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Treatment of Generalized Anxiety Disorder with Nose to Brain Drug Delivery of Natural Drugs, a mini review

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Keywords

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Abstract:

Generalized anxiety disorder (GAD) is one of the common mental disorders. Natural drugs often have the advantages of abundant resources, good efficacy and low side effects, which can be used as potential drugs for multi-targeted treatment of GAD. Nose to brain drug delivery (NBDD) enables natural drugs to target the central nervous system through the nasal cavity and bypass the blood-brain barrier to reach the brain directly. Substantial experimental studies confirmed that NBDD can go through intracellular and extracellular pathways, and then reach the brain and spinal cord through the olfactory nerve and trigeminal nerve to exert a synergistic therapeutic effect. This paper reviews the literature and clinical application studies concerning NBDD of natural drug at home and abroad, and analyzes the research progress of NBDD treatment mode for GAD as well as its advantages over oral drugs from the perspectives of applications, action mechanism, characteristics, etc. It further illuminates the problems and deficiencies that still exist in NBDD, as well as the methods and directions of formulation optimization, in order to provide a reference for the research and development of brain-targeted NBDD systems targeting GAD, further develop potential natural drugs for the treatment of GAD, provide natural, safe and innovative alternative therapies for GAD, and new ideas for the improvement of nasal preparation.

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Introduction

Generalized anxiety disorder (GAD), a common subtype of anxiety disorder, is primarily characterized by excessive anxiety, autonomic dysfunction and motor restlessness [1]. Reportedly, the lifetime prevalence of GAD in China was 4.66%, among which about 45.49% GAD patients were profoundly affected in terms of activities of daily living [2]. Many deficiencies exist in current drug therapies that have limited their wide application. Oral administration, in particular, has a significant first pass effect, causing low bioavailability accompanied by multi-system side effects. Therefore, interruption of the treatment could occur due to patient intolerance to side effects caused by oral administration.

Nose to brain drug delivery (NBDD) is an effective administration method with high efficacy, small side effects, and low addiction by incremental dose titration, it could significantly reduce the over-antagonism effect and improve the safety of the overdose victim [3]. NBDD can bypass the blood-brain barrier (BBB) to target the brain without the first pass effects in the liver, which has advantages of non-invasiveness, fast action and convenience. Natural drugs have a long history of treating brain diseases through NBDD. According to *Li Yue Pian Wen*, croton oil and *Gleditsia sinensis* powder can be burned to deliver to the nasal cavity as smoke to treat unconscious stroke patients; the incense from burning of agilawood and sandalwood can be applied to treat heatstroke patients accompanied by syncope; *Carthamus tinctorius* and vinegar can be decocted to to deliver to the nasal cavity as smoke to treat syncope caused by abnormal blood flow [4]. With the successful application of acute administration of neurosteroid nasal spray PH94B for treating adult social anxiety disorder in phase III clinical trials [5], the transnasal brain-targeted drug delivery system has received more and more attention and become a research hotspot.

1. Pathological mechanism of GAD and application status of NBDD

GAD has complicated pathogenesis, which contains hyperfunction of 5-Hydroxytryptamine (5-HT) system and decreased volume of hippocampus, dysfunction of gamma-aminobutyric acid type A receptors, as well as neuroendocrine system instability and neural structure changes (such as functional and structural local changes and anomalous connection of multi-region and multi-network in the whole brain). Hyperfunction of 5-HT system combined with decreased volume of hippocampus is one of the neural hypotheses of GAD [6-7], and 5-HT reuptake inhibitor has been primarily applied to treat GAD [8-9]. Meanwhile, the volume of gray matter in amygdala is increased significantly, which is positively correlated with the severity of anxiety [10-11]. By means of brain imaging technology, it has been identified that eugenol and other aromatic substances can reach central nervous system (CNS), and deposit amygdala and hippocampus through inhalation to play an anti-anxiety role [12]. It has been documented that dysfunction of gamma-aminobutyric acid type A receptors can trigger GAD, and benzodiazepines can quickly exert anti-anxiety effects by binding to this receptor [13]. Nose to brain transfer through lipid-based nanosystems can improve the targeting of benzodiazepines to brain and promote efficiency of drug delivery. One of the causes of GAD is the functional and structural local changes and anomalous connection of multi-region and multi-network in the whole brain [14-15]. However, NBDD can enable drugs to bypass BBB to reach brain, act on relevant brain areas, and reduce anxiety symptoms in patients. The nasal application of eletriptan hydrobromide emulsifiable granules and amiloride has been proved as a safe and efficient nose to brain transfer, and enable fast action [16-17].

In recent years, the clinical efficacy of NBDD has been testified by several clinical trials. Atomization inhalation and airway instillation possessing high bioavailability have been perceived as a safe and effective method of sedation in children for relieving pain and reducing anxiety [18]. Zhao Ji revealed that 20 minutes (min) before separation of mother and child, the intranasal administration of sufentanil (1

μg·kg^{-1}, 2 μg·kg^{-1}) can effectively relieve preoperative anxiety of child patients, and elevate the degree of sedation and analgesia of drugs and compliance of child patients [19]. Lu Junhua et al. identified that nasal drip of Esketamine (1 mg·kg^{-1}) mitigates preoperative anxiety of children with high safety [20]. Luo Xin et al. found that 30 min before surgery, the intranasal administration of dexmedetomidine hydrochloride has sedation and anxiety-relieving effects [21]. Kou et al. confirmed that the intranasal administration of neuropeptide oxytocin at low doses and low frequencies has the potential to treat GAD [22-23]. Nicholas et al. pointed out that intranasal administration of morphine and midazolam sprays in the management of patients receiving palliative care in the community have shown efficacy and safety [24].

2. The application status of traditional Chinese medicine (TCM)

Clearing channels and collaterals through intranasal administration" is an important method of TCM to treat brain diseases through NBDD[25]. TCM believes that there is a certain pathway between the nose and the brain. *Corrections on the Errors of Medical Works-theory of human brain* recorded that "the nose is connected to the brain and the smell is reflected in the brain", and "inspiration and memory depend on the brain instead of the heart" [25-26]. In *Jingyue's Complete Works Vol.13 Nature Collection-Schema of Miscellaneous Patterns*, qi is an inner energy of human beings [26], can pass through nose which is connected to brain, and when poison enters the brain, it will invade all meridians (a three-dimensional structure within the human body) and infect the person [27]. *Complete Library in the Skin and External Diseases* pointed out that the nose is in the middle of the face and responsible for life-long blood circulation. Nostrils are orifices of the lung, through which qi can go up to the brain and down to the lung [27-28]. Meanwhile, According to *Plain Questions-on Essentials for Pulse-Taking and Pulse Subtlety*, the brain is the place where the essence (consciousness, thinking and emotions of human) gathers[28], and if the head droops and the eye cells are sunken, the spirit which is the master and regulator of human life activities will be declined[28]. Accordingly, syndrome of orifices confused by phlegm and neurological disorders are the key of GAD pathogenesis [1]. In TCM, treating GAD through nose to brain pathway is an effective method.

The volatile oil of many natural drugs can play an anti-anxiety role through regulating CNS. *In-vivo* studies on animal models have verified the anxiolytic effects of these essential oils and the interactions of their major components with central nervous system receptors[29]. The volatile oil of *Cyperus rotundus* can modulate central cholinergic system, increase Hippocampal monoamine transmitter 5-HT, and mitigate the anxiety behaviors of mice exposed to chronic restraint stress [30]. Essential oil from styrax can elevate the level of 5-HT in the limbic system such as the hippocampus, increase brain-derived neurotrophic factors, and alleviate anxiety-like behaviors in mice with acute and chronic stress [31]. The anti-anxiety role of volatile oil from agilawood may be associated with the regulation on the secretion of neurotransmitters and the expression of receptor and transporter proteins [32]. Essential oil from mint reduces anxiety in patients with acute coronary syndrome in the emergency department via affecting the limbic system, hypothalamus, and piriform cortex [33]. The volatile oil of Piper nigrum EO possesses a dual anxiolytic and antidepressant-like effect through the possible involvement of serotonergic transmission[34].

In some oils, such as lavender, geranium, rosemary, the number of identified components ranges from 450 to 500 [35]. Studies have shown synergistic anxiolytic effects of the constituents due to activation of the different receptors. For the olfactory system, when the signals are transferred to the olfactory bulb and the brain, chemical

components of essential oils (e.g. lavender, lemon and bergamot) can communicate signals to the olfactory system, activate olfactory receptors but also non-olfactory receptors, can directly activate gamma aminobutyric acid receptors and transient receptor potential channels and stimulate the brain to exert neurotransmitters (e.g. serotonin and dopamine), thereby further regulating mood[36-37].

When natural drugs with a molecular weight of less than 300 exert effects through NBDD, its efficacy is not significantly affected by physicochemical property [32]. The volatile oil of natural drugs is fat-soluble with small molecular weight and strong volatility, which can be absorbed by the brain through blood-brain barrier without limitation from physicochemical property, and generate effects rapidly. Some volatile oil components not only easily cross the blood-brain barrier, but also promote the absorption of other effective substances. For example, borneol, as a TCM with special affinity to some meridians, improves the permeability of blood-brain barrier and facilitates the entry of drugs into brain; geniposide combined with fragrance components including muscone and borneol flakes can be applied to promote the bioavailability of brain tissue, increase the transport volume across the blood-brain barrier monolayer, and the action mechanism of geniposide is possibly associated with the ability of muscone and borneol flakes to open the tight connections of blood-brain barrier cells [38-39].

3. The mechanism, advantages, disadvantages and optimization method of NBDD in GAD

3.1 Action of mechanism

NBDD is achieved through intranasal pathway and nose to brain pathway to reach the brain in treating GAD. Intranasal pathway consists of intracellular pathway and extracellular pathway. In intracellular pathway, odor molecules enter nasal cavity, which are firstly accepted and recognized by olfactory cells on nasal mucosa through the endocytosis of olfactory cells, and then are transferred from axon to synapse fissure in the olfactory bulb, followed by exocytosis of drugs. This transsynaptic process is repeated by the olfactory epithelium of the nasal cavity containing bipolar olfactory cells, whose slender axons at the base form olfactory nerves within the lamina propria. Then, the olfactory nerves enter olfactory bulb in CNS through cribriform plate of ethmoid bone [40-41], and connect nose, brain and spinal cord [42], thus distributing drugs to other regions in the brain [43]. Figure 1 displayed the process, which was adapted from the study of Chen et al. [44].

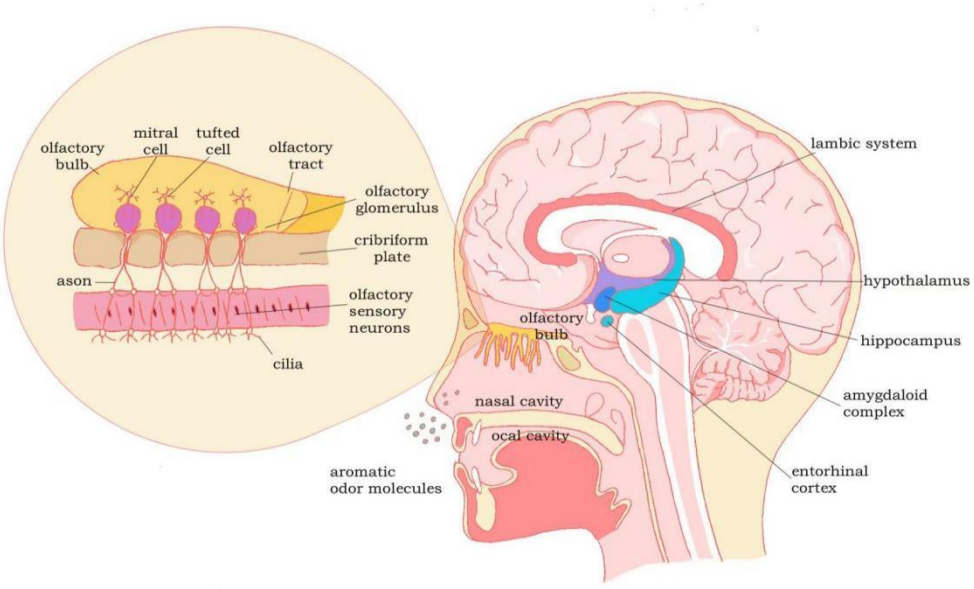

Fig.1 The main sites and pathways of absorption of the drug through the olfactory bulb.

In extracellular pathway, the drug first crosses the nasal epithelium through the paracellular space, in which the olfactory perineurium fluid communicates with the cerebrospinal fluid in the subarachnoid space via the perineural space, so that the nasal administered drug may be absorbed into the olfactory bulb or cerebrospinal fluid through nasal mucosa, bypass the BBB and be directly transferred into CNS [41].

There are two distinct neural pathways in nasal cavity and brain to construct nose to brain pathway. One pathway generates psychological and physiological reactions through transmitting signals by olfactory nerve to tissues including hippocampus and analyzing signals in cerebral cortex. The other pathway connects nose and brain through both ends of the trigeminal nerve. Of them, the eye nerve branches and maxillary nerve branches of one end extend to the epithelial cells of the nasal olfactory area and respiratory area, and the other end enters CNS through pons and locates in nuclei tractus spinalis nervi trigemini of the brainstem [43]. Olfactory nerve and trigeminal pathways connect nose, brain and spinal cord, which allows nasal administration to bypass the BBB and reach the brain, avoids the first pass effect of viscera, and thus successfully reduces dosage of administration and systemic adverse reactions. Figure 2 described the specific pathways, which was adapted from the study of ZHA [45].

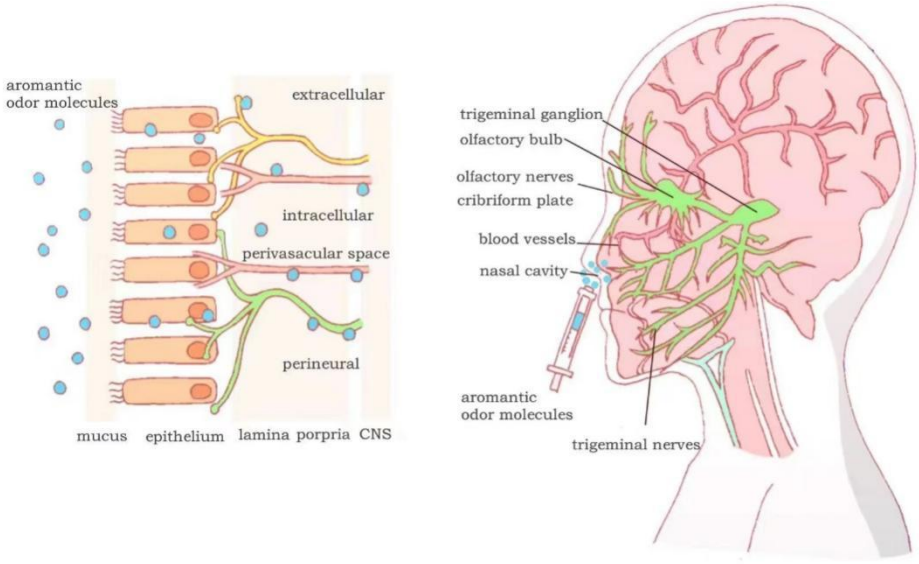

Fig.2 Olfactory nerve and trigeminal pathways and absorption pathways of drugs administered nasally. Blue dots refer to small molecule drugs.

3.2 Unique advantages of NBDD for treating GAD

Ample evidence revealed that natural drugs and their active components can holistically treat brain-related diseases through several targets, and prevent complications[46]. NBDD has the significant advantage of being able to bypass BBB, and considerable studies identified NBDD of natural drugs can markedly elevate the bioavailability of drugs (Table 1).

Table 1 The effect of NBDD on improving the bioavailability of drugs in the brain

No.	Drugs	Sources	Drug form	BTE	DTP	Clinical application	Ref
1	Huperzine A	Lycopodium alkaloids extracted from *huperzia serrata*	Temperature-sensitive glycol liposome gel	133.58 %	25.14 %	Promoting CNS targeting, and repairing nerve by stimulating the expressions of neurotrophic factors	[47-49]
2	Resveratrol	Non-flavonoid polyphenol components from *polygonum cuspidatum*	Nano-suspension	458.20 %	78.18 %	Improving lipopolysaccharide-induced anxiety behaviors through mitigating neuroinflammation and promoting hippocampal autophagy	[50]
3	Sempervirine	Yohimbine-type alkaloids existing in *Gelsmium elegans*	Chitosan microemulsion temperature-sensitive gel	261%	74.96 %	Achieving slow-release, controlled-release and target administration, exerting anti-tumor, analgesic, anxiolytic and so on.	[51-52]
4	Puerarin	Isoflavone compound extracted from the dry rhizome of *Pueraria mirifica*	Solution	132.25 %	/	Protecting nerves and resisting anxiety through boosting dopaminergic cell proliferation and affecting different molecular targets	[53-54]
5	Curcumin	Yellow polyphenol compounds from ginger	Microemulsion *in situ* gel	39%	/	Alleviating anxiety-like behaviors induced by dextran sodium sulfate through modulating specific gut microbiota	[55-56]
6	Salvianolic acid B	Effective components from the dry rhizome of *salvia miltiorrhiza*	Cubic liquid crystalline nanoparticles	/	/	Impacting the hippocampus, protecting brain and improving model learning and memory during neuroprotection and nerve regeneration modulation	[57-58]
7	Baicalin	Flavonoids compounds extracted from the rhizome of	Submicron emulsion of phytosome	788%	72%	Improving the mitochondrial structural damage of hippocampal neurons and exerting	[59-61]

		scutellaria baicalensis				anti-anxiety effects through affecting the mitochondrial autophagy of the hippocampus in mice	
8	Berberine	Isoquinoline alkaloids extracted from *coptis chinensis* and *cortex phellodendri*	Hydrochloric acid preparation	166.67	/	Exerting anti-anxiety effect and preventing damaged neurons from re-entering the cell cycle through regulating the 5-HT system	[62-63]
9	Ginsenoside Rg3	Tetracyclic triterpenoid saponins from natural ginseng	Chitosan microsphere	/	/	Anxiolytic-like effects are associated with normalization of neurosteroid biosynthesis, serotonergic system, and HPA axis dysfunction	[64-65]
10	Panax Notoginseng Saponins	Active components from *Panax notoginseng*	Nasal gel spay	/	81.06 %	Reducing the level of brain-derived neurotrophic factors, improving the plasticity of γ-aminobutyric acid nerves, and decreasing the susceptibility to anxiety in elderly mice	[66-67]
11	Asiaticoside	A pentacyclic triterpenoid saponin derived from *Centella asiatica*	Thiolated chitosan nanocomposite	/	89.44 %	Bypass the BBB, enhanced delivery of Centella to the CNS, can be beneficial in anti-anxiety	[68-69]
12	Mesembrine alkaloids	Alkaloids of the South African medicinal plant *Mesembryanthemum tortuosum*	Tablets	/	/	The binding of the alkaloids with the serotonin transporter lead an anxiolytic-like effect in zebrafish larvae	[70-73]

*BTE: Brain targeting efficiency, DTP: Percentage of the direct transfer from nose to brain

3.3 Problems of treating GAD through NBDD

3.3.1 Differences of the proportion of nasal mucosa in various organisms

At present, the basic research on NBDD is mainly based on animal experiments, and experimental animals of different genera or species are significantly different in nose, microscopical anatomy and histology [74]. Hence, anxiety animal model cannot completely reflect the complexity and severity of patients' symptoms [75]. The nasal mucosa covering olfactory area accounts for 50% of the total area of nasal cavity, while human

olfactory epithelium only covers 6% of a small area of the top of nasal cavity [76]. Human mucociliary clearance is 64-65 times slower than that of rats, possibly leaving more time for absorption [77]. Nasal administration of neuropeptide S can mitigate anxiety and prolongs memory in rats at doses lower than subcutaneous injection [78], but the effects have not been replicated in human body. Monkey has similar nasal cavity and brain structure with human, but human has relatively small olfactory area that restricts the efficiency of drug delivery to CNS [76]. Hence, successful preclinical data cannot guarantee the success of treatment, and more detailed clinical research is required [79].

3.3.2 Nasal mucosal toxicity and cerebral neurotoxicity

The mechanism of NBDD involves the stimulation and damage to nasal mucosal epithelial cells. By means of confocal laser scanning microscopy, the detection of the drug delivery and cell morphology revealed that many drugs and excipients are toxic to nasal mucosa and mucosal cilia. NBDD can elevate the bioavailability of Propranolol and propafenone suspension, but their strong ciliotoxicity may damage nasal mucosal surface [80-82]. Borneol flakes and muscone can open the tight connection of BBB cells and promote drug delivery to brain, but may also lead to normal secretion of mucoprotein in nasal cavity and increase of inflammatory factor release [83]. 5% polysorbate combined with 17% propylene glycol can completely dissolve the volatile oil of *radix bupleuri* and *coptis chinensis*, but the dosage is large and has obvious ciliotoxicity [84]. Saponins accelerant can not only relatively strongly stimulate nasal mucosa, but also trigger severe hemolysis and damage red blood cells [58]. Hence, drug concentration and dosage form should be appropriately controlled during administration. Yang li et al. indicated that nasal atomization inhalation of TCM improves the mucociliary transport function in chronic nasosinusitis [85], implying that atomization inhalation of TCM can alleviate the damage of NBDD to nasal mucosa.

When the drug is absorbed into the brain through nasal cavity, some components without brain-related pharmacodynamic action also penetrate BBB with the drug and are absorbed into the brain, which have notable neurovirulence. The enhanced activity of thrombolytic tissue-type plasminogen activator, which is applied to treat ischemic stroke, in CNS can strengthen the permeability of BBB and deteriorate the stroke outcome [86].

3.3.3 Low transfer capacity of drug delivery into brain

Some brain-targeted preparation has small drug loading capacity [87]. After NBDD of berberine hydrochloride, the plasma concentration and bioavailability of drugs are elevated; however, the amount of brain tissue deposits is low, which is limited by the dosage [62]. The bioavailability of intranasal nalbuphine nearly reaches 50%, and the intranasal dose of 0.4 $mg \cdot kg^{-1}$ provides pain control comparable to intravenous doses of 0.1-0.2 $mg \cdot kg^{-1}$ [88].

3.4 Optimization of preparation

3.4.1 Improving intranasal deposition

Drugs entering nasal cavity can easily be systematically degraded by substantial enzymes in the nasal secretions [89]. The ciliated cells of the nasal mucosal epithelium are cyclically excreted in the mucus layer towards the pharyngeal side, so that the drug is catabolized in the digestive tract [90]. Appropriate mucosal adhesive polymers and enzyme activity inhibitors can reduce mucociliary clearance rate, increase adhesion time of drugs, suppress intranasal degradation of drugs, and elevate the amount of drugs being delivered into brain to meet the needs of clinical treatment [91-92], which has been applied to optimize the drug delivery through nose.

Natural biodegradable materials (such as gelatin, starch, and albumin) can be applied as bioadhesive preparation, which tightly connect with nasal mucosa through water swelling and surface wetting, produce bioadhesion effects, and prolong the action time of drugs in the nasal cavity [93]. A study conducted by

Xu et al. develop a nano thermoresponsive hydrogel (nanogel) to allow the encapsulation of icariin for intranasal administration in order to increase the amount of drug that reaches the brain, and to verify its antidepressant-like activity [94]. The inhibitor of cytochrome P450 enzymes augments the penetration of melatonin in nasal mucosa [95], and relieves the anxiety of patients during surgery [96]. The preparation of microspheres based on natural polysaccharides can minimize the effect of mucociliary clearance and achieve slow release [97]. P-glycoprotein inhibitor remarkably elevates drug uptake rate and the deposit quantity in brain [98]. Nasal injection of enkephalin synzyme inhibitor can inhibit rapid extracellular damage and enhance the analgesic effect on rodents [14, 99-100].

3.4.2 Setting carrier system

During NBDD, polar drugs and several macromolecular substances have poor membrane penetrability, and can easily be cleared rapidly and be absorbed by abundant capillaries in the nasal cavity [99-100]. Solid lipid nanoparticles and nanostructured lipid carriers, as superior carriers for NBDD, have high biocompatibility, and can optimize nose to brain delivery through increasing bioavailability and site-specificity, which have been widely studied to act as alternatives to conventional dosage forms for improving drug bioavailability [101-102].

Dauricine protects nerve cells by suppressing oxidative stress response and reducing cell apoptosis, which functions as an auxiliary to alleviate anxiety-like behaviors of Alzheimer mice. It has been confirmed that nasal administration of dauricine loaded on graphene oxide nanoparticles can effectively elevate brain targeting efficiency and bioavailability [103]. Nasal administration of curcumin-like nanoparticles greatly ameliorates anxiety-like behaviors induced by dextran sodium sulfate, which has higher bioavailability than oral administration [104]. Thiolated chitosan nanoparticles of buspirone hydrochloride for brain delivery through intranasal route can be an effective treatment of GAD [105].

4. Current types and characteristics of dosage forms for anti-anxiety through NBDD

At present, the research on the processed anti-anxiety NBDD preparations including targeting preparation and sustained release preparation is relatively mature [106]. Compared with other common dosage forms such as tablet and injection, the dosage form delivered through nose develops well, although it occupies a small proportion. Anti-anxiety preparations delivered through nose primarily contain essential oil preparation that is prepared based on the volatility of the drug, nasal spray preparation prepared by atomization technology, temperature-sensitive gel preparation, nanoparticle preparation, etc. The strengths and weaknesses of these preparations can be seen in Table 2.

Table 2 Current types of anti-anxiety preparations for nasal administration

Types of preparations	Strengths	Weaknesses	References
Spray preparation	Administering drugs through nose at microgram doses, with high safety, uniform distribution and rapid absorption	Difficult to form an ideal atomization, and to completely reach absorption site	[107-108]
Volatile oil	High permeability, low toxicity and rapid metabolism without reserve. Easy to penetrate BBB by virtue of small molecular weight	Complicated components, worse water solubility, strong stimulation and prone to oxidation	[109-111]

Temperature-sensitive gel	Contributing to the adhesion of drugs in nasal mucosa, prolonging the action time of drugs in the body and increasing local drug concentration	Its sustained-release effect failing to meet the clinical demand, and imperfect evaluation criteria.	[112-114]
Polymer nanoparticle	Elevating the brain-targeting efficiency and utilization of drugs, preventing drug losses and delivering drugs directly to the brain	Easy oxidization, low encapsulation rate, instability and unfavourable storage	[115-116]
Liposome nanoparticles	Having high biocompatibility, controlled release property and stability, easy to be degraded, and possessing low toxicity to nasal mucosa	A limited ability to solubilize hydrophilic molecules, low drug encapsulation efficiency	[117-121]

Absorption enhancer is commonly used to assist the above nasal administration preparations to promote the transmembrane property of drugs and enhance drug absorption, so as to help drugs achieve ideal therapeutic efficacy. Notably, the absorption-promoting effect of absorption enhancer has a direct association with drug concentration and dosage [122]. Currently, there are limited absorption enhancers for intranasal preparations that have been approved for marketing. Comprehensively analyzing the characteristics of dosage forms to promote the research on absorption enhancer can improve the development of nasal administration preparations.

5. Conclusion and expectation

NBDD has a unique advantage of bypassing BBB to achieve brain targeting. The current research should explore novel strategies to improve the treatment of natural drug NBDD for GAD through clarifying how to stimulate response system, increase the permeability of the nasal cavity and elevate therapeutic efficiency, and minimize side effects.. It is believed that nose to brain targeting drug delivery will have a broad development prospect.

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Conflict-of-Interest

The authors declare no conflicts of interest.

Authors' contributions

Conceptualization: B.F.S; Data curation: E.A.A; Formal analysis: W.Q.G; Methodology: J.L.G; Writing – original draft: B.F.S; Writing – review and editing: E.A.A; All authors have read and agreed to the published version of manuscript.

Ethics approval and consent to participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Material

Not applicable.

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