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Antidepressants and nose-to-brain delivery: drivers, restraints, opportunities and challenges

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Why is nose-to-brain delivery considered to be a strategy that directly allows the access of antidepressants to the brain? In which circumstances can the intranasal pathway be applicable? Are there any requirements to follow? What triggers the antidepressant market? Which constraints are imposed during discovery programs? What opportunities can arise and what is their current status of development? Are they already translated into clinical practice? Which challenges are expected from recent development strategies? This review aims at providing a critical appraisal of nose-to-brain delivery of antidepressants, framed within a comprehensive analysis of drivers, restraints, opportunities and challenges.

Introduction

Depression is a common mental disorder, affecting >300 million people of all ages globally, and this number is rising at a fast pace. Depression is the leading cause of disability worldwide, which is a significant contributor to the overall global burden of the disease [1]. These considerations reveal that depression has a major, international, clinical, public health and economic impact. The growth in the number of young adults affected by some form of depression is as high as 8%. These numbers become even more worrisome when, despite the dozens of drugs with proven antidepressant efficacy available in clinical practice, more than 50% of depressed patients do not respond to the first-line pharmacological treatment and 30% fail to achieve remission following several pharmacological interventions [2].

Why is this the case? One of the major reasons behind treatment failure relies on the existence of the blood-brain barrier (BBB), which remains a bottleneck in brain drug development. Recent approaches regarding transport across the BBB have revealed an improved prediction of the response to antidepressant therapy [3–5]. In fact, a determining characteristic for the effectiveness of central drugs is their ability to cross this biological barrier. The BBB is complex and includes endothelial cerebral cells that express efflux transmembrane proteins, particularly those from the ATB-binding cassette family, which mainly include P-glycoprotein (P-gp) and breast-cancer-resistant protein (BCRP) [6]. These transporters restrict the access of lipophilic compounds to the brain and they have been found to be overexpressed in the brain of refractory patients [7]. Antidepressant drugs have been recently identified as substrates, inhibitors and inductors of P-gp, although their interaction with BCRP remains currently unknown [8]. Because an effective therapy with antidepressant drugs depends on drug concentrations at the biophase (brain), conventional oral and parenteral therapies become limited because they require the drug to cross the BBB. In the light of the above facts, there is an emergent need for new effective dosage forms that controllably release the drug directly into the brain, decreasing their systemic exposure, adverse effects, drug–drug interactions (DDIs) and, ultimately, circumvent pharmacoresistance issues.

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The intranasal route has been highlighted as a potential strategy, because it provides direct nose-to-brain drug transport, offering enhanced targeting ability and reduced systemic side-effects. But is this pathway indiscriminately applicable to all chemical entities or are there any requirements to follow? Note that low-solubility, labile, low-permeant and/or less potent drugs can require additional efforts to develop formulations other than the conventional solutions or suspensions. In this context, nanosystems and triggered formulations are considered to be promising approaches, because they can afford protection of the drugs from chemical and/or metabolic degradation, enhancing drug solubility, prolonging drug nasal residence time, delivering the drug exactly where it should be absorbed or facilitating the transport through biological membranes. In turn, other strategies involving the use of peptides and stem cells arise as potential novel modalities for the treatment of depression. What is their current status of development? Are they available to translate to clinical practice?

The main purpose of the present review is to understand the drivers, restraints, opportunities and challenges in promoting efficient brain targeting when applying intranasal drug administration for the treatment of depression and prevention of pharmacoresistance. For that, a systematic bibliographic search and analysis was performed, critically addressing study designs, formulation properties and reporting quality.

Search methodology

The articles considered for data analysis were obtained via searches in the Web of Science™ database, using the following terms: depression AND (intranasal OR nasal OR nose to brain) AND (nanoemulsion$ OR microemulsion$ OR emulsion$ OR nanostructured OR nanoparticle$ OR nanosystem$ OR liposome$). The date of the last search was 5th February 2019 and no publication filters were applied. The clinicaltrialsregister.eu and clinicaltrials.gov databases were also accessed to retrieve potential molecules and/or treatments under clinical assessment underlying 'depression AND intranasal' keywords.

Overview of intranasal delivery of antidepressants

Drivers and restraints

The rising number of patients, in the awareness level of the disease state and clinical needs, pose a steady opportunity for growth of existing therapies and open new avenues in the antidepressant field [9]. The poor outcomes in terms of efficacy and safety profiles of current antidepressants have fueled the development of surrogate drugs and delivery systems that act faster, better and stronger, with fewer side effects [10–13]. Moreover, the increased number of antidepressant patent expirations and the consequent pipeline weakening are expected to hamper the market growth. Developing intranasal drug products could pave the way to boost the introduction of 'super generics', by providing the possibility of a faster onset and enhanced efficacy in the relief of depressive symptoms, thus driving toward the introduction of new antidepressant therapies and market growth [8,14].

Opportunities

Intranasal drug delivery has been pinpointed as a reliable and direct method to bypass the BBB [15,16]. Indeed, owing to the unique direct connection between the brain and the nasal cavity mediated by the olfactory epithelium, intranasal administration is the only route through which the brain is in connection with the outside environment [17]. This particular neural connection has sparked attention for the delivery of a wide variety of drug molecules, ranging from small to large molecules, such as nucleotides, peptides, proteins and even stem cells, to the brain. In parallel, formulation approaches have been developed to prevent enzymatic degradation and enhance the pharmacological effects, without systemic absorption and toxicity in the major peripheral organs (Fig. 1) [18,19].

Formulation approaches

Among the available options [20,21], nanosystems are labeled as an excellent vehicle for direct transport of drug to the brain, because they afford protection of the drug from biological and chemical hazards and prevent the efflux of the drug, thus increasing drug brain concentration. Several types of nanocarriers with a size range 10–300 nm (nanogels, lipid nanoparticles, polymeric nanoparticles, liposomes, nanoemulsions and microemulsions) have been designed for the delivery of a wide variety of antidepressant drugs across the olfactory pathway to the brain. Supported by numerous animal studies, the intranasally delivered nanosystems have been shown to enhance brain uptake, improve pharmacological activity or therapeutic efficacy and reduce the side-effects of drugs, when compared with conventional drug

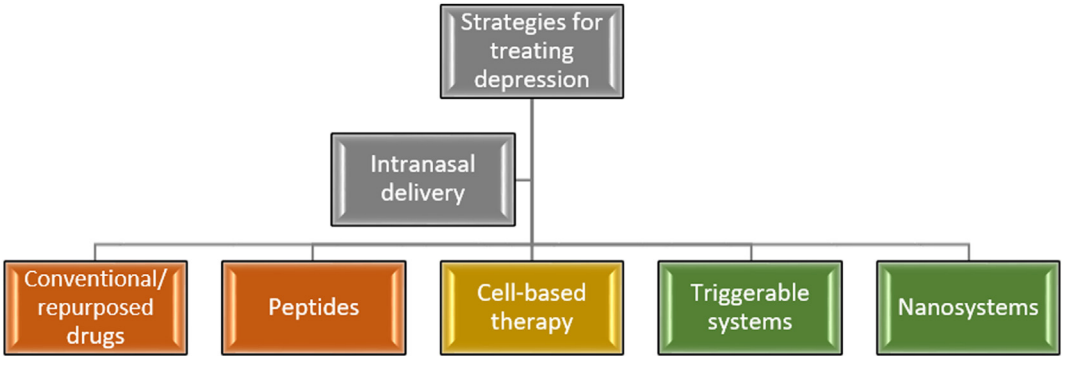

FIGURE 1

New strategies involving the intranasal route for the treatment of depression. These can be directed either to the active pharmaceutical ingredient (drug repositioning or macromolecules e.g., peptides), formulation approaches encompassing triggerable or nanosystems or, alternatively, advanced therapies (e.g., cellular approaches).

delivery systems [18]. This can be ascribed to their ability to prevent extracellular transport by P-gp efflux proteins. In addition to this, their small size potentially enables nanoparticles to be transported transcellularly through olfactory neurons to the brain via the various endocytic pathways of sustentacular or neuronal cells in the olfactory membrane, as previously described. They can also prevent mucosa drying by trapping moisture [17]. An in-depth analysis of literature (Table 1) indicates that the choice of the intranasal route (when compared with the intravenous and/or oral routes) and the simultaneous use of carrier nanosystems (when compared with intranasal simple solutions) are advantageous for brain delivery of a large set of antidepressant drugs or classes. Moreover, this is consistent with the assumptions of providing a faster onset of action along with a prolonged duration of action.

Despite the scarce data pool that precludes a robust and statistically significant analysis, a favorable trend is denoted when the drug is encapsulated in nanoparticles, irrespective of their nature. Among the most represented nanosystem classes, polymeric nanoparticles, in particular chitosan-based nanosystems, are one of the most frequently explored. Note that chitosan has the peculiarity to serve a dual purpose: to provide the matrix for drug encapsulation and, simultaneously, to improve nasal residence time owing to its intrinsic mucoadhesive properties. In turn, lipid nanocarriers comprising solid lipid-based matrix systems (e.g., nanostructured lipid carriers), emulsion derivatives, such as nanoemulsions and microemulsions, or vesicular systems, such as liposomes, have also been explored for intranasal delivery of several antidepressants.

Taking venlafaxine hydrochloride (VLF) as an example, this dual-action antidepressant drug that belongs to the serotonin–norepinephrine reuptake inhibitor (SNRI) pharmacotherapeutic group has been encapsulated in parallel using either nanostructured lipid carriers [22], chitosan [23] or alginate–chitosan nanoparticles [24]. VLF is a widely used antidepressant, being commercially available as immediate and controlled-release tablets and capsules. Nevertheless, VLF is a hydrophilic compound that presents a limited BBB permeability, short half-life (4–5 h), extensive hepatic effect and low oral bioavailability (45%), thus requiring a frequent administration to ensure a blood level for therapeutic concentration. Moreover, oral therapy provides a slow onset of action, and clinical side-effects like tachycardia, increased blood pressure, fatigue, headache, dizziness, sexual dysfunction and dry mouth [25]. Therefore, the nasal route arises as an appealing alternative to VLF oral administration. Note, however, that reported research has disclosed some necessary prerequisites for intranasal delivery nanosystems for the nose-to-brain transportation of drugs. In particular, they should be designed to provide a longer residence time in the nasal cavity to overcome nasal mucociliary clearance and facilitate rapid transport of the drug across the nasal mucosa.

Chitosan-based nanoparticles claim both attributes. As observed by Haque *et al.*, alginate–chitosan or chitosan nanoparticles significantly enhanced the VLF concentration in the brain, having promoted a drug-targeting efficiency (DTE%) of VLF NP_{IN} nearly twofold higher than the corresponding VLF solution (Table 1). Such findings were ascribed to the summation of several factors, including the increase in absorption time caused by the reduction of nasal mucociliary clearance, enhanced permeation across nasal respiratory mucosa, modulation of P-gp efflux transporters present on the BBB and contribution of paracellular transport through tight junction modulation between the cells [23,24]. The encapsulation of VLF was also studied by Dange *et al.*, who developed a jellified nanostructured lipid carrier (NLC) formulation [22]. This alternative nanosystem led to a faster onset of action and prolonged VLF release, also revealing significant improved locomotor activity and swimming time in depressed rats when compared with the corresponding VLF solution. The increase in the viscosity along with the colloidal nature of the system (150 nm, PI of 0.271) could be major reasons for the enhanced performance. These findings are also in concurrence with previous reported results for VLF chitosan/VLF alginate-chitosan NPs formulations, supporting the use of mucoadhesive nanoformulations to favour nose to brain uptake of drugs.

Interestingly, other chitosan chemical modifications, such as the covalent attachment of thiol groups to the primary amino groups of chitosan, have been explored aiming at increasing mucoadhesiveness and permeation properties, along with *in situ* gelling features, without compromising drug biodegradability. Supported by this strategy, Singh *et al.* developed thiolated chitosan nanoparticles (TCSNs) for the intranasal delivery of selegiline hydrochloride, a MAOi that, like other antidepressant drugs, exhibits a very significant first-pass metabolism and low bioavailability, together with severe side-effects and high potential to develop DDIs [26,27]. In a global appraisal, TCSNs were found to provide more-significant outcomes than the corresponding unmodified chitosan nanoparticles, leading to a reduction in oxidative stress along with a restoration of the activity of the mitochondrial complex. Pertaining to behavioral parameters, a drastic reduction in the duration of immobility was observed, evidencing that TCNs successfully restored the impaired locomotor activity and the normal sucrose consumption [27].

Similar patterns have also been reported for other nanocarrier formulations, with alternative antidepressant drugs. This is the case for the use of NLCs as solid-lipid matrix-based systems for the encapsulation of duloxetine. Duloxetine is considered as the first SNRI that ensures rapid and sustained efficacy in the treatment of emotional and physical symptoms of depression. Concomitantly, it promises treatment of physical symptoms that accompany major depressive disorder (MDD), such as aches, pains and gastrointestinal disturbance [16]. Duloxetine is marketed under tablet and capsule dosage forms. Nevertheless, it is acid-labile at gastric pH and, after oral administration, it undergoes hepatic first-pass metabolism, presenting a systemic bioavailability of only 50% [28]. Additionally, oral administration of the drug also causes side-effects, including nausea, dry mouth, headache, dizziness, orthostatic hypotension and fatigue. NLCs are a second and smarter generation of lipid nanoparticles, consisting of a matrix composed of a blend of solid and liquid (oils) lipids, stabilized by an aqueous surfactant solution. This characteristic leads to the creation of a less ordered structure, thus providing them with an increased drug-loading capacity and improved physical stability [29]. Their lipophilic and biocompatible and biodegradable nature places them as interesting candidates for nose-to-brain drug delivery. The intranasal administration of duloxetine-loaded NLCs (DLX-NLC) exhibited more than a six-times higher concentration of DLX in the brain (0.82% ID/g, percent injected dose per gram of tissue) when compared with the intravenous administration

TABLE 1

Formulation approaches for intranasal delivery of antidepressant drugs

Antidepressant drug/class	Dosage form	Method of preparation	Characterization	%DTE[a]/%DTP[b]	*Ex vivo*/*in vivo* studies	Relevant therapeutic outcomes	Refs
Nanosystems							
Venlafaxine hydrochloride SNRI	Chitosan (CS) nanoparticles	Ionic gelation of chitosan with sodium tripolyphosphate (TPP)	PS = 167 ± 6.5 nm PI = 0.367 ± 0.045 ZP = +23.83 ± 1.76 mV Yield = 71.42 ± 3.24% DL = 32.25 ± 1.63% EE = 79.3 ± 2.6%	508.59/80.34	*Ex vivo* permeation studies using porcine nasal mucosal membrane (Franz cells) Pharmacodynamic studies (Wistar rats): • modified forced swim test •locomotor activity test Qualitative localization and biodistribution studies by confocal laser scanning microscopy Pharmacokinetic analysis	VLF brain/blood ratios for VLF_{IV}, VLF_{IN}, VLF-CS NPs_{IN} were 0.0293, 0.0700 and 0.1612, respectively, at 0.5 h, indicative of better brain uptake of VLF chitosan NPs Mucoadhesive VLF-CS NPs enhanced the uptake of venlafaxine to the brain when delivered by IN route Significant quantity of VLF was quickly and effectively delivered to the brain by IN administration of mucoadhesive NPs of venlafaxine The higher DTE and DTP of VLF chitosan NPs as compared to other formulations suggest better efficacy in treatment of depression	[23]
Venlafaxine hydrochloride SNRI	Alginate-chitosan nanoparticles (AG-NPs)	Ionotropic pre-gelation of polyanion (AG) with calcium chloride ($CaCl_2$) followed by polycationic crosslinking by CS	PS = 173.7 ± 2.5 nm PI = 0.391 ± 0.045 ZP = +37.4 ± 1.74 mV Solid structure and spherical to subspherical shape DL = 26.74 ± 1.40% EE = 81.3 ± 1.9% *In vitro* VLF release from AG NPs = 85.6 ± 1.87% over a period of 24 h	VLF AG-NPs = 425.77/76.52	Pharmacodynamic studies (Wistar rats): • forced swimming test • locomotor activity test Biodistribution studies by confocal laser scanning fluorescence microscopy (rhodamine 123) Blood and brain pharmacokinetic studies	AG NPs were able to control the release of VLF beyond 24 h VLF AG-NPs IN treatment significantly improved the behavioral analysis parameters i.e., swimming, climbing and immobility in comparison to the $VLF\ solution_{IN}$ and $VLF\ tablet_{oral}$ The IN VLF AG-NPs improved locomotor activity when compared with $VLF\ solution_{IN}$ and $VLF\ tablet_{oral}$ Greater brain:blood ratios (30 min) for VLF $AG\text{-}NPs_{IN}$ in comparison to $VLF\ solution_{IN}$ and $VLF\ solution_{IN,}$	[24]
Desvenlafaxine SNRI	PLGA-chitosan nanoparticles	Emulsion solvent evaporation method	PS = 172.5 ± 10.2 nm PI = 0.254 ± 0.02 ZP = +35.63 ± 8.25 mV EE = 76.4 ± 4.2% DL = 30.8 ± 3.1% *In vitro* DVLF release from NPs 77.21 ± 3.87% (pH 7.4) and 76.32 ± 3.54% (pH 6.0) over a period of 24 h	DVF NPs = 544.23/81.62 DVF = 202.41/50.59	*Ex vivo* permeation studies on porcine nasal mucosa Pharmacodynamic studies (Wistar rats) • Stress-induced model: forced swimming test • Drug-induced model: reserpine reversal test Biochemical estimation of serotonin, noradrenaline and dopamine Blood and brain pharmacokinetic studies	PLGA-CS NPs IN administration significantly reduced the symptoms of depression and enhanced the level of monoamines in the brain in comparison with orally administered DVLF It enhanced the pharmacokinetic profile of DVLF in brain together with their brain:blood ratio at different time points	[31]

TABLE 1 (*Continued*)

Antidepressant drug/class	Dosage form	Method of preparation	Characterization	%DTE[a]/%DTP[b]	*Ex vivo*/*in vivo* studies	Relevant therapeutic outcomes	Refs
Duloxetine SNRI	NLC	Melting dispersion technique (high shear homogenization followed by ultrasonication and lyophilization)	PS = 137.2 ± 2.88 nm ZP = −31.53 ± 11.21 mV EE = 79.15 ± 4.17% DL = 9.73 ± 3.22% Spherical shape	DLX-NLC 757.74/86.80 DLX solution 287.34/65.12	Biodistribution studies (Wistar rats) Pharmacokinetic studies Gamma-imaging studies	IN administration exhibited about 8-times higher concentration of DLX in brain when compared with the intravenous administration of DLX solution The scintigraphy images were consistent with the biodistribution and pharmacokinetic studies, having revealed a high uptake of DLX into the brain	[16]
Paroxetine SSRI	Nanoemulsion (o/w type)	Spontaneous emulsification technique	PS = 58.47 ± 3.02 nm PDI = 0.339 ± 0.007 ZP = −33 mV Spherical droplets Transmittance = 100.60 ± 0.577% Refractive index = 1.412 ± 0.003 Viscosity = 40.85 ± 6.40 cP NE showed a 2.57-fold enhancement in permeation in comparison to paroxetine suspension	-	*Ex vivo* permeation studies using porcine nasal mucosal membrane (Franz cells) Pharmacodynamic studies (Wistar rats): • forced swimming test • locomotor activity test Biochemical estimation • GSH • TBARS	Treatment of depressed rats with paroxetine nanoemulsion IN significantly improved the behavioral activities in comparison to paroxetine suspension (oral) Biochemical estimation results revealed that the prepared nanoemulsion was effective in enhancing the depressed levels of glutathione and decreasing the elevated levels of TBARS	[32]
Selegiline hydrochloride MAOi	Thiolated chitosan nanoparticles (TCSN)	Ionic gelation method	PS = 215 ± 34.71 nm ZP = +17.06 mV EE = 70 ± 2.71% TCN were found to have 80% cumulative release (13 h)	–	Pharmacodynamic studies (Wistar rats): • forced swim and tail suspension test • sucrose preference test • locomotor activity Measurement of drug concentration in the brain Biochemical estimation: estimation of protein; nitrite; lipid peroxidation; reduced glutathione; catalase; mitochondrial enzyme complex estimation; complex I (NADH dehydrogenase activity); complex II (succinate dehydrogenase activity); complex III (MTT activity); complex IV (cytochrome c oxidase)	TCSNs successfully attenuated the oxidative stress and restored the activity of the mitochondrial complex *in vivo* A drastic reduction in the duration of immobility was seen in an evaluation of behavioral parameters, showing that TCNs successfully restore the impaired locomotor activity Normal sucrose consumption was found on treatment	[27]
Mirtazapine (MTZ) Tetracyclic antidepressant	Microemulsion (ME) and mucoadhesive microemulsion (MMME)		[MTZ] =26 mg/mL ME: PS = 14.17 ± 0.14 nm ZP = −16.9 ± 0.21 mV Conductivity = 0.128 ± 0.012 mS/cm Viscosity: 125.8 ± 0.24 cP MMME: PS = 23.79 ± 0.62 nm ZP = 5.98 ± 0.21 mV Conductivity = 0.251 ± 0.012 mS/cm Viscosity = 249.3 ± 0.24 cP	–	Pharmacodynamic studies (Wistar rats): • despair swim test • locomotor activity • elevated plus maze test	Brain:blood uptake ratios were found to be highest for mirtazapine MMME, followed by mirtazapine ME post-intranasal administration compared to oral delivery of ME Significant ($p < 0.05$) reduction in the assessed pharmacodynamic parameters was observed after IN administration of MMME against control group	[33]

TABLE 1 (*Continued*)

Antidepressant drug/class	Dosage form	Method of preparation	Characterization	%DTE[a]/%DTP[b]	*Ex vivo*/*in vivo* studies	Relevant therapeutic outcomes	Refs
Quercetin Flavonol	Liposomes	Lipid thin film formation and extrusion	PS = 173 ± 0.04 nm ZP = −17.43 ± 0.31 mV EE = 87.4 ± 7.1%	–	Pharmacodynamic studies (Wistar rats): • elevated plus maze test • Morris water maze test	Quercetin liposomes showed anxiolytic and cognitive-enhancing effects A lower dose and a faster rate were observed with IN quercetin liposomes when compared with oral quercetin, conventional and liposomal	[34]
Triggerable systems							
Venlafaxine hydrochloride SNRI	*In situ* mucoadhesive thermoreversible gel Lutrol® F127	Cold method	Drug content = 97.65 – 98.24% pH = 4.5 – 6.5 Mucoadhesive strength = 900 − 1200 dyn/cm^2 Release = 97.85 – 99.15%	–	*Ex vivo* permeation studies across sheep nasal mucosa (Franz cells) Pharmacodynamic study in rats Forced swim test Measurement of locomotor activity	Venlafaxine hydrochloride was more effective as an antidepressant by nasal route as *in situ* gel nasal drops in comparison to oral administration of equivalent dose	[30]
Doxepin Tricyclic antidepressant	Thermoreversible biogels/chitosan and glycerophosphate or poly(ethylene) glycol	–	[Dox] =5 mg/mL Gelation time = 7 min Gelation temperature = 37 °C pH = 6.5 Drug release = 50% (8 h)	–	*Ex vivo* permeation studies across sheep nasal mucosa (Franz cells) *In vivo* assessment of the activity counts and immobility time	Gels showed good mucoadhesion, enhanced drug permeation and provided prolonged *in vitro* release at 37 °C Efficacy of the formulation in treated groups was inferred from the measured pharmacodynamic parameter and histopathological reports of formulation-treated groups showed no significant local toxicity	[35]
Fluoxetine hydrochloride SSRI	Ion sensitive *in situ* nasal gel (gellan gum and HPMC)	–	Drug content = 99.79 ± 0.29% (1%) pH = 5.81 ± 0.02 Viscosity = 54.35 ± 0.24 cP Highest drug release = 94.24 % (240 min)	-	*Ex vivo* permeation studies across sheep nasal mucosa (Franz cells) Pharmacodynamic studies (rats): • force swim test • locomotor activity test	Locomotor activity and forced swim test study revealed that the *in situ* gel treated rats showed significant responses as compared to control group	[36]
Combined systems							
Venlafaxine hydrochloride SNRI	Nanostructured lipid carrier (NLC) gel	Emulsion solvent diffusion and evaporation method-ultrasonication	PS = 151.83 nm PI = 0.271 ZP = −8.08 mV DL = 34.3 ± 2.2%	–	*Ex vivo* permeation studies using sheep nasal mucosal membrane (Franz cells) Pharmacodynamic studies (Wistar rats): • modified forced swim test • locomotor activity test	NLC-based gel showed a rapid onset along with a prolonged duration of action as compared with pure drug solution and NLC dispersion	[22]
Tramadol HCl (centrally acting synthetic opioid)	Chitosan nanoparticles embedded in a Pluronic® and HPMC-based mucoadhesive thermoreversible gel (*in situ* gel)	Ionic gelation method	PS = 152.0 ± 9.6 nm PI = 0.143 ± 0.003 ZP = +31 ± 2.21 mV EE = 85 ± 3.23% Controlled release of entrapped drug: 90% NPs *vs.* 39.4% NP gel at 480 min	-	Pharmacodynamic studies (Wistar rats): • forced swim test • sucrose preference test Assessment of brain oxidative stress (estimating reduced form of glutathione, nitrite and increasing levels of catalase and lipid peroxidation)	Significant increase in locomotor activity, body weight as compared to control group Glutathione and catalase levels significantly increased, whereas lipid peroxidation and nitrite level was found to be decreased after IN administration	[37]

Abbreviations: PS, particle size; ZP, zeta potential; PI, polydispersity index; VLF, venlafaxine; IN, intranasal; CS, chitosan; NPs, nanoparticles; DVLF, desvenlafaxine; MAOi, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; NADH, nicotinamide adenine dinucleotide; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-H-tetrazolium bromide; PLGA, polylactide-co-glycolide; TBARS, thiobarbituric acid reactive substances; GSH, glutathione; DLX, duloxetine; ME, microemulsion; Dox, doxepin.

[a] %DTE: drug targeting efficiency represents the time average partitioning of drug between brain and plasma and is calculated by $(AUC_{brain}/AUC_{blood})_{IN}/(AUC_{brain}/AUC_{blood})_{IV} \times 100$.

[b] %DTP: direct transport percentage represents the percentage of drug directly transported to the brain through the olfactory and trigeminal neural pathway and is calculated by $B_{IN} - B_X/B_{IN} \times 100$ wherein $B_X = B_{IV} - P_{IV}) \times P_{IN}$ corresponds to the brain AUC fraction contributed by systemic circulation through the BBB following intranasal administration; B_{IV} stands to the AUC_{brain} following intravenous administration, P_{IV} to the AUC_{blood} following intravenous, B_{IN} to the AUC_{brain} following intranasal administration and P_{IN} to the AUC_{blood} following intranasal administration.

(0.134% ID/g) of DLX solution ($p < 0.10$). The higher concentration of duloxetine found in the brain was attributed to the direct pathway of transport (neuronal and non-neuronal) from nose to brain. The uptake of duloxetine in the brain and other organs was also visualized following intranasal administration of radiolabeled formulations (99mTc-DLX-NLC suspension and 99mTc-DLX solution), having revealed an increased radiation intensity from the radiolabeled formulation in the brain region for DLX-NLC suspension as compared with that for DLX solution. In summary, (i) the intranasal administration provided a higher duloxetine concentration in the brain than that obtained through the intravenous route and (ii) the intranasal lipid nanocarriers promoted higher concentrations than the intranasal DLX solution [16]. Other lipidic nature nanocarriers, encompassing microemulsions, nanoemulsions and liposomes, have been employed for intranasal antidepressant delivery. Despite, in general, a smaller particle size, when compared with solid-matrix (polymeric or lipidic) nanoparticles, this feature did not necessarily correlate with superior performance in terms of nose-to-brain delivery.

Options involving the use of triggerable systems, in particular those that are thermoresponsive, like *in situ* gelling formulations, have also been explored for the intranasal delivery of antidepressants. Again, the increased residence time in the nasal mucosa from the higher viscosity led to better performance, when compared with the corresponding solutions. An example wherein this strategy was successfully employed is reported in [30], describing co-formulated venlafaxine with the thermoresponsive polymer Lutrol® F127 and an array of mucoadhesive polymers (Carbopol® 934 P, HPMC K4M, PVP K30, sodium alginate, tamarind seed gum and carrageenan) [30]. For the optimal Lutrol® F127 concentration (18%), gel properties were further refined by adjusting mucoadhesive concentrations. A decrease in the $T_{sol-gel}$ along with an increase in mucoadhesive strength of the produced gels were observed when the mucoadhesive concentration was augmented. Optimized formulations with $T_{sol-gel}$ temperature within the range of 30–33 °C displayed an almost total permeation of VLF across sheep nasal mucosa at 150 min. *In vivo* pharmacodynamics studies demonstrated the superiority of the intranasal formulation, highlighting its antidepressant effectiveness when compared with the respective oral congener [30].

A cross-functional analysis of the formulation approaches is shown in Table 1, taking the immobility time extracted from the forced swim test because the common behavioral outcome (that is, difference in the immobility time of animals administered with the tested versus the reference formulation) indicates, in general, a superior performance when a nanosystem is employed as the strategy, in comparison with an *in situ* gelling system. However, the use of other outcomes, such as %DTE and direct transport percentage (%DTP), would be preferable to provide a more robust analysis regarding the direct nose-to-brain delivery. Among the strategies developed for enhancing direct nose-to-brain antidepressant drug transport, it was also noticed that the use of enhancers and ligands is not yet a reality that has been overly explored.

Drug repurposing

The strategy of drug repurposing has emerged as an attractive method to tackle several diseases, including depression. The opportunity of reusing drugs already approved for other indications (drug repositioning) can shorten R&D timelines by up to 3–5 years, with a higher probability of success when compared with complex, longstanding *de novo* drug discovery [38]. Underlying the clinical trials search involving 'intranasal' AND 'depression' keywords (on 5th February 2019), 21 results were found in the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search) and 24 in the ClinicalTrials.gov NIH database (https://clinicaltrials.gov/) (Table 2). A transversal analysis of the pipeline products identified ketamine, esketamine and oxytocin as the most-studied repurposed drugs.

Several clinical studies have demonstrated that ketamine and esketamine could be potential candidates to produce a rapid-onset antidepressant effect in treatment-resistant depression. Note that nearly one-third of patients with MDD do not respond to the existing antidepressants; and responders commonly take weeks to months to achieve a significant effect. This clear unmet need requires rapidly acting and more-effective treatments [39].

In clinical proof-of-concept studies, ketamine and esketamine revealed a rapid, significant antidepressant effect and the probable anti-suicidal effect that was transient when limited to a single administration [40]. Apart from the clinical outcomes, the inherent challenges of intravenous (from a logistics point-of-view, hospital admission and consultation with an anesthesiologist are required) or oral (reduced bioavailability) esketamine administration have prompted its intranasal delivery as a preferred and more convenient route for patient self-administration. Indeed, intranasal esketamine has been reported to produce a pharmacokinetic profile similar to that obtained with higher doses that were intravenously administered [41]. The relatively rapid onset of action and increased bioavailability of the drug once intranasally administered are attributable to the rich vasculature and relatively high systemic absorption of esketamine via the nasal mucosa [42]. The clinical evidence favoring an antidepressant effect and better tolerability profile associated with intranasal esketamine led the FDA to assign this drug a breakthrough therapy designation [43]. That justifies the boost in the clinical trials underway with intranasal esketamine because, if the outcomes retrieved are positive, approval will be granted. In this context, Janssen recently received approval from the FDA for esketamine nasal spray (Spravato®) new drug application for treatment-resistant depression in adults [44,45].

Oxytocin, a neuropeptide synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, has also been proposed for intranasal delivery as a potential treatment for anxiety and depressive disorders (Table 2). However, the lack of trials investigating the efficacy of intranasal oxytocin on core symptoms of anxiety and depression is a reality, and further studies considering larger samples and long-term administration are still required [46].

Interestingly, ongoing investigations into intranasal drug delivery have garnered attention regarding the insulin molecule, despite somewhat controversial findings [47]. Alterations in insulin availability and/or insulin receptor sensitivity and availability have been pinpointed as relevant to the function of neural structures underlying pathological aspects of MDD. Results from previous preclinical and clinical studies have revealed that intranasal acute administration of insulin exerts pro-cognitive effects across all subdomains of cognitive function, manifested by, for example, improvements in the subjective rating of mood as well as altering the stress response in healthy and medically affected individuals

TABLE 2

List of clinical trials involving licensed drugs with potential to be repurposed as antidepressant drugs for depression treatment (not exhaustive)

Drug intervention	Sponsor	Full title	Medical condition	Population age	Main objective of the trial	Trial protocol	EudraCT-number/ ClinicalTrials.gov identifier
Ketamine hydrochloride 50 mg/mL Solution for infusion *vs.* placebo	Department of Psychiatry, Helsinki University Central Hospital	The effect of intranasal ketamine on suicidality in severely depressed and suicidal patients Randomized, placebo-controlled study	Depression	Adults	To investigate the effect of ketamine on suicidality and mood in patients with major depression and severe suicidality who are waiting for ECT treatment series to begin	FI (ongoing)	2014-002451-26
Esketamine hydrochloride – nasal solution – 140 mg/mL plus duloxetine hydrochloride 30 mg escitalopram 10 mg or venlafaxine hydrochloride 75 mg Oral treatment *vs.* placebo (nasal spray)	Janssen-Cilag International NV	A randomized, double-blind, multicenter, active-controlled study of intranasal esketamine plus an oral antidepressant for relapse prevention in treatment-resistant depression	Treatment-resistant major depression	Adults	To assess the efficacy of intranasal esketamine plus an oral antidepressant compared with an oral antidepressant (active comparator) plus intranasal placebo in delaying relapse of depressive symptoms in subjects with TRD who are in stable remission after an induction and optimization course of intranasal esketamine plus an oral antidepressant	DE (completed) BE (completed) PL (completed) ES (completed) HU (completed) CZ (completed) SK (completed) IT (completed)	2014-004586-24
Nasal spray hydrochloride esketamine 56 mg *vs.* placebo	Janssen-Cilag International NV	A double-blind, doubly-randomized, placebo-controlled study of intranasal esketamine in an adaptive treatment protocol to assess safety and efficacy in treatment-resistant depression (SYNAPSE)	Treatment-resistant major depression	Adults	To assess the efficacy and dose response of intranasal esketamine (panel A: 28 mg, 56 mg, 84 mg; panel B: 14 mg and 56 mg) compared with placebo in improving depressive symptoms in participants with treatment-resistant depression (TRD), as assessed by a change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score for the combined periods in the double-blind treatment phase	BE (ongoing)	2013-004005-11
Esketamine hydrochloride 28 mg, 56 mg or 84 mg	Janssen-Cilag International NV	A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety and tolerability of intranasal esketamine plus an oral antidepressant in elderly subjects with treatment-resistant depression	Treatment-resistant major depression	Elderly	To evaluate the efficacy of switching elderly subjects with treatment-resistant depression (TRD) from a prior antidepressant treatment (to which they have not responded) to flexibly-dosed intranasal esketamine (28 mg, 56 mg or 84 mg) plus a newly initiated oral antidepressant compared with	SE (completed) BE (completed) ES (ongoing) LT (completed) FI (completed) BG (completed) IT (completed)	2014-004588-19
Nasal solution – 140 mg/mL	Janssen-Cilag International NV	A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety and tolerability of flexible doses of intranasal esketamine plus an oral antidepressant in adult subjects with treatment-resistant depression	Treatment-resistant major depression	Adults	switching to a newly initiated oral antidepressant (active comparator) plus intranasal placebo, in improving depressive symptoms, as assessed by the change from baseline in the MADRS total score from day 1 (pre-randomization) to the end of the 4-week double-blind induction phase	DE (completed) PL (completed) ES (completed) CZ (completed)	2014-004585-22

TABLE 2 (*Continued*)

Drug intervention	Sponsor	Full title	Medical condition	Population age	Main objective of the trial	Trial protocol	EudraCT-number/ ClinicalTrials.gov identifier
Esketamine hydrochloride – Nasal solution – 140 mg/mL *vs.* duloxetine hydrochloride 30 mg escitalopram 10 mg sertraline hydrochloride 50 mg venlafaxine hydrochloride 75 mg Oral treatment *vs.* placebo (nasal spray)	Janssen-Cilag International NV	A randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety and tolerability of fixed doses of intranasal esketamine plus an oral antidepressant in adult subjects with treatment-resistant depression	Treatment-resistant major depression	Adults	BE (completed) SK (completed) HU (completed) PL (prematurely ended)	2014-004584-20	
Esketamine hydrochloride – nasal solution – 140 mg/mL plus duloxetine hydrochloride 30 mg, escitalopram 10 mg or venlafaxine hydrochloride 75 mg Oral treatment *vs.* placebo (nasal spray)	Janssen-Cilag International NV	An open-label long-term extension safety study of intranasal esketamine in treatment-resistant depression	Treatment-resistant major depression	Adults, elderly	To assess the safety and tolerability of intranasal esketamine in subjects with TRD, with special attention to the following: • potential long-term effects on cognitive function • treatment-emergent adverse events (TEAEs), including TEAEs of special interest • post-dose effects on heart rate, blood pressure, respiratory rate and blood oxygen saturation • potential effects on suicidal ideation/behavior	DE (ongoing) GB (ongoing) BE (ongoing) ES (ongoing) PL (ongoing) HU (ongoing) CZ (ongoing) SK (ongoing) LT (ongoing) AT (ongoing) FI (ongoing) BG (ongoing)	2015-003578-34
Esketamine hydrochloride – nasal solution – 140 mg/mL plus duloxetine hydrochloride 30 mg, escitalopram 10 mg or venlafaxine hydrochloride 75 mg Oral treatment *vs.* placebo (nasal spray)	Janssen-Cilag International NV	An open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression	Treatment-resistant major depression	Adults, elderly	To assess the long-term safety and tolerability of intranasal esketamine plus a newly initiated oral antidepressant in subjects with TRD, with special attention to the following: • potential effects on cognitive function • potential treatment-emergent symptoms of cystitis and/or lower urinary tract symptoms • potential withdrawal and/or rebound symptoms following cessation of intranasal esketamine treatment	SE (completed) BE (completed) DE (completed) ES (ongoing) AT (completed) PL (completed) BG (completed) LT (completed) FI (completed) IT (completed)	2014-004587-38
Oxytocin 16 IU nasal spray, solution *vs.* placebo	Istituto Per L'infanzia Burlo Garofolo	Synergic effects of oxytocin and psychotherapy in postpartum depression Randomized controlled study	Postpartum depression	Adults	To evaluate the efficacy of the administration of intranasal oxytocin in conjunction with psychotherapy in women with postpartum depression	IT (ongoing)	2008-001913-51

TABLE 2 (*Continued*)

Drug intervention	Sponsor	Full title	Medical condition	Population age	Main objective of the trial	Trial protocol	EudraCT-number/ ClinicalTrials.gov identifier
Insulin nasal spray *vs.* placebo nasal spray	Toronto Western Hospital Toronto, Ontario, Canada	Effect of intranasal insulin on depressive symptoms in major depressive disorder	Major depressive disorder	Adults	To determine whether adjunctive intranasal insulin will exert an antidepressant effect when compared to placebo in adults with major depressive disorder (MDD), insufficiently responsive conventional antidepressants	Completed	NCT00570050

[48,49]. Notwithstanding, the rapidity and mechanisms underlying the overall improvement of cognitive function over time, in particular the manner insulin interacts with neurobiological targets (i.e., insulin receptors in the brain), have yet to be clarified [47,50]. By encouraging this mechanism, drug repurposing development programs present as models for the discovery of new antidepressants, also providing a pathway to understanding the pathophysiology of treatment-resistant depression in patients, thereby contributing to the elucidation of mental illness. Ultimately, it could enable drug development progress toward new compounds with novel mechanisms of action (similar to those presented here).

Neuropeptides

Dozens of brain neuropeptides act in concert to regulate physiological behavior and functions, comprising modulatory effects on conventional neurotransmitter systems [51]. In this context, the intranasal route of administration has become a practical, noninvasive tool in human and rodent studies, offering the opportunity to explore the effect of several neuropeptides on diverse aspects of social and nonsocial behaviors, emotion and neuronal activation patterns. Apart from oxytocin, other neuropeptides have emerged with promising anxiolytic effects [52–56]. Some of them and their respective achievements are summarized in Table 3. Despite still being at the preclinical stage, these studies enlarge the range of therapeutic entities with strong potential to generate treatments capable of multiplicative impact among patients with drug-resistant depression.

Cellular-based therapy

Cellular-based therapy has emerged as a recent modality for the effective delivery of a variety of drugs. This therapy usually involves macrophages and many types of stem cells as carriers for brain delivery. In particular, mesenchymal stem cells (MSCs) can be easily isolated and expanded from bone marrow and even from adipose tissue. MSCs are pluripotent adult stem cells that can promote neurogenesis by differentiating into neural lineages (e.g., neurons and glial cells), as well as by expressing neurotrophic factors [such as brain-derived neurotrophic factor (BDNF), β-nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1)] that enhance the survival and differentiation of neural progenitor cells [60,61]. Depression has been associated with impaired neurogenesis in the hippocampus and dentate gyrus, therefore MSCs have been suggested as candidates for treating a variety of neurodegenerative diseases, including depressive disorders.

Some studies have been performed to assess the therapeutic potential of MSCs in rat animal models for depression [62,63]. Aiming to address MSCs and intranasal delivery, one can cite the work of Nijboer *et al.*, who studied the therapeutic potential of intranasally administered bone-marrow-derived MSCs relatively late post-insult, using a rat endovascular puncture model for subarachnoid hemorrhage (SAH) [64]. Note that depression affects nearly half of SAH patients during the first year of recovery, and is associated with poor quality of life [65]. Six days after induction of SAH, rats were randomly submitted to MSCs or vehicle treatment through nasal administration. The intranasal MSC treatment was associated with a significant improvement in the sensorimotor and mechanosensory function at 21 days after SAH. It also led to a sharp decrease in SAH-induced activation of astrocytes and microglia and macrophages in the lesioned hemisphere. Interestingly,

TABLE 3

Some examples of neuropeptides and respective impact on depression-like behaviors

Peptide	Main findings	Refs
BDNF-HA2TAT/AAV	IN administration of BDNF-HA2TAT/AAV to normal mice displayed anti-depression effect in forced swimming test when the delivery lasted relatively longer The AAV applied to mice subjected to chronic mild stress through intranasal administration for 10 days also alleviated depression-like behaviors	[57]
Glucagon-like peptide II	PAS-CPPs-GLP-2 (IN) exhibited antidepressant-like effects in the forced swim test (FST) and tail suspension test in naive mice as well as adrenocorticotropic-hormone-treated mice, in contrast to PAS-CPPs-GLP-2 (IV) and the GLP-2 derivative containing CPPs without a PAS (CPPs-GLP-2) (IN), which did not affect the immobility time in the mouse FST FITC-labeled PAS-CPPs-GLP-2 (IN) but not FITC-labeled CPPs-GLP-2 (IN) was distributed through the mouse brain after the FST session PAS-CPPs-GLP-2 is effective for IN delivery to the brain, and could be useful in the clinical treatment of major depression	[58]
Neuropeptide Y	NPY (IN) treated rats had lower anxiety-like behavior than vehicle treated rats as indicated by more entries into open arms and fewer into closed arms, lower anxiety index, higher risk assessment and unprotected head dips and reduced grooming time NPY (IN) led to reduced depressive-like behavior, assessed by forced swim test NPY (IN) reversed several behavioral impairments triggered by the traumatic stress of SPS and has potential for noninvasive PTSD therapeutic intervention	[55]
	NPY attenuated anxiety and depressive behavior Strong preclinical proof-of-concept for intranasal NPY and probable MC4R antagonists as promising noninvasive early pharmacological interventions to prevent development of PTSD and comorbid disorders	[56]
Neuropeptide S	Nasal NPS (4–40 nmol applied topically on the rhinarium) facilitated object discrimination in a dose-dependent manner The anxiolytic effect of NPS on the elevated plus-maze could be confirmed after nasal administration (40 nmol); by contrast, identical doses of subcutaneously injected NPS failed to produce corresponding behavioral effects in both tests Nasal application of NPS could represent a viable therapeutic approach for NPS treatment of patients with psychiatric illnesses, such as anxiety or panic disorders	[59]

Abbreviations: BDNF, brain-derived neurotrophic factor; PTSD, posttraumatic stress disorder; PAS, penetration accelerating sequence; CPP, cell-penetrating peptide; GLP-2, glucagon-like peptide II; PAS-CPPs-GLP-2, GLP-2 derivative containing cell-penetrating peptides and a penetration accelerating sequence; FITC, fluorescein isothiocyanate; NPS, neuropeptide S; SPS, single prolonged stress.

MSC administration promoted a decrease in the SAH-induced depression-like behavior, along with a restoration of tyrosine hydroxylase expression in the substantia nigra and striatum. Such findings consubstantiate the pivotal role of intranasal MSC administration in the reversion of the damaging consequences of SAH insult, encompassing regeneration of the cerebral lesion, functional recovery and treatment of depression-like behavior as the main comorbidity. Based on the reported examples, it can therefore be postulated that MSCs serve as an appealing modality for treating depressive disorders.

Challenges

Depression is a multifactorial disease, thereafter the progress of therapy development is intrinsically slowed down by the influence of several challenges. Intranasal drug delivery has been advantageously labeled as a noninvasive route of administration, wherein the drugs are less susceptible to enzymatic or acidic degradation and first-hepatic metabolism than if orally delivered. In addition, nasal mucosa offers an extensive vascularization and direct brain access, which, together with a large surface area (ascribed to the numerous microvilli of ciliated and nonciliated cells), results in an enhanced drug permeability and rapid onset of therapeutic action. It should be emphasized, however, that absorption and bioavailability of drugs across the nasal mucosa can be impacted, and somehow reverted, by factors such as: (i) rapid drug elimination prompted by mucociliary clearance (5 mm/min for healthy humans); (ii) limited administration volume (25–200 μl); and (iii) the presence of enzymes that degrade, despite to a much lesser extent than the gastrointestinal tract, protein and peptide drugs [66]. All these physiological aspects must be considered when choosing the appropriate formulation strategy.

Pertaining to the pharmaceutical product development pipeline, most of the nanosystem-based formulations, along with the use of neuropeptides and cellular-based therapies, remain at a preclinical stage, far from clinical practice. Several barriers, mainly regulatory issues, are posed, addressing safety and quality aspects, as well as stringent quality requirements that need to be overcome to support their translation to the market. For example, despite formulation of nanosystems being considered as a promising approach, attributable to their multiple benefits, the understanding of the factors that influence their efficient brain targeting through the intranasal route remains incomplete [67]. In turn, regarding cellular therapy marketing approval, the lack of common principles that facilitate the convergence of regulatory approaches, ensuring the smooth, efficient evaluation and regulation or surveillance of products, as well as the existence of production facilities based on sound scientific principles, can be pointed out *a priori* [68].

The pharmaceutical industry is witnessing increased pressure to introduce innovative and efficient processes for manufacturing active drug products, which directly includes delivery devices. In the coming years, the design of more-complex and automated delivery devices will be demanded to warrant accurate and repeatable intranasal dosing. The complex geometry of the nasal cavity is in itself a big challenge to promote effective delivery of drugs beyond the nasal valve. As such, new efforts are needed to make this noninvasive route of delivery more efficient and popular.

Concluding remarks

Depression is a multifactorial disease, so treatments addressing the multiple facets of the disease are desirable. In this context, the current range of therapeutic opportunities is wide and outcomes

can be boosted if some of these approaches are combined. The direct intranasal drug transportation to the brain can benefit from nanocarrier-based formulations. However, despite the noticeable number of studies and the encouraging results achieved over the past decade, the use of nanocarriers in clinics remains in its infancy. In turn, MSCs are at the forefront in intranasal delivery, representing a future research vista to treat depressive disorders. The overall analysis, herein performed, indicates that repurposed drugs essentially feed antidepressant clinical development programs. Interestingly, esketamine nasal spray was recently approved as the first intranasal prescription medicine for treatment-resistant depression in adults. These findings corroborate that nose-to-brain drug delivery could provide a strong effective solution for treatment-resistant depression.

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