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Short Communication

Pharmacological Aspects of Nose-to-Brain Drug Delivery Systems: Discussion on Current Commercial Outlook

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The treatment of CNS disorders is quite challenging due to the blood-brain barrier (BBB), which hinders the therapeutic entity from reaching the brain after subsequent oral and parenteral administration. At present, nose-to-brain drug delivery has heightened interest as a promising non-invasive route that bypasses numerous obstacles, enabling more direct access *via* the olfactory and trigeminal neural pathways [1]. These editorial reviews the pharmacological principles of the nose-to-brain system, recent technologies, and the commercial landscape.

The nasal cavity consists of the respiratory and olfactory regions and the trigeminal nerve pathways. There is a direct connection between the brain's olfactory bulb and olfactory epithelium present at the upper part of the nasal cavity that allows certain drugs to bypass the BBB. Analogously, the extension of the trigeminal nerve permits drug delivery to the brainstem and the spinal cord region [2]. These direct routes speed up brain access than oral or parenteral administration, making nose-to-brain an ideal route for acute neurological conditions like seizures, migraines, and drug overdose. Nevertheless, mucociliary clearance, enzymatic degradation, and the nasal mucosal barrier can cease the absorption and brain targeting [2,3]. The nose-to-brain drug delivery occurs *via* different transports like paracellular, transcellular, neuronal, and perineural diffusion. The transport mechanism relies on the molecular size, lipophilicity, and physicochemical properties of the formulation. To conquer the nasal delivery barriers, innovative pharmaceutical technologies are utilised, which include mucoadhesive polymers, permeation enhancers, enzyme inhibitors, and nanocarriers involving liposomes and nanoemulsions. These formulations provide gradual release, enhanced bioavailability, and diminished systemic side effects [4].

The intranasal drug delivery gives a higher bioavailability of certain drugs by bypassing the hepatic first-pass metabolism [5]. However, absolute brain bioavailability remains low with many of the drugs still absorbed systemically. It is a critical challenge to achieve steady and reproducible targeting to olfactory/trigeminal areas. Frequent intranasal administration raises safety concerns, nasal mucosal irritation, olfactory function loss, and local immune reactions to biologics [6].

Numerous products utilizing nasal administration are on the market, but not all are specifically labeled or engineered for nose-to-brain. Here are a few examples: Narcan® Naloxone nasal spray for opioid overdose, Imitrex® Sumatriptan nasal spray for migraine, Zomig® Zolmitriptan nasal spray for migraine, and Nicotrol® Nicotine nasal spray for smoking cessation (Figure 1). Still, many of these are not explicitly designed to target the olfactory and/or trigeminal neural pathway, and their pharmacological action may be largely systemic rather than completely brain targeted.

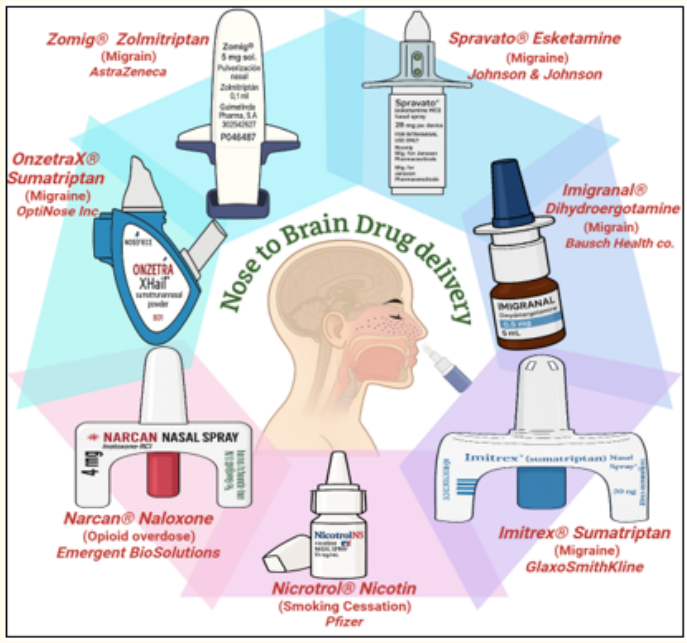

Figure 1: *Illustration of the nose-to-brain drug delivery system (respiratory route) and a commercial nasal spray.*

Currently, various devices have been invented and patented for nose-to-brain delivery. Impel NeuroPharma's POD™ device assists in delivering a formulation to the upper nasal cavity by pressurized air, VersiDoser®, and VRx2™, a patented product of Mystic Pharmaceuticals for controlled and targeted nasal dosing, while a US patent has been received for precision intranasal delivery to Rocket Science Health Corporation [7-9]. Use of insulin for Alzheimer's disease, ketamine, and esketamine for depression, as well as neuropeptides and antibodies for Parkinson's disease, Huntington's chorea, and Glioblastoma by the nose-to-brain route, is under the clinical pipeline. Along with these mucoadhesive gels, nanoparticles, and thermos-responsive systems are the representatives of advanced formulation under clinical assessment [10-12].

In spite of the advantages, nose-to-brain drug delivery is facing challenges like deposition of drug in the respiratory region and not in the olfactory region, alteration in human anatomy, degradation of biologics, and regulatory concerns, as it requires robust pharmacokinetic, pharmacodynamic, and imaging datasets, production, and scalability issues [3].

The future of nose-to-brain drug delivery appears highly promising, particularly for acute CNS disorders, where rapid onset of action and minimal systemic exposure are essential. The favourable diseases involve seizure, psychosis, cluster headache, and overdose of neurotoxins. Intelligent drug delivery systems use advanced nanoparticles that respond to environmental triggers, targeting specific brain regions with precision. Digital health platforms with integrated sensors enable better treatment monitoring and personalization. Biomarker research and imaging techniques are crucial for tracking medication effectiveness. Successful commercial solutions will combine innovative formulations with precise delivery methods, supported by patents and clinical data. Success in this market depends on regulatory approval, cost-effectiveness, ease of use, and patient compliance. Nose-to-brain delivery systems that prove superior to traditional methods in both efficacy and cost will likely dominate the market.

Conclusively, nose-to-brain drug delivery offers a promising pathway for treating central nervous system disorders by bypassing the BBB. While challenges exist, advances in formulation and delivery methods continue driving progress. With proven success through approved intranasal medications and ongoing research developments, this administration route is poised to become crucial for CNS therapeutics, especially in urgent medical situations.

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