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Review Article

# NANO CARRIER DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF COGNITIVE DYSFUNCTION IN DEPRESSION-AN OVERVIEW ON THE NANO FORMULATIONS TARGETING TO THE BRAIN

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**ABSTRACT**

To review and discuss the current therapeutic strategies available for the management of cognitive dysfunction in major depressive disorder with special emphasis on novel therapeutics based on nanotechnology like nano carrier delivery systems. The method entailed a review of research articles, review articles, and other internet-sourced materials. Journals, articles, and reports were thoroughly searched for the efficacy and safety of nanotechnology based newer drug delivery approaches for the management of cognitive dysfunction in major depressive disorder. The information obtained during the literature search aided in comprehending the scenario. Several new nanomedicines and nanotechnology based drug delivery systems for improving the efficacy of new and old drugs used for the management of cognitive dysfunction in major depressive disorder were reviewed. There is a dearth of sufficient studies which focus on cognitive domain in depression. Nanomedicines and nanotechnology based drug delivery systems holds tremendous potential in the management of cognitive impairment in depression as well as other neuropsychiatric disorders. It is imperative to conduct advanced studies in this regard for better therapeutic outcomes in the management of such patients.

**Keywords**: Major depressive disorder, Cognitive dysfunction, Nano drugs, Nano formulations, Nano carriers


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## INTRODUCTION

Cognitive dysfunction is one of the primary sign of the clinical manifestation of depression and is one of the major causes of functional deterioration in patients with major depressive disorder [MDD]. The response of the patients to antidepressant medications may be good in clinical practise, but cognitive impairment persist as residual symptom. These cognitive symptoms appear to have a significant impact not only on patient's functional ability, but also on the risk of recurrence of the disease [1, 2]. In recent years, evidence has emerged that the elemental cause of the disease is dysfunction of circuits other than the known aminergic neurotransmitter systems, such as glutamatergic pathways; furthermore, the impact of other pathogenic mechanisms, for example, loss of synaptic plasticity in those areas involved in emotion and affect regulation, has emerged [3-5]. This has fuelled interest in new molecules capable of interfering with these pathways and mechanisms, which are known to have established roles in cognitive processes. However, current medications for depression have seldom been shown to be effective in treating cognitive disorders. Rather, they are found to aggravate the cognitive decline [6]. Recently, vortioxetine has surfaced a promising drug which act on the serotonergic system via a unique mechanism. After being shown to improve cognitive performance in various animal models and clinical trials, this drug with a distinct pharmacological profile was approved for use in the European Union as well as in the United States in 2013 for the treatment of MDD in adult patients (dose 5 to 20 mg/day). The recommended starting dose was 10 mg/day for patients more than 65 y and 5 mg/day for patients aged more than 65 y. The European Medicines Agency [EMA] updated its data on vortioxetine's clinical efficacy in 2015, stating that its efficacy cognitive improvement and global functioning and the drug was later approved by Food and Drug Administration [FDA] for the management of cognitive dysfunction in MDD. Vortioxetine has been found to produce significant improvement in symptoms of depression as well as cognition from a large number of clinical trials [7-10].

According to studies, vortioxetine has a linear pharmacokinetic profile [11]. When administered by oral route, approximate bioavailability is 75%, independent of food consumption. It has a high binding rate to plasma proteins [98%] and this will not vary between normal people or who have renal or hepatic impairment. Its plasma concentration spikes after 7 to 11 h of oral ingestion, and plasma half-life was obtained to be 57 to 66 h. It has an observable distribution volume of approximately 2,600 L, implying that it is a lipophilic substance with widespread distribution in the extravascular compartment. The pharmacological profile of vortioxetine is attributed to the unmodified molecule. The liver is where the majority of the drug is metabolised. Several cytochrome p450 isozymes like CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6 are involved in its metabolism. The primary enzyme that catalyzes the conversion the drug into its metabolite which is inactive is CYP2D6. Hvenegaard *et al.* discovered that Vortioxetine levels were twice as high in slow CYP2D6 metabolizers as they were in fast metabolizers [12].

However no major developments have emerged since the approval of vortioxetine for the management of cognitive impairment in MDD. The blood-brain barrier [BBB] complicates permeation to target sites in brain cells significantly. To overcome the BBB, it has been proposed to use the nanocarrier systems. Polymeric nanoparticles, solid lipid nanoparticles [SLN], nanostructured lipid carriers [NLC], nanoemulsions, nanogels, carbon nanotubes, and liquid crystalline nanoparticles with neuroprotective properties are currently being studied as forms of nanotherapy for neuropsychiatric disorders [13].

In this update, we will present recent developments in the promising areas of nanotherapy in the field of cognitive dysfunction in patients with MDD. We will discuss in detail about [i] the physiology of drug transport across BBB [ii] Current evidences on nano drugs for cognitive dysfunction in MDD, [iii] future prospects of nano drugs for management of cognitive dysfunction in MDD.

### The physiology of drug transport across the blood brain barrier

In spite of major advances in recognising the molecular and cellular mechanisms of neuropsychiatric illnesses and the advancement of therapeutic approaches, effective drug delivery to the central nervous system continues to be a significant challenge today. The BBB is the most significant impediment to drug transport to the brain. The BBB is responsible for transporting nutrients and oxygen from the blood to the brain as well as protecting the CNS from toxic chemicals. Vascular endothelium, glial cell, perivascular macrophages, and pericytes make up the BBB. Tight junctions between endothelial cells, which form the proteins occludins, claudins, and adhesion molecules, which s formr edcause the BBB's

impermeability to many molecules [14]. Controlled BBB permeability is provided by endothelial cell tight junctions, a specialised extracellular matrix, and a basement membrane composed of collagen IV type, laminin, fibronectin, tenascin, and proteoglycans [15-17].

Passive or transcellular diffusion, facilitated diffusion, and active transport are the most studied substance transport pathways through the BBB. Active and passive diffusion transport substances across cells. There are three types of active molecule transport systems in the BBB: receptor-mediated transport, which transports macromolecules; carrier proteins, which transfer sugars, amino acids, organic anions as well as cations, neurotransmitters, and metabolites; and active transport by peptides of the adenosine triphosphate binding cassette family. P-glycoprotein and other adenosine triphosphate binding cassette proteins render the BBB impermeable to pharmaceuticals [18].

The current challenge is indeed the development of substances that will cross the BBB to treat CNS disorders. The drug's levels must accrue in the appropriate body region and remain stable for a prolonged time period if the drug should have an appropriate therapeutic effect [19]. To reduce side effects, the drug concentration in other organs and tissues must be kept as low as possible. The presence of BBB significantly hinders transfer of drugs into the CNS. The presence of BBB necessitates the development of newer therapeutic strategies for the treatment of central nervous system disorders.

To overcome this problem several strategies have been devised by researchers, such as disruption of the integrity of the tight contacts by osmotic disruption as shown by Kavineni *et al.* using intraarterial infusion of hyperosmolar mannitol [20] or chemical disruption [21, 22], vasoactive drugs like TNF-α [23, 24], IFN-γ [25], directed ultrasound [26], direct injection into brain tissue by intrathecal [27] or intraventricular route [28, 29], intranasal delivery [30], administration of biodegradable substances [31], nanoparticle delivery [32], delivery via interstitial wafers [33] and microchips [19, 34].

Among the most effective techniques for overcoming BBB is the use of carriers for drug loading that, due to their small size, have the ability to cross the BBB. This has the ability to increase bioavailability while decreasing side effects. The nanoparticles [NP] are transported across the blood brain barrier via several mechanisms, the most important of which is transient opening of the BBB caused by nanoparticle induced effects such as stimulus from the bioactive component on the nanoparticle surface or due to nano-effects or nano-toxicity. Other mechanisms are the surface of capillary endothelium will facilitate adsorption of nanocarrier conjugates which will cause release of drug from the carrier, which further leads to increase in concentration gradient of the drug and diffusion into the brain. The nanocarriers may also directly penetrate the brain tissue by transcytosis, endocytosis and exocytosis [35-37].

The NPs ability to penetrate the BBB has paved the way to the development of a spectrum of nanoparticles like polymeric NPs which are based on natural or synthetic polymers like alginate, chitosan, gelatin, cellulose, polyacrylate, polycaprolactone [PCL], polylactic acid [PLA], polyethylenimine [PEI], Polyethylene glycol [PEG], nanocapsules or dendrimers etc; lipid based NPs like liposomes, nanoemulsions; inorganic NPs like mesoporous silica NPs, gold NPs, carbon nanotubules, and iron oxide NPs, quantam dots and new class based on nucleolipid nanoparticles. A schematic illustration of different classes of nanoparticles according to their chemical composition has been depicted in fig. 1.

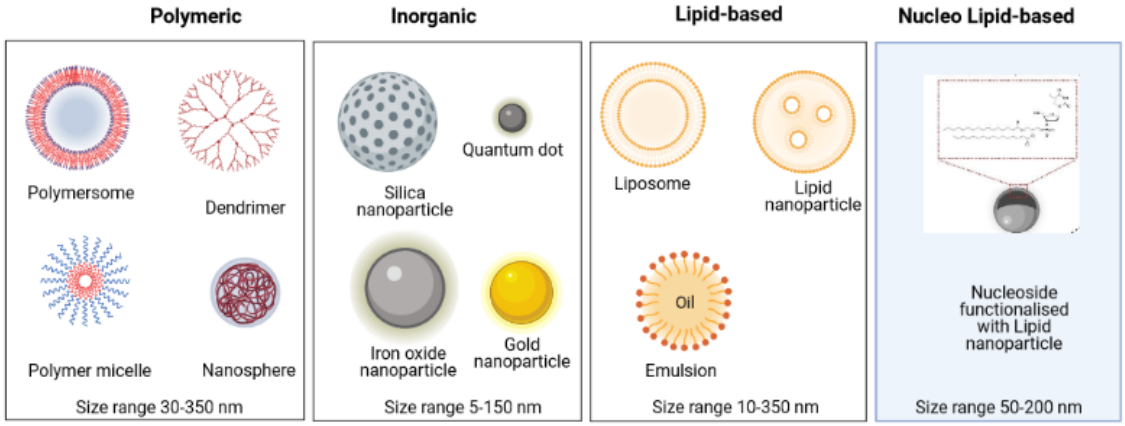


**Fig. 1: Schematic illustration of different classes of nanoparticles according to their chemical composition [Created with BioRender.com]**

Current evidences on Nano drugs for cognitive dysfunction in MDD

In spite of variety of drugs for the management of symptoms of depression, the cognitive functions are not adequately addressed by any of these antidepressant drugs. The response to treatment is determined by the drug concentration in the CNS. Cognitive dysfunction in depression can be produced as a result of the disease itself or due to the medication effects [1].

Currently there are no FDA approved nanodrug with targeted delivery to the brain, but there are promising results from several studies which indicate the potential of this delivery system in the immediate future. In the section below, we shall review about the various nanoforms of the classical drugs of depression and their application in cognitive dysfunction.

**(i) Monoamine oxidase-A [MAO-A] inhibitors**

Tranylcypromine was loaded into polymeric micellar in-situ nasal gel and sucessfullly formulated enabled direct delivery to brain by Shilpa *et al.* [38]. Our literature search found that Singh *et al.* in 2016 had studied the use of thiolated chitosan nanoparticles for enhancing transnasal delivery of MA0-B inhibitors like Selegiline with promising results in rats and had proposed the probable use of thiolated chitosan nanoparticles for delivery to brain via nasal route for antidepressant effects [39]. Intranasal delivery transported via olfactory or trigeminal route had emerged as a recent trend in the non-invasive delivery of drugs targeting the brain with a wide spectrum of applications in several disorders including neuropsychiatric disorders [40-42].

**(ii) Tricyclic antidepressants [TCAs]**

Amitriptyline, doxepin and imipramine, which are among the most frequently used TCAs, encapsulated with poly [lactic-co-glycolic] acid [PLGA] as polymer was investigated for analgesic and antiallodynic effect and resulted in long lasting and better effects. This holds for further research in its utility in neuropsychairic disorders, particularly depression [43].

**(iii) Selective serotonin reuptake inhibitors [SSRIs]**

Several SSRIs have been investigated nanoformualtions like paroxetine, fluoxetine, escitalopram [44-47]. Among these fluoxetine was investigated as an *in-situ* gelling system for nose to brain delivery with

increased release, mucoadhesive strength and might result in enhanced patient compliance [48]. Paroxetine delivered intranasally as a nanoemulsion via olfactory region remarkably improved behavioural activities comapared to paroxetine suspension. It was also found that the nanoformulation significantly enhanced depressed levels of glutathione and decreased elevated levels of TBARS (Thiobarbituric acid reactive substances) [49]. All of these with promising results need further investigations [50, 51]. Among all the antidepressant drugs SSRIs have been the most interesting drug candidates for the researchers. However our literature survey couldn't find any of the above studies considering cognitive improvement as an endpoint.

**(iv)Serotonin Nor epinephrine Reuptake Inhibitors [SNRIs]**

Venlafaxine hydrochloride was formulated as a thermogelling polymer as an insitu mucoadhesive thermoreversible gel resulted in more effective behavioural improvements [52] Venlafaxine formulated as chitosan spray dried microparticles for controlled delivery has also promising results [53]. Desvenlafaxine has also been evaluated in nanoformulations with remarkable results [54].

**(v) Serotonin Antagonist and Reuptake Inhibitors [SARIs]**

This class of drugs include trazadone and nefazodone. Trazadone loaded into nanoform showed enhanced delivery of the drug compared to pure substance [55, 56].

**(vi)Others**

Other drugs like Agomelatine which has antidepressant property due to its blockade of 5HT2C receptors has shown increased therapeutic effect when loaded into nanoform and administered intranasally by loading of agomelatine loaded with poly-lactic-co-glycolic acid nanoparticles [57]. Ahmad *et al.* and shinde *et al.* has shown better permeability and enhanced brain delivery of Agomelatine NPs [58, 59].

**Future prospects for nano drugs for cognitive dysfunction in depression**

Vortioxetine is an effective antidepressant with multimodal mechanisms like inhibition of serotonin reuptake and activating receptors. In a clinical trial in adult patients aged between 18 to 65 y with recurrent MDD and a current depressive episode, evaluation of vortioxetine in a dose of 10 or 20 mg/day was found efficacious than the placebo [60]. This drug with proven efficacy in cognitive dysfunction in depression if formulated into nanoform can ensure better penetration, sustained action and patient compliance.

Duloxetine is another drug which has been studied as an antidepressant with pro-cognitive effects in MDD in subpopulations ranging from young patients to middle-aged. Duloxetine, produced remarkable enhancement of cognition, especially, speed of psychomotor functions, in an open-label trial of 12 w duration [61].

Long term SSRI treatment has also been found to reduce mild cognitive impairment to Alzheimer dementia in patients with MDD [62]. Mathews *et al.*, in their systematic review and meta-analysis found that SSRIs/SNRIs give promising results on memory than tricyclic antidepressants [TCAs], but had almost same result on working memory as Norepinephrine-Dopamine Reuptake Inhibitors [NDRIs]. Sertraline, when compared to fluoxetine, was found to have more positive effect on psychomotor speed within the SSRI class [63].

Ketamine has been found to exert a fast-acting antidepressant action in MDD subpopulations that fail to respond to treatment with conventional antidepressants. Ketamine has been suggested to improve neurocognitive symptoms in Treatment Resistant Depression [TRD], hence it could be used effectively as an antidepressant in sub-anaesthetic doses. However, there were concerns that ketamine might impair recall for previously learned information, but evidence in control participants has shown that ketamine does not affect recall for previously learned material and ketamine treatment has not been associated with impairments in executive function [64, 65].

EPO [erythropoietin] is a glycoprotein secreted by the kidneys that stimulates the production of red blood cells in the bone marrow. EPO has established vital roles in the central nervous system like neurodevelopment, adult neurogenesis, and neuroprotection. Its role in haemopoiesis has already been very well established. Hippocampal EPO has been shown to improve cognitive performance in a variety of disease models by exerting neuroprotective and neurotrophic effects [66, 67].

From the above it is evident that different nanocontainer formulations are under development for the treatment of depression. To summarise nanoformulations have a high potential for use in the treatment of depression because they provide a platform with very good penetration potential, targeted transmission, and enhanced safety and efficacy. Simultaneously all these formulations should be evaluated for cognitive improvement as well, which then can provide flourishing opportunities in the research activities in this domain. Nanotechnology has emerged as a promising approach for delivery of drugs for neuropsyachiatric disorders. However our search couldn't find the exploration of the above antidepressant drugs for cognitive improvement as a core research objetive. It is imperative that animal studies investigating the effectives of nanoforms of antidepressants should have cognitive changes as one of the secondary endpoint. However several other neuroprotective drugs have been evaluated in nanoformulations like curcumin, edaravone and nerve growth factors in neurodegenerative diseases like stroke, epilepsy, parkinsonism, alzheimers disease and brain tumors [52]. Most of these molecules have been successfully nanostructured for therapeutic applications [68]. Gold nanoparticles were shown to protect cognitive impairments, oxidative damage, and inflammation in a rat model of Alzheimer's disease sporadic dementia. [69]. Similarly cholesterol loaded nanoparticles was shown to improve synaptic and cognitive function in mice model of Huntington's disease after intraperitoneal injection suggesting the potential of this new route of drug administration to cross the BBB [70].

In another study by Abd-Allah *et al.* for management of insulin resistance induced cognitive defects, ascorbic acid and nicotinamide chitosan nanoparticles were found to have superior therapeutic effects compared to the conventional delivery forms [71]. Likewise there are several studies exploring the cognitive dysfunction in neurodegenerative conditions but there is a paucity of researches and evidences with regard to cognitive dysfunction in depression. We researchers should use the potential of nanotechnology in formulating new antidepressant drugs which will benefit the patient community.

Intra-nasal insulin was investigated as a pro-cognitive drug for the management of mood and mental disorders. Intranasal insulin therapy, for example, has been shown to improve cognition in both bipolar disorder and Alzheimer dementia. The presence of MDD has been linked to insulin availability and insulin receptor sensitivity [72-74].

Several vitamins like Vitamin-B [75], Vitamin D [76] and other multivitamins [77] and fatty acids like n-3 PUFA [78] have also been evaluated in the management of cognitive dysfunction and all these holds tremendous potential in nanoforms.

**CONCLUSION**

Cognitive dysfunction is one of the main pathological feature of MDD which is often underappreciated and not properly evaluated in the disorder's diagnosis and management. It is a key factor mediating the outcome of the patient with respect to psychosocial and functional domains, with implications for productivity at work. The evaluation of subjective and objective cognition metrics is inevitable and critical for better outcomes in patients with MDD. Conventional methods to managing cognitive dysfunction in MDD are grossly inadequate, with poor response rates to both first-and second-line antidepressant medications. The pharmacological treatment options primarily focus on the restoration of MDD mood symptoms, but research shows that remitted patients also have clinically significant cognitive impairments that negatively impact the patient's function and quality of life.

This situation has led to the emergence of new formulations that have enhanced delivery and sustained action for exerting

precognitive effects. Nanotechnology based formulations and nanocarriers holds tremendous potential in this regard. But we need to move further from preclinical studies for systemic use of these formulations. Several studies have demonstrated astounding results as discussed above as well as several other drug candidates are there which have not yet been tried in nano forms. Hence in future, we should focus more on development of such formulations.

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**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICT OF INTERESTS**

Declared none

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