nanodevices for modeling neuromorphic networks. Thus, manufactured nanodevices also account as biotracers for tracking and modulating the treatment strategies [55].

## NANOPARTICLES AND BLOOD BRAIN BARRIER

BBB is a semi-permeable membrane made up of endothelial cells between blood and the brain. They are highly selective for the movement of ions and molecules between blood and the brain. Endothelial cells are arranged tightly, which limits the entry of large molecules, hydrophilic molecules, and microorganisms. The entry into the brain through BBB depends on several factors, including the diameter of molecules, the structure of the molecule, charge on the surface, liposolubility [56]. The proteins on the surface of the endothelial cells participate in the permeability. One such example is P – Glycoprotein. Any nanoparticle can penetrate the BBB (Fig. 1). However, the carriers made up of biodegradable polymers can penetrate very easily due to their stability. These types of polymers can easily escape the reticuloendothelial system (RES), providing more time for the drug to reach the target site. The toxicity of these types of nanocarriers is also negligible, motivating researchers to work more on these systems [57].

## NANOASSISTED DRUG DELIVERY

There are different varieties of nanoparticles that are being used in drug delivery systems, especially to cross the BBB. Drugs are available already with certain nanoformulations. A lot more drugs are being investigated and are in clinical trials [58].

### *Polymeric Nanoparticles*

Currently, there are several research efforts to associate psychiatric medicaments with polymeric nanoparticles in progress. The main objective of the research is to either improve the bioavailability and therapeutic effect of the antipsychotic drug or to decrease its adverse effects caused due to prolonged administration of antipsychotics, such as the extrapyramidal side effect. One of the most widely used drugs in psychiatry is haloperidol, which has become a fundamental part of the treatment for various psychiatric illnesses such as schizophrenia and acute psychosis [59]. The nanoformulation of biomaterials such as Polylactic acid (PLA) and Polylactic-co-glycolic acid (PLGA) loaded with haloperidol was synthesized using homogenization and Sonication methods by A. Budhian, *et al.* in 2007 [60]. The synthetic procedures used by those authors are also useful to synthesize other hydrophobic drug polymers conjugates and for designing nanosystems of different sizes, structures, and payload content. Hence, this methodology might provide further development of many nanocarriers loaded with psychiatric medicaments leading to a therapeutical effect at a great satisfactory level with negligible adverse effects. If in case these observations are successful, this would open new avenues for multiple clinical trials of nanoformulated

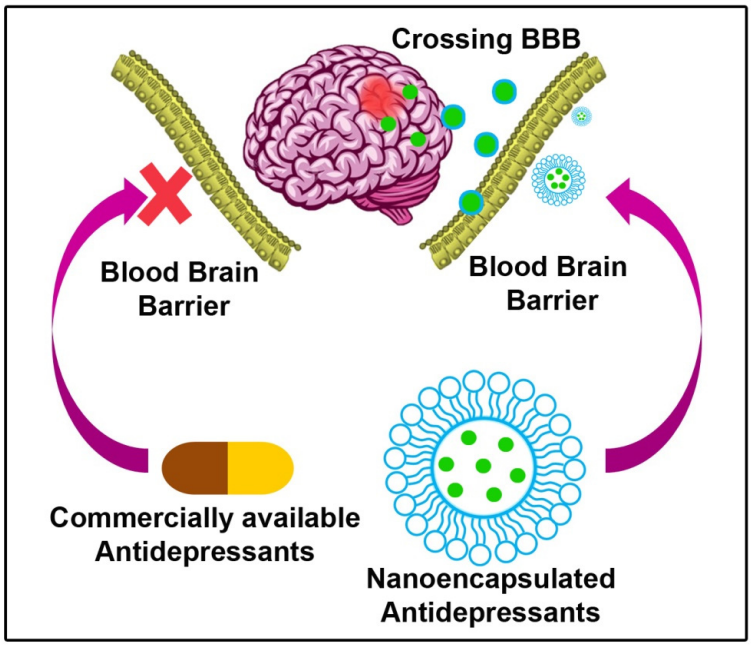


Fig. 1. Improving the drug-carrying strategy with Nanocarriers.

antipsychotic drugs [61]. Nanoformulation of certain antipsychotic drugs such as haloperidol, olanzapine, paliperidone palmitate, clozapine, risperidone and their clinical potential in treating psychological aspects was discussed by Muthu *et al.* [62]. Since risperidone is another commonly used antipsychotic drug, in another study, Muthu *et al.* have successfully developed a nanoparticle formulation of Polylactic-co-glycolic acid with risperidone using the nanoprecipitation method to synthesize the nanoparticle and Poloxamer-407 as the polymeric stabilizer. This combination of drugs has been tested on animals. The results showed an excellent antipsychotic effect by efficiently passing through BBB due to the active accumulation of the metabolite 9-hydroxy risperidone [63]. Lopez-Maldonado *et al.* developed a novel green synthesis of polymer nanocomposite (Chitosan-Alginate-Triprophylphospate). The physiochemical evaluation of the polymer composites showed significantly greater pharmacological performance with excellent absorption and minimal dentrimental effects, thus could provide controlled delivery system and improving the performance of psychic therapies [64].

*Solid- lipid-based nanoparticles*

Recently, several research studies have focused on investigating the possibility of producing nanosystems for targeted drug delivery to the brain, which would encapsulate antidepressant drugs, thereby increasing the bioavailability (Table-2). Similarly, the main objective of nanotechnology is to increase the effectiveness and decrease the toxicity of antipsychotics [65]. Valproic acid used in the treatment of bipolar disorder consists of potentially toxic metabolites, which is usually the major limiting factor, which was readily reduced by stabilization with dextran and polysorbate 85-coated nanoparticles. This experiment was conducted by Darius et al., who studied the brain tissue kinetics of mice after administration in 2000. This combination of the drugs is the first used drug as a mood stabilizer [66]. Another antidepressant for treating depression is Duloxetine. It is a serotonin-norepinephrine reuptake inhibitor (SNRI) available with solid lipid nanoformulation. This serves as one of the effective antidepressants and is used in first-line treatment [67].

*Surfactant based nanoparticles*

Nanoparticles are renowned for their large surface-to-volume ratio, which leads to several advantages over bulk materials. A surfactant is a surface-active agent. Thus, the presence of surfactants will lower the surface tension of the nanoparticles. Surfactant-based nanoparticles act as a novel drug delivery system. Liposomes and niosomes are well-known surfactant-based successful delivery systems. Liposomes are spherical-shaped vesicles consisting of a lipid bilayer surrounding an aqueous core. Niosomes are usually synthesized with uncharged single-chain surfactant and cholesterol; meantime, liposomes are synthesized with double chain phospholipids. Liposomes are known to improve the therapeutic index of the encapsulated drug and deliver them to the diseased site, thereby increasing the bioavailability. In 2017, Nikolay Dimov *et al.* synthesized liposomes that can be tailored to the desired size. The methodology followed by the authors is more precise, and such produced liposomes are toxic-free. Niosomes are well known to escape the BBB and RES uptake. The other major advantage of using niosome for drug delivery vehicles is that they can encapsulate poorly absorbable drugs. With the available research data, niosome serves as one of the best suitable nanocarriers for antidepressants [68, 69].

**FUTURE PERSPECTIVE**

The future of psychiatric treatments depends on nanotechnology (Table 4). Besides nanoformulated drugs and contrast agents for psychiatric illness, advanced research focuses on the application of nanotechnology for the theranostic approach. It is believed that a single nanomaterial can act as both biomarker and drug simultaneously. Many nanoformulated antidepressant drugs are already under laboratory research practice. Statistics of research conclude that nanotechnology will become a common psychiatric practice very soon [77]. The biodegradable polymeric nanoparticle serves as the core material in nanopsychiatry. The polymeric nanoparticles are biodegradable and can be easily synthesized. The possibility of manufacturing a conjugate with inorganic nanoparticles and antipsychotic medicament is less due to the lack of research data on the behavior of such conjugates in the bodily system. Many other branches of treatment use gold and iron oxide nanoparticles for encapsulating the drug moiety, for example, cancer. Iron oxide nanoparticles are being widely used as a contrast medium for MRI in

Table 4. Nanoformulated antidepressants.

| S. No. | Generic Medication | Nanoparticle System | Pharmacological class | Disorder treated | Ref. |
|---|---|---|---|---|---|
| 1. | Clozapine | Solid lipid nanoparticles | Antipsychotic agent | Schizophrenia | [70] |
| 2. | Duloxetine | Solid lipid nanoparticles | Antidepressant SSNRI (Selective Serotonin-norepinephrine Reuptake Inhibitor) | Major Depressive Disorder (MDD) | [71] |
| 3. | Haloperidol | PLA (Polylactic acid) or PLGA [poly (lactic-co-glycolic acid)] | Antipsychotic agent | Schizophrenia, Tourette syndrome, Mania, Bipolar disorder, Delirium. | [72] |
| 4. | Risperidone | PLGA [poly (lactic-co-glycolic acid)] | Antipsychotic agent | Schizophrenia, Bipolar disorder, Autistic disorder. | [73] |
| 5. | Mirtazapine | Methyl cellulose-based system | Antidepressant NaSSA (Noradrenergic and specific serotonergic antidepressant) | Major Depressive Disorder(MDD), Obsessive compulsive disorder, Anxiety disorder | [74] |
| 6. | Valproic acid | Dextran-stabilized polysorbate 85-coated nanoparticles | Anticonvulsant or Anti-epileptic medicine | Bipolar disorder, Seizure disorders, Epilepsy. | [75] |
| 7. | Venlafaxine | Chitosan nanoparticles | Antidepressant SSNRI (Selective Serotonin-norepinephrine Reuptake Inhibitor) | Major Depressive Disorder(MDD), Anxiety disorder, Panic disorder, Social phobia. | [76] |

diagnosing tumors. Since there is no reported dead toxicity of using gold and iron oxide nanoparticles inside the bodily system, they are now in the formulation of psychiatric medicaments. In many countries, anxiolytics are the most commonly prescribed psychiatric medication. Anxiolytics such as benzodiazepines, Lorazepam, Diazepam, and Midazolam are generally used in the treatment of anxiety, panic disorders, insomnia, obsessive-compulsive disorder, etc. Conjugation of these drugs to nanoparticles, in turn, has a positive impact on biodistribution and bioavailability. Designing nanosystems with unique physical and chemical characteristics could help in understanding the morphological aspects of the brain cortex and typical psychic functions. A complete understanding of brain function and structure might help in not just designing new drugs but also in the prevention of disorders. Nanocarriers with surfactants like liposomes and niosomes are extremely beneficial, starting from the ease of synthesizing with completely satisfactory therapeutic effects with a negligible level of toxicity.

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## CONFLICT OF INTEREST

There are no conflicts to declare

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