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Trans-Nasal Delivery: A Review of Opportunities and Challenges to Cross the Blood Brain Barrier

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Review Article

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ABSTARCT

Trans-nasal drug delivery offers great potential to treat an array of unmet medical needs in CNS (Central Nervous System) disorders that affect millions of people today. The ability of many drugs to cross the BBB (Blood Brain Barrier) is constrained by their physiochemical properties, leading to sub-therapeutic concentrations in the CNS as well as problematic side effects due to systemic drug exposure.

This review aims to inform the reader about both the opportunities and challenges associated with trans-nasal delivery of therapies across the BBB to treat CNS disorders. Areas covered will include physiochemical barriers, formulations, delivery devices, quantifying uptake and transition from current pre-clinical work to successful human clinical trials and the paper incorporates current literature on the subject.

Much of the underlying research and pre-clinical work has been successfully executed in trans-nasal drug delivery to target CNS diseases. The main challenge lies in the transition from animal to human clinical studies establishing robust regulatory dossiers that will satisfy the regulators that these therapies are both efficacious and safe to treat the target CNS diseases at a commercial scale.

Keywords: Blood brain barrier; Central nervous system; Device; Formulation; Nasal; Translation

INTRODUCTION

For millions of patients suffering today with CNS diseases, their treatments are frequently sub-optimal due to the fact that many such therapies bring with them unwanted side-effects due to systemic exposure. The most commonly prescribed CNS therapies today are anti-Alzheimer's, antidepressants, antiepileptics, antipsychotics, anti-Parkinson's and pain management agents. Associated side effects are widely reported with the most common ones being hypertension, sedation, motor instability, gastro-intestinal effects, arrythmia, skin conditions, cardiovascular issues, seizures, hepatotoxicity and fatigue [1]. The majority of drugs cannot easily cross the BBB due to their physicochemical properties and therefore cannot access the targeted CNS tissues [2-4]. As a consequence of the above challenges, the trans-nasal route with its numerous advantages could provide a promising route for the delivery of drugs to the central nervous system. Trans nasal delivery of drugs to the CNS *via* the neuronal pathways would avoid the gastro-intestinal system and other key organs in the systemic pathway that can lead to the unwanted side effects detailed above. However, trans nasal delivery of drugs to the CNS *via* the systemic circulation and subsequently the BBB could still bring some unwanted systemic side effects.

The trans-nasal route is a non-invasive or minimally invasive way of administration to the CNS and could provide an alternative to the intravenous and oral routes. In traditional routes such as parenteral and oral administration, the drugs must firstly find their way into the systemic circulation and must then cross the BBB or the Blood-Cerebral Spinal Fluid Barrier (BCSFB) in order to enter the CNS. These two barriers represent the largest interface between blood and brain extracellular fluids, prevent the free paracellular diffusion of polar molecules by complex morphological features, including tight junctions that interconnect the endothelial and epithelial cells, respectively. The BBB and the BCSFB are formed by brain endothelial cells and choroid plexus epithelial cells, respectively [5]. Delivering the drugs *via* the nasal cavity will avoid hepatic first-pass metabolism and drug degradation in the gastrointestinal tract, and this pathway could be an alternative to parenteral administration, which could be a benefit for biological therapies such as proteins, peptides, monoclonal antibodies and nucleic acids. In addition, drug transport along olfactory and/or trigeminal nerves within the nasal cavity, may facilitate direct penetration into the CNS.

LITERATURE REVIEW

It is 40 years since the first reported passage of drugs from the nasal cavity to the CSF was documented. A plethora of over 1000 publications have since been recorded where authors have been evaluating the passage of drugs from the nasal cavity to the brain, CNS or CSF. However, it is somewhat disappointing to note that there is not even a single FDA-approved therapy for treatment of CNS disorders that is administered by the trans-nasal route and supported with convincing proof of direct transport *via* the nose to CNS.

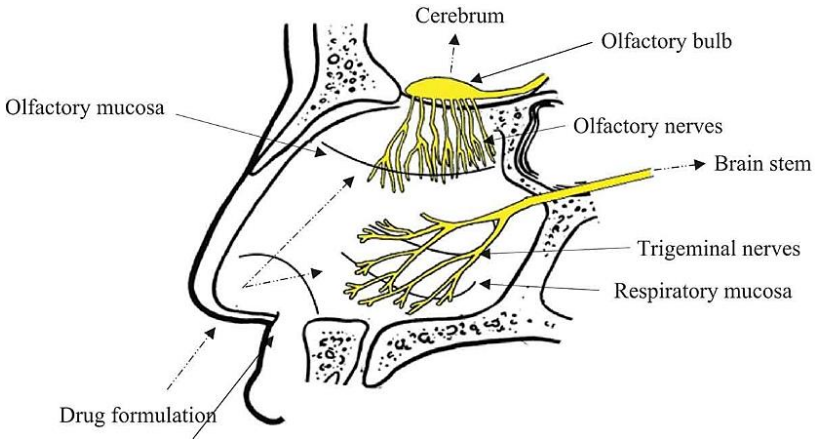
Drugs mainly cross the BBB by passive diffusion and a small number of compounds can also enter the brain mediated by receptors or transporters highly expressed on the BBB. For passive transport it is generally advised that they be less than ~400 Da molecular weight, they should be largely nonpolar (uncharged), and not multi-cyclic in structure. However, a large number of compounds that one would like to deliver to the CNS do not fit within these constraints, imparting serious difficulties to the development of CNS therapies. In fact, 98% of drug molecules do not cross the BBB in suitable therapeutic quantities. Certain compounds can traverse the BBB by receptor mediated transport *via* receptors located in the BBB epithelium such as INSR (insulin), TfR1 (transferrin), IGFR (insulin growth factor), LDLR (lipoprotein) etc. [3]. Compounds of varying low molecular size can also cross the BBB by use of active mediated transport, e.g. ABC (P-glycoprotein, cholesterol), SLC (solute carriers, amino acids,

organic anions) and both the above routes can influence and be used to adjust the transport of compounds across the BBB [6].

Numerous physiological barriers stand on the way of trans-nasal delivery to the CNS including the nasal vestibule, nasal valve, epithelial tight junctions, efflux transporters, nasal metabolism, mucociliary clearance, the limited surface area of the olfactory region, presence of drug-specific target receptors/transporters, and the BBB itself [6]. Born et al. were the first to report details of trans-nasal drug delivery to the CNS as far back as 2002, whereby vasopressin, melanocortin and insulin were administered as intranasal solutions to human subjects, and increased levels of all these drugs were detected in the CSF 10 minutes after dosing with maximum levels recorded 80 minutes after administration [7]. This pioneering study has given rise to numerous clinical studies whereby the trans-nasal route has been evaluated for an array of disease indications.

The olfactory epithelium has long, non-motile cilia extending into the upper part of the nasal cavity [8]. This is the only place in the body where the CNS is in direct contact with the outside environment. The olfactory mucosa has about 6 million neurons and each olfactory neuron has one specific receptor. These olfactory neurons die and regenerate-perhaps the best-known neurons with that ability likely resulting from their exposure to inhaled chemicals - with a lifecycle of 30-60 days as shown in Figure 1 [9].

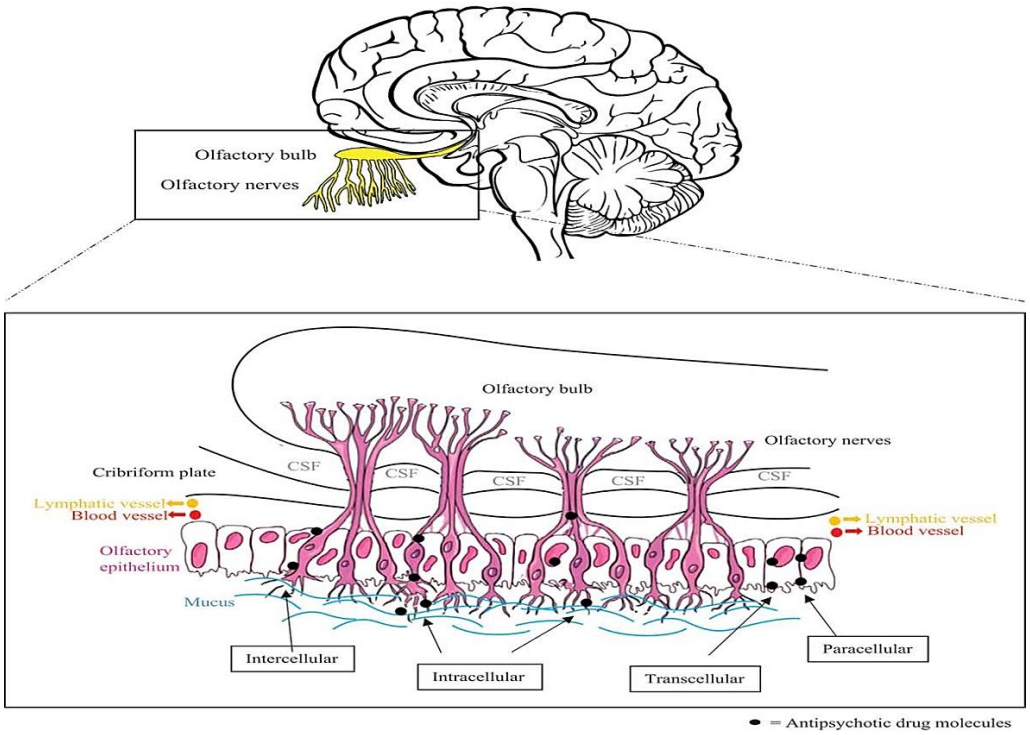
Figure 1. Neuronal targets for trans-nasal transport. It should be noted that the depth of nerve penetration into the nasal cavity will vary from patient to patient.



The respiratory mucosa is ciliated with a cyclical nasal clearance time of 15-20 minutes. It has a rich supply of blood vessels and therefore good access for transport to the systemic blood circulation and the mucosal thickness here is 0.03 cm to 0.5 cm.

The precise mechanism by which active compounds travel from the nasal mucosa to the CNS is not yet fully understood or proven. As illustrated in Figure 1, trans-nasal delivery is thought to take place *via* the olfactory and trigeminal nerves. The olfactory nerves and trigeminal nerves have the potential to transport active ingredients to the olfactory bulb and the brain stem respectively. The olfactory nerve pathway draws particular attention in many studies due to its close proximity to the CSF, its restricted blood supply and hence, lower systemic absorption, as well as a potentially faster rate of uptake due to the relatively shorter olfactory nerves themselves. Perineural spaces exists around the olfactory nerves which allow the CSF to communicate with the nasal mucosa [10]. This provides another route (olfactory/nasal lymphatic) by which drugs can pass from the nasal cavity to the CSF/CNS is shown in Figure 2 [11].

Figure 2. Proposed olfactory transport routes.



There are two principal routes for trans nasal drug delivery to the CNS, the nasal neuronal pathway and the systemic pathway [12]. Figure 2 illustrates the four main potential transport routes for active drug transport along the olfactory and trigeminal nerves. The four proposed pathways are intercellular, intracellular, transcellular and paracellular routes in the olfactory nerves, and this process is thought to occur similarly for the trigeminal pathway [8]. Drugs targeting the CNS *via* the intercellular route will make their way between the epithelial cells by receptor-mediated mechanisms and will have the added challenge of passing through any tight junctions they may come across between the epithelial cells. Alternatively, drugs moving *via* the intracellular pathway will travel within the olfactory neurons (or trigeminal neurons) themselves by way of endocytosis and will eventually reach the synapses at the olfactory bulb or brain stem. Another potential transport route, the transcellular route, will see the molecules entering the epithelial layer *via* endocytosis, traversing the cell itself and then exiting the epithelial layer *via* exocytosis. The paracellular route transports the drug along the nerves by the simple process of diffusion. In addition, perivascular transport also allows for drug molecules to be transported to the brain once they have crossed the nasal mucosa into the olfactory region [12].

It should be noted that drugs moving *via* the paracellular, intercellular or transcellular avenues may also end up in other locations such as blood vessels, lymphatic vessels or CSF, and consequently are at risk of systemic absorption [13]. The transcellular and intracellular routes are more likely favoured by lipophilic active ingredients. Extracellular transport is considered to occur rapidly, e.g., ~30 min, whereas intracellular processes may take hours to days. Transport to other brain areas after entry to the brain (e.g., to the mid brain from the olfactory bulb or to the brain stem from the trigeminal nerve) is thought to be mainly either by extracellular convective bulk flow or *via* perivascular routes [14,15]. Alternatively, drugs could make their way into the systemic circulation from the nasal cavity and, where feasible, could cross the BBB and enter the CNS [12].

Drug delivery devices for trans-nasal therapies

Delivery devices, both for liquids and powders, for trans-nasal delivery are well covered in the literature, (see Table 1), with mention of several devices in various publications [6,9]. They all claim to be capable of delivering trans-nasally *via* neuronal routes, but none have human clinical data to back up these claims to date. Delivery devices can influence trans-nasal drug delivery and some important aspects should be considered such as: Delivered dose (liquid or powder), spray angle, spray velocity and site of deposition [16]. The interface of the device with the patient is important, such as ease of use or compliance. Suitable devices may need to be considered for specific groups such as paediatric or geriatric patients, to manage aspects such as actuation force [17].

Table 1. Examples of nasal spray devices associated with trans-nasal delivery [9].

Device (manufacture)	Dosage form	Characteristics
EDS (Optinose)	liquid, powder	marketed devices, single, multiple dose
Sipnose (Sipnoce)	liquid, powder	in development single, multiple dose
Naltos (Nanometrics)	powder	in development, single dose
POD (Impel)	liquid, powder	marketed liquid device (HFA propellant), multiple dose
SMI (Medspray)	liquid	in development, single, multiple dose
UDSL, UDSP (Aptar)	liquid, powder	marketed devices, single dose
Veridoser (Mystic)	liquid, powder	in development, single, multiple doses
ViaNase (Kurve)	liquid	in development, multiple dose

Overcoming the barriers

Literature reviews of the many publications claiming trans-nasal to CNS transport led the reviewers to comment that encouraging data had been generated with both insulin and orexin, based on MRI (magnetic resonance imaging) imaging and/or clinical response, but that "convincing, unequivocal proof of N2B (nose to brain) transport was still missing in humans, largely due to methodological and ethical considerations" [13]. Insulin has been the most studied large molecular weight 5808 Da peptide. Most of these studies on Insulin have focused on the clinical outcomes of trans nasal Insulin delivery and not specifically on the precise nasal to CNS transport. The presence of insulin receptors in the olfactory bulb, hippocampus, hypothalamus, and lower brainstem, makes it an ideal candidate for nose-to-brain delivery [9]. Insulin is known to bind to these receptors and increased levels of Insulin in human CSF have been reported after 60 mins [18]. Insulin's therapeutic effects in the CSF/CNS are improved memory and general cognition as well as enhanced cerebral glucose metabolism [19]. The focus of trans nasal research has not been solely on high molecular weight compounds and numerous other studies related low molecular weight entities for therapies such as brain tumours are reported in the literature [4,20]. Although there have been promising preclinical, or clinical case study results reported, these have yet to be subjected to large scale, randomized clinical trial investigations in humans in order to provide definitive proof of this mode of drug delivery [21]. Several pathways for human trans-nasal to CNS delivery have been proposed based on pre-clinical studies. However, evidence gathered from animal studies is not readily transferable to humans due to fundamental anatomical and physiological differences between species.

In rodents the olfactory epithelium may cover as much as ~50% of their nasal cavity as opposed to ~10% as is the case in humans (Table 2). Many animal experimental studies are likely conducted by highly trained and experienced technicians administrating formulations to anesthetized animals in the backword position. The significantly

different olfactory epithelial surface area to body weight ratio in humans as compared to other animal species make it very difficult to easily translate preclinical to clinical situations.

Table 2. Nasal cavity differences amongst spieces [22].

Species	Body weight (kg)	Nasal cavity volume cm^3	Nasal cavity surface area cm^2	Olfactory epithelium %	Olfactory epithelium cm^2
Mouse	0.03	0.03	25	47	1.37
Rat	0.25	0.26	13.4	50	6.75
Rabbit	3	6	61	10	6
Human	70	25	160	8	12.5

Clinical studies should take into consideration both the surface area of an animal's olfactory mucosa and its surface area to weight ratio. Till-date there is no clear consensus to measure the direct CNS uptake of drugs in humans *via* the trans-nasal route, and in addition, there will be an obligation to carry out significant longer-term safety and efficacy studies to establish the true benefits of such therapies.

Rodents are employed in the majority of *in vivo* models reported in the literature. The respiratory mucosa in rodents cover about 50% of the nasal cavity, whereas in humans it can account for up to 80%–90% of the nasal cavity [22]. One factor to keep in mind in translating preclinical animal studies to human studies is the fact that the entire CSF volume of rats is totally replaced every hour (i.e., 24 times a day), whereas in humans the CSF is turned over every 5 hours (i.e., 4–5 times a day) [23]. Such differences should be taken into account when interpreting trans-nasal *in vivo* model studies [24].

Another factor that can limit the translation of trans-nasal drug delivery from animals to humans is the fact that the majority of preclinical investigations on nasal drug delivery to the CNS are performed with experimental designs that could produce local nasal injury and membrane disruption, owing to the nasal instillation of very large volumes of drug formulations [3]. The volume of the nasal cavity in humans is 15-20 mL, but is only 0.3 mL in the rat, and 0.03 mL in the mouse. The nasal administration of a volume greater than 1% of the volume of the nasal cavity in rodents would be the equivalent <250 µl in a human study, which are much greater than the typical volumes used in todays' nasal products and could potentially lead to local injury. A nasal administration volume of 1% of the nasal cavity volume would be 4 µL in the rat and 0.3 µL in the mouse. Most literature studies indicate that the nasal administration volumes in preclinical nasal drug delivery research are 1-2 log orders higher than the above levels and are not realistic in terms of transitional pre-clinical work to bridge the gap to human studies [3]. In an effort to minimize dose size and maximize drug content, there is work ongoing to develop solid nasal dose formulations using approaches like composite solid microparticles, dry powder microspheres and spray dried powders [25].

There can be numerous quantitative and qualitative differences between human and animal spices including; nasal surface area coverage, olfactory region size and location, airflow rates, nasal capillaries, cerebral blood flow, brain tissue binding, CSF turnover and intracerebral distribution. As a consequence, there is a significant challenge in order to successfully translate such preclinical evidence [6].

One key aspect in order to successfully accomplish safe and effective trans-nasal delivery will be developing suitable formulations as they will steer the absorption pathways that the drug will follow. The molecular weight of the API (Active Pharmaceutical Ingredient) as well as the absorption pathway taken will determine the eventual bioavailability of any therapy. There is an inverse relationship between percent drug absorbed and molecular weight

in the nasal cavity. Trans-nasal transport to the CNS will depend on the physicochemical characteristics of the drug coupled to the physiology of the human nose.

The use of nanoparticles and solution penetration enhancers improves the delivery to the CNS *via* the trans-nasal route and because there are limitations in dose volume, these technologies are likely to play a key role in the future. Nanoparticles fall into three general classes, -polymer, e.g., dendrimers, miscellas, protein, -lipid, e.g., liposomes, solid lipid nanoparticles, exosomes, -non-polymeric, e.g., caron nanotubes, metallic [3]. It has been shown that nasal drug transport by such systems is achieved by various mechanisms [26]. Nano-formulations can further be separated into nanoparticles, nanoemulsions and nanosuspensions [11]. Work is ongoing to clarify aspects such as accumulation of nanoparticles in the body and their biodegradation. The literature reports small amount of drug delivered, estimated at ~0.1% of the dose at the Cmax, and yet clear pharmacological effects have been observed in human and animal studies and this would lead one to believe that in some cases the dose delivered by this route may only need to be 0.1–1% of an oral dose to be effective [4,9].

Another key challenge is related to drug deposition on the nasal mucosa and absorption which needs to overcome the body's natural defence mechanism, such as ciliary clearance. The anatomical location of the olfactory epithelium is another limitation of this delivery route since the dosage form must first be able to reach this site. Metabolic enzymes present in the olfactory mucosa must also be considered when designing a formulation for the trans-nasal route [6]. Consequently, much work has been done on intranasal formulations in order to make them biocompatible, odourless and to avoid rapid elimination due to mucociliary clearance and/or enzymatic degradation [2]. Employment of permeation and absorption enhancers, cell-penetrating molecules, mucoadhesive and mucopenetrating agents, enzyme inhibitors, hydrogel systems, and nanoparticulate drug delivery systems or a combination of different above strategies have been studied to try and overcome the nasal cavity's natural defences. In addition to the approaches to enhance drug absorption to the CNS *via* the nasal cavity mentioned above there have been studied including; chemical modification of therapeutic agents, i.e. PEG or transport ligands (conjugates to aid absorption and drug stability), vasoconstriction (reduce absorption into the blood/systemic), devices (target the drug to optimal areas of the nasal cavity), polymeric carriers, lipid carriers (carriers provide protective encapsulation and transport), emulsions (increase delivery efficiency), thermogels (prolong contact with nasal surfaces), amongst others [26,27]. In order to enhance the absorption of drugs with larger molecular weights, e.g., >4k Da, researchers have looked at the addition of permeation enhancers to trans-nas al formulations. Permeation enhancers can aid the uptake of both low and high molecular weight drugs *via* numerous potential mechanisms including: hydrophilic pore generation, increasing membrane fluidity and tight junction permeability, hydrophilic pore augmentation and decreasing viscosity and enzymatic activity [6]. Numerous mucoadhesive agents such as carbopol, the chitosan family and starch microspheres have indicated improved permeation of a wide range of active ingredients by opening tight junctions as well as improving adhesion and extending residence time on the nasal mucosa [27].

The body has a natural defence system, glycosylated membrane proteins, located in the nasal mucosa and these act as multidrug resistance pumps across the nasal mucosa and BBB effecting transport elimination [3]. One strategy to by-pass this natural barrier would be to use nano-carriers to encapsulate and protect the active ingredients from biological and chemical breakdown an enhancing absorption rates. Much work is being conducted currently on nano-carriers as they have numerous potential benefits including the fact that some, but not all, are biodegradable, have good physiochemical stability and can be used with a range of small molecules and biologics

such as peptides, proteins and nucleic acids [2,6]. In addition, Nano-carriers are capable of sustained or controlled release of APIs. Although nano-carrier materials offer numerous potential advantages there are still remain many questions to address such as evaluating their interaction with brain tissues, long term safety and their elimination process [2]. There is growing interest in delivering biologics *via* the trans-nasal route and this will bring its own challenges. One potentially important advantage of trans nasal delivery is the opportunity to target high molecular weight treatments, such as neuropeptides and therapeutic cells to the CNS [22]. Even if the nose harbours a relatively low metabolic environment, drug metabolism in the nasal cavity could be considered a major barrier for trans-nasally delivered peptides, proteins or nucleic acids. Enzymes such as cytochrome-P450, endopeptidases, and exopeptidases present in the nasal respiratory and olfactory mucosa could generate local nasal enzymatic degradation and therefore potentially restrict drug absorption of such biologic compounds.

Quantifying uptake in the CNS

One challenge of trans-nasal drug delivery is to find suitable ways to measure transport to the CNS as well as effective and pertinent measures of clinical efficacy, bioavailability, safety etc. Conducting risky and invasive CNS clinical trials on healthy volunteers would be deemed ethically unacceptable. Brain imaging could be employed as an alternative to brain or CNS sampling to determine trans-nasal delivery and its effectiveness in clinical and preclinical trials. Less invasive alternative methods to determine trans-nasal delivery are also being considered, such as changes in brain metabolism, selective insulin impairment, changes in brain blood flow and neuromodulation although these kinds of techniques will be compound specific [6]. Brain imaging can be done by several techniques including PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging). MRI based methods can be used to look at arterial spin labelling which in turn can measure cerebral blood flow [28]. Brain metabolism measurement techniques have been used to assess changes in cerebral glucose metabolism using 18F fluorodeoxyglucose PET during trans nasal human clinical trials [19]. These alternative approaches will need to be vigorously explored so that the requisite evidence of trans-nasal delivery to the CNS in humans can be truly proven. These would be considered secondary or surrogate clinical measurements in humans and not 'direct' evidence of trans-nasal transport. Supporting evidence of trans-nasal delivery in humans has also been historically recorded whereby increased concentrations of vasopressin, melanocortin and insulin were reported in both CSF and the systemic circulation following intranasal administration in healthy subjects [7]. Imaging or tracking of movement of suitably labelled compounds from the nasal cavity to the human CNS could also bring strong supporting evidence for this route of administration.

Studies to elucidate aspects of both bioavailability and biodistribution following trans-nasal drug delivery often involves preclinical studies on animals with supplementary support being contributed from studies using human nasal casts models, imaging, theoretical modelling, and on a very much smaller scale, human CSF/CNS sampling and testing [29,30]. Nasal cast models are generated from cadavers or 3D CT (Computed Tomography) or MRI files from human subjects. They are mostly used for realistic *in vitro* nasal deposition work in order to ascertain where the formulation droplets or particles are delivered within the nasal cavity and can aid understanding as to whether the drug uptake would be likely *via* the systemic or CNS route [29]. Theoretical modelling can involve approaches such as CFD (Computational Fluid Dynamics) or mathematical modelling and can help elucidate various aspects of importance in trans nasal drug delivery such as deposition, influence of air flow or even mucociliary clearance [31]. More advanced modelling techniques are emerging which help in enhancing *in vivo* drug bioavailability which integrate numerous key elements such as carrier/mucosa interaction models, mucous layer penetration modelling

and PBPK models, so as to predict CNS/CSF delivery [26]. There are very few studies that detail human CSF sampling related to trans-nasal delivery as such studies are ethically challenging, invasive and carry high risks for the human volunteers. Methodology described for such studies report strict controls within neurology departments, IV (intravenous) controls (indwelling arterial forearm cannula) and CSF sample withdrawals (cisternal or lumber CSF drain tap) taken at intervals of 0, 5, 10, 20, 30, 40, 60, 120 and 180 mins with samples analysed by HPLC (High-Performance Liquid Chromatography) or radioimmunoassay [32]. One such study looked at both hydroxocobalamin (hydrophilic) and melatonin (lipophilic) nasal delivery on separate days. Results demonstrated that nasal administration of these compounds to humans lead to rapid rise in both blood and CSF levels, but they did not demonstrate direct transport from the nasal cavity to the CSF [32].

One of the most widely studied and reported drug in RCTs (Randomized Clinical Trials) is Insulin [18,19,33]. Nasal delivery of Insulin has the potential to improve memory, cognition, and even appetite control. Insulin has a relatively high molecular weight (~5.8K Da), and numerous studies have demonstrated that such peptide molecules can be absorbed through specialized pathways incorporating receptor-mediated transcytosis as well as passive diffusion. Human clinical studies have shown evidence of successful trans-nasal insulin delivery through the use of CSF measurements, cerebral blood flow measurements, MRI, functional disability scales, and cognitive tests in healthy, diabetic, and Alzheimer's disease populations. Other studies have also indicated that nasally delivered insulin can increases cerebral metabolism, influence brain-pancreas communications, can decrease endogenous glucose production, without affecting lipid content or triglyceride secretion.

Based on human clinical trial evidence, there are >80 clinical studies with evidence suggesting insulin and other substances can be delivered directly into the CNS *via* the trans-nasal pathways [6]. Some caution should be employed in interpreting this evidence as these human studies have limitations such as lack of randomization, blinding, or they are case studies only. Large scale RCTs are needed to fully confirm this mode of drug delivery with associated convincing evidence of both safety and efficacy.

Transitional challenges

One of the biggest remaining challenges for trans nasal drug delivery to treat CNS disorders remains the translation of preclinical animal work to effective human clinical trials. There is very little evidence related to human testing as compared to animal studies currently and dosing volumes, especially, are not aligned or relevant for translation to human dosing [27].

Both liquid and powder formulations have been investigated with regard to trans-nasal drug delivery to the CNS. Some studies have tried to bridge the transitional gap between animals and humans by using Non-Human Primate (NHP) models [34]. Studies looking at three distinct formulations/delivery modes (nasal liquid, nasal powder and intravenous) for sumatriptan delivery to the CNS/CSF following nasal delivery have tried to address this gap. The model used both liquid and powder nasal unit dose devices (UDS, Aptar Pharma) and samples were evaluated by collecting serial blood and Cerebrospinal Fluid (CSF) samples and performing quantifications for the model sumatriptan compound. The model revealed that the plasma concentration *vs*. time of the dry powder resulted in the highest Cmax while the liquid nasal spray with permeation enhancer resulted in the earliest Tmax. The dry powder formulation had the highest AUC (Area Under the Curve) dose and bioavailability, respectively. The concentration *vs*. time profile for the CSF again showed the dry powder to have the highest Cmax. However, in the CSF the dry powder had an earlier Tmax than the liquid nasal spray. This kind of work will be essential in closing the transitional gap in trans-nasal drug delivery in future and will eventually help in understanding what doses may be

needed in humans in order to achieve effective therapeutic levels in the brain [24]. Safety aspects related to areas such as mucosal and olfactory toxicity, brain neurotoxicity, excipients including nano-carriers and their corresponding degradation pathways and elimination are yet to be resolved and will be key components of any regulatory submissions [2,24].

Limitations related to qualitative and quantitative differences between animal and human anatomy, physiology and metabolism will have to be resolved. These key aspects can be resolved by current advances being made in the areas of pre-clinical PKPD modelling that will aid in predicting safety and effectiveness of clinical study design [6]. Advances have been made in developing predictive PKPD models, one example being remoxipride where IV and intra-nasal administration were successfully translated from rodents to humans whereby the PKPD relationship developed could adequately predict levels measured in humans [35]. Some of the key remaining challenges in the translational area are: Clearly identifying the absorption and transportation routes; integration of differences in animal *vs* human nasal characteristics including nasal metabolism and active transport as well as the impact of formulations on absorption profiles. Advances in brain *in vivo* imaging techniques will ease the transition from animal to NHP and human clinical studies [28]. The most sensitive techniques are hypothesized to be PET/MRI as they provide high tissue contrast and good spatial resolution [6].

CONCLUSION

Trans-nasal drug delivery can bypass the BBB, leading to a non-invasive, convenient, and patient-friendly administration route with precise drug targeting, and fewer systemic side effects. However, the clinical translation of intranasal optimized formulations still has a long way to go. Many aspects such as mucociliary clearance, enzymatic degradation of the drug, scaling-up and stability of the specialized formulations, residence, uptake, mucosal toxicity, accidental infection (viral or bacterial) and brain neurotoxicity are typical limitations associated with this drug delivery mode.

Numerous studies indicate that the main routes are the direct transport of drugs to the brain through neuronal pathways such as olfactory or trigeminal nerves and the indirect transport of drugs through the vasculature and lymphatic system. Nevertheless, the exact mechanisms of drug transport have not been fully elucidated yet, and it's not clear if one single mechanism or several mechanisms may participate in the transport process. As of today, nasal drug delivery to treat CNS disorders is a developing area with great potential but some key challenges still remain to overcome. The advantages of this route are numerous including; it could meet many unmet medical needs in the CNS field by by-passing the BBB and avoiding injections, gastrointestinal and renal API degradation; targeting the CNS directly and minimizing systemic side effects and easily (self) administered and low concentrations of actives could be effective. Trans-nasal drug delivery to treat CNS disorders may be on the verge of finally getting real proof in humans. The major challenging are difficulties associated with areas including; difficulty in targeting the olfactory zone (~10% area); the role of the trigeminal nerve is not established; one may need penetration enhancers or preservatives; there is a need to overcome mucociliary clearance and enzymatic degradation; there will be complicated and ethically challenging clinical studies to perform; unknown regulatory pathways with a possibility of toxicity or long term safety (olfactory) issues; there is a lack of bridging from animal to human clinical studies and we are still lacking large definitive human randomized clinical trial proof to truly establish the nasal route to effectively and safely treat CNS disorders.

Future clinical studies are also needed to address issues such as optimal drug doses, formulation, devices, safety and time windows for trans-nasal delivery therapies. Additionally, clinical investigators should continue to develop

pre-clinical translational pharmacokinetics-pharmacodynamics modelling to improve the safety and effectiveness of the human clinical studies they design.

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