Guerra *et al. J Transl Genet Genom* 2022;6:304-21
DOI: 10.20517/jtgg.2022.08

Journal of Translational Genetics and Genomics

Review

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Neurogenic dysphagia: current pharmacogenomic perspectives

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How to cite this article: Guerra J, Naidoo V, Cacabelos R. Neurogenic dysphagia: current pharmacogenomic perspectives. *J Transl Genet Genom* 2022;6:304-21. https://dx.doi.org/10.20517/jtgg.2022.08

Received: 17 Mar 2022 **First Decision:** 17 May 2022 **Revised:** 18 May 2022 **Accepted:** 30 May 2022 **Published:** 1 Jul 2022

Academic Editor: Shu-Feng Lei **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Neurogenic dysphagia (ND) is characterized by a swallowing disorder where nervous system, muscle, and neuromuscular diseases are involved. *DRD1*, *COMT*, *BDNF*, and *APOE* are genes that may have a predictive role in the occurrence and evolution of ND. Many drugs that improve swallowing or can induce or exacerbate swallowing difficulties are related to dopamine metabolism and substance P. These pharmacological treatments for ND include dopamine precursors (levodopa), dopamine agonists (amantadine, apomorphine, cabergoline, and rotigotine), and TRP channel activators (capsaicin, piperine, and menthol). Since treatment outcomes are highly dependent on the genomic profiles of ND patients, personalized treatments should rely on pharmacogenetic procedures to optimize therapeutic interventions. Knowledge of the pharmacogenetic profiles of these drugs would minimize the occurrence of adverse drug reactions (especially to antidopaminergic medications) that may induce dysphagia and optimize pharmacological treatment that can ameliorate it. This knowledge should also be applied to the use of medications that control symptoms associated with dysphagia, such as sialorrhea, xerostomia, reflux, or hiccups.

Keywords: Oropharyngeal dysphagia, neurogenic dysphagia, pharmacogenomics, dopamine, dopaminergics, antidopaminergics, TRP genes

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INTRODUCTION

Neurogenic dysphagia (ND) refers to any swallowing disorder associated with central and peripheral nervous system conditions, as well as muscle and neuromuscular diseases. ND is linked to multiple degenerative and nondegenerative congenital, traumatic, vascular, neoplastic, and iatrogenic disorders as diverse as cerebral palsy, traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's syndromes, myasthenia gravis (MG), and myositis[1]. Based on clinical observations, ND can be classified into the following seven distinct phenotypes, which are particularly useful when etiological diagnosis is in doubt: (i) premature bolus spillage; (ii) delayed swallowing reflex, both characteristic of stroke; (iii) predominance of residue valleculae, common in patients with Parkinson's disease; (iv) predominance of residue in the piriform sinus, characteristic of myositis, motor neuron disease, or brainstem stroke; (v) pharyngolaryngeal movement disorder, observed in patients with parkinsonism and stroke; (vi) fatigable swallowing weakness in individuals with myasthenia gravis; and (vii) complex disorder, as occurs in ALS[2].

The importance of dysphagia stems mostly from the increased risk of death caused by aspiration pneumonia, and conditions related to dehydration or malnutrition[3,4]. In addition to these factors, aging reduces the frequency of spontaneous swallowing[5]. To ensure proper diagnosis and management of ND, it is mandatory to: (i) obtain a complete medical history; (ii) perform screenings that assess the risk of aspiration (e.g., a swallowing test with water and other consistencies); (iii) conduct counseling tests and clinically evaluate dysphagia by videofluoroscopy (VFSS), swallowing endoscopy (FEES), or manometry, and other additional tests such as ultrasonography or electromyography); (iv) perform treatments based on dietary therapeutic interventions, behavioral interventions, oral hygiene measures, neurostimulation, pharmacotherapy, and surgical treatments[6]. In this third step, the management of special groups such as tracheostomized patients and patients with nasogastric tubes is of particular interest[6].

The treatment of ND is mainly based on rehabilitation therapies performed by speech therapists and other non-pharmacological approaches. However, some medications may be effective in improving impairment during the different phases of swallowing[6,7]. The majority of medications used to treat oropharyngeal dysphagia have a general effect on swallowing function that is independent of the underlying neurological disease; this allows for standardized use[8]. Pharmacotherapy, however, produces limited results and should therefore not be used as a stand-alone treatment, but rather as an adjunct to other therapies[8]. Furthermore, medications such as antidopaminergic agents, anticholinergic drugs, or benzodiazepines induce or exacerbate dysphagia[9-12].

In view of these considerations, research into specific ND-related genes may be useful in the prognosis of this condition. Because pharmacogenetics also plays a key role in both the diagnosis and the correct pharmacological management of patients with dysphagia, to increase the benefit of compounds that can improve swallowing difficulty and minimize the risk with the use of dysphagia-inducing drugs, in this review, we highlight these ND mechanisms from a pharmacogenomic perspective.

DOPAMINE AS A NEUROTRANSMITTER

Dopamine is a neurotransmitter of high relevance in the swallowing process. Its precursor, L-DOPA, is synthesized from the essential amino acid tyrosine or indirectly through phenylalanine, a non-essential amino acid. Dopamine β-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine (NE), and NE is then converted into epinephrine by phenylethanolamine N-methyltransferase with S-adenosyl-L-methionine as the cofactor. Dopamine is degraded by monoamine oxidase (MAO-A and MAO-B), catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase (ALDH), which act

sequentially[13].

Dopamine is synthesized and acts primarily in the central nervous system (CNS). Dopaminergic neurons project to different brain regions along the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways. Dopamine exerts its effects by binding to five G-protein-coupled receptors (D1-D5); of these, D1 receptors are the most abundant in the CNS. These receptors are divided into D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors. D1-like receptors exert a stimulatory effect through sodium channels or an inhibitory effect through potassium channels. At the peripheral level, dopamine does not cross the blood–brain barrier and is synthesized independently. Dopamine is present in plasma as dopamine sulfate, and only a small unconjugated amount can be synthesized by peripheral tissues[14,15].

DOPAMINE AND SWALLOWING

The swallowing process requires, at least in part, dopamine activity and its binding to its receptors[16]. Although most dopamine receptors would theoretically be relevant to ND, the role of the dopamine D1 receptor (DRD1) is particularly important in this condition. For example, DRD1 antagonists alter the swallowing reflex and reduce substance P (SP) levels in peripheral organs[17]. Specifically, in the striatum in an animal model of Huntington's chorea, *Drd1a*, *SP,* and *dynorphin* expression is downregulated, whereas the expression of the dopamine D2 receptor (*Drd2*) and enkephalin is upregulated after ablation of D1 receptor-expressing cells[18]. In this animal model, the resulting phenotype includes swallowing disturbances and poor oromotor coordination with tongue protrusion[18]. This role of *DRD1* has also been observed in certain single nucleotide polymorphisms (SNPs) in humans. The *DRD1* rs4532 polymorphism confers a worse prognosis of swallowing function in individuals over the age of 65 following a stroke. Other SNPs, such as *DRD2* rs1800497 and *DRD3* rs6280, do not appear to be involved in ND[19]. Moreover, interactions between the *COMT* rs165599 and *BDNF* rs10835211 polymorphisms are linked to dysphagia with increasing age; the effect of the SNP rs10835211 heterozygosity is dependent on the status of SNP rs165599[20].

The use of dopaminergic agonists in the treatment of neurogenic dysphagia

Levodopa, rotigotine, cabergoline, apomorphine, and amantadine are dopamine agonists that have been used generically to treat a variety of neurological conditions associated with oropharyngeal dysphagia[8]. The drug that provides the best outcome is controversial because of conflicting outcomes across different studies. However, among these, levodopa is the most widely used, and it is also used to evaluate the swallowing response during the Fiberoptic Endoscopic Evaluation of Swallowing (FEES) test[21,22]. Most studies have focused on the effect of dopaminergic agonists in Parkinson's disease, and several publications show that these drugs improve dysphagia, especially in the oral phase and, to a lesser extent, in the pharyngeal phase[23-25]. This clinical improvement is related to swallowing alterations due to nigrostriatal dopamine deficits and to other structures such as the pedunculopontine nucleus or the medulla[23]. In a small group of patients, an improvement in bolus fragmentation, vallecular stasis, and laryngeal penetration was observed, together with a shortening of the swallowing phase; these findings are associated with an improvement in bucco-linguo-facial motility[26]. Paradoxically, and despite most articles reporting a beneficial effect, one clinical trial showed that levodopa could worsen dysphagia by inhibiting brainstem reflexes[27]. Overall, however, the results appear to support its use in PD patients despite the lack of high-quality evidence[28]. Although dopaminergic agonists have a modest effect on the motor symptoms of progressive supranuclear palsy, they help some patients improve their swallowing[21]. However, these drugs can also be employed in acquired neurological conditions. Following a lacunar stroke involving the basal ganglia, for example, levodopa decreases the risk of aspiration by shortening the latency of the swallowing reflex, as shown after examining the submental electromyographic activity and the visual observation of the laryngeal movement[29]. This reduction, according to monocentric randomized trials in which imaging and

physical signs were evaluated, is also observed with other dopamine agonists such as cabergoline and amantadine; the elderly population, in particular, may benefit from treatment with dopamine agonists[30,31].

The search for new compounds to treat ND also includes natural supplements that contain dopamine, for use mainly in groups where dosage or side effects may be contraindicated, such as children or the elderly. Natural sources of dopamine include *Mucuna pruriens*, *Vicia faba*, or *Musa cavendishii*[32-34]. In fact, several studies in patients with Parkinson's disease reveal the effectiveness of these treatments with extracts derived from these products; these compounds reduce the risk of adverse effects such as dyskinesias as well as induce epigenetic and pharmacoepigenetic modifications[35,36].

Pharmacogenetics of dopaminergic agonists in the treatment of neurogenic dysphagia

Anti-ND drugs exhibit different specific pharmacogenetic profiles [Table 1][37]. All of the medications used to treat ND show, among others, *DRD1* as a mechanistic gene and the binding of drugs to this receptor. All of the anti-ND drugs have *COMT* as substrates, where *COMT* shortens the activity of these dopaminergic drugs[38]. Moreover, the *COMT* rs4680 polymorphism may induce motor complications such as dyskinesia during treatment with levodopa[38-40]. Levodopa also has *DBH* as substrate[37]. *ADORA2A* SNPs and *HOMER1* variants are associated with L-DOPA-induced adverse motor (e.g., dyskinesia) and psychotic symptoms[41,42]. A haplotype integrating -141CIns/Del, rs2283265, rs1076560, C957T, TaqIA, and rs2734849 polymorphisms at the *DRD2/ANKK1* gene region is linked to L-DOPA-induced motor dysfunction[43]. SLC6A3 is a genetic modifier of the treatment response to L-DOPA[44]. The multi-drug resistance gene (*MDR1*) C1236T polymorphism may also influence pharmacotherapy[45] and SNPs in genes that encode the dopamine transporter (*DAT*; *SLC6A3*) and the vesicular monoamine transporter 2 (*VMAT2*; *SLC18A2*)[46]. Despite the fact that dopamine agonist therapy has applicability in other ND diseases, these studies focus on Parkinson's disease, which limits inferences in other acquired or degenerative neurological illnesses.

Antidopaminergics and neurogenic dysphagia

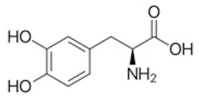
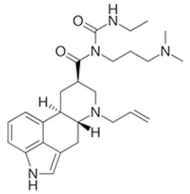
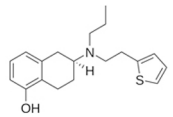
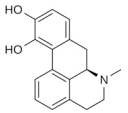
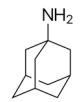
In a significant number of cases, the causes of ND can be induced or exacerbated by certain drugs[9-11]. Many patients with different neurological conditions are treated with antidopaminergic medication[10,11]. Adverse reactions are especially frequent in senescence and are relevant since they are reversible, and dysphagia may be the only or the predominant extrapyramidal symptom. Although it is recommended that drug intake be minimized as much as possible, this is not feasible in many cases. It is therefore recommended that the drug dose be adjusted to avoid the aforementioned side effects. Knowing the pharmacogenetic profiles of these drugs is, therefore, very important to therapeutic strategies[37] [Table 2].

Antipsychotics, as antidopaminergic medications, are primarily metabolized through *CYP1A2/2D6/3A4/2C19*[47]. Of these, *CYP2D6* is the most relevant because 40% of these neuroleptics are major substrates of this enzyme. *CYP2D6*, however, is associated with side effects. Other genes such as *HTR2A*, *SLC18A2, GRIK3,* and *DRD2* are linked to extrapyramidal reactions[48]. Drugs that exert an antidopaminergic effect on *DRD1* are of particular interest. In ND, *DRD1* is the pathogenic gene that is involved in the pharmacogenomic response to haloperidol, aripiprazole, olanzapine, quetiapine, or risperdone. Other *DRDs (not DRD1)* pathogenic variants mediate the adverse effects of antipsychotic drugs such as sulpiride, domperidone, and metroclopramide, causing oropharyngeal dysphagia; this suggests that other dopamine- and non-dopamine pathways mediate blocking of the swallowing phase[37].

TRANSIENT RECEPTOR POTENTIAL CHANNEL (TRP) GENES

Transient receptor potential (TRP) channel genes encode ion channels that are classified into two broad groups: (i) Group 1 includes TRPC (canonical), TRPV (vanilloid), TRPVL (vanilloid-like), TRPM

Table 1. Pharmacogenetics of dopaminergic agonists in the treatment of neurogenic dysphagia

Drug	Properties	Pharmacogenetics
	Name: Levodopa IUPAC Name: l-Tyrosine-3-hydroxy Molecular Formula: $C_9H_{11}NO_4$ Molecular Weight: 197.19 g/mol Mechanism: Levodopa circulates in the plasma to the blood–brain barrier, where it crosses and is then converted by striatal enzymes to dopamine. Carbidopa inhibits the peripheral plasma breakdown of levodopa by inhibiting its carboxylation, and thereby increases available levodopa at the blood–brain barrier Effect: Antiparkinsonian agents, dopamine precursors	Pathogenic genes: *ANKK1, BDNF, LRRK2, PARK2* Mechanistic genes: *CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1* Metabolic genes: Substrate: *COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DBH, DDC, G6PD, MAOB, TH, UGT1A1, UGT1A9* Transporter genes: *SLC22A1, SLC6A3, SLC15A1 (inhibitor). SLC16A10 (inhibitor), SLC7A5, SLC7A8* Pleiotropic genes: *ACE, ACHE*
	Name: Cabergoline IUPAC Name: Ergoline-8β-carboxamide, N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonil]-6-(2-propenyl) Molecular Formula: $C_{26}H_{37}N_5O_2$ Molecular Weight: 451.60 g/mol Mechanism: A long-acting dopamine receptor agonist. Has high binding affinity for dopamine D2-receptors and lesser affinity for D1, α1- and α2-adrenergic, and serotonin (5-HT1 and 5-HT2) receptors. Reduces serum prolactin concentrations by inhibiting release of prolactin from the anterior pituitary gland (agonist activity at D2 receptors) Effect: Antiparkinsonian agents, ergot-derivative dopamine receptor agonists	Pathogenic genes: *BDNF, GSK3B* Mechanistic genes: *ADRA1A, ADRA1B,ADRA1D, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, AKT1, BDNF, CNR1, DRD1, DRD2, DRD3, DRD4, DRD5, GSK3B, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C, HTR7* Metabolic genes: Substrate: *COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4 (minor), CYP3A5, DDC* Transporter genes: *ABCB1*
	Name: Rotigotine Molecular Formula: $C_{19}H_{25}NOs$ Molecular Weight: 315.47 g/mol Mechanism: A non-ergot dopamine receptor agonist with specificity for D3-, D2-, and D1-dopamine receptors. Although the precise mechanism of action of Rotigotine is unknown, it is believed to be due to stimulation of postsynaptic dopamine D2-type autoreceptors within substantia nigra in brain, leading to improved dopaminergic transmission in motor areas in basal ganglia, notably caudate nucleus/putamen regions Effect: Antiparkinsonian agents, non-ergot-derivative dopamine receptor agonists	Pathogenic genes: *ANKK1, BDNF, LRRK2* Mechanistic genes: *CCK, CCKAR, CCKBR, DRD1, DRD2, DRD3, DRD4, DRD5, GRIN2A, GRIN2B, HCRT, HOMER1, LMO3, OPRM1, HTR1A, ADRA2B* Metabolic genes: Substrate: *COMT, MAOB, CYP3A4, CYP2D6* Inhibitor: *CYP2D6, CYP2C19* Transporter genes: *SLC22A1, SLC6A3* Pleiotropic genes: *ACE, APOE*
	Name: Apomorphine Molecular Formula: $C_{17}H_{17}NO_2HCl_{1/2}H_2O$ Molecular Weight: 312.79 g/mol Mechanism: Stimulates postsynaptic D2-type receptors within the caudate-putamen in the brain Effect: Antiparkinsonian agents, non-ergot-derivative dopamine receptor agonists	Pathogenic genes: *PARK2* Mechanistic genes: *ADRA2A, ADRA2B, ADRA2C, CALY, DRD1, DRD2, DRD3, DRD4, DRD5, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C* Metabolic genes: Substrate: *COMT, CYP1A2 (minor), CYP2B6, CYP2C9 (minor), CYP2C19 (minor), CYP2D6, CYP3A4 (minor), CYP3A5, DDC, UGT1A1, UGT1A9, SULT1A1, SULT1A2, SULT1A3, SULT1E1, SULT1B1* Inhibitor: *CYP1A2 (weak), CYP2C19 (weak), CYP3A4 (weak)* Transporter genes: *SLC18A2*
	Name: Amantadine IUPAC Name: Tricyclo[3.3.1.13,7]decan-1-amine, hydrochloride Molecular Formula: $C_{10}H_{17}NHCl$ Molecular Weight: 187.71 g/mol Mechanism: Antiparkinsonian activity may be due to inhibition of dopamine reuptake into presynaptic	Pathogenic genes: *PARK2* Mechanistic genes: *CCR5, CXCR4, DRD1, DRD2, GRIN3A, CHRNA3, CHRNA4, CHRNA7* Metabolic genes: Substrate: *COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DDC, UGT1A1, UGT1A9*

neurons or by increasing dopamine release from presynaptic fibers Effect: Antiparkinsonian agents, adamantanes, dopamine agonists	Inhibitor: *MAOB* Transporter genes: *SLC22A1 (Substrate/inhibitor), SLC22A2 (Substrate/inhibitor)*

(melastatin), TRPS (soromelastatin), TRPN (no mechanoreceptor potential C), and TRPA (ankyrin); (ii) Group 2 consists of TRPP (polycystic) and TRPML (mucolipin)[49]. Some of these targets represent a therapeutic strategy of interest for dysphagia by stimulating areas that evoke the swallowing reflex. Group 1 genes are the most relevant where *TRPV1*, *TRPA1,* and *TRPM8*, for example, are involved in stimulation of thermal sensitivity and the release of CGRP and inflammatory mediators[50]. These receptors are expressed on trigeminal, vagal, and glossopharyngeal nerve terminals; these nerves are critical in the swallowing process[51,52]. Three compounds of clinical relevance in ND that stimulate these receptors are capsaicin, piperine, and menthol. Capsaicin increases the frequency of spontaneous swallowing by stimulating TRPV1 receptors, piperine stimulates TRPV1/A1 receptors, and menthol stimulates TRPM8 receptors[53,54]. A recent meta-analysis revealed the effectiveness of TRP channel agonists in treating ND[55]. Capsaicin produces the highest therapeutic outcomes by lowering the risk of laryngeal penetration and pharyngeal residue and increasing bolus velocity[54]. Capsaicin also induces the release of SP, a neurotransmitter involved in amplifying the inflammatory response and nociceptive sensitization. Since *DBH* inhibits capsaicin, a pharmacogenetic study in patients with variants of interest is mandatory[37]. As mechanistic genes, *TRPV1* Val585Ile and *UCP2* -866 G/A variants correlate with the capsinoid therapeutic response[56]. All three, but mainly capsaicin, inhibit *CYP* group enzymes (*CYP3A4, CYP2C9,* and weak in *CYP2D6*). Furthermore, capsaicin and piperine inhibit *CYP1A2*[57]. *In silico,* piperine weakly inhibits CYP2D6 WT and CYP2D6*53[58]. Capsaicin and the other compounds, in addition to exhibiting large heterogeneity in their metabolic genes, exert anti-inflammatory effects by modulating pleiotropic genes such as *TNF* and*ILs*[37] [Table 3].

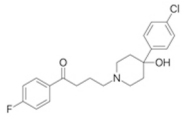
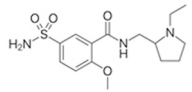
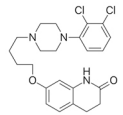
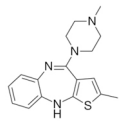
OTHER DRUGS USED IN NEUROGENIC DYSPHAGIA

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit substance P degradation[59]. These drugs reduce the cough threshold and subsequently can be used in aspiration prophylaxis; however, results from studies on perindopril, lisinopril, or imidapril are inconclusive[59-61]. Imidapril is effective in controlling dysphagia after stroke[30]. In one study, levetiracetam was beneficial to the recovery of dysphagia in post-stroke patients[62]. Several reports describe the usefulness of cough provocation tests with irritants (citric acid, tartaric acid, and mannitol) as a diagnostic tool[63-65], but it remains to be determined whether such agents are useful for treating dysphagia. Table 3 shows the pharmacogenetic profiles of other drugs used to treat ND[37]. It should furthermore be noted that drugs used to treat ND (including dopaminergic agonists) may influence neuroplasticity and axonal regrowth or sprouting to improve, for example, the level of consciousness that would facilitate swallowing[66].

OTHER GENES RELATED TO NEUROGENIC DYSPHAGIA

Few reports have linked other genes to dysphagia. However, the *BDNF* gene has been studied the most in this regard; the influence of the *COMT* gene on symptomatic dysphagia has been previously discussed[20]; rs6265 polymorphisms exert disparate effects on pharyngeal stimulation in healthy subjects[67] and appear to influence a better prognosis in swallowing after stroke or poor tolerance to esophageal electrostimulation in carriers of the *Met* allele[68-70]. Furthermore, a study with a large sample of elderly individuals showed that e4 homozygous *APOE* carriers have low swallowing evaluation scores[71]. Finally,

Table 2. Pharmacogenetics of antidopaminergic drugs and the risk of neurogenic dysphagia

Drug	Properties	Pharmacogenetics
	Name: Haloperidol IUPAC Name: 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one Molecular Formula: $C_{21}H_{23}ClFNO_2$ Molecular Weight: 375.864223 g/mol Mechanism: Haloperidol is a butyrophenone antipsychotic which blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in brain. Depresses release of hypothalamic and hypophyseal hormones. Believed to depress reticular activating system Effect: Antipsychotic agent, Serotonergic antagonist, Dopaminergic antagonist, antiemetic, antidyskinesia agent, sedative effects, hypotension	Pathogenic genes: *ADRA1A, ADRA2A, ADRA2B, ADRA2C, BDNF, DRD1, DRD2, DRD3, DRD4, DTNBP1, GRIN2B, HTR2A* Mechanistic genes: *ANKK1, BDNF, COMT, DRD1, DRD2, DRD3, DTNBP1, GRIN2A, GRIN3B, GRIN2C, GRIN2B, SLC6A3, MCHR1, SLC18A2, HTR2C, SIGMAR1, HRH1, CHRM3, HTR1A, HTR6, HTR7* Metabolic genes: Substrate: *CBR1, CYP1A1 (minor), CYP1A2 (minor), CYP2A6, CYP2C8 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4/5 (major), CYP3A7, GSTP1, UGT1A9* Inhibitor: *CYP2D6 (moderate), CYP3A4 (moderate)* Transporter genes: *ABCB1 (substrate/inhibitor), ABCC1, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SLC6A3* Pleiotropic genes: *CHRM2, FOS, GSK3B, HRH1, HTR2A, HTT, IL1RN*
	Name: Sulpiride. IUPAC Name: N-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxy-5-sulfamoylbenzamide Molecular Formula: $C_{15}H_{23}N_3O_4S$ Molecular Weight: 341.42582 g/mol Mechanism: It is a selective antagonist at postsynaptic D2 and D3 receptors. It appears to lack effects on norepinephrine, acetylcholine, serotonin, histamine, or GABA receptors. It also stimulates secretion of prolactin. Effect: Antipsychotic agent, dopaminergic antagonist, antidepressant effect, antiemesis, sedation (> 600 mg/day), dopamine reuptake inhibition (< 200 mg/day), antiemesis, antimigraine effects, antivertiginous activity, prolactin-releasing stimulation	Pathogenic genes: *DRD2, DRD3, DRD4* Mechanistic genes: *DRD2, DRD3, DRD4, PRLH, CA2, CA3* Metabolic genes: Substrate: *CYP1A2, CYP2B1, CYP3As* Inhibitor: *BCHE, CYP1A2, CYP2B1, CYP3As* Transporter genes: *SLC22A1, SLC22A2, SLC47A1, SLC47A2, SLC22A3, ABCB1, ABCG2*
	Name: Aripiprazole. IUPAC Name: 7-{4-[4-(2,3-dichlorophenyl) piperazin-1-yl]butoxy}-1,2,3,4-tetrahydroquinolin-2-one Molecular Formula: 448.38538 g/mol Molecular Weight: $C_{23}H_{27}Cl_2N_3O_2$ Mechanism: Partial agonist at the D2 and 5-HT1A receptors, and as an antagonist at the 5-HT2A receptor Effect: Antipsychotic agent, H1-receptor antagonist, serotonergic agonist	Pathogenic genes: *DRD1, DRD2, DRD3, DRD4, HTR1A, HTR2A, HTR2C* Mechanistic genes: *ADRA1A, ADRA1B, ADRA2A, ADRA2B, ADRA2C, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, CALy, GSTP1,DRD1, DRD2, DRD3, DRD4, HRHs, HTR1A, HTR1B, HTR1D, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR6, HTR7, CYP1A1* Metabolic genes: Substrate: *CYP1A2, CYP2A6, CYP2D6 (major), CYP3A4 (major), CYP2C8, CYP2C9, CYP2C19, CYP3A5, FMO3, UGT1A4* Inhibitor: *CYP2D6, CYP3A4, CYP2C19* Transporter genes: *ABCB1*
	Name: Olanzapine. IUPAC Name: 5-methyl-8-(4-methylpiperazin-1-yl)-4-thia-2,9-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),3(7),5,8,10,12-hexaene Molecular Formula: $C_{17}H_{20}N_4S$ Molecular Weight: 312.4325 g/mol Mechanism: It displays potent antagonism of serotonin 5-HT2A and 5-HT2C, dopamine D1-4, histamine H1 and α1-adrenergic receptors, moderate antagonism of 5-HT3 and muscarinic M1-5 receptors, and weak binding to GABA-A, BZD, and β-adrenergic receptors. Effect: Antipsychotic agent, GABA modulator, muscarinic antagonist, serotonin uptake inhibitor, dopaminergic antagonist, serotonergic antagonist, histamine antagonist, antiemetic activity	Pathogenic genes: *COMT, DRD1, DRD2, DRD3, DRD4, GRM3, HTR2A, HTR2C, LPL* Mechanistic genes: *ABCB1, ADRA1A, ADRA1B, ADRB3, AHR, BDNF, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, COMT, DRD1, DRD2, DRD3, DRD4, DRD5, GABRs, GRIN2B, HRH1, HTR2A, HTR2C, HTR3A, HTR6, HRH1,LEP, RGS2, RGS7, SLC6A4, STAT3, TMEM163* Metabolic genes: Substrate: *COMT, CYP1A2 (major), CYP2C9, CYP2D6 (major), CYP3A4, CYP3A5, FMO1, FMO3, GSTM3, TPMT, UGT1A1, UGT1A4, UGT2B10* *Inhibitor: CYP1A2 (weak), CYP2C9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP3A4 (weak)* Inducer: *GSTM1, MAOB, SLCO3A1*

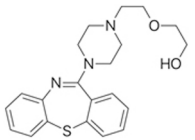
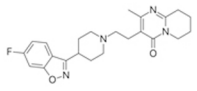
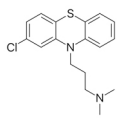
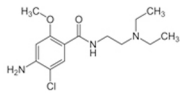
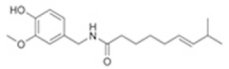
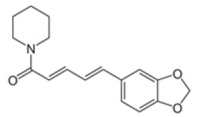
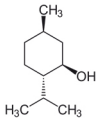
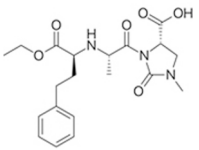
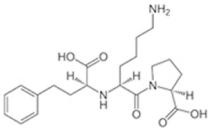
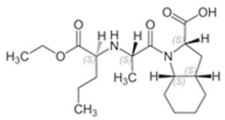
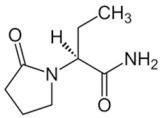
		Transporter genes: *ABCB1 (substrate/inhibitor), KCNH2, SLC6A2, SLC6A4, SLCO3A1* Pleiotropic genes: *APOA5, APOC3, GNB3, LEP, LEPR, LPL*
	Name: Quetiapine IUPAC Name: 2-[2-(4-{2-thia-9-azatricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,9,11,13-heptaen-10-yl}piperazin-1-yl)ethoxy]ethan-1-ol Molecular Formula: $C_{46}H_{54}N_6O_8S_2$ Molecular Weight: 883.08636 g/mol Mechanism: Antagonist at multiple neurotransmitter receptors: serotonin 5-HT1A and 5-HT2, dopamine D1 and D2, histamine H1, and adrenergic α1- and α2-receptors. Effect: Antipsychotic agent, Adrenergic antagonist, histamine antagonist, serotonergic antagonist, dopaminergic antagonist, sedative activity, orthostatic hypotension	Pathogenic genes: *ADRA2A, DRD1, DRD2, DRD4, HTR1A, HTR2A, RGS4* Mechanistic genes: *ADRA1s, ADRA2A, ADRA2B, ADRA2C, BDNF, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, DRD4, HRH1, HTR1A, HTR1B, HTR1D, HTR1E, HTR2A, HTR2B, HTR2C, HTR6, HTR7* Metabolic genes: Substrate*: CYP2D6 (minor), CYP3A4/5 (major), CYP3A7,CYP2C19* Transporter genes: *ABCB1 (substrate/inhibitor), KCNE1, KCNE2, KCNH2, KCNQ1, SCN5A, SLC6A2 (inhibitor)*
	Name: Risperdone IUPAC Name: 3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidin-4-one Molecular Formula: $C_{23}H_{27}FN_4O_2$ Molecular Weight: 410.484483 g/mol Mechanism: Antagonist at multiple neurotransmitter receptors: serotonin 5-HT1A and 5-HT2, dopamine D1 and D2, histamine H1, and adrenergic α1- and α2-receptors. Effect: Antipsychotic agent, H1-receptor antagonist, dopaminergic antagonist, alpha-adrenergic antagonist, serotonergic antagonist, somnolence, orthostatic hypotension	Pathogenic genes: *ADRA2A, BDNF, COMT, DRD1, DRD2, DRD3, DRD4, GRM3, HTR2A, HTR2C, HTR7, PON1, RGS4* Mechanistic genes: *ADRA1A, ADRA1B, ADRA2B, ADRA2C, DRD1, DRD2, DRD3, DRD4, FOS, HRH1, HTR1A, HTR2A, HTR2C, HTR3A, HTR3C, HTR6, HTR7, NR1I2, STAT3* Metabolic genes: Substrate: *COMT, CYP2D6 (major), CYP3A4/5 (minor)* Inhibitor: *CYP2D6 (weak), CYP3A4 (weak)* Inducer: *MAOB* Transporter genes: *ABCB1 (substrate/inhibitor), KCNH2, SLC6A4* Pleiotropic genes: *APOA5, BDNF, RGS2*
	Name: Chlorpromazine IUPAC Name: [3-(2-chloro-10H-phenothiazin-10-yl)propyl]dimethylamine Molecular Formula: $C_{17}H_{19}ClN_2S$ Molecular Weight: 318.86416 g/mol Mechanism: Blocks postsynaptic mesolimbic dopaminergic receptors in the brain. Has actions at all levels of CNS, particularly at subcortical levels; also acts on multiple organ systems. It also exhibits weak ganglionic blocking, has a strong α-drenergic blocking effect, and depresses the release of hypothalamic and hypophyseal hormones. Depresses the reticular activating system Effect: Antipsychotic agent, dopaminergic antagonist, antiemetic, anticholinergic effects, sedative effects, antihistaminic effects, anti-serotonergic activity, hypotension	Pathogenic genes: BDNF, DRD1, DRD2, DRD3, DRD4, HTR2A Mechanistic genes: ADRA1A, ADRA1B, CHRM1, CHRM2, CHRM3, DRD1, DRD2, DRD3, DRD4, DRD5, HRH1, HRH4, HTR1A, HTR2A, HTR2C, HTR6, HTR7, KCNH2, SMPD1, CALM1 Metabolic genes: Substrate: CYP1A2*(minor)*, CYP2A6, CYP2C9, CYP2C19, CYP2D6*(major)*, CYP3A *(minor)*, FMO1, UGT1A3, UGT1A4 Inhibitor:CYP1A2, CYP2D6*(strong)*, CYP2C19, CYP2E1 *(weak)*, CYP3A4, DAO, BCHE Inductor: CYP3A4 Transporter genes: *ABCB1 (substrate/inhibitor), ABCB11 (inhibitor), CFTR* Pleiotropic genes: *ACACA, BDNF, FABP1, LEP, NPY*
	Name: Metoclopramide IUPAC name: 27. Benzamide, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy-, monohydrochloride, monohydrate, Molecular formula: $C_{14}H_{22}ClN_3O_2$ HCl H Molecular Weight: : 354.2 g/mol Mechanism: Blocks dopamine receptors and (when given in higher doses) also blocks serotonin receptors in chemoreceptor trigger zone of CNS. Enhances response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions. Increases lower esophageal sphincter tone Effect: Prokinetic agents, antiemetic	Pathogenic genes: *DRD2* Mechanistic genes: *DRD2, CHRM1, HTR4, HTR3A* Metabolic genes: Substrate: *CYP2D6 (minor), CYP3A4, CYP1A2 (minor)* Inhibitor: *CYP2D6 (strong)* Transporter genes: *ABCB1* Pleiotropic genes: *ACHE*

Table 3. Pharmacogenetics of other drugs in the treatment of neurogenic dysphagia

Drug	Properties	Pharmacogenetics
	Name: Capsaicin IUPAC name: 6-Nonenamide, (E)-N-[(4-hydroxy-3-methoxy-phenyl) methyl]-8-methyl. Molecular Formula: $C_{18}H_{27}NO_3$. Molecular Weight: 305.41 g/mol Mechanism: Induces release of substance P (main chemomediator of pain impulses from the periphery) from peripheral sensory neurons, depletes the neuron of substance P (after repeated stimulation), and prevents reaccumulation. Effect: Skin and Mucous Membrane Agents, local anesthetics, topical	Pathogenic genes: *DBH, MPO, BCHE, TACR2* Mechanistic genes: *TRPV1, PHB2, ABCB1, ACOX1, ACSL3, ALOX5, CFTR, F2, FOS, HTR1D, NOS3, NPC1, PPARA, TAC1, TGFB1, UCP2* Metabolic genes: Substrate: *GLU, CYP2E1 (minor), UGT1A1, UGT1A7, UGT1A9, UGT1A10, GSTP1* Inhibitor: *CYP3A4 (strong), CYP2C9, CYP2D6 (weak), PTGS2, MPO, CYP1A2 (strong), CYP1A2 (strong), CYP19A2 (strong), CYP2E1, DBH, BCHE* Inductor: *CYP1A1, CYP1A2* Transporter genes: *ABCB1* Pleiotropic genes: *TNF*
	Name: Piperine IUAC name: (2E,4E)-5-(2H-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one. Molecular Formula: $C_{17}H_{19}NO_3$ Molecular Weight: 285.34 g/mol Mechanism: An alkaloid isolated from the plant *Piper nigrum* that has a role as an NF-kappaB inhibitor, a plant metabolite, a food component, and a human blood serum metabolite. It is a member of benzodioxoles, an N-acylpiperidine, a piperidine alkaloid, and a tertiary carboxamide. Effect: Skin and mucous membrane agents, local anesthetics, topical	Mechanistic genes: *TRPV1, TRPA1, NR1I2, FOS* Metabolic genes: Substrate: *CYP1A1* Inhibitor: *CYP3A4, CYP2C9, CYP2D6 (weak)* Transporter genes: *ABCB1 (inhibitor)* Pleiotropic genes: *TNF, IL1B, IL6*
	Name: Menthol IUPAC name: (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol Molecular Formula: $C_{10}H_{20}O$ Molecular Weight: 156.26 g/mol Mechanism: A local anesthetic with counterirritant qualities, widely used to relieve minor throat irritation. Menthol also acts as a weak κ-opioid receptor agonist. Effect: Skin and mucous membrane agents, local anesthetics, topical	Mechanistic genes: *TRPM8, TOP1, FOS* Metabolic genes: Substrate: *CYP2A6*
	Name: Imidapril IUPAC name: (4S)-3-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid;hydrochloride Molecular Formula: $C_2H_{27}N_3O_6$ Molecular weight: 405,44 g/mol Mechanism: Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Effect: Angiotensin-converting enzyme inhibitors	Mechanistic genes: ACE, *AGT, AGTR1, BDKRB2, CES1, CES2, NOS3*
	Name: Lisinopril IUPAC name: L-Proline, 1-[N 2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, dihydrate, (S) Molecular Formula: $C_{21}H_{31}N_3O_{52}H_2O$ Molecular Weight: 441.52 g/mol Mechanism: Competitive inhibitor of angiotensin-converting enzyme (ACE). Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Effect: Angiotensin-converting enzyme inhibitors	Mechanistic genes: *ACE, ACE2, REN, AGT; BDKRB2, MMP3, NOS3, NPPA* Metabolic genes: Substate: *CYP3A4/5 (major)*

	Name: Perindopril IUPAC name: 1H-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2α,3aβ,7aβ]]- Molecular Formula: $C_{19}H_{32}N_2O_5$ $C_4H_{11}N$ Molecular Weight: 441.60 g/mol Mechanism: A prodrug for perindoprilat, which acts as competitive inhibitor of angiotensin-converting enzyme. Prevents c conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, and causes an increase in plasma renin activity and reduction in aldosterone secretion. Effect: Angiotensin-converting enzyme inhibitors	Mechanistic genes: *SFRP4, ACE, AGT, AGTR1, MMP2, TGFB1* Metabolic genes: Substate: *BCHE* Transporter genes: *SLC15A1, SLC15A2*
	Name: Levetiracetam IUPAC name: 1-Pyrrolidineacetamide, α-ethyl-2-oxo-, (α S)- Molecular Formula: $C_8H_{14}N_2O_2$ Molecular Weight: 170.21 g/mol Mechanism: The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission. Effect: Anticonvulsants, miscellaneous	Mechanistic genes: *SV2A, CACNA1B, MT-TK* Metabolic genes: Unknown: *CYP2D6, CYP3A4* Transporter genes: *ABCB1*

The T allele of rs17601696 (parent gene *FGFR2*) is reported to be associated with ND[72].

PHARMACOGENETICS OF DRUGS EMPLOYED IN OTHER ASSOCIATED OROPHARYNGEAL SYMPTOMS IN NEUROGENIC DYSPHAGIA

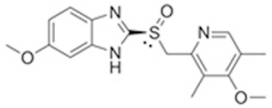
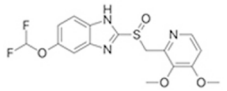
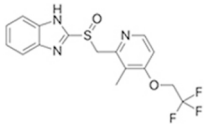
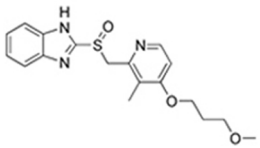
Together with strategies aimed at controlling ND, it is also important to manage those factors that may exacerbate symptoms and increase the risk of aspiration. Many patients with CNS conditions exhibit sialorrhea, hiccups, xerostomia, or reflux with swallowing difficulties. Prior to considering systemic drugs, it is recommended that local treatment or physical measures be initiated first [Table 4][37].

Sialorrhea

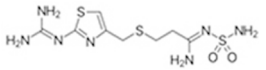
The most used treatments for the control of hypersalivation in patients with neurological damage are based on their anticholinergic profiles. This includes a heterogeneous group of drugs such as amitriptyline, scopolamine, glycopyrronium chloride, trihexyphenidyl, atropine, or thiopium bromide. These anticholinergic agents present an added benefit in the control of other motor symptoms, as occurs in patients with Parkinson's disease[73]. However, their main drawback is the occurrence of frequent side effects that include sedation, cognitive deficits, constipation, urinary retention, tremor, and blurred vision. Within a population where the prevalence of dementia is high, elderly patients often use drugs with anticholinergic effects, and frequently in combination. Furthermore, in this patient population, polymedication may mask symptoms that are misdiagnosed as pathology unrelated to drug toxicity[74].

Concerning the pharmacogenetic profile, anticholinergic drug exposure shows associated variants located at chromosome 3p21.1 locus, with the top SNP rs1076425 in the inter-alpha-trypsin inhibitor heavy chain 1 (*ITIH1*) gene[75]. Subjects with *CYP2D6/CYP2C19* PM phenotype increase the risk of adverse reactions due to increased serum drug concentrations[76]. In contrast, polymorphisms of the *ARGEF10, ADRB3, ROCK2,* and *CYP3A4* genes in the cholinergic

Table 4. Pharmacogenetics of drugs in associated symptoms and neurogenic dysphagia

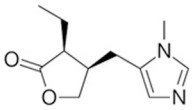
Drug	Properties	Pharmacogenetics
	Name: Omeprazole IUPAC name: 1H-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl] Molecular Formula: $C_{17}H_{19}N_3O_3S$ Molecular weight: 345.42 g/mol Mechanism: Concentrates in acid conditions of parietal cell secretory canaliculi. Forms active sulfenamide metabolite which irreversibly binds to and inactivates hydrogen-potassium ATPase (proton or acid pump), blocking final step in secretion of hydrochloric acid. Acid secretion is inhibited until additional hydrogen-potassium ATPase is synthesized, resulting in prolonged duration of action. Suppresses *H. pylori* in duodenal ulcer and/or reflux esophagitis infected with organism. Effect: Antiulcer agents and acid suppressants, proton-pump inhibitors, substituted benzimidazole	Mechanistic genes: *ATP4A, AHR, ADH1C, ALDH3A1, AHR, ATP4A, ATP4B, CASR, CBR1, CFTR, CHRM3, FMO1, HRH2, MMP2, NR1I2, NR1I3, RRAS2, SNAP25, SSTR2* Metabolic genes: Substrate: *CYP1A1, CYP2C8 (minor), CYP2C9 (minor), CYP2C18 (minor), CYP3A4 (major), CYP2C19 (major), CYP2A6 (minor), CYP2D6 (minor)* Inhibitor: *CYP1A2 (moderate), CYP2C9 (moderate), CYP2D6 (moderate), CYP3A4 (moderate), CYP2C19 (strong)* Inducer: *CYP1A1, CYP1A2, CYP1B1, CYP3A4, CYP2B6* Transporter genes *ABCG2 (inhibitor), ABCC3 (inducer), ABCB1, ABCC6 (substrate/inhibitor), ABCC6, UGT1A1*
	Name: Pantoprazole IUPAC name: (1) 1H-Benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl] Molecular Formula: $C_{16}H_{15}F_2N_3O_4S$. Molecular weight: 383.37 g/mol Action: Suppresses gastric acid secretion by inhibiting parietal cell H+/K+ ATP pump Effect: Antiulcer agents and acid suppressants, proton-pump inhibitors, substituted benzimidazole	Mechanistic genes: *ATP4A, DDAH1, ABCC2, CASR, CHRM3, HRH2, IL1B, PPAs, SNAP25, SSTR2* Metabolic genes: Substrate: *CYP3A4 (major), CYP2C19, CYP2C19 (major), CYP2D6 (minor), SULTs, UGTs* Inhibitor: *CYP2C19 (strong),CYP1A2 (weak), CYP2C9 (moderate), CYP2D6 (weak), CYP3A4 (moderate)* Inducer: *CYP1A2, CYP3A4* Transporter genes: *ABCB1 (substrate/inhibitor), ABCG2 (substrate/Inhibitor), SLC22A8 (inhibitor)*
	Name: Lansoprazole IUPAC name: 1H-Benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]- Molecular Formula: $C_{16}H_{14}F_3N_3O_2S$ Molecular Weight: 369.36 g/mol Mechanism: Decreases acid secretion in gastric parietal cells through inhibition of (H +, K +)-ATPase enzyme system, blocking final step in gastric acid production Effect: Antiulcer agents and acid suppressants, proton-pump inhibitors, substituted benzimidazole	Mechanistic genes: *ATP4A; CASR, MAPT, CYP1A1, CYP1B1, HRH2, SNAP25, SSTR2* Metabolic genes: Substrate: *CYP2C8 (major), CYP2C9 (major), CYP2C18 (major), CYP2C19 (major), CYP3A4/5 (major); POR* Inhibitor: *CYP2C9, (moderate), CYP2C19 (strong), CYP3A4 CYP2D6 (moderate), CYP2E1 (moderate), CYP3A4 (moderate), PPA1* Inducer: *CYP1A2, CYP1A1, CYP1B1, CYP2C9, CYP3A4* Transporter genes: *ABCG2 (inhibitor), ABCB1 (substrate/inhibitor), SLC22A8 (inhibitor), SLC22A1, SLC22A2, SLC22A3*
	Name: Rabeprazole IUPAC name: 1H-Benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl] Molecular Formula: $C_{18}H_{20}N_3NaO_3S$ Molecular weight: 381.42 g/mol Action: Suppresses gastric acid secretion by inhibiting parietal cell H+/K+ ATP pump Effect: Antiulcer agents and acid suppressants, proton-pump inhibitors, substituted benzimidazole	Mechanistic genes: *ATP4A, DDAH1, ATP4B, CASR, CHRM3, HRH2, HTR1D, NR1I2, SNAP25, SSTR2* Metabolic genes: Substrate: *CYP3A4 (major), CYP2C19 (major), CYP2D6 (major)* *Inhibitor: CYP2C9 (moderate), CYP2C8 (moderate), CYP2C19 (strong), CYP2D6 (moderate)*

Transporter genes: *ABCB1 (substrate/inhibitor), ABCG2 (substrate/inhibitor), SLC22A8 (inhibitor)*



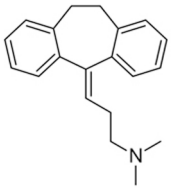
Name: Famotidine
IUPAC name: Propanimidamide, N′-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-
Molecular formular: $C_8H_{15}N_7O_2S_3$
Molecular weight: 337.45 g/mol
Action: Famotidine works by reducing the amount of acid in the stomach, thereby reducing pain and allowing the ulcer to heal, and through a competitive inhibition of histamine at H2 receptors of gastric parietal cells, which inhibits gastric acid secretion.
Effect: Antiulcer agents and acid suppressants, histamine H2-antagonists

Pathogenic genes: *HRH2*
Mechanistic genes: *HRH2, CAT, FOS*
Metabolic genes:
Inhibitor: *CYP1A2*
Transporter genes: *SLC22A6, SLC22A8 (Substrate/inhibitor), SCL22A2 (Inhibitor), SLC47A1 (Inhibitor)*



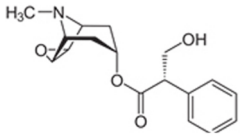
Name: Pilocarpine
IUPAC name:. 2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)methyl]-, monohydrochloride, (3S-cis)-
Molecular Formula: $C_{11}H_{16}N_2O_2$
Molecular weight: 244.72 g/mol
Mechanism: Directly stimulates cholinergic receptors in eye causing miosis (by contraction of iris sphincter) and loss of accommodation (by constriction of ciliary muscle) and lowering of intraocular pressure (with decreased resistance to aqueous humor outflow)
Effect: Antiglaucoma agents, miotics, cholinergic agonists

Pathogenic genes: *BDNF*
Mechanistic genes:*CHRM3,CHRM1, CHRM2, CHRM4 BDNF; CHRNs; FOS; GRIA3*
Metabolic genes: Substrate: *CYP1A2 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (minor)*
Inhibitor: *CYP2A6, CYP3A4 (weak), CYP2A6 (weak), CYP2E1 (weak)*



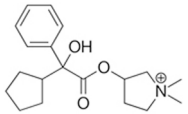
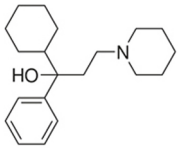
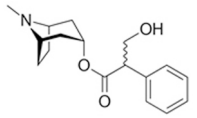
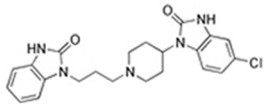
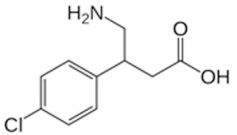
Name: Amitriptyline
IUPAC Name: dimethyl(3-{tricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,11,13-hexaen-2-ylidene}propyl)amine
Molecular Formula: $C_{20}H_{24}ClN$
Molecular Weight: 313.86426 g/mol
Mechanism: Increases synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibiting their reuptake in the presynaptic neuronal membrane
Effect: Adrenergic uptake inhibition, antimigraine activity, analgesic (nonnarcotic) activity, antidepressant action

Pathogenic genes: *ABCB1, GNB3, HTRs, NTRK2, SLC6A4, TNF*
Mechanistic genes: *ADRA1A, ADRA1B, ADRA1D, ADRA2A, HTRs, HRH1, HRH2, HRH4, SIGMAR1, NTRK1, NTRK2, OPRD1, OPRK1, OPRM1*
Metabolic genes: Substrate: *CYP1A2 (minor), CYP2B6 (minor), CYP2C8, CYP2C9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4/5 (major), GSTP1, UGT1A3, UGT1A4, UGT2B10*
Inhibitor: *CYP1A2 (moderate), CYP2C9 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak)*
Transporter genes: *ABCB1 (substrate/inhibitor), ABCC2 (inhibitor), ABCG2 (inhibitor), KCNA1, KCNE2, KCNH2, KCNQ1, KCNQ2, KCNQ3, SCN5A, SLC6A2, SLC6A4*
Pleiotropic genes: *FABP1, GNAS, GNB3, NTRK1, TNF*



Name: Scopolamine
IUPAC Name: Benzeneacetic acid, α-(hydroxymethyl)-, 9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester, hydrobromide, trihydrate, [7(S)-(1α,2β,4β,5α,7β)]-
Molecular Formula: $C_{17}H_{21}NO_4HBr_3H_2O$
Molecular weight: 438.31 g/mol
Mechanism: Competitively inhibits acetylcholine and other cholinergic stimuli at autonomic effectors innervated by postganglionic cholinergic nerves and, to a lesser extent, on smooth muscles that lack cholinergic innervation. Doses used to decrease gastric secretions likely to cause dryness of mouth (xerostomia). Antagonizes histamine and serotonin
Effect: Anticholinergic agents, antimuscarinics/antispasmodics

Mechanistic genes: *CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, CHRNA4, CHRNB2, SI*
Metabolic genes: *Substrate:CYP3A4*

	Name: Glycopyrrolate IUPAC Name: Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, bromide Molecular Formula: $C_{19}H_{28}BrNO_3$ Molecular Weight: 398.33 g/mol Mechanism: Blocks action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and CNS Effect: Anticholinergic agents, antimuscarinics/antispasmodics	Mechanistic genes: *CHRM1, CHRM2, CHRM3, CHRM4, CHRM5* Metabolic genes: Substrate: *CYP1A2, CYP2B6, CYP2C9, CYP2D6,*CYP2C18, CYP2C19, CYP3A4 Transporter genes: *SLC22A2, SLC47A1*
	Name: Trihexyphenidyl IUPAC Name: 1-Piperidinepropanol,α-cyclohexyl-α-phenyl Molecular Formula: $C_{20}H_{31}NO$ Molecular Weight: 301,46 g/mol Mechanism: Exerts direct inhibitory effect on parasympathetic nervous system. It also has a relaxing effect on smooth musculature, exerted both directly on muscle itself and indirectly through parasympathetic nervous system (inhibitory effect) Effect: Antiparkinsonian agents, anticholinergic agents	Pathogenic genes: *PARK2* Mechanistic genes: *CHRM1, CHRM2, CHRM3, CHRM4, CHRM5*
	Name: Atropine IUPAC Name: Benzeneacetic acid, α-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, endo-(-) Molecular Formula: $C_{17}H_{23}NO_3$ Molecular Weight: 289.37 g/mol Mechanism: Blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and CNS. Increases cardiac output, dries secretions. Reverses the muscarinic effects of cholinergic poisoning Effect: Mydriatics, anticholinergic agents, antimuscarinics/antispasmodics, antidote	Mechanistic genes: *CHRM1, CHRM2; CHRM3, CHRM4, CHRM5, CHRNA4, CHRNB2, FOS, GLRA1, PTGS2, TP53* Transporter genes: *ABCB11* Pleiotropic genes: *ACHE, CES1*
	Name: Domperidone IUPAC name: 2H-Benzimidazol-2-one, 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro- Molecular Formula: $C_{22}H_{24}ClN_5O_2$ Molecular weight: 425.91 g/mol Mechanism: Has peripheral dopamine receptor blocking properties. Increases esophageal peristalsis; lowers esophageal sphincter pressure, gastric motility, and peristalsis; and enhances gastroduodenal coordination, therefore facilitating gastric emptying and decreasing small bowel transit time Effect: Prokinetic agents, dopamine antagonist	Pathogenic genes: *DRD2, DRD3* Mechanistic genes: *DRD2, DRD3* Metabolic genes: Substrate: *CYP3A5 (major), CYP3A7, CYP3A4 (major), CYP1A2 (minor), CYP2B6 (minor), CYP2C8 (minor), CYP2D6 (minor), CYBs (major)* Transporter genes: *ABCB1*
	Name: Baclofen IUPAC name: Butanoic acid, 4-amino-3-(4-chlorophenyl)- Molecular Formula: $C_{10}H_{12}ClNO$ Molecular weight: 213.66 g/mol Mechanism: Inhibits the transmission of mono/polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals Effect: GABA-derivative skeletal muscle relaxants	Mechanistic genes: *GABBR1, GABBR2, CXCR4, CFTR* Transporter genes: *ABCC9, ABCC12, SLC28A1*

pathway do not appear to significantly modify parameters related to clinical improvement[77].

Xerostomia

The first line of treatment for xerostomia is to employ local therapies (artificial saliva, sialogogues), avoiding the use of systemic medications (pilocarpine) as the first choices due to their common negative effects. Side effects include blurred vision, bronchoconstriction, hiccup, sweating, hypotension, bradycardia,

cutaneous vasodilatation, nausea, diarrhea, or increased urinary frequency[78]. Polymorphisms in *CYP2A6* modify the pharmacokinetics of this drug, where the clearance of pilocarpine is significantly lower. *In vivo*, these slow metabolizers have two inactive *CYP2A6* alleles: *CYP2A6**4A, *CYP2A6**7, *CYP2A6**9, or *CYP2A6* *10[79].

Pharyngolaryngeal reflux

Proton-pump inhibitors (PPI) and H2 receptor antagonists show improvements in gastro-esophageal reflux disease-like symptoms, being PPIs more effective in subjects with negative endoscopic findings[80]. CYP2C19 is the most prominent of the PPI-metabolizing enzymes; *CYP2C19*-specific single nucleotide polymorphisms reduce clearance proportionally and increase exposure and prolong proton-pump inhibition. Differences in *CYP2C19*-mediated metabolism lead to marked interpatient variability in acid suppression, drug–drug interaction potential, and clinical efficacy[81-84]. This phenomenon has also been observed with *CYP3A4*, but to a lesser degree[82].

Hiccup

Pharmacologically, multiple drugs with different targets are available to control hiccups. Baclofen is a drug commonly used in intractable hiccups[85]. The *ABCC9* SNP (rs11046232, heterozygous AT versus reference TT genotype) is associated with a two-fold increase in oral baclofen clearance[86]. Allelic variants with the *ABCC12, SLC28A1,* and *PPARD* SNPs generate variable responses in cerebral palsy[86]. Chlorpromazine, domperidone, and metoclopramide can also be useful. However, since these are antidopaminergic drugs, they should be prescribed with caution because they may worsen dysphagia. Domperidone would be recommended amongst these medications because of its limited transit through the blood–brain barrier and exceptional central effects[87]. Paradoxically, metoclopramide and other antidopaminergic drugs may be beneficial by reducing nausea and vomiting in patients with ND, and therefore the risk of aspiration. In these cases, dose adjustment and patient selection are essential due to the risk of adverse effects[45].

CONCLUSION

Treatment of ND must be comprehensive and multidisciplinary. Pharmacological treatments are support tools for other therapeutic measures. Dopamine is the main neurotransmitter implicated in these swallowing disorders. Of the genes that encode dopaminergic receptors, *DRD1* is the most important in the prediction and treatment of ND. Other genes such as *COMT* and *DBH* have also been considered in the management of ND. Polymorphisms in dopaminergic and antidopaminergic agents are associated, respectively, with undesired or insufficient effects and increased risk of swallowing impairment. SP is another main factor in the treatment of ND, which can be altered with antidopaminergic agents. SP degradation is blocked with TRP channel agonists such as capsaicin, piperine, menthol, and ACE inhibitors. Genetic variants influence the therapeutic response of TRP channel agonists. When symptoms coexist that can worsen dysphagia and increase the risk of aspiration (e.g., reflux, xerostomia, sialorrhea, and hiccups), it is recommended to carefully associate other medications with ND treatment due to the risk of adverse effects, which may even include swallowing disorders. Dose adjustment and choice of drug in polypharmacy patients is one of the main objectives of a pharmacogenetic analysis.

DECLARATIONS

Acknowledgments

Joaquin Guerra would like to thank Dante Doncel Guerrero for being the source of inspiration to develop this article.

Authors' contributions

Made substantial contributions to conception and design of the review and interpretation: Guerra J
Read, adjusted and approved the final manuscript: Naidoo V, Cacabelos R

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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