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REVIEW

The promise and pitfalls of intranasally administering psychopharmacological agents for the treatment of psychiatric disorders

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Accumulating research demonstrates the potential of intranasal delivery of psychopharmacological agents to treat a range of psychiatric disorders and symptoms. It is believed that intranasal administration offers both direct and indirect pathways to deliver psychopharmacological agents to the central nervous system. This administration route provides a unique opportunity to repurpose both old drugs for new uses and improve currently approved drugs that are indicated for other administration routes. Despite this promise, however, the physiology of intranasal delivery and related assumptions behind the bypassing of the blood brain barrier is seldom considered in detail in clinical trials and translational research. In this review, we describe the current state of the art in intranasal psychopharmacological agent delivery research and current challenges using this administration route, and discuss important aspects of nose-to-brain delivery that may improve the efficacy of these new therapies in future research. We also highlight current gaps in the literature and suggest how research can directly examine the assumptions of nose-to-brain delivery of psychopharmacological agents in humans.

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INTRODUCTION

Despite the increasing prevalence[1] and cost[2] of psychiatric illness, the development of new therapeutic agents has slowed dramatically.[3,4] Few novel drugs have been brought to market in the past four decades,[5] and pharmaceutical companies are spending less on the development of psychiatric treatments.[3] Indeed, only 7% of developed psychiatric treatments reach the market.[6] The molecular targets of psychopharmacological drugs have remained unchanged for over five decades,[7] in spite of enormous efforts to base drug development on druggable targets discovered through research in disease pathophysiology. As the development of novel therapeutics seems to be more complicated than anticipated, researchers have been encouraged to investigate the improvement of existing pharmacological treatments,[8] either by repurposing old targets into new indications or improving the delivery and form of existing therapeutics to improve efficacy, compliance and adverse side effects. From a drug development perspective, using drugs already approved for other indications can significantly reduce the resources and time required before the product is in the market.[9]

The past decade has seen a renewed focus on the intranasal route to deliver drugs for psychiatric disorders and symptoms. Intranasal administration is believed to offer both direct and indirect pathways to deliver psychopharmacological agents to the central nervous system (CNS)[10] that is crucial for brain diseases. Direct nose-to-brain transport via olfactory and trigeminal nerve pathways[11–13] after intranasal deposition and absorption on the olfactory and respiratory epithelia[14] provides a noninvasive means of circumventing the blood brain barrier (BBB), a crucial obstacle for drug delivery to the CNS.[15] Moreover, intranasal administration of therapeutics targeted to the CNS provides substantial advantages in terms of treatment efficacy over other routes. In comparison with other administration routes, intranasal administration may offer ease of use, reduced systemic exposure, faster drug onset,[16] increased compliance[17] and greater bioavailability by avoiding first-pass metabolism.[18]

In spite of the advantages of intranasal administration, there are currently no approved indications for intranasal administration of any medication in psychiatry. A search of clinical trial registries, however, reveals a growing interest in delivering psychopharmacological agents intranasally to treat psychiatric illness (Figure 1). As shown, many of these trialed intranasal medications are already indicated for other conditions (for example, oxytocin (OT) for milk ejection, ketamine for sedation). In response to this recent interest, we proposed methods of drug form and administration that may improve the consistency of intranasal delivery for clinical trials.[17] Such recommendations were based on insufficient publically available data, highlighting a need for much greater knowledge to advance this important field.

Recent reviews have described nose-to-brain delivery pathways[19,20] and summarized the potential of intranasal administration of compounds to treat psychiatric illness.[21–23] However, research is yet to combine these approaches or provide a summary of results from registered clinical trials. Thus, the encompassing goal of this review is to integrate work from the fields of rhinology, physiology, neuroscience and clinical psychiatry. Evidence for intranasal delivery to the CNS to treat brain-based illnesses is presented, along with associated challenges with this

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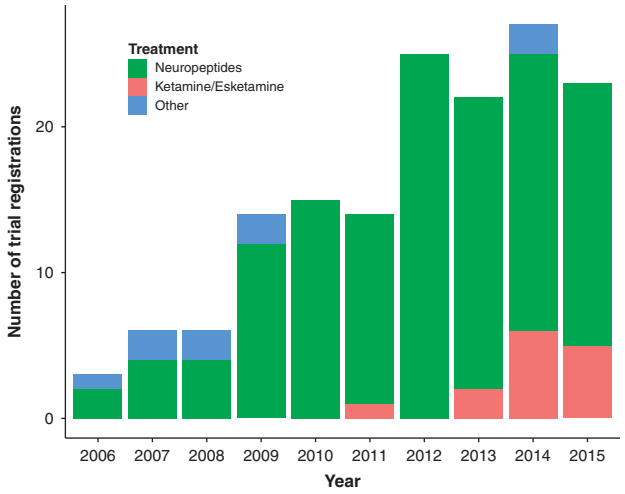

Figure 1. Registered trials of intranasal psychotropics. Derived from a search of the US National Institutes of Health (http://www.clinicaltrials.gov/), European Medicines agency (https://www.clinicaltrialsregister.eu/) and Australian National Health and Medical Research Council (http://www.anzctr.org.au/) clinical trial registries between 2006 and 2014. Neuropeptides, oxytocin, vasopressin and neuropeptide Y; Other, haloperidol, buprenorphine, droperidol and insulin. As the search was performed in August 2015, the number of registrations in 2015 is only representative up to this point in time.

administration route. A greater understanding of potential physiological barriers to efficacious delivery will improve future trials. Finally, we provide a summary of registered clinical trials of intranasal treatments in psychiatry and make suggestions for future research. This will help build a greater understanding of these drug delivery mechanisms that have considerable potential for improved treatment.

HOW DO INTRANASALLY ADMINISTERED THERAPEUTICS REACH AND INFLUENCE THE CNS?

Intranasal transport to the CNS is by no means a recent idea, with reports from more than a century ago indicating that the poliomyelitis virus uses this route to enter the CNS.[24,25] Following this work, a range of other viruses were also found to enter the CNS via the nasal cavity such as Yellow fever,[26] Herpes simplex encephalitis[27] and Hepatitis.[28] Since these early reports, over 40 different substances have been shown to travel from nose to brain in animals,[29] and nasal delivery is now used for vaccines.[30] These animal experiments, which have used various techniques including radiolabeling[31–33] and microscopy,[34] have revealed both direct and indirect routes to the CNS via the nasal cavity.

Direct CNS transport via the nasal cavity

There are two primary means that substances can be transported via olfactory and trigeminal nerve fibers (Figure 2); extracellular and intracellular transport. Intracellular transport from deposition on the olfactory epithelium occurs via substance absorption by olfactory sensory neurons,[12] otherwise known as endocytosis. Hydrophobic molecules with a lower molecular weight are more likely to use this mode of transport. These olfactory sensory neurons receptors, which number up to six million,[35] extend into the mucous layer of the olfactory epithelia of the upper posterior nasal cavity, thus accessing the external environment. Converging olfactory cell axons arrange into bundles, forming the fila olfactoria, that enter the skull through a gap in the ethmoid bone to the olfactory bulbs.[36,37] As the olfactory receptor cells are first-order neurons, there are no synapses between receptors cells in the olfactory epithelium and the brain.[38] Extracellular delivery, which favors hydrophilic molecules with larger molecular weight, via paracellular diffusion can also occur from both the olfactory and respiratory epithelia.[13] In the case of olfactory nerve fibers, extracellular delivery can take place within a direct, continuous channel from the olfactory epithelium to the olfactory bulb that is formed by ensheathing cells surrounding olfactory nerve fibers.[39] Extracellular transport may also be facilitated by rapidly regenerating olfactory sensory neurons.[13] Together, converging evidence suggests that intranasal administration can be used to deliver drugs to the human brain by bypassing the BBB that is a barrier to large, peripherally administered molecules entering the CNS.[15]

Animal tracer molecule and radiolabeling studies provide the most direct mammalian evidence of intranasally administered substances traveling down nerve fiber routes to the CNS. Early work used protein tracers, such as Albumin labeled with Evans blue (961 Da) and horseradish peroxidase (34 100 Da) to determine the route and destination of intranasally administered proteins. Kristensson and Olsson[40] administered both of these tracers intranasally in mice, reporting that the axons of olfactory sensory neurons took up both tracer proteins that traveled to the olfactory bulbs. Balin *et al.*[13] later replicated this finding using horseradish peroxidase in rodents and extended this observation to primates.

In addition, research suggests that the hormone insulin-like growth factor-I (IGF-I) travels to the brain via olfactory and trigeminal nerve pathways.[11] In this study, intranasal and intravenous (i.v.) administration of radiolabeled IGF-I ([^{125}I]-IGF-I) was compared, with similar peripheral concentration achieved with both administration methods. It is likely that similar concentration after intranasal delivery was achieved through systemic uptake via the highly vascularized nasal cavity.[41,42] Regardless of these similar levels, over 100 times more of the intranasally administered [^{125}I]-IGF-I was detected in the CNS after intranasal administration, strongly suggesting bypass of the BBB. Moreover, high concentrations were observed in both the trigeminal and olfactory nerve fibers, demonstrating the dual pathways of [^{125}I]-IGF-I delivery to the CNS. Both destinations of these nerve fibers, the olfactory bulb and the brainstem, also showed high concentrations of [^{125}I]-IGF-I after intranasal administration. Importantly, there was no increase in radioactivity in the cerebrospinal fluid (CSF) after [^{125}I]-IGF-I administration, suggesting direct delivery to the brain rather than delivery across the BBB. Intranasal administration of [^{3}H]-Dopamine also shows similar results, with increased central radioactivity after intranasal, but not intravenous delivery, in mice[43] and monkeys[44] CNS effects with intranasal but not i.v. administration indicates that intranasal administration offers improved delivery of drugs centrally. Importantly, a range of radiolabeled substances with relatively large molecular weights have been shown to have the highest levels in the trigeminal nerve after intranasal administration, followed by the olfactory bulb.[45]

Indirect CNS transport via the nasal cavity

Intranasally delivered molecules can also travel to the brain via indirect routes across the BBB (Figure 2). In particular, molecule deposition on the nasal mucosa facilitates uptake to the surrounding capillary networks that drain into systemic circulation.[42,46] The nasal mucosa offers faster uptake compared with other mucous membranes on the body, such as the buccal mucosa.[47] Thus, intranasal administration is another way of rapidly delivering the drug into systemic circulation,[16,48] avoiding the first-pass effects of the liver.[49] Once in systemic circulation, substances can cross into the CSF[50] and then across the BBB

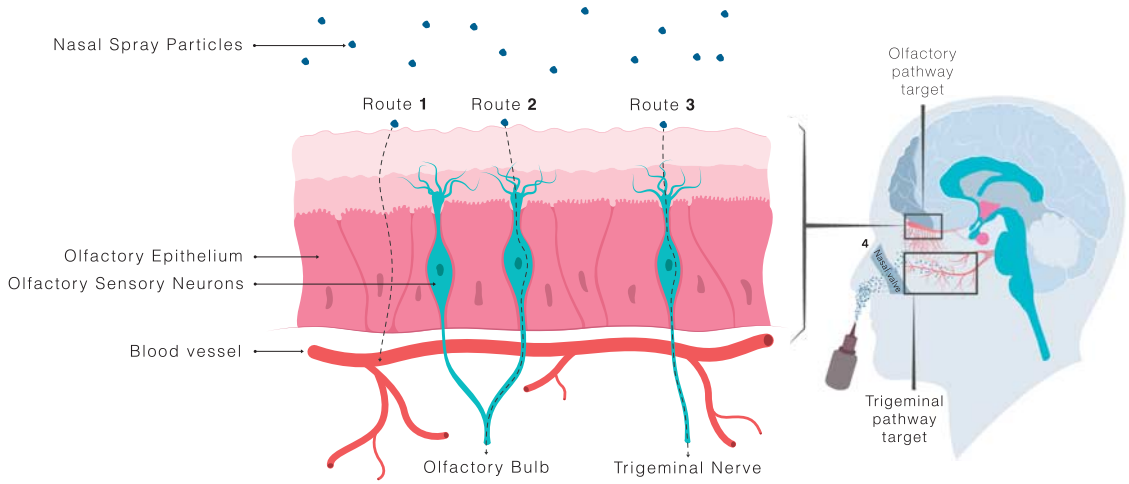

Figure 2. Delivery of intranasally administered agents to the central nervous system (CNS). Psychopharmacological agents delivered intranasally can reach central destinations indirectly via blood capillary absorption (1), and directly via olfactory (2) and trigeminal (3) nerve fiber routes. These direct transport target areas lie in the upper and posterior areas of the nasal cavity beyond the nasal valve (4). Reproduced from Quintana *et al.*[10] with permission.

depending on molecule characteristics. The lipophilicity of a drug is related to how easily they can cross the BBB via passive diffusion.[51,52] This association also extends to peptides, with lipophilicity reported to be the most important physicochemical factor contributing to BBB penetration.[53] Intranasal administration of radiolabeled OT in monkeys increases radiation levels in the choroid plexus but not the brain.[54,55] Although this could have been because of slow distribution of the compound in the brain, this is indicative of the intranasal compound filtering into the CSF (for which the choroid plexus is the source of filtration and production) via lymphatic drainage. Delivery to the CNS via exposure to oral mucosa (that is, buccal administration) has also been explored for a number of compounds in an effort to avoid first-pass metabolism;[56] however, this route appears to have poorer absorption in comparison with nasal mucosa.[16] Intranasally delivered therapeutics might also indirectly reach the brain via delivery to systemic circulation and then across the BBB, depending on the molecular weight. This type of delivery is thought to occur from blood capillary uptake in the nasal cavity.[42,57]

INTRANASAL DELIVERY CONSIDERATIONS

Side effects and compliance

Compared with oral and i.v. routes, intranasal administration is attractive for many reasons, including ease of use, rapid absorption and reduced systemic exposure and thus fewer side effects. Intranasal administration is noninvasive, and this is particularly appealing for pediatric and acute emergency psychiatric indications. Unsurprisingly, patients report a preference for intranasal insulin instead of i.v. delivery.[58] Recent trials of twice-daily intranasal OT administration for 6 weeks in adolescents and adults with early psychosis[59] and 8 weeks in adolescents with an autism spectrum disorder[60] also report that repeated nasal sprays have been well tolerated. Intranasal ketamine has also been reported to be well tolerated in patients with major depressive disorder[61] and chronic pain.[62] Noninvasiveness is also attractive for chronic administration if this can be used in place of intramuscular and i.v. injections, as this may improve patient comfort, increase compliance[17] and reduce the risk of needle-stick injuries.[63]

Improved drug onset time

Independent of nose-to-brain delivery, intranasal administration offers faster drug onset because of the circumvention of first-pass metabolism via the highly vascularized nasal cavity that is supplied by internal and external carotid arteries. The nasal mucosa is well suited for rapid absorption, with faster absorption than the large intestine and the buccal cavity.[16] For instance, Miller *et al.*[18] compared the pharmacokinetics of intranasal haloperidol with i.v. and intramuscular administration in an open-label study. In addition to increased bioavailability, intranasal haloperidol also reached peak levels quicker than intramuscular administration, which is the indicated administration route.

Challenges for intranasal delivery

There are four important and reciprocal intranasal CNS delivery challenges crucial for drug efficacy that are seldom considered in detail. The first is the delivery route of intranasally administered drugs. Substances delivered through the nose can putatively enter the CNS directly via trigeminal nerve fibers and olfactory nerve fibers and indirectly through systemic circulation.[11,46,64–67] The geneses of these direct olfactory and trigeminal nerve pathways, the olfactory and respiratory epithelia, are located in the difficult to reach upper posterior region of the nasal cavity, underscoring the need for direct intranasal delivery when directly targeting the CNS. A better understanding of these routes and destinations can help improve the delivery of psychopharmacological drugs to central targets. Second, physicochemical factors such as stability,[68] lipophilicity[69] and molecular weight[70] can also influence intranasal drug delivery. For instance, only molecules with smaller sizes (< 500 Da) and lower lipophilicity ($\log P < 3.5$) are purported to easily cross the BBB via systemic circulation.[69,70] However, there is animal evidence that larger molecules can travel via the trigeminal and olfactory pathways.[65] Third, nasal cavity physiology can also limit the accuracy and consistency of intranasal drug administration.[14] Fourth, similar and reliable spray deposition and bioavailability also needs to be achieved; however, there is a dearth of work on the variability of bioavailability for intranasal psychopharmacological agents in comparison with i.v. and oral dosage that is needed for the intranasal route to be a viable alternative to other routes. There seems to be less control over dosing with intranasal delivery of high molecular weight drugs in comparison with other routes (for example, i.v.) because of the

differing absorption rates and delivery destinations of the various nasal epithelia described above.[71] For instance, as the pharmaceutical target of oral medications is gastrointestinal metabolism, the patient only needs to swallow the medication to ensure uptake. Similarly, for i.v. and intramuscular administration, the goal is to simply introduce the medication into systemic circulation. However, given the different intranasal pathways described previously, it is more difficult to consistently target nose-to-brain areas in the nasal cavity.

Obstacles for consistent delivery and pharmacodynamic response

There are many impediments for intranasally administered spray to reach target delivery regions that are often not considered that may reduce the efficacy of intranasal treatments due to poor dosing control. The mucosa located in the nasal vestibule (the nasal cavity area easily accessible by a finger) has almost no absorption properties. Consequently, any drugs delivered here would probably not have any opportunity for direct transport to the CNS but perhaps a small chance of systemic absorption. The olfactory epithelium is difficult for drug molecules to reach, as it is located at the top of the nasal cavity even beyond the reach of inspiratory airflow (Figure 2). Moreover, this target region is quite small, $\sim$5–10 cm^2 in humans.[72,73] Other environmental factors, such as inhaled substance abuse, may also inhibit intranasal drug uptake because of nasal cavity damage.[74]

The nasal valve is the most narrow section of the nasal airway (Figure 2), yet it exerts some of the broadest influence on overall nasal cavity physiology.[75] Although there has been debate on the exact constituents of the nasal valve,[76] this structure is best conceptualized as the point of greatest inspiratory flow resistance,[77] containing both cartilaginous and bony valve segments. Owing to its location, the nasal valve presents a barrier between the nostril and target delivery regions in the upper posterior nasal cavity.[14,78] Despite the importance of the nasal valve in respiratory physiology being recognized for over a century,[79,80] it is seldom taken into account in intranasal administration studies. Nasal health also plays a role in response to intranasal drug administration due to congestion and blockage, modulating delivery effectiveness that can change from day to day.[81] Other factors that can limit spray deposition beyond the nasal valve that vary between individuals include septal deviation,[82] nasal polyps and mucosal inflammation[83]—that can be assessed via physical examination. Although nasal cavity dimensions appear to be stable from week to week in healthy individuals,[84] this has yet to be investigated in psychiatric populations. More research is needed to clarify how these factors may affect the dose delivered to the brain. Thus, it is recommended that the nasal cavity is assessed before initiating drug administration.

Because of the physiology of the nasal cavity, sniffing during administration may influence pharmacodynamic response to intranasal psychopharmacological agents. Indeed, the concept of sniffing is so synonymous with intranasal administration that many researchers have described hand-actuated spray administration as a sniff, instead of a spray. There are two important points with sniffing that may influence whether intranasally administered substances reaches the deep nose-to-brain targets in the nasal cavity. First, sniffing creates negative pressure within the nasal airway that constricts or even collapses the nasal valve. Second, sniffing draws the deposited spray particles along the floor of the nasal cavity that misses crucial nose-to-brain regions located on the upper wall of the cavity. Sniffing may also contribute to the bitter taste often reported by participants because of the liquid traveling past taste buds on the base of the tongue,[85] as a sniff draws the administered liquid down to the gastrointestinal tract. Together, the nasal cavity milieu and factors relating to nasal health, sniffing and spray deposition may modulate drug deposition on the olfactory and respiratory epithelia.[86]

Experimental methods to improve nasal spray delivery

Considering the related roles of nasal anatomy and physiology, experimental methods require careful design to improve deposition beyond the nasal valve, thus increasing the likelihood of treatment response. Indeed, recent data indicate that nasal valve dimensions are associated with intranasal OT treatment response.[84] We have previously made a number of recommendations to improve nasal spray administration studies, including physical examination of participants and standardization of nasal spray administration.[17] Following these guidelines may reduce the impact of variance in nasal anatomy and physiology.

Relatedly, various new technologies have been developed to overcome these nasal delivery challenges and purportedly improve nose-to-brain delivery of molecules. Drug absorption and transfer may be improved by enhancing spray formulations by using mucoadhesive gels[87] or nanocarriers with surface modification.[88] Administration devices have also been created to improve nose-to-brain drug transfer, such as a nasal atomizer,[89] a pressurized metered dose inhaler[90] and a Breath Powered nasal spray device.[14] Of these three approaches, only the latter has provided evidence of spray deposition in the upper posterior nose-to-brain targets in the nasal cavity via gamma scintigraphy.[14,91] Moreover, the Breath Powered device is also designed to expand the narrow nasal valve and prevent drip down to the gastrointestinal tract as the intraoral pressure created by the device elevates the soft palate, isolating the nasal cavity from the rest of the respiratory system and preventing any sniffs occurring during the spray administration. Together, these elements may improve response to psychopharmacological agents by facilitating greater delivery to the upper posterior nasal cavity. Early evidence supports nose-to-brain transfer of OT using this device.[84] However, further research is needed to demonstrate the superiority of intranasal administration over other administration methods.

CURRENT TREATMENTS

To summarize clinical research of intranasal psychopharmacological agents, a systematic search of three clinical trial registries (US National Institutes of Health, European Medicines agency and the Australian National Health and Medical Research Council) was performed using the following search terms: intranasal AND (oxytocin OR ketamine OR esketamine OR vasopressin OR insulin OR buprenorphine OR haloperidol OR neuropeptide Y OR antipsychotic). Published trial results in peer-reviewed journals are presented in Table 1 and summarized below.

Oxytocin

The neuropeptide OT has attracted the largest body of work investigating intranasal psychopharmacological agents. The i.v. OT is commonly used to initiate parturition;[92,93] however, this delivery method has only been used in one trial in psychiatric illness[94,95] and another in healthy adults.[84] Because of the vital role of OT in milk let-down,[96] intranasally administered OT is also indicated to assist mothers with breastfeeding in some countries.[97] OT is a relatively large (1008 Da) hydrophilic molecule that may limit its ability to cross the BBB.[15,98] Molecular weight holds a particular relevance given the inverse relationship between this and drug absorption in hydrophilic molecules.[99] However, direct transport via olfactory and trigeminal nerve fibers would still be viable transport routes to the CNS.[11] Although animal evidence suggests that OT may still cross the BBB in little amounts,[100] the use of intranasal administration circumvents the BBB, increasing CNS OT concentration in rodents[101] and humans.[102]

Table 1. Published and registered clinical trials of intranasal psychotropics

Study and registry ID	*Treatment*	*Administration regime*	*Sample size*	*Study population*	*Outcome*
Anagnostou *et al.*,[110] NCT00490802	Oxytocin	6 weeks, twice daily	19	ASD	No significant changes in the primary outcome measures after correcting for baseline differences but improvement in secondary social cognition measures
Caccioti-Saija *et al.*,[120] ACTRN 12612000190808	Oxytocin	6 weeks, twice daily	52	Early psychosis	No benefit of OT to improve social cognition compared to placebo. Increased use of OT was, however, associated with reductions in negative symptoms
Dadds *et al.*,[148] ACTRN 12609000513213	Oxytocin	4 days, once daily	38	ASD	OT did not improve social cognition
Davis *et al.*,[115] NCT0131227	Oxytocin	Single administration	23	Schizophrenia	OT improved performance in a higher-level social cognitive task
Eckstein *et al.*,[149] NCT02156661	Oxytocin	Single administration	62	Healthy adults	OT facilitated the extinction of conditioned fear
Einfeld *et al.*,[119] ANZCTR 12609000982213	Oxytocin	8 weeks, twice daily	30	Prader – Willi syndrome	OT had no benefit in target behaviors
Fang *et al.*,[112] NCT01856530	Oxytocin	Single administration	54	Social anxiety disorder	Attachment style moderated the effects of OT on social behaviors and cognition
Groppe *et al.*,[106] EudraCT 2009-015538-30	Oxytocin	Single administration	28	Healthy adults	OT significantly enhanced neural activation in response to cues signaling social reward or punishment
Guastella *et al.*,[150] ACTRN 12606000362594	Oxytocin	Single administration	69	Healthy adults	OT enhanced encoding of positive social information
Guastella *et al.*,[151] ACTRN 12607000256471	Oxytocin	Single administration four times	25	Social anxiety disorder	OT improved positive evaluations of appearance and speech performance as treatments progressed
Guastella *et al.*,[109] ACTRN 12609000368235	Oxytocin	Single administration	16	ASD	OT improved performance on a social cognition task
Guastella *et al.*,[60] ACTRN 12609000513213	Oxytocin	8 weeks, twice daily	50	ASD	Results did not suggest clinical efficacy. However, caregivers who believed their child had been assigned OT, regardless of drug assignment, reported greater benefit than those who believed their child received placebo
Guastella *et al.*,[113] ACTRN 12609000528257	Oxytocin	Single administration	21	Schizophrenia	OT improved performance on higher-order social cognition tasks
Lapidus *et al.*,[61] NCT01304147	Ketamine	Single administration	18	Major depression	Patients demonstrated improvement in depressive symptoms after ketamine treatment
Lee *et al.*,[114] NCT00884897	Oxytocin	3 weeks, twice daily	28	Schizophrenia	Symptomology did not improve. However, odor identification improved.
MacDonald *et al.*,[117] NCT01081249	Oxytocin	Single administration	17	Depression	OT increased anxiety but improved performance on a social cognition task
McIntyre *et al.*,[152] NCT00314314	Insulin	6 weeks, four times daily	43	Bipolar disorder	Insulin administration significantly improved a single measure of executive function
McRae-Clark *et al.*,[116] NCT01335789	Oxytocin	Single administration	16	Cannabis dependence	OT reduced craving and anxiety
Muin *et al.*,[118] EudraCT 2011-001310-34	Oxytocin	As needed	30	Women with sexual dysfunction	OT improved sexual function and depression symptoms
Quintana *et al.*,[84] NCT01983514	Oxytocin	Single administration	16	Healthy adults	Low-dose OT reduced anger ratings of ambiguous facial stimuli
Striepens *et al.*,[107] NCT01606462 NCT01607970	Oxytocin	Single administration	70	Healthy adults	OT inhibited amygdala response to negative stimuli and enhanced the impact of aversive social information

Abbreviations: ASD, autism spectrum disorders; OT, oxytocin.

After recognizing the role of OT in social behavior revealed by animal experiments,[103,104] research began to investigate the repurposing of this neuropeptide to treat psychiatric disorders characterized by poor social functioning. The first study to investigate OT in psychiatric illness used i.v. administration, revealing a decrease in repetitive autism spectrum disorder symptoms[95] and an increase in the retention of social cognition.[94] Subsequent research has evaluated intranasal OT in registered trials in healthy controls[84,105–107] and for the treatment of a number of psychiatric conditions including autism spectrum disorder[60,108–111] anxiety disorders,[112] psychosis spectrum disorders,[59,113–115] drug dependence,[116] depression,[117] sexual dysfunction[118] and Prader–Willi syndrome[119] (Table 1). The results of these trials have been mixed so far. For instance, some of these trials have reported that intranasal OT improves symptoms in autism spectrum disorder and psychosis spectrum disorders,[109,113,115] whereas others report no difference compared with placebo.[60,108,120] These varied results may point to differences in study populations,[121] placebo effects[60] and administration methods.[17,120]

A systematic review of 11 brain imaging studies suggests intranasal OT modulates neural activity in the temporal lobes and amygdala in response to social stimuli,[122] consistent with delivery to the brain. These neural responses have a functional impact as temporal lobe and amygdala circuitry underlie social cognition and behavior.[123] Changes in neural activity have been shown to correspond to behavior. For instance, reciprocation in a trust game corresponds with increased activity in the insula and right putamen after OT administration.[124] Moreover, changes in cerebral blood flow after intranasal oxytocin administration are also observed in neural networks underpinning social behavior and cognition[125] that are also rich in OT receptors.[126]

Although these results identify neural regions that facilitate intranasal OT response, these areas may not necessarily represent intranasal OT delivery destinations. Nevertheless, research in rodents indicates that intranasal OT administration increases OT concentration of microdialysates sampled from the amygdala and hippocampus.[101] Practical considerations render sampling of microdialysates from humans difficult. However, CSF samples can provide a broad measure of central OT concentrations. For instance, Striepens *et al.*[102] collected CSF and blood after intranasal OT administration. Analysis revealed a modest elevation of CSF OT concentration 75 min after intranasal administration. The observed 64% increase in CSF concentrations compared with placebo was much less than the 216–255% increase observed in plasma concentrations. Similar CSF concentration increases have also been observed after intranasal administration in macaques.[127,128] Unlike blood plasma, CSF OT levels are not related to brain tissue concentration 45 min after administration.[101] This is consistent with the delayed peak concentration of CSF OT observed in animals[129] and humans[102] compared with blood plasma pharmacokinetics. Nevertheless, although the mechanisms and underlying central OT delivery are poorly understood,[130] the behavioral and brain imaging data are consistent with central OT delivery.[131]

Ketamine

Ketamine is a high-affinity *N*-methyl-D-aspartate receptor agonist that has been used for some time for sedation, particularly in children.[132,133] Ketamine is well suited for intranasal administration considering its high lipophilicity and relatively low (238 Da) molecular weight.[134] Intranasally administered ketamine has demonstrated a bioavailability of 45–50% (ref. 135 and 136) that is greater than bioavailabilities after oral (20%), sublingual (30%) or suppository administration (30%).[135] Consequently, larger doses of intranasal ketamine are needed to achieve similar bioavailability to i.v. ketamine. In response to the unfolding role of the glutamate system in depression,[137] research has evaluated the potential of ketamine as a novel antidepressant. Intriguingly, intranasal ketamine has been shown to improve depressive symptoms.[61] In this crossover study, 18 patients with depression received 50 mg of intranasal ketamine or saline treatment. Compared with placebo, there was a significant improvement in depressive symptoms a day after intranasal ketamine treatment, with minimal adverse effects. Although research is yet to directly compare intranasal ketamine and i.v. ketamine administration, the results of this study were comparable to past research examining the impact of i.v. ketamine on depression symptoms.[138]

There are two important points relevant to intranasal administration that speak to this route's strengths and weaknesses: (1) blood concentration of ketamine was lower after intranasal administration compared with i.v.,[139,140] suggesting reduced peripheral exposure with comparable CNS response, and (2) a lower proportion of responders compared with i.v., highlighting the variable response to intranasal administration. Other work has shown similar pharmacokinetics between intranasal and i.v. administration.[135] In addition, a number of studies have been conducted with intranasal ketamine for nonpsychiatric indications. For instance, intranasal ketamine has been shown to stop familial hemiplegic migraine[141] and reduce chronic pain,[62] suggesting a wide variety of potential uses.

Antipsychotics

Although there are no reported results from registered trials of intranasal antipsychotics, these medications are of interest considering the need for treatments with rapid onset and reduced side effects. Antipsychotics can successfully pass the BBB after oral administration because of their high lipophilicity. However, intranasal administration may offer more rapid delivery to the CNS. Early research has investigated the intranasal administration of haloperidol.[18] The data from this study indicated that that intranasal absorption was twice as fast as intramuscular administration, which is particularly relevant in emergency and acute contexts. Moreover, intranasal administration in emergency contexts may also be safer as the risk of needle-stick injury is reduced.[63,142,143] Animal research has also shown more rapid uptake with intranasal administration of a risperidone mucoadhesive nanoemulsion intranasal administration in comparison with i.v. risperidone.[48] Most research has examined the efficacy of intranasal antipsychotics because of their fast-acting properties—especially relevant in emergency contexts—rather than any specific need to bypass the BBB considering their high lipophilicity. Moreover, direct delivery to the brain may require a lower dose that would reduce the peripheral concentration, thus reducing the impact of side effects. This has a large clinical potential, as current selection of antipsychotic agents in a clinical context are based primarily on the side-effect profile.[144]

FUTURE RESEARCH AND CONCLUSIONS

To comprehensively explore the potential of intranasal administration for repurposing old therapeutics,[8] this treatment route needs to be compared directly with i.v. or oral administration in psychiatric populations, in a double-dummy and double-blind manner, for safety and efficacy.[10,130] To date, one study has compared nasal delivery of a molecule (that is, ketamine) with other routes in three adults, but only in a preliminary open-label design.[135] In addition, levels of CSF OT have been compared after i.v. and intranasal OT administration in rhesus monkeys, revealing that the i.v. route did not increase CSF OT.[145] Finally, a recent trial in healthy adults compared intranasal and i.v. delivery of OT with placebo in a double-dummy, double-blind, crossover design.[84] Regardless of similar peripheral OT concentration after both delivery modalities, social cognitive effects were only observed after intranasal delivery consistent with nose-to-brain delivery

instead of systemically circulating molecules crossing into the CNS. Future work should make these comparisons in psychiatric populations, along with measures of the concentration level of the administered molecule to assess systemic exposure. Future research also needs to determine the optimal doses of intranasal administration in target populations.[10] Research in healthy controls has shown that at least for OT, a lower dose may be more efficacious than higher doses.[84]

Advances in intranasal administration may be accelerated by the standardization of administration methods that facilitate direct delivery to the brain. In this review, we have shown that reaching deposition targets in the nasal cavity require careful methods that encourage upper and posterior delivery beyond the nasal valve barrier. Moreover, stricter standardization will improve the reproducibility of research and may reduce variation in response to intranasal treatment. In addition, careful measurement of related physiology will help build a greater understanding of how these molecules exert their observed effects. This includes not only the brain, which is a growing research area with OT,[146] but also peripheral processes. Although brain is the target of psychiatric treatments, it is important to consider indirect effects via peripheral systems, particularly the cardiac autonomic system, that may contribute to the modulation of behavior, cognition and affect after intranasal treatments.[147]

Here we have highlighted the promise of intranasal delivery of psychopharmacological agents by providing a summary of current applications and its distinct advantages over other drug delivery routes. These benefits underscore the unique opportunity provided by intranasal administration to repurpose old therapeutics for new purposes. However, more work is required to better determine the underlying mechanisms of this delivery route to improve intranasal administration methods. An enhanced understanding of the above-mentioned features of nose-to-brain delivery may improve the efficacy and reliability of these novel therapies for psychiatric disorders in future research.

CONFLICT OF INTEREST

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