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

Daniel S. Quintana, Ph.D. [1*], Adam J. Guastella, Ph.D. [2], Lars T. Westlye, Ph.D. [1, 3], Ole A. Andreassen, MD., Ph.D. [1]

[1] NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, University of Oslo, and Oslo University Hospital, Oslo, Norway
[2] Brain and Mind Center, Central Clinical School, University of Sydney, Sydney, Australia
[3] Department of Psychology, University of Oslo, Oslo, Norway

*** Corresponding Author:** Daniel S. Quintana, NORMENT, KG Jebsen Centre for Psychosis Research, Building 49, Oslo University Hospital, Ullevål, Kirkeveien 166, PO Box 4956 Nydalen, N- 0424 Oslo, Norway, Ph: +47 97 56 88 85, fax: +47 23 02 73 33, email: daniel.quintana@medisin.uio.no

Keywords: intranasal administration, treatment, psychopharmacology, oxytocin, ketamine, antipsychotics

Word count:
Abstract: 166 words
Article: 4722 words
Figures: 2
Tables: 1

Abstract

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, 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.

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. Since 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 on the market [9].

The last 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], which 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 non-invasive means of circumventing the blood brain barrier (BBB), which is 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 to 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 medications 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 (e.g., oxytocin 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 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 central nervous system?

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 radiolabelling [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 fibres (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, which 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 fibres, extracellular delivery can take place within a direct, continuous channel from the olfactory epithelium to the olfactory bulb, which 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, which is a barrier to large, peripherally administered molecules entering the CNS [15].

Animal tracer molecule and radiolabelling studies provide the most direct mammalian evidence of intranasally administered substances travelling 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, which travelled to the olfactory bulbs. Balin and coworkers [13] later replicated this finding using horseradish peroxidase in rodents and extended this observation to primates.

Additionally, 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 (IV) administration of radiolabelled 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 fibres, 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 IV administration indicates that intranasal administration offers improved delivery of drugs centrally. Importantly, a range of radiolabelled 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 to 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] then across the BBB 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 radiolabelled oxytocin (OT) in monkeys increases radiation levels has in the choroid plexus, but not the brain [54, 55]. While this could have been due to slow distribution of the compound in the brain, this is indicative of the intranasal compound filtering into the CSF (for which the choroid plexus in the source of filtration and production) via lymphatic drainage. Delivery to the CNS via exposure to oral mucosa (i.e., 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 to 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 to oral and IV routes, intranasal administration is attractive for many reasons, which include ease of use, rapid absorption, and reduced systemic exposure and thus fewer side-effects. Intranasal administration is non-invasive, which is particularly appealing for pediatric and acute emergency psychiatric indications. Unsurprisingly, patients report a preference for intranasal insulin instead of IV

delivery [58]. Recent trials of twice-daily intranasal OT administration for six weeks in adolescents and adults with early psychosis [59] and eight 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]. Non-invasiveness is also attractive for chronic administration if this can be used in place of intramuscular and IV 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 due to the circumvention of first-pass metabolism via the highly vascularized nasal cavity, which 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 and colleagues [18] compared the pharmacokinetics of intranasal haloperidol with IV 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 fibres, 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 to IV and oral dosage, which is needed to 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 to other routes (e.g., IV) due to 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 GI metabolism, the patient only needs to swallow the medication to ensure uptake. Similarly, for IV 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, which 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 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 it is quite small, at approximately 5-10cm^2 in humans [72, 73]. Other environmental factors, such as inhaled substance abuse, may also inhibit intranasal drug uptake due to nasal cavity damage [74].

The nasal valve is the most narrow section of the nasal airway (Figure 2), yet exerts some of the broadest influence on overall nasal cavity physiology [75]. While 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 recognised for over a century [79, 80] its 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, which 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] – which can be assessed via physical examination. While 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 prior to initiating drug administration.

Due to 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. Firstly, sniffing creates negative pressure within the nasal airway that constricts or even collapses the nasal valve. Secondly, sniffing draws the deposited spray particles along the floor of the nasal cavity, which 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 due to the liquid travelling past taste buds on the base of the tongue [85] as a sniff draws the administered liquid down to the gastrointestinal (GI) 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, which includes 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 (U.S. 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. IV 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]. Due to 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, which 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 fibres would still be viable transport routes to the CNS [11]. While 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].

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 IV administration, revealing a decrease in repetitive autism spectrum disorder (ASD) 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 for a number of psychiatric conditions including ASD [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 ASD and psychosis spectrum disorders [109, 113, 115], whereas others report no difference compared to 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], which is 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], which 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 and coworkers [102] collected CSF and blood after intranasal OT administration. Analysis reveled a modest elevation of CSF OT concentration 75 minutes after intranasal administration. The observed 64% increase in CSF concentrations compared to 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 minutes after administration [101]. This is consistent with the delayed peak concentration of CSF OT observed animals [129] and humans [102] compared to blood plasma pharmacokinetics. Nevertheless, while the mechanisms and underlying central OT delivery are poorly understood [130], the behavioral and brain imaging data is consistent with central OT delivery. [131]

Ketamine

Ketamine is a high-affinity *N*-methyl-D-aspartate receptor agonist, which 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% [135, 136], which 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 IV 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 to placebo, there was a significant improvement in depressive symptoms a day after intranasal ketamine treatment, with minimal adverse effects. While research is yet to directly compare intranasal ketamine vs. IV ketamine administration, the results of this study were comparable to past research examining the impact of IV ketamine on depression symptoms [138].

There are two important points relevant to intranasal administration which speak to this route's strengths and weaknesses; (i) blood concentration of ketamine was lower after intranasal administration compared to IV [139, 140], suggesting reduced peripheral exposure with comparable CNS response, and (ii) a lower proportion of responders compared to IV, which highlights the variable response to intranasal administration. Other work has shown similar pharmacokinetics between intranasal and IV [135]. In addition, a number of studies have been conducted with intranasal ketamine for non-psychiatric 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 due to their high lipophilicity. However, intranasal administration may offer more rapid delivery to the CNS. Early research has

investigated the intranasal administration of haloperidol [18]. While bioavailability was similar to intramuscular and IV administration, the data indicated intranasal absorption was twice as fast, 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 IV risperidone [48]. Most research has examined the efficacy of intranasal antipsychotics due to its fast-acting properties – especially relevant in emergency contexts – rather than any specific need to bypass the BBB considering its high lipophilicity. Moreover, direct delivery to the brain may require a lower dose, which would reduce the peripheral concentration and 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 IV or oral administration in psychiatric populations, in a double-dummy and double-blind fashion, for safety and efficacy [10, 130]. To date, one study has compared nasal delivery of a molecule (i.e., ketamine) with other routes in three adults, but only in a preliminary open-label design [135]. Additionally, levels of CSF OT have been compared after IV and intranasal OT administration in rhesus monkeys, revealing that the IV route did not increase CSF OT [145]. Finally, a recent trial in healthy adults

compared intranasal and IV delivery of OT compared to 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. Additionally, careful measurement of related physiology will help build a greater understanding of how these molecules exert their observed effects. This includes the brain, which is a growing research area with OT [146], but also peripheral processes. Although the brain is target of psychiatric treatments it is important to consider indirect effects via peripheral systems, particularly the cardiac autonomic system, which 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 statement: Daniel S. Quintana, Lars T. Westlye, and Ole A. Andreassen are investigators in a project studying oxytocin's effects after intranasal delivery partnered by OptiNose AS (Oslo, Norway) and funded by a BIA grant (219483) from the Research Council of Norway. Adam J. Guastella is an investigator in a project investigating oxytocin's effects partnered by OptiNose AS and funded by a Linkage Grant from the Australian Research Council. The funders and partner had no influence in the ideas contained in the manuscript and no role in the writing of the manuscript.

References

1. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS *et al.* Grand challenges in global mental health. *Nature* 2011; **475**(7354)**:** 27-30.

2. Bloom DE, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S *et al.* The global economic burden of noncommunicable diseases: Program on the Global Demography of Aging; 2012.

3. Miller G. Is pharma running out of brainy ideas. *Science* 2010; **329**(5991)**:** 502-504.

4. Abbott A. Novartis to shut brain research facility. *Nature* 2011; **480**(7376)**:** 161-162.

5. Insel T, Voon V, Nye J, Brown VJ, Altevogt B, Bullmore E *et al.* Innovative solutions to novel drug development in mental health. *Neurosci Biobehav Rev* 2013; **37**(10)**:** 2438-2444.

6. Pangalos MN, Schechter LE, Hurko O. Drug development for CNS disorders: strategies for balancing risk and reducing attrition. *Nature Reviews Drug Discovery* 2007; **6**(7)**:** 521-532.

7. Hyman SE. Revolution stalled. *Sci Transl Med* 2012; **4**(155)**:** 155cm111-155cm111.

8. Chong CR, Sullivan DJ. New uses for old drugs. *Nature* 2007; **448**(7154)**:** 645-646.

9. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003; **22**(2)**:** 151-185.

10. Quintana DS, Alvares GA, Hickie IB, Guastella AJ. Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model. *Neurosci Biobehav Rev* 2015; **49:** 182-192.

11. Thorne RG, Pronk GJ, Padmanabhan V, Frey I, W H. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal

pathways following intranasal administration. *Neuroscience* 2004; **127**(2)**:** 481-496.

12. Thorne RG, Emory CR, Ala TA, Frey II WH. Quantitative analysis of the olfactory pathway for drug delivery to the brain. *Brain Res* 1995; **692**(1)**:** 278-282.

13. Balin BJ, Broadwell RD, Salcman M, El-Kalliny M. Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, and squirrel monkey. *J Comp Neurol* 1986; **251**(2)**:** 260-280.

14. Djupesland PG, Skretting A, Winderen M, Holand T. Breath Actuated Device Improves Delivery to Target Sites Beyond the Nasal Valve. *The Laryngoscope* 2006; **116**(3)**:** 466-472.

15. Pardridge WM. CNS drug design based on principles of blood-brain barrier transport. *J Neurochem* 1998; **70**(5)**:** 1781-1792.

16. Yamamoto A, Iseki T, Ochi-Sugiyama M, Okada N, Fujita T, Muranishi S. Absorption of water-soluble compounds with different molecular weights and

[Asu< sup> 1.7</sup>]-eel calcitonin from various mucosal administration sites. *J Control Release* 2001; **76**(3)**:** 363-374.

17. Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, Disinger HM *et al.* Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology* 2013; **38**(5)**:** 612-625.

18. Miller JL, Ashford JW, Archer SM, Rudy AC, Wermeling DP. Comparison of intranasal administration of haloperidol with intravenous and intramuscular administration: a pilot pharmacokinetic study. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2008; **28**(7)**:** 875-882.

19. Meredith ME, Salameh TS, Banks WA. Intranasal Delivery of Proteins and Peptides in the Treatment of Neurodegenerative Diseases. *The AAPS journal* 2015**:** 1-8.

20. Miyake MM, Bleier BS. The blood-brain barrier and nasal drug delivery to the central nervous system. *American journal of rhinology & allergy* 2015; **29**(2)**:** 124-127.

21. Kaminsky BM, Bostwick JR, Guthrie SK. Alternate Routes of Administration of Antidepressant and Antipsychotic Medications. *Ann Pharmacother* 2015**:** 1060028015583893.

22. Jiang Y, Li Y, Liu X. Intranasal delivery: circumventing the iron curtain to treat neurological disorders. *Expert Opin Drug Deliv* 2015; (ahead-of-print)**:** 1-9.

23. Andrade C. Intranasal drug delivery in neuropsychiatry: focus on intranasal ketamine for refractory depression. *The Journal of clinical psychiatry* 2015; **76**(5)**:** e628-631.

24. Flexner S. The mode of infection in epidemic poliomyelitis. *Journal of the American Medical Association* 1912; **59**(15)**:** 1371-1372.

25. Clark PF, Fraser FR, Amoss HL. The relation to the blood of the virus of epidemic poliomyelitis. *The Journal of experimental medicine* 1914; **19**(3)**:** 223-233.

26. Findlay G, Clarke L. Infection with neurotropic yellow fever virus following instillation into the nares and conjunctival sac. *The Journal of Pathology and Bacteriology* 1935; **40**(1)**:** 55-64.

27. Slavin HB, Berry GP. Studies on herpetic infection in mice: II. The pathways of invasion of the central nervous system after intranasal instillation of virus in suckling mice. *The Journal of experimental medicine* 1943; **78**(4)**:** 315.

28. Perlman S, Barnett E, Jacobsen G. Mouse hepatitis virus and herpes simplex virus move along different CNS pathways. *Coronaviruses*. Springer1993, pp 313-318.

29. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? *J Drug Target* 1998; **5**(6)**:** 415-441.

30. Sharma S, Mukkur T, Benson HA, Chen Y. Pharmaceutical aspects of intranasal delivery of vaccines using particulate systems. *J Pharm Sci* 2009; **98**(3)**:** 812-843.

31. Henriksson J, Tallkvist J, Tjälve H. Uptake of nickel into the brain via olfactory neurons in rats. *Toxicol Lett* 1997; **91**(2)**:** 153-162.

32. Chen X, Fawcett J, Rahman Y, Ala T, Frey I. Delivery of nerve growth factor to the brain via the olfactory pathway. *J Alzheimers Dis* 1998; **1**(1)**:** 35-44.

33. Ross T, Martinez P, Renner J, Thorne R, Hanson L, Frey II W. Intranasal administration of interferon beta bypasses the blood–brain barrier to target the central nervous system and cervical lymph nodes: a non-invasive treatment strategy for multiple sclerosis. *J Neuroimmunol* 2004; **151**(1)**:** 66-77.

34. Shipley M. Transport of molecules from nose to brain: transneuronal anterograde and retrograde labeling in the rat olfactory system by wheat germ agglutinin-horseradish peroxidase applied to the nasal epithelium. *Brain Res Bull* 1985; **15**(2)**:** 129-142.

35. Doty RL, Bromley SM. Chapter 7 - Cranial Nerve I: Olfactory Nerve. In: Goetz CG (ed). *Textbook of Clinical Neurology (Third Edition)*. W.B. Saunders: Philadelphia, 2007, pp 99-112.

36. Roth G. Sensory Systems: The Coupling between Brain and Environment. *The Long Evolution of Brains and Minds*. Springer2013, pp 165-192.

37. Kalogjera L, Dzepina D. Management of smell dysfunction. *Curr Allergy Asthma Rep* 2012; **12**(2)**:** 154-162.

38. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol* 2008; **63**(1)**:** 7-15.

39. Li Y, Field PM, Raisman G. Olfactory ensheathing cells and olfactory nerve fibroblasts maintain continuous open channels for regrowth of olfactory nerve fibres. *Glia* 2005; **52**(3)**:** 245-251.

40. Kristensson K, Olsson Y. Uptake of exogenous proteins in mouse olfactory cells. *Acta Neuropathol (Berl)* 1971; **19**(2)**:** 145-154.

41. Dhuria SV, Hanson LR, Frey II WH. Intranasal delivery to the central nervous system: Mechanisms and experimental considerations. *J Pharm Sci* 2009**:** n/a-n/a.

42. Wolburg H, Wolburg-Buchholz K, Sam H, Horvát S, Deli MA, Mack AF. Epithelial and endothelial barriers in the olfactory region of the nasal cavity of the rat. *Histochem Cell Biol* 2008; **130**(1)**:** 127-140.

43. Dahlin M, Bergman U, Jansson B, Björk E, Brittebo E. Transfer of dopamine in the olfactory pathway following nasal administration in mice. *Pharm Res* 2000; **17**(6)**:** 737-742.

44. Anand Kumar T, David G, Kumar K, Umberkoman B, Krishnamoorthy M. A new approach to fertility regulation by interfering with neuroendocrine pathways. *Neuroendocrine Regulation of Fertility, Editor: Anand Kumar, TC; Karger, Basel* 1976**:** 314-322.

45. Alcalá-Barraza SR, Lee MS, Hanson LR, McDonald AA, Frey WH, McLoon LK. Intranasal delivery of neurotrophic factors BDNF, CNTF, EPO, and NT-4 to the CNS. *J Drug Target* 2010; **18**(3)**:** 179-190.

46. Chow HHS, Chen Z, Matsuura GT. Direct transport of cocaine from the nasal cavity to the brain following intranasal cocaine administration in rats. *J Pharm Sci* 1999; **88**(8)**:** 754-758.

47. Anderson M, Tambe P, Sammons H, Mulla H, Cole R, Choonara I. Pharmacokinetics of buccal and intranasal lorazepam in healthy adult volunteers. *Eur J Clin Pharmacol* 2012; **68**(2)**:** 155-159.

48. Kumar M, Misra A, Babbar A, Mishra A, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. *Int J Pharm* 2008; **358**(1)**:** 285-291.

49. Grant I, Nimmo W, Clements J. Pharmacokinetics and analgesic effects of im and oral ketamine. *Br J Anaesth* 1981; **53**(8)**:** 805-810.

50. Wallum B, Taborsky Jr G, Porte Jr D, Figlewicz D, Jacobson L, Beard J *et al.* Cerebrospinal Fluid Insulin Levels Increase During Intravenous Insulin Infusions in Man. *The Journal of Clinical Endocrinology & Metabolism* 1987; **64**(1)**:** 190-194.

51. Foster K, Roberts M. Experimental methods for studying drug uptake in the head and brain. *Curr Drug Metab* 2000; **1**(4)**:** 333-356.

52. Hansch C, Clayton JM. Lipophilic character and biological activity of drugs II: The parabolic case. *J Pharm Sci* 1973; **62**(1)**:** 1-21.

53. Banks WA, Kastin AJ. Peptides and the blood-brain barrier: lipophilicity as a predictor of permeability. *Brain Res Bull* 1985; **15**(3)**:** 287-292.

54. Smith AL, Freeman SM, Voll RJ, Young LJ, Goodman MM. Investigation of an F-18 oxytocin receptor selective ligand via PET imaging. *Bioorg Med Chem Lett* 2013; **23**(19)**:** 5415-5420.

55. Smith AL, Freeman SM, Voll RJ, Young LJ, Goodman MM. Carbon-11 N-methyl alkylation of L-368,899 and in vivo PET imaging investigations for neural oxytocin receptors. *Bioorg Med Chem Lett* 2013; **23**(3)**:** 902-906.

56. Bartlett JA, van der Voort Maarschalk K. Understanding the oral mucosal absorption and resulting clinical pharmacokinetics of asenapine. *AAPS PharmSciTech* 2012; **13**(4)**:** 1110-1115.

57. DeSesso JM. The relevance to humans of animal models for inhalation studies of cancer in the nose and upper airways. *Quality Assurance (San Diego, Calif)* 1993; **2**(3)**:** 213-231.

58. Frauman AG, Cooper ME, Parsons BJ, Jerums G, Louis WJ. Long-term use of intranasal insulin in insulin-dependent diabetic patients. *Diabetes Care* 1987; **10**(5)**:** 573-578.

59. Cacciotti-Saija C, Langdon R, Ward PB, Hickie IB, Scott E, Naismith SL *et al.* A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. *Schizophr Bull* 2015; **41**(2)**:** 483-493.

60. Guastella AJ, Gray KM, Rinehart NJ, Alvares GA, Tonge BJ, Hickie IB *et al.* The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: a randomized controlled trial. *Journal of Child Psychology and Psychiatry* 2015; **56**(4)**:** 444-452.

61. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L *et al.* A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder. *Biol Psychiatry* 2014; **76**(12)**:** 970-976.

62. Carr DB, Goudas LC, Denman WT, Brookoff D, Staats PS, Brennen L *et al.* Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain* 2004; **108**(1)**:** 17-27.

63. Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T *et al.* Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. *The Journal of emergency medicine* 2005; **29**(3)**:** 265-271.

64. Jansson B, Björk E. Visualization of In Vivo Olfactory Uptake and Transfer Using Fluorescein Dextran. *J Drug Target* 2002; **10**(5)**:** 379-386.

65. Baker H, Spencer RF. Transneuronal transport of peroxidase-conjugated wheat germ agglutinin (WGA-HRP) from the olfactory epithelium to the brain of the adult rat. *Exp Brain Res* 1986; **63**(3)**:** 461-473.

66. Nonaka N, Farr SA, Kageyama H, Shioda S, Banks WA. Delivery of Galanin-Like Peptide to the Brain: Targeting with Intranasal Delivery and Cyclodextrins. *J Pharmacol Exp Ther* 2008; **325**(2)**:** 513-519.

67. Danielyan L, Schäfer R, von Ameln-Mayerhofer A, Bernhard F, Verleysdonk S, Buadze M *et al.* Therapeutic Efficacy of Intranasally Delivered Mesenchymal Stem Cells in a Rat Model of Parkinson Disease. *Rejuvenation Res* 2011; **14**(1)**:** 3-16.

68. Lai M, Topp E. Solid-state chemical stability of proteins and peptides. *J Pharm Sci* 1999; **88**(5)**:** 489-500.

69. Waterhouse RN. Determination of lipophilicity and its use as a predictor of blood–brain barrier penetration of molecular imaging agents. *Mol Imaging Biol* 2003; **5**(6)**:** 376-389.

70. Pardridge WM. Drug and gene delivery to the brain: the vascular route. *Neuron* 2002; **36**(4)**:** 555-558.

71. Adjei A, Sundberg D, Miller J, Chun A. Bioavailability of leuprolide acetate following nasal and inhalation delivery to rats and healthy humans. *Pharm Res* 1992; **9**(2)**:** 244-249.

72. Proctor DF. The upper airways. I. Nasal physiology and defense of the lungs. *The American review of respiratory disease* 1977; **115**(1)**:** 97-129.

73. Weiss L. *Cell and Tissue Biology: A Textbook of Histology*. Lippincott Williams & Wilkins1988.

74. Schweitzer VG. Osteolytic sinusitis and pneumomediastinum: deceptive otolaryngologic complications of cocaine abuse. *The Laryngoscope* 1986; **96**(2)**:** 206-210.

75. Jones N. The nose and paranasal sinuses physiology and anatomy. *Advanced drug delivery reviews* 2001; **51**(1)**:** 5-19.

76. Wexler DB, Davidson TM. The nasal valve: a review of the anatomy, imaging, and physiology. *Am J Rhinol* 2004; **18**(3)**:** 143-150.

77. Bridger G, Proctor D. Maximum nasal inspiratory flow and nasal resistance. *The Annals of otology, rhinology, and laryngology* 1970; **79**(3)**:** 481-488.

78. Aggarwal R, Cardozo A, Homer J. The assessment of topical nasal drug distribution. *Clinical Otolaryngology & Allied Sciences* 2004; **29**(3)**:** 201-205.

79. Uddströmer M. On the Physiology of the Nasal Respiration. *Acta Otolaryngol (Stockh)* 1940; **28**(s42)**:** 15-59.

80. Mink PJ. Le nez comme voie respiratoire. *Presse Oto-Laryng Belge* 1903; **2**(421).

81. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. *Advanced drug delivery reviews* 1998; **29**(1)**:** 3-12.

82. Merkus P, Ebbens FA, Muller B, Fokkens WJ. Influence of anatomy and head position on intranasal drug deposition. *European Archives of Oto-Rhino-Laryngology and Head & Neck* 2006; **263**(9)**:** 827-832.

83. Djupesland PG, Mahmoud RA, Messina JC. Accessing the brain: the nose may know the way. *Journal of Cerebral Blood Flow & Metabolism* 2013; **33**(5)**:** 793-794.

84. Quintana DS, Westlye LT, Rustan ØG, Tesli N, Poppy CL, Smevik H *et al.* Low dose oxytocin delivered intranasally with Breath Powered device affects social-cognitive behavior: a randomized 4-way crossover trial with nasal cavity dimension assessment. *Translational Psychiatry* 2015; **5**(e601)**:** 1-9.

85. Sato K, Endo S, Tomita H. Sensitivity of three loci on the tongue and soft palate to four basic tastes in smokers and non-smokers. *Acta Otolaryngol (Stockh)* 2002; **122**(4)**:** 74-82.

86. Homer J, Raine C. An endoscopic photographic comparison of nasal drug delivery by aqueous spray. *Clinical Otolaryngology & Allied Sciences* 1998; **23**(6)**:** 560-563.

87. Perez AP, Mundiña-Weilenmann C, Romero EL, Morilla MJ. Increased brain radioactivity by intranasal 32P-labeled siRNA dendriplexes within in situ-forming mucoadhesive gels. *Int J Nanomedicine* 2012; **7:** 1373.

88. Kanazawa T. Brain delivery of small interfering ribonucleic acid and drugs through intranasal administration with nano-sized polymer micelles. *Medical devices (Auckland, NZ)* 2015; **8:** 57.

89. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A *et al.* Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch Neurol* 2012; **69**(1)**:** 29-38.

90. Hoekman JD, Ho RJ. Enhanced analgesic responses after preferential delivery of morphine and fentanyl to the olfactory epithelium in rats. *Anesth Analg* 2011; **113**(3)**:** 641.

91. Djupesland PG, Skretting A. Nasal Deposition and Clearance in Man: Comparison of a Bidirectional Powder Device and a Traditional Liquid Spray Pump. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2012; **25**(5)**:** 280-289.

92. Blanks AM, Thornton S. The role of oxytocin in parturition. *BJOG: An International Journal of Obstetrics & Gynaecology* 2003; **110**(s20)**:** 46-51.

93. Fuchs A-R, Fuchs F, Husslein P, Soloff MS, Fernstrom MJ. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. *Science* 1982; **215**(4538)**:** 1396-1398.

94. Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L *et al.* Oxytocin Increases Retention of Social Cognition in Autism. *Biol Psychiatry* 2007; **61**(4)**:** 498-503.

95. Hollander E, Novotny S, Hanratty M, Yaffe R, DeCaria CM, Aronowitz BR *et al.* Oxytocin Infusion Reduces Repetitive Behaviors in Adults with Autistic and Asperger's Disorders. *Neuropsychopharmacology* 2003; **28**(1)**:** 193-198.

96. Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, Matzuk MM. Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. *Proceedings of the National Academy of Sciences* 1996; **93**(21)**:** 11699-11704.

97. Ruis H, Rolland R, Doesburg W, Broeders G, Corbey R. Oxytocin enhances onset of lactation among mothers delivering prematurely. *BMJ* 1981; **283**(6287)**:** 340-342.

98. McEwen BB. Brain–fluid barriers: relevance for theoretical controversies regarding vasopressin and oxytocin memory research. *Adv Pharmacol* 2004; **50:** 531-592.

99. Fisher A, Brown K, Davis S, Parr G, Smith D. The effect of molecular size on the nasal absorption of water-soluble compounds in the albino rat. *J Pharm Pharmacol* 1987; **39**(5)**:** 357-362.

100. Neumann ID, Landgraf R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci* 2012; **35**(11)**:** 649-659.

101. Neumann ID, Maloumby R, Beiderbeck DI, Lukas M, Landgraf R. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. *Psychoneuroendocrinology* 2013; **38**(10)**:** 1985-1993.

102. Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W *et al.* Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. *Scientific reports* 2013; **3**.

103. Nelson E, Panksepp J. Oxytocin mediates acquisition of maternally associated odor preferences in preweanling rat pups. *Behav Neurosci* 1996; **110**(3)**:** 583.

104. Popik P, Vetulani J, Van Ree JM. Low doses of oxytocin facilitate social recognition in rats. *Psychopharmacology (Berl)* 1992; **106**(1)**:** 71-74.

105. Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE *et al.* Oxytocin facilitates the extinction of conditioned fear in humans. *Biol Psychiatry* 2014.

106. Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Gründer G *et al.* Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. *Biol Psychiatry* 2013; **74**(3)**:** 172-179.

107. Striepens N, Scheele D, Kendrick KM, Becker B, Schäfer L, Schwalba K *et al.* Oxytocin facilitates protective responses to aversive social stimuli in males. *Proceedings of the National Academy of Sciences* 2012; **109**(44)**:** 18144-18149.

108. Dadds MR, MacDonald E, Cauchi A, Williams K, Levy F, Brennan J. Nasal oxytocin for social deficits in childhood autism: A randomized controlled trial. *J Autism Dev Disord* 2014; **44**(3)**:** 521-531.

109. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ *et al.* Intranasal Oxytocin Improves Emotion Recognition for Youth with Autism Spectrum Disorders. *Biol Psychiatry* 2010; **67**(7)**:** 692-694.

110. Anagnostou E, Soorya L, Chaplin W, Bartz J, Halpern D, Wasserman S *et al.* Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: a randomized controlled trial. *Molecular autism* 2012; **3**(1)**:** 16.

111. Andari E, Duhamel J-R, Zalla T, Herbrecht E, Leboyer M, Sirigu A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *PNAS* 2010; **107**(9)**:** 4389-4394.

112. Fang A, Hoge EA, Heinrichs M, Hofmann SG. Attachment Style Moderates the Effects of Oxytocin on Social Behaviors and Cognitions During Social Rejection Applying a Research Domain Criteria Framework to Social Anxiety. *Clinical Psychological Science* 2014**:** 2167702614527948.

113. Guastella AJ, Ward PB, Hickie IB, Shahrestani S, Hodge MAR, Scott EM *et al.* A single dose of oxytocin nasal spray improves higher-order social cognition in schizophrenia. *Schizophr Res* 2015.

114. Lee MR, Wehring HJ, McMahon RP, Linthicum J, Cascella N, Liu F *et al.* Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: results from a randomized double blind placebo controlled pilot study. *Schizophr Res* 2013; **145**(1)**:** 110-115.

115. Davis MC, Lee J, Horan WP, Clarke AD, McGee MR, Green MF *et al.* Effects of single dose intranasal oxytocin on social cognition in schizophrenia. *Schizophr Res* 2013; **147**(2)**:** 393-397.

116. McRae-Clark AL, Baker NL, Moran-Santa Maria M, Brady KT. Effect of oxytocin on craving and stress response in marijuana-dependent individuals: a pilot study. *Psychopharmacology (Berl)* 2013; **228**(4)**:** 623-631.

117. MacDonald K, MacDonald TM, Brüne M, Lamb K, Wilson MP, Golshan S *et al.* Oxytocin and psychotherapy: a pilot study of its physiological, behavioral and subjective effects in males with depression. *Psychoneuroendocrinology* 2013; **38**(12)**:** 2831-2843.

118. Muin DA, Wolzt M, Marculescu R, Rezaei SS, Salama M, Fuchs C *et al.* Effect of long-term intranasal oxytocin on sexual dysfunction in premenopausal and postmenopausal women: a randomized trial. *Fertil Steril* 2015.

119. Einfeld SL, Smith E, McGregor IS, Steinbeck K, Taffe J, Rice LJ *et al.* A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome. *American Journal of Medical Genetics Part A* 2014; **164**(9)**:** 2232-2239.

120. Cacciotti-Saija C, Langdon R, Ward PB, Hickie IB, Scott EM, Naismith SL *et al.* A Double-blind Randomized Controlled Trial of Oxytocin Nasal Spray and

Social Cognition Training for Young People With Early Psychosis. *Schizophr Bull* 2014**:** sbu094.

121. Bakermans-Kranenburg M, Van Ijzendoorn M. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Translational psychiatry* 2013; **3**(5)**:** e258.

122. Wigton R, Jocham Radua PA, Averbeck B, Meyer-Lindenberg A, McGuire P, Shergill SS *et al.* Neurophysiological effects of acute oxytocin administration: systematic review and meta-analysis of placebo-controlled imaging studies. *Journal of psychiatry & neuroscience: JPN* 2015; **40**(1)**:** E1.

123. Adolphs R. The neurobiology of social cognition. *Curr Opin Neurobiol* 2001; **11**(2)**:** 231-239.

124. Rilling JK, DeMarco AC, Hackett PD, Thompson R, Ditzen B, Patel R *et al.* Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. *Psychoneuroendocrinology* 2012; **37**(4)**:** 447-461.

125. Paloyelis Y, Doyle OM, Zelaya FO, Maltezos S, Williams SC, Fotopoulou A *et al.* A Spatiotemporal Profile of In Vivo Cerebral Blood Flow Changes Following Intranasal Oxytocin in Humans. *Biol Psychiatry* 2014.

126. Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA. Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience* 2013; **253**(C)**:** 155-164.

127. Dal Monte O, Noble PL, Turchi J, Cummins A, Averbeck BB. CSF and Blood Oxytocin Concentration Changes following Intranasal Delivery in Macaque. *PLoS ONE* 2014; **9**(8)**:** e103677.

128. Chang SW, Barter JW, Ebitz RB, Watson KK, Platt ML. Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (Macaca mulatta). *Proceedings of the National Academy of Sciences* 2012; **109**(3)**:** 959-964.

129. Kendrick K, Keverne E, Hinton M, Goode J. Cerebrospinal fluid and plasma concentrations of oxytocin and vasopressin during parturition and vaginocervical stimulation in the sheep. *Brain Res Bull* 1991; **26**(5)**:** 803-807.

130. Leng G, Ludwig M. Intranasal oxytocin: myths and delusions. *Biol Psychiatry* 2015.

131. Quintana DS, Woolley JD. Intranasal oxytocin mechanisms can be better understood but its effects on social cognition and behavior are not to be sniffed at. *Biol Psychiatry* in press.

132. Goldman RD. Intranasal drug delivery for children with acute illness. *Current Drug Therapy* 2006; **1**(1)**:** 127-130.

133. Howes M. Ketamine for paediatric sedation/analgesia in the emergency department. *Emergency medicine journal: EMJ* 2004; **21**(3)**:** 275.

134. Barceloux DG. Ketamine. *Medical Toxicology of Drug Abuse*. John Wiley & Sons, Inc.2012, pp 110-119.

135. Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N *et al.* Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* 2003; **24**(1)**:** 37-43.

136. Malinovsky J, Servin F, Cozian A, Lepage J, Pinaud M. Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; **77**(2)**:** 203-207.

137. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 2012; **62**(1)**:** 63-77.

138. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM *et al.* Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* 2014.

139. Horacek J, Brunovsky M, Novak T, Tislerova B, Palenicek T, Bubenikova-Valesova V *et al.* Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect. *Psychol Med* 2010; **40**(09)**:** 1443-1451.

140. Zarate Jr CA, Brutsche N, Laje G, Luckenbaugh DA, Venkata SLV, Ramamoorthy A *et al.* Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* 2012; **72**(4)**:** 331-338.

141. Kaube H, Herzog J, Käufer T, Dichgans M, Diener H. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. *Neurology* 2000; **55**(1)**:** 139-141.

142. Wolfe T, Barton E. Nasal drug delivery in EMS: reducing needlestick risk. *JEMS: a journal of emergency medical services* 2003; **28**(12)**:** 52-63.

143. Barton ED, Ramos J, Colwell C, Benson J, Baily J, Dunn W. Intranasal administration of naloxone by paramedics. *Prehosp Emerg Care* 2002; **6**(1)**:** 54-58.

144. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F *et al.* Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet* 2013; **382**(9896)**:** 951-962.

145. Modi ME, Connor-Stroud F, Landgraf R, Young LJ, Parr LA. Aerosolized oxytocin increases cerebrospinal fluid oxytocin in rhesus macaques. *Psychoneuroendocrinology* 2014; **45:** 49-57.

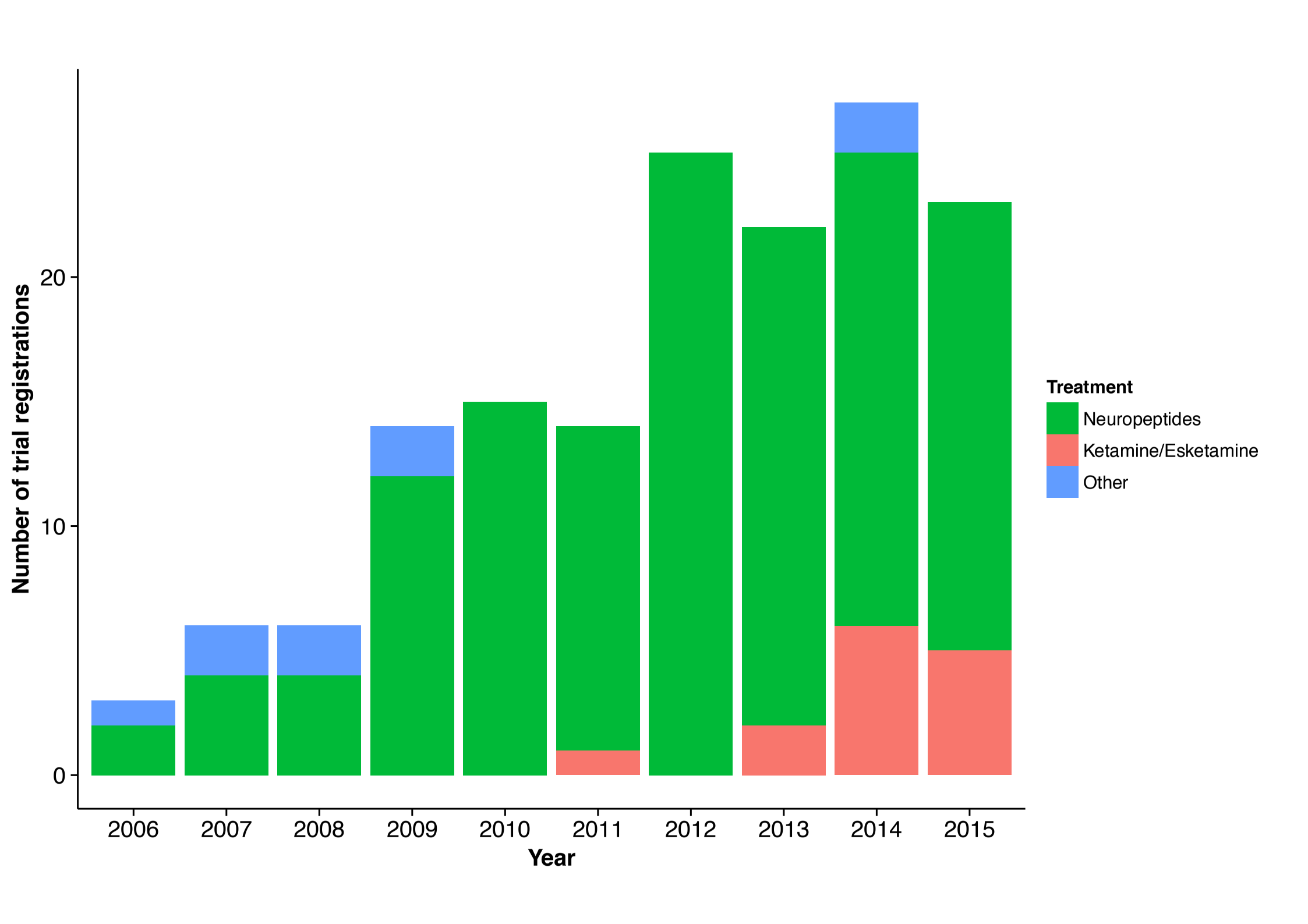
146. Bethlehem RAI, van Honk J, Auyeung B, Baron-Cohen S. Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. *Psychoneuroendocrinology* 2013; **38**(7)**:** 962-974.

147. Quintana DS, Kemp AH, Alvares GA, Guastella AJ. A role for autonomic cardiac control in the effects of oxytocin on social behavior and psychiatric illness. *Front Neurosci* 2013; **7**.

Figure captions

Figure 1 caption. Registered trials of intranasal psychotropics. Derived from a search of the U.S. 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.

Figure 2 caption. Delivery of intranasally administered agents to the CNS. Psychopharmacological agents delivered intranasally can reach central destinations indirectly via blood capillary absorption (1), and directly via olfactory (2) and trigeminal (3) nerve fibre 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.


Number of trial registrations
0
10
20
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Year
Treatment
Neuropeptides
Ketamine/Esketamine
Other

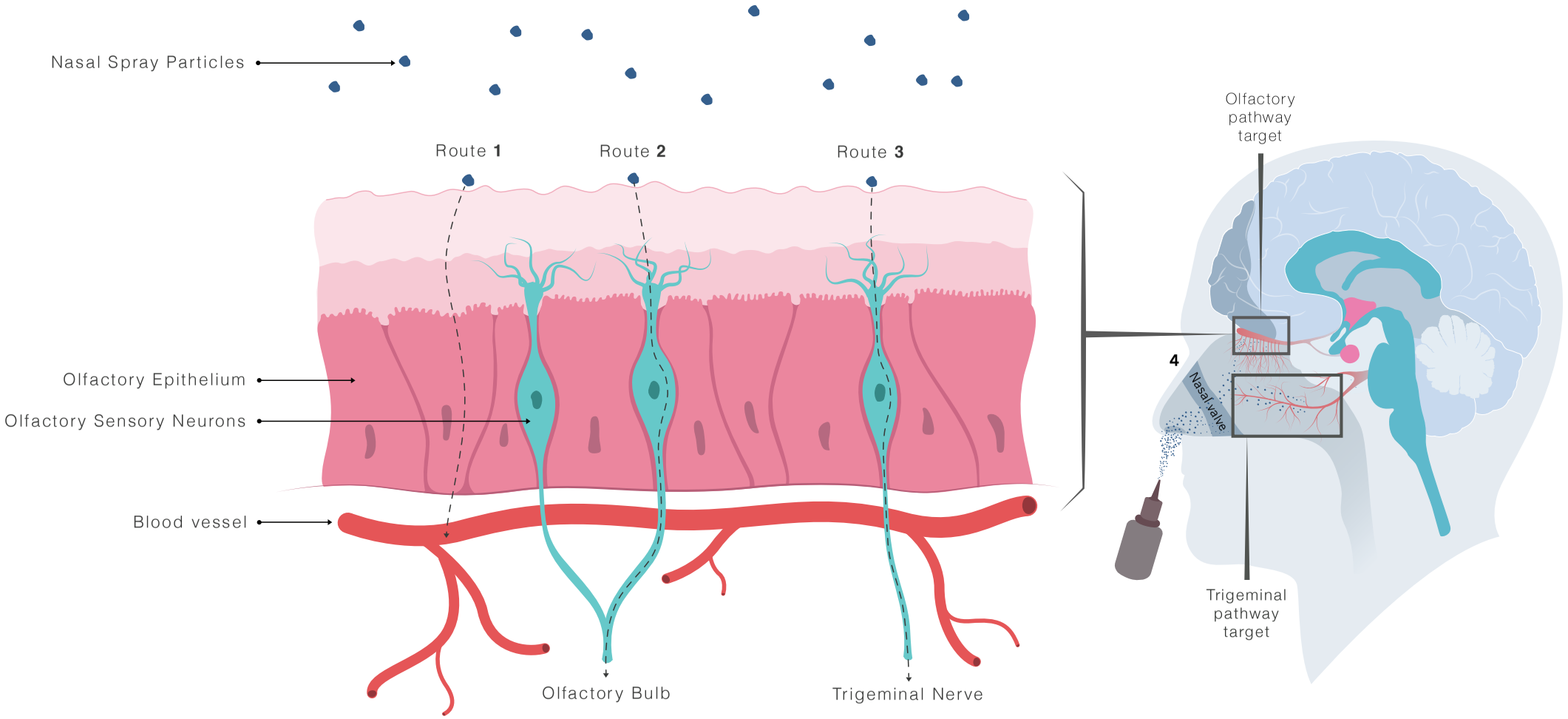

Nasal Spray Particles
Route 1
Route 2
Route 3
Olfactory Epithelium
Olfactory Sensory Neurons
Blood vessel
Olfactory Bulb
Trigeminal Nerve
Olfactory pathway target
4
Nasal valve
Trigeminal pathway target

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., (2012) - 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., (2014) - 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., (2013) - ACTRN 12609000513213	Oxytocin	4 days once-daily	38	ASD	Oxytocin did not improve social cognition
Davis et al., (2013) - NCT0131227	Oxytocin	Single administration	23	Schizophrenia	Oxytocin improved performanc in a higher-level social cognitive task
Eckstien et al., (2014) - NCT02156661	Oxytocin	Single administration	62	Healthy adults	Oxytocin facilitated the extinction of conditioned fear
Einfeld et al., (2014) - ANZCTR 12609000982213	Oxytocin	8 weeks twice-daily	30	Prader-Willi syndrome	OT had no benefit in target behaviors
Fang et al., (2014) - NCT01856530	Oxytocin	Single administration	54	Social anxiety disorder	Attachment style moderated the effects of oxytocin on social behaviors and cognitions
Groppe et al. (2013) - 2009-015538-30	Oxytocin	Single administration	28	Healthy adults	Oxytocin significantly enhanced neural activation in response to cues signaling social reward or punishment
Guastella et al., (2010) - ACTRN 12609000368235	Oxytocin	Single administration	16	ASD	Oxytocin improved performance on a social cognition task
Guastella et al., (2015) - 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., (2015) - ACTRN 12609000528257	Oxytocin	Single administration	21	Schizophrenia	OT improves performance on higher-order social cognition tasks
Lapidus et al., (2015) - NCT01304147	Ketamine	Single administration	18	Major depression	Patients demonstrated improvement in depressive symptoms after ketamine treatment
Lee al., (2013) - NCT00884897	Oxytocin	3 weeks twice-daily	28	Schizophrenia	Symptomology did not improve. However, odour identification improved.
MacDonald et al., (2013) - NCT01081249	Oxytocin	Single administration	17	Depression	Oxytocin increased anxiety and non-verbal during a therapy session but improved performance on a social cognition task

McIntyre et al., (2012) - NCT00314314	Insulin	6 weeks four times daily	43	Bipolar disorder	Insulin administration significantly improved a single measure of executive function
McRae-Clark et al., (2013) - NCT01335789	Oxytocin	Single administration	16	Cannabis dependence	Oxytocin reduced craving and anxiety
Muin et al, (2015) - 2011-001310-34	Oxytocin	As needed	30	Women with sexual dysfunction	Oxytocin improved sexual function and depression symptoms
Quintana et al., (2015) - NCT01983514	Oxytocin	Single administration	16	Healthy adults	Low-dose oxytocin reduced anger ratings of ambiguous facial stimuli
Striepens et al., (2012) - NCT01606462 NCT01607970	Oxytocin	Single administration	70	Healthy adults	OT inhibited amygdala response to negative stimuli and enhanced the impact of aversive social information

Note: ASD = autism spectrum disorders