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Precision nanomedicine for anxiety: challenges,opportunities, and future directions in targeted drug delivery

Precision nanomedicine for anxiety: challenges, opportunities, and future directions in targeted drug delivery

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Abstract

Nanoparticle-based drug delivery system represents one of the challenging strategies suggested to improve anxiety disorder therapeutic approaches, clinic challenges of delayed action, side effect-free designing and poor patient compliance. Traditional pharmacological agents can increase drug bioavailability and target specific brain regions, whereas nanoparticle-mediated controlled release offers enhanced precision and sustained action. The others in this review concentrate on several kinds of nanoparticle, including lipid-based, polymeric-metallic, and responsive nanoparticles, their use in anxiety medication. In addition, emphasis is placed on precision medicine that pertain the delivery of treatment based on an individual's genetic, environmental and lifestyle aspects. Also, it is looked into how artificial intelligence is being integrated into personalized nanoparticle formulations. Toxicity, regulatory hurdles and scalability are briefly discussed and future directions on smart and biodegradable nanoparticles are underlined. The present review highlights advantages of nanoparticle treatments and outlines a future direction of precision nanomedicine for anxiety.

Keywords: Anxiety, Controlled release, Drug delivery, Nanoparticles, Precision medicine

1. Introduction

Anxiety disorders refer to a classification of mental disorder encompassing excessive fear and worry that interfere with daily activities. Occurs globally, anxiety disorders represent a major mental health problem [1,2]. The most common mental health issue afflicts millions around the world. These disturbances profoundly impact social, occupational and having an impaired quality of life [3]. The burden of high prevalence and adverse impact makes it an important focus area in health system hence need for proven interventions [3,4] Figs. 1 and 2.

1.1. Limitations of current pharmacological treatments

Despite having effective treatments like Cognitive Behavioral Therapy (CBT) and different pharmacological options, most people are still not treated [2,4]. This underscores the need for greater mental health awareness and services worldwide. Pharmacological treatments for anxiety are wasteful, referring to low efficacy, delayed onset of action, high side effect burden and poor compliance [5]. Commonly used drug classes like benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) are often cited, and provide examples of challenges that include dependency, tolerance, limited long-term efficacy [5,6] Fig. 3.

2. Nanoparticles as a Novel Solution

Nanoparticles seem to be a recent step in precision treatment of anxiety disorders and improve delivery accuracy. Engineered nanoparticles can be formulated that boost bioavailability and home to specific brain regions hence reducing side-effects rendered by conventional pharmacological therapy [7,8]. Moreover, using the external magnetic forces magnetic nanoparticles (MNPs) have the ability to direct themselves and are able to release drugs in a

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controlled manner [9]. In the tailored delivery of therapeutic interventions, nanoparticles can overcome the shortfalls of existing treatment mode and generate more efficacious and personalized treatment for anxiety disorders [8,10].

The purpose of the review article is to shift the potential of nanomaterials in improving our treatment to anxiety disorders by tackling the current limitations in drug delivery and sustainability [11]. It investigates if nanoparticle therapeutics can augment drug bioavailability, especially by exploiting new delivery routes like the intranasal one that circumvents blood brain barrier and escalate therapeutic effects [12,13]. The review discussed here asserts the importance of introducing nanometric emulsions and multifunctionalities nanoparticles to safeguard the drug against degradation and cater to controlled release in form of faster onset followed by longer-lasting effects [14,15]. Hence, the review pursues and fosters the research conducted by nanomedicine working to impart personalized anxiety management related solutions through which mental health care can be switched gradually [16].

2.1. Precision medicine and its importance in tailoring treatments to individual patients

Precision medicine is an emerging model in healthcare that specifically considers each patient as individual using genomic, environmental and lifestyle factors *versus* the traditional drug/patient model [17]. This approach improves the efficiency and safety of treatment thereby reducing side effects and enhancing patient adherence [18,19]. Evaluation of personalized treatments like nanoparticle-based drug delivery systems characterize how precision medicine can facilitate better outcomes by increasing success rates while minimizing side effects [17,19,20].

2.2. Role of nanoparticles in precision medicine

Nanotechnology as a potential to develop novel drug delivery systems targeting those brain regions implicated in pathways of anxiety as will minimize off-target side effects. Engineered nanoparticle (lipid based and polymeric) can exert a better therapeutic acceptability than conventional methods [7,21]. Additionally, biosynthesized nanoparticles provide a biocompatible choice, improve drug stability and bioavailability with biofunctionalization by therapeutic agents based on a personalized patient profile [22]. This patient-centric philosophy not only produces the most optimal drug formulations but also illustrates an opportunity for controlled release mechanisms [23,24]. Nanotechnology combined with artificial intelligence (AI) could facilitate

List of abbreviations

CBT	Cognitive Behavioral Therapy
SSRIs	Selective Serotonin Reuptake Inhibitors
MNPs	Magnetic Nanoparticles
AI	Artificial Intelligence
nm	Nanoparticles
BBB	Blood Brain Barrier
CNS	Central Nervous System
SLNs	Solid Lipid Nanoparticles
PLGA	Poly Lactic-co-glycolic acid
PEG	Poly Ethylene Glycolate
RNA	Ribonucleic Acid
FDA	Food and Drug Administration
EA	European Agency
GMP	Good Manufacturing Practices
BNPs	Biodegradable nanoparticles

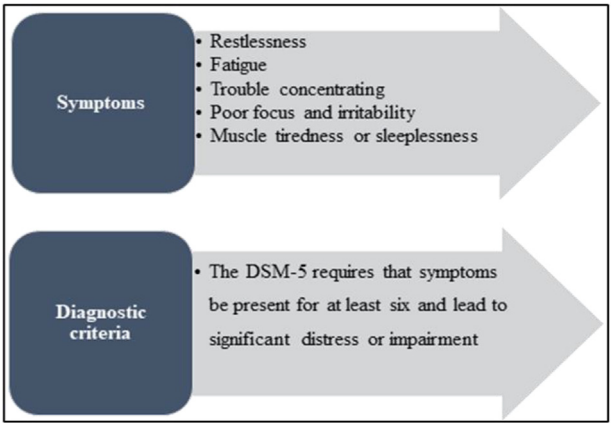

Fig. 2. Common symptoms and diagnostic criteria for anxiety.

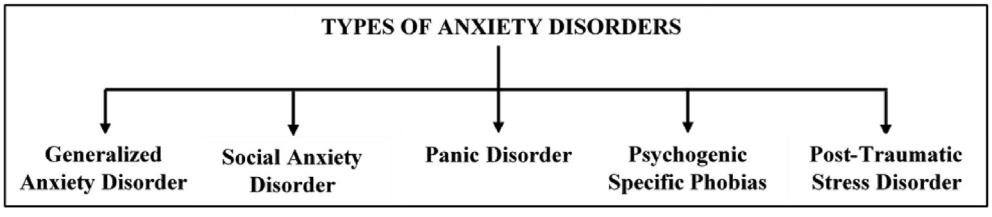

Fig. 1. Different types of anxiety.

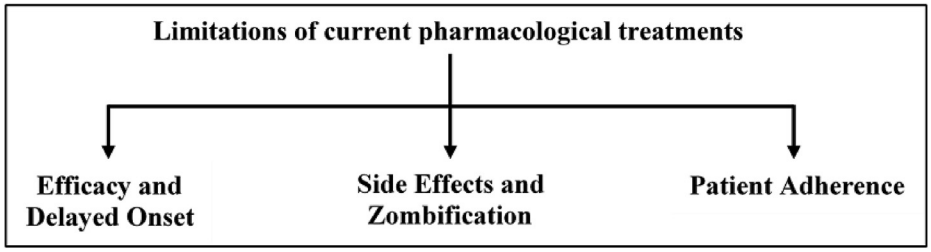

Fig. 3. Limitations of current pharmacological treatments.

individualized therapy and meet the specific patient requirements for mental health management [21].

3. Overview of nanoparticles

Nanoparticles (1-100 nm in size) are nano range particles with special properties such as surface/volume ratio and can be functionalized with particular molecules for improved performance in many applications [25,26]. Their nano size can help with enhanced solubility and penetrability, especially of biological barriers such as blood brain barrier (BBB) [27]. This is essential for any drug delivery systems oriented at central nervous system (CNS) disorders [28]. The use of polymeric, lipid-based and metallic nanoparticles provides a diversity to the available therapeutic options hence how they selectively tackle anxiety disorders or brain-related conditions indicative of their potency in the contemporary practice [27,28].

Nanoparticles have become an interesting tool for anxiety treatment due to their capacity to improve systemic drug delivery and accessibility to certain brain areas. Different types of nanoparticles such as lipid-based, polymeric, metallic and dendritic differs in terms of their properties providing exceptional approaches dealing with a variety of billions more challenging dilemma in BBB transport and enhancing the treatment efficacy-systems [29–32] Fig. 4.

4. Types of Nanoparticles Relevant to Anxiety Treatment

4.1. Lipid-based nanoparticles

4.1.1. Liposomes

The spherical vesicles help to improve solubility and bioavailability of drugs. They are also biocompatible and easily able to pass through BBB [29,30].

4.1.2. Solid lipid nanoparticles (SLNs)

They can include hydrophilic and lipophilic drugs, facilitating their use in anxiety treatment [31,33].

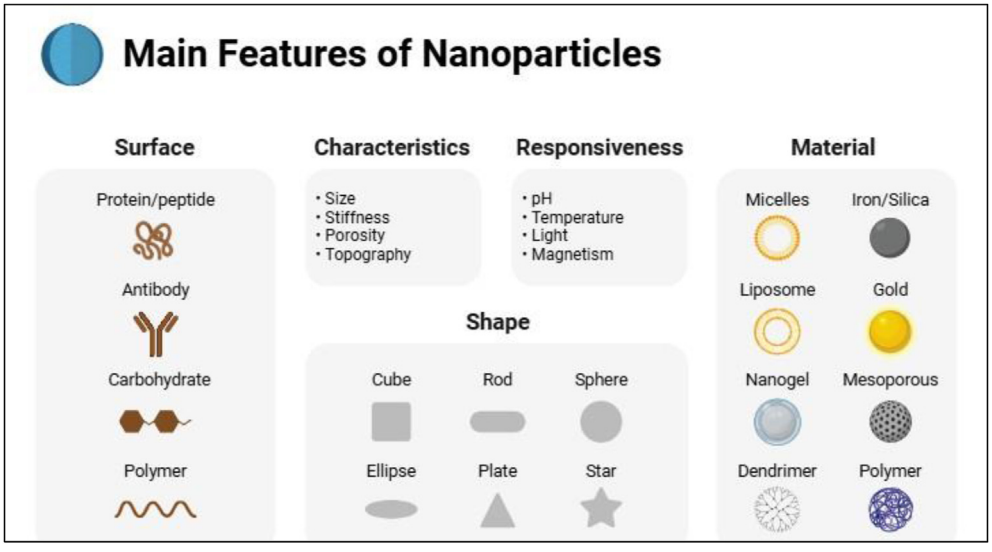

Fig. 4. Main features of nanoparticles.

4.2. Polymeric nanoparticles

4.2.1. PLGA (Poly lactic-co-glycolic acid)

Degradable copolymer used for releasing the drug at a controlled rate and can be modified to target specific mode of therapy. Flexibility and versatility are in its nature, compatible with different CNS disorders [11].

4.2.2. PEGylated systems

These nanoparticles increase circulation time and reduce immunogenicity thereby improving drug targeting to the brain [11].

4.3. Metallic nanoparticles

Gold and silver Nanoparticles: The special properties of these nanoparticles can be used as targeted drug delivery system and imaging in anxiety treatment [11].

4.4. Dendrimers

Highly branched polymers which can be used for specific drug loading and release control, subsequently used in the field of neuro-targeted therapy [11].

4.5. Nanogels

Polymeric networks that contain drugs and release them in response to external stimulus, thus providing a controlled release and improved targeting [11].

5. Role of Nanoparticles in Neurological Applications

Nanoparticles for neurological applications are ideal due to their small size which enable a good passage through the blood-brain barrier (BBB) and also helped in drug delivery to the brain; most of these sized nanomaterials can be used therapeutically to overcome BBB [34]. Their nanoscale platforms enhance the solubility and therefore enhance stability of therapeutics [27,32,35] In addition, the nanoparticles can be additionally functionalized with one or multiple targeting ligands for site-specific delivery to regions of brain known to drive anxiety regulation thus reducing side effects [11,36]. Their biocompatibility and controlled release mechanism offer prolonged therapeutic effects, which is why they are a very promising platform for long term treatment strategies [11,27,37,38].

6. Nanoparticles in Anxiety Treatment

6.1. Targeted drug delivery

Nanoparticle could be used to improve drug delivery for anxiety pathologies so they can efficiently migrate through the blood-brain barrier (BBB) and bind to specific brain receptors like GABAergic and serotonergic which mediate anxiety or mood regulation [39]. In addition, the surface modifications (ligand, charge adjustment) further improve their ability to cross the BBB and enable site-specific delivery to the brain zones related to anxiety regulation [27,40]. Intranasal delivery and other novel methods for targeting olfactory neural pathways through BBB, have been proposed as alternative routes to mediating neuropsychiatric disorders as well [40].

6.2. Sustained and controlled release

Sustained delivery of drugs through nanoparticles has resulted with significant improvement in therapeutic performance and less frequent dosing. Nanoparticles are engineered with a release scheme that prevents batch-to-batch variations and therefore allows surface carrying optimization [27,41,42]. They act as a controlled release system, minimizing the peaks and troughs seen with traditional dosing methods which are associated with side effects, especially in anxiety management [43]. For example, polymeric nanoparticles can be optimized for particular release kinetics thereby making drugs more soluble and stable for sustained action [27,41,43].

6.2.1. Examples of anti-anxiety drugs with nanoparticles

The use of nanotechnology in drug delivery systems have improved therapeutic efficacy of anti-anxiety drugs. Nanoparticles can do wonders for benzodiazepines, by allowing for the easy transfer across blood-brain barrier (BBB) [27] and hence contribute to both rapid as well controlled delivery, so as to lower the dependence and side effect profile of these drugs [12]. The poor solubility of SSRIs that solve by nanocarriers improves their absorption and supplies higher drug concentrations at brain level could lead to increasing therapeutic effects [40,44]. Taken together, nanoparticle-based delivery of these therapeutics ameliorates several challenges associated with drug solubility, bioavailability and controlled release thereby improve therapeutic management of anxiety [45,46].

7. Ongoing Research in Treatment of Anxiety

New evidence of the nanoparticles-based therapy to anxiolysis *via* novel delivery routes namely intranasal route was reviewed in recent studies [12]. This work shows that by using intranasal nanogels, it is possible to increase not only therapeutic bioavailability but also provide a direct way of drug delivery into the brain and avoid the well-known barriers of oral routes [13,47]. For example, quercetin which is a natural anxiolytic that resulted in increased loading and pharmacological efficacy of this compound when incorporated into the polymeric nano capsules demonstrated noticeable and compared very favorably in terms of safety and bioavailability to the existing patented formulation [47]. *In vivo* study of quercetin-loaded polymeric nano capsules as a novel platform for intranasal delivery of anxiety treatment further revealed faster onset and sustained therapeutic effects of these nanoparticle-based systems than current standard of care containing formulations [13]. Therefore, nanoparticles in drug delivery are a great step towards the management of anxiety disorders [12].

7.1. Recent advances in nanoparticle-based intranasal drug delivery systems for the treatment of anxiety and depression

Anxiety and depressive disorders are two of the most prevalent and disabling disorders worldwide, with hundreds of millions affected. Standard treatments are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), benzodiazepines and other psychotropic drugs. Although these treatments are useful in certain conditions, their efficacy can be constrained by slow onset of action, limited brain penetration across the blood-brain barrier (BBB), systemic side effects, poor bioavailability and patient-compliance related problems.

In the past years, the use of nanotechnology for intranasal delivery has attracted much attention in order to circumvent these problems. The olfactory and trigeminal nerves bypass BBB through the intranasal route to offer a non-invasive, rapid delivery of therapeutic molecules directly to the brain (CNS). In combination with nanoparticle carriers, this approach provides a novel vehicle to improve the solubility, stability and brain bioavailability of a wide variety of synthetic and natural drugs.

This section of the review highlights some of the significant developments in the use of nanoparticle-mediated intranasal drug delivery systems to treat anxiety and depression.

A. Quercetin-loaded Polymeric Nanocapsules for Anxiolytic Therapy

The first investigation using intranasally administered quercetin was recently published in Scientific Reports as quercetin-loaded polymeric nanocapsules for anxiety treatment. Quercetin is a plant flavonoid and possesses strong antioxidative, anti-inflammatory, and neuroprotective activities. Nevertheless, clinical usefulness of pterostilbene has been hindered by its low solubility and poor penetration through the BBB.

In order to overcome this obstacle, quercetin was incorporated into polymeric nanoencapsulated systems using biodegradable and biocompatible materials. The nanosystem was subsequently administered intranasally thus enabling the direct delivery of the drug into the brain. Behavioral studies in animal models showed large decrease of anxiety-like behaviours and increased drug accumulation in the brain compared with oral administration.

This study is important for several reasons. First, it illustrates the feasibility of using dietary polyphenols in CNS therapy when combined with nanotechnology. Second, it highlights the utility of polymeric carriers in protecting bioactive compounds and facilitating controlled drug release [47].

B. Fluoxetine-loaded Pegylated Chitosan Nanoparticles for Depression and Cognitive Enhancement

In an investigation published in Life Sciences, an intranasal delivery system was designed and optimized for fluoxetine-loaded pegylated chitosan nanoparticles to enhance the treatment of depressive disorders. Fluoxetine is a well-established SSRI that has been commonly used for major depressive disorder and anxiety disorders. Nonetheless, oral fluoxetine is subjected to first-pass metabolism and a delayed therapeutic effect.

To obviate this limitation, fluoxetine was loaded into chitosan nanoparticles, which is a mucoadhesive and also safety and able to improve the nasal residence time drug. In addition, PEG was applied to enhance solubility and absorption.

Chronic stress models of rats were intervened by the administration of the nanoparticle. The experiment resulted in clear amelioration of depressive symptoms, decrease of anxiety-like behaviour, and improvement of spatial memory. Additionally, high brain-derived neurotrophic factor (BDNF) and less demyelination in brain sections suggested potential neuroprotective effects.

This combination provides two benefits: a pharmacokinetic enhancer with brain targeting, and an optimized pharmacodynamics through neurotropic effects. It is an advancement in the implementation of antidepressant agents with reduced systemic toxicity [48].

C. Quercetin Transferosomal Thermosensitive Gel for Intranasal Delivery

Another significant progress in nasal drug delivery is the report of quercetin-loaded transferosomal gel prepared by the authors and reported in Pharmaceutics. Transferosomes are highly deformable lipid vesicles that can traverse stringent biological barriers in nose, and in combination with thermo-sensitive gels, they provide a sustained and mucoadhesive drug system for nasal delivery.

The latter system was used in this hybrid system to be applied intranasally with quercetin. The gel remained in the state of liquid at room temperature and it solidified as highly viscous gel when it touched to the nasal mucosa. This characteristic would ensure nasal retention and minimize mucociliary clearance.

Animal studies demonstrated significant improvements in both anxiety and depression models. Additionally, the formulation led to a controlled release of quercetin, sustained over a period of time, which resulted in prolonged therapeutic action. Brain tissue analysis confirmed elevated drug concentrations in hippocampal and cortical regions.

The successful combination of transferosomal vesicles and thermosensitive gels exemplifies a strategic approach to improving the pharmacological action of herbal agents in CNS disorders [49].

D. Dantrolene-loaded Nanoparticles for Neuroinflammation-induced Anxiety and Depression

One preclinical study was conducted to repurpose dantrolene, a muscle relaxant, for neuroinflammation-mediated anxiety and depression, through local intranasal delivery of nanoparticles. Neuroinflammation is now widely admitted as a pathogenic factor in psychiatric disorders, so that anti-inflammatory compounds appear as relevant therapeutic tools.

In the present study, dantrolene was loaded into the nanoparticles and was given intra-nasally to the mice injected with lipopolysaccharide (LPS) an endotoxin, leads inflammation and depression-like symptoms. The therapy significantly decreased behavioural manifestations of anxiety and depression, and brain cytokine levels.

This strategy extends the utilization of anti-inflammatory drugs and like-wise non-traditional CNS drugs for treatment of mental health disorder and unveils a new therapeutic use empowered by nanotechnology [50] Table 1.

8. Innovative Systems Combined with Imaging Agents for Diagnosis

Emerging nanoparticle-based systems with the capability for a broader treatment of anxiety are reaching a focus level [51]. Metal-organic frameworks and other nanoparticle have been designed to

Table 1. Summary of nanoparticle-based intranasal formulations for anxiety and depression.

S. No.	Formulation/Drug	Nanocarrier Type	Purpose/Effect	Key Outcomes
1	Quercetin-loaded polymeric nanocapsules	Polymeric nanocapsules	Anxiolytic therapy using antioxidant-rich quercetin	Enhanced brain targeting, reduced anxiety behavior in animal models, improved solubility [47]
2	Fluoxetine-loaded PEGylated chitosan NPs	PEGylated chitosan nanoparticles	Treatment of depression and cognitive improvement	Improved antidepressant effect, enhanced spatial memory, neuroprotection via BDNF upregulation [48]
3	Quercetin-loaded transferosomal thermogel	Transferosomes + thermosensitive gel	Dual therapy for anxiety and depression with controlled release	High nasal retention, sustained release, increased brain levels of quercetin, behavioral improvement [49]
4	Dantrolene-loaded nanoparticles	Unspecified polymeric nanoparticles	Anti-neuroinflammatory therapy for depression/anxiety induced by neuroinflammation	Reduced pro-inflammatory markers, significant behavioral recovery in LPS-induced mouse models [50]

efficiently translocate mRNA or siRNA into the brain where it causes profound gene silencing and protein modulation essential for anxiety homeostasis [52,53]. The nano size of these particles allows for the protection of RNA degradation and *in vivo* delivery towards specified brain regions overcoming issues, such as instability and immune responses [54]. Furthermore, conjugation of nanoparticles with imaging agents (e.g., quantum dots and gold nanoparticles) allows real-time tracking of drug delivery and therapeutic action [27,55]. Polymeric nanoparticles and lipid-based nanoparticles have been very promising to enhance the delivery of drugs to the Brain that means improve clinics and reduction in side effects [56]. While metallic nanoparticles provide an original approach to gene therapy, stimuli-responsive nanoparticles may help in developing individualized treatment strategies. Together, all these represent the scaffolding necessary for significant disease advancements in anxiety treatment [22,27,28,44] Table 2.

9. Challenges and Limitations

9.1. Toxicity concerns

Nanoparticles bioaccumulate in numerous organs, inducing long term health effects like cognitive impairment and worsened anxiety symptoms due to neurotoxicity [57,58]. Satisfying biocompatibility and regulation clearance from the body is a formidable goal, otherwise long-term retention can escalate toxicity [59]. Although surface modifications, e.g., PEGylation, could be employed to mitigate the toxicity, new hurdles are introduced [58]. Prognostic safety assessment must be performed in pre-clinical studies [59,60].

9.2. Ethical and regulatory issues

There are substantial obstacles including manufacturing and safety as well as ethical issues, the clinical translation of nanoparticles for anxiety treatment has to overcome to be integrated in the establishment-transformation pipeline/regulatory approval process [61]. Taking preclinical elegance from the bench to the clinic is further complicated by requirements of scalable manufacturing and stable nanoparticle platforms that demand protocol standardization in order to reproduce and validate safety [62,63]. Although there are high regulatory barriers to entry, nanoparticles need to pass stringent safety and efficacy testing to be allowed on par with the FDA/EAs yet lack of specific nanomedicine drug or device classification-based guidelines muddy their classification properties [64,65]. The regulatory arena is catching up with these nuances and adapted to some extent, with moves made at harmonization of guidelines and increased collaboration between stakeholders to facilitate safe and effective nanomedicine practices [59,63].

9.3. Manufacturing and scalability

Production scaling up from lab to industrial levels render uniformity in size, shape and surface properties is difficult [66,67]. Strict quality control is necessary to make sure drugs work as claimed [68]. GMP compliance is also proving a regulatory challenge for nanotechnology due complexity of the matter [69]. Precise manufacturing, advanced manufacturing techniques with automated quality control, cost-effective scalable production methods and standardization efforts can address the challenges in nanoparticle manufacturing as well as

Table 2. Summary of the different nanoparticle systems employed in anxiety treatment.

Drug/ Nutraceutical	Nanoparticle Type	Route of Administration	Mechanism of Action	Animal Model/Outcome	References
Diazepam	Solid lipid nanoparticles (SLNS)	Oral	Enhanced BBB permeability and sustained release	Reduced anxiety-like behavior in elevated plus maze (EPM) test	[90]
Quercetin	Polymeric nanocapsules	Intranasal	Improved bioavailability and nose-to-brain delivery	Faster onset and prolonged effect vs oral quercetin	[47]
Fluoxetine	Lipid-based nanoparticles	Oral	Enhanced solubility and BBB penetration	Greater serotonin uptake inhibition; improved anxiolytic effect	[91]
Alprazolam	Polymeric nanoparticles (PLGA)	Intranasal	Controlled release; reduced systemic exposure	Improved efficacy and reduced sedation	[92]
Curcumin	Gold nanoparticles	IV	Antioxidant & anti-inflammatory; modulated GABA/BDNF expression	Reduced oxidative stress and anxiety biomarkers	[93]

scalability. The bottleneck for scalability and reproducibility is microfluidics as well in continuous flow processing to up-scale the nanoparticle production. They are somehow precise control over size, shape and surface of nanoparticle which has been showing the use of microfluidic platforms operating at different driving flow rates [70]. Microfluidics technology further allows for spatially-controlled manipulation of microchannel geometries and fluid dynamics [71]. Real-time monitoring of nanoparticle properties performed by automated quality control systems are essential to keep track and comply with quality specifications [72]. Cost-saving production methods are being investigated to facilitate the use of biodegradable abundant materials which can decrease the manufacturing cost but have the same biocompatibility [73,74].

10. Future Prospectives

10.1. Smart nanoparticles

A nanoparticle solution that is smart to the brain is essential for future anxiety treatment as it enables localized, real-time drug delivery with on demand response to specific brain signals or biomarkers of stress [75]. The nanoparticles can be designed to identify on endogenous triggers, such as electrical activity or neurotransmitter levels and release drugs in a controlled and localized manner within the brain [76]. These nanobelts will enable precise therapy that matches the patient's real-time demands *via* actions based on specific brain signals and hence promise better treatment efficacy [77].

Finally, the nanocarrier specifically designed for stress biomarker silent delivery as cortisol or neuropeptides releases give such on-demand treatment to curb or prevent full-blown anxiety exacerbation in its positive flare-up. This is consistent with the tenets of personalized medicine in that it aims to deliver drug treatment regiments to individual patient formulated according to their intimate biomarker data or brain activity profiles thus, most likely improving both treatment efficacy and patient compliance [78]. Novel stimuli-responsive nanomaterials, which are capable for both endogenous and exogenous stimulus-response behavior have the key to reach a higher level of specificity and control in drug delivery systems [79]. With further research, some of these innovations may change the face of anxiety treatment bringing on more adaptive and responsive therapies that suit psychiatric disorders best adapted to the dynamic nature [80].

10.2. Artificial intelligence and computational models

The development of patient-tailored nanocarriers for anxiety treatment by means of artificial intelligence (AI) and computational model is a major step towards personalized medicine. AI algorithms helps to design the optimum particle size, shape and surface properties of nanoparticles accompanied by drug loading in order to improve therapeutic efficacy with as little side effect [81,82]. Whereas, computational models that simulate *in silico* nanoparticle behavior inside the human body facilitating the prediction of whether the particles will cross the blood-brain barrier for targeted receptors [83,84]. Thus, the personalized adhesive takes into account hereditary predisposition and treatment responses enabling to design successful treatment strategies.

10.3. Biodegradable nanoparticles

Biodegradable nanoparticles (BNPs) are natural and therefore will be eliminated *via* normal procedure by body in the long term. These nanoparticles that are usually made from biocompatible materials, can break down to nontoxic products that can easily be excreted or metabolized, therefore avoid tissue retention [85,86]. In comparison to non-biodegradable counterparts, BNPs substantially decrease the incidence of long-term toxicity and clear the risk of later interventions to remove stigmatizing particles from the body [27,51]. However, extensive additional clinical trials are needed before BNPs can be considered for treating anxiety and other cognitive disorders [27] Fig. 5.

10.4. Combinatorial therapies

The role of nanotechnology in enabling combinatorial therapies for anxiety treatment is to a great extent mediated by delivering traditional anxiolytics and gene therapies (siRNA or CRISPR) in one formulation *via* engineered nanoparticles synchronously [87,88]. The dual action of drug and gene therapy can complement limitations of conventional treatments, with immediate symptom alleviation alongside gene modulators for stress regulation [27,89]. Yet, co-delivery remains a hurdle with very high demand for precise control from minimal to maximal release profiles, the potential immune response, and the multifarious requirement of packaging nanoparticles that effectively conceal and release two loaded payloads [40,88]. Next-generation nanoparticle designs with multi-layered structures are likely to improve the efficacy of dual functionality in enhancing anxiety management [27].

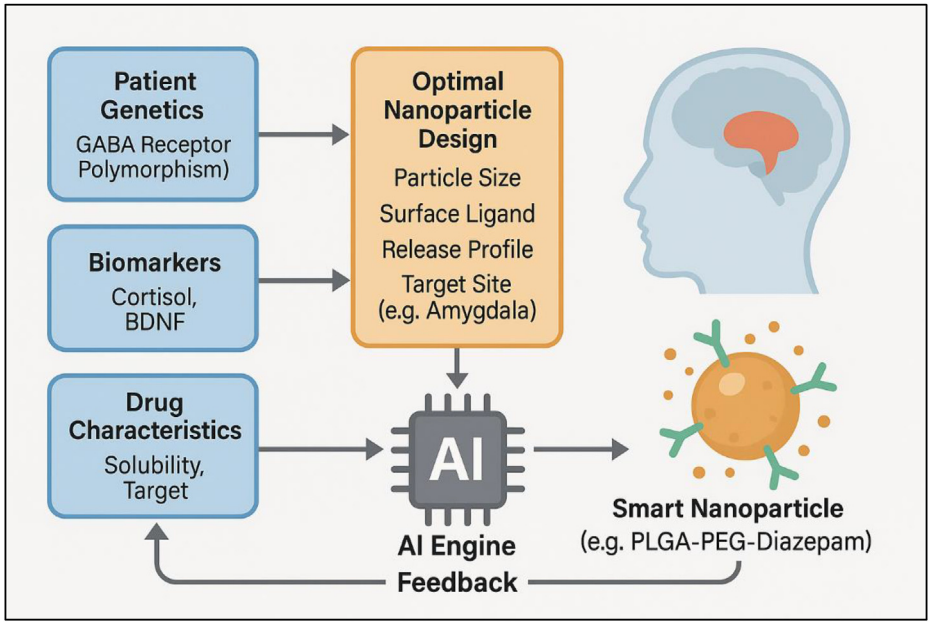

Fig. 5. This figure shows how AI uses patient-specific data—such as genetics, biomarkers, and drug properties—to design personalized nanoparticles that deliver anxiety medication directly to the brain, improving targeting and treatment outcomes through real-time feedback.

11. Conclusion

This review article discusses the potential of nanoparticle-based therapies for improving the treatment of anxiety disorders. Current pharmacological treatments for anxiety, such as benzodiazepines and SSRIs, have limitations including delayed onset of action, side effects, and poor patient compliance. Nanoparticles can enhance drug delivery to the brain, increase bioavailability, and enable targeted delivery to specific brain regions, thereby improving therapeutic efficacy and reducing side effects. The review covers various types of nanoparticles, including lipid-based, polymeric, metallic, responsive nanoparticles, and their applications in anxiety treatment. It also highlights the importance of precision medicine and the role of artificial intelligence in designing personalized nanoparticle formulations. Recent advances in intranasal delivery of nanoparticle-based anxiolytic drugs are discussed. The review emphasizes the need for further research to address challenges such as toxicity, regulatory hurdles, and scalability of nanoparticle manufacturing. Future directions include the development of smart, biodegradable nanoparticles and the integration of drug and gene therapy approaches for improved anxiety management.

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