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Neuropsychiatric Disease and Treatment

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/dndt20

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To cite this article: Ivy Cheng, Adeel Hamad, Ayodele Sasegbon & Shaheen Hamdy (2022) Advances in the Treatment of Dysphagia in Neurological Disorders: A Review of Current Evidence and Future Considerations, Neuropsychiatric Disease and Treatment, , 2251-2263, DOI: 10.2147/NDT.S371624

To link to this article: https://doi.org/10.2147/NDT.S371624

Published online: 14 Oct 2022.

Neuropsychiatric Disease and Treatment

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REVIEW

Advances in the Treatment of Dysphagia in Neurological Disorders: A Review of Current Evidence and Future Considerations

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Abstract: Dysphagia, which refers to difficult and/or disordered swallowing, is a common problem associated with various neurological diseases such as stroke, motor neuron diseases and neurodegenerative diseases. Traditionally, dysphagia treatments are either compensatory, which includes modifications of bolus texture or feeding posture, or rehabilitative, which includes behavioral exercises and sensory stimulation. Despite being widely adopted in clinical practice, recent views have challenged the clinical efficacy of these treatments due to the low level of evidence supported by mainly non-controlled studies. As such, with advancements in technology and scientific research methods, recent times have seen a surge in the development of novel dysphagia treatments and an increasing number of robust randomized controlled clinical trials. In this review, we will review the clinical evidence of several newly introduced treatments for dysphagia in the last two decades, including rehabilitative exercises, biofeedback, pharmacological treatments, neuromodulation treatments and soft robotics. Despite the recent improvements in the quality of evidence for the efficacy of dysphagia treatments, several critical issues, including heterogeneity in treatment regimens, long-term treatment effects, underlying mechanisms of some neuromodulation treatments, and the effects of these techniques in non-stroke dysphagia, remain to be addressed in future clinical trials.

Keywords: dysphagia, neuromodulation, pharmacology, rehabilitation, review, treatment

Introduction

Swallowing describes the process of propulsion of food from the oral cavity to the stomach. It is considered a complex neuromuscular process that needs the coordination of more than 25 muscle pairs (Table 1).[1] The process of swallowing is traditionally divided into three mutually dependent stages, namely the oral, pharyngeal and esophageal stages. The oral stage is considered voluntary and may be further subdivided into the oral preparatory and propulsive stages. The oral preparatory stage prepares the bolus for swallowing by concurrently breaking down solid material into a size suitable for subsequent propulsion through the coordinated actions of the tongue, teeth and cheeks while mixing the partially prepared matter with saliva to form a cohesive bolus. The formation of an appropriate bolus constitutes the end of the oral preparatory stage. The propulsive stage involves first positioning the bolus of fluid on the superior surface of the tongue. The tip of the tongue then flexes forcing the bolus toward the pharynx.[1] The latter two stages of swallowing are considered increasingly automatic and involuntary, allowing the bolus to safely and effectively pass through the pharynx avoiding the adjacent airway, and ultimately enter the stomach.[2] The physiological actions at each stage of swallowing, the muscles involved in each action and the innervation of these muscles are summarized in Table 1.

The complex process of swallowing is mediated by the central nervous system and involves dynamic interactions and coordination between the sensory and motor neural pathways. Recent literature utilizing functional magnetic resonance imaging (fMRI) and other brain imaging modalities has demonstrated that the cortex is involved in the act of

Received: 15 August 2022
Accepted: 8 October 2022
Published: 14 October 2022

Table 1 Different Stages of Swallowing, Muscle Involvement and Innervation at Each Stage and Potential Treatment Options for Disorders at Each Stage

Stages of Swallowing	Action	Muscles Involved	Innervation	Potential Treatment Options*
Oral preparatory	• Voluntary • Fluid: containment of fluid within oral cavity • Solid: mastication to break down larger bolus and mix it with saliva to form a cohesive bolus	• Orbicularis oris • Buccinator • Risorius • Lip elevators • Lip depressors • Superior and inferior longitudinal muscles of tongue • Transverse and vertical muscles of tongue • Genioglossus • Hyoglossus • Styloglossus • Palatoglossus • Temporal • Masseter • Lateral pterygoid • Medial pterygoid	• Facial Nerve (CN VII) • Glossopharyngeal (CN IX) • Hypoglossal (CN XII)	• Bolus texture modification • Rehabilitative exercises that involve lip and tongue muscles[+] • Rehabilitative exercises with biofeedback • NMES • TRP channel agonists
Oral propulsive	• Voluntary • Positioning the bolus of fluid on the superior surface of the tongue • The tip of the tongue then forces the bolus toward the pharynx.			
Pharyngeal	• Involuntary • Soft palate elevates to seal the opening of nasopharynx • Vocal cords and arytenoids abduct to seal the opening of trachea • Epiglottis inverts to cover the laryngeal vestibule • Hyoid bone and larynx move superiorly and anteriorly which widens and elevates the pharynx and the upper esophageal sphincter (UES)	• Tensor veli palatine • Palatoglossus • Palatopharyngeus • Levator veli palatine • Musculus uvulae • Anterior digastric • Geniohyoid • Stylohyoid • Styloglossus • Superior, middle and • inferior pharyngeal constrictors • Palatopharyngeus • Palatoglossus	• Mandibular branch of trigeminal nerve (CN V3) • Pharyngeal branch of vagus nerve (CN X) • Inferior alveolar nerve • Hypoglossal nerve (CN XII) • Facial nerve (CN VII) • Vagus nerve (CN X)	• Rehabilitative exercises with biofeedback • EMST • CTAR • NMES • TRP channel agonists • PES • rTMS • tDCS
Esophageal	• Bolus travel downward along the esophagus by esophageal peristalsis and gravity • Lower esophageal sphincter relaxes, allowing bolus to enter the stomach	• Cricopharyngeus • upper esophageal sphincter • lower esophageal sphincter	• Vagus nerve (CN X)	• Esophageal endoprosthetic stents to expand the esophagus in patients with esophageal strictures

Notes: *Treatment options that have been discussed in this review. [+]Clinical efficacy to improve swallowing has not been established.
Abbreviations: CN, cranial nerve; NMES, neuromuscular electrical stimulation; TRP, transient receptor potential, EMST, expiratory muscle strengthening training; CTAR, chin-tuck against resistance; PES, pharyngeal electrical stimulation; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

swallowing.[3] Studies indicate that neuronal activity is observed in several distinct cortical loci during swallowing of saliva or water.[4] A recent review on the cerebral control of swallowing that summarised the neuroimaging evidence from literature in healthy adults showed that cortical regions including primary motor cortex, primary sensory cortex, insula, cingulate cortex, supplementary motor area, premotor cortex, auditory cortex, inferior frontal gyrus, parietooccipital and prefrontal cortex, operculum, putamen, thalamus, global pallidus, internal capsule, cerebellum, corpus callosum, basal ganglia, caudate, pons and midbrain, inferior parietal lobule are activated during swallowing (For detailed analysis and discussion, please refer to the review by Cheng et al, 2022).[5]

The oral and pharyngeal regions are known to have sensory fibres innervating the mucosa, submucosal, and muscle regions, where numerous mechanical receptors which are sensitive to touch and pressure, chemical receptors which may respond to taste and water, stretch or length receptors, and receptors responding to pain and temperature are located.[6] The receptors located in the larynx and epiglottis have been found to be largely free ending with a chemosensory component and possibly also taste sensing. When these receptors are triggered, sensory signals are generated and transmitted through the afferent neural pathways to lower level circuitry in the brainstem and then rostrally to subcortex and cortex.[5] Once the signal is processed, motor signals are generated in the primary motor cortex (primarily) which are transmitted through the efferent neural pathways to the peripheral muscles in which the execution of swallowing takes place.[5] Sensory inputs are therefore important for the initiation and regulation of motor sequences of swallowing.[5]

It is known from current literature on human studies that small amounts of food begin to be transported to the pharynx during mastication and processing of food in the oral cavity.[7] During the pharyngeal stage of swallowing, the posterior oral cavity and the oropharynx form a functional space, where food is squeezed past the faucial pillars.[8] Traditionally, it is believed that food propelled through the pillars triggers the pharyngeal swallow and the reflexive physiological mechanisms via its interactions with the innervated mucosa overlying them. However, recent studies have updated our knowledge regarding the initiation of the swallowing reflex. Stephen et al found that some older healthy adults initiated the swallow reflex after the bolus head has reached the faucial pillars and below the tongue base and mandibular ramus (TMI) without penetration or aspiration.[9] Furthermore, a large-scale study with 195 healthy adults identified substantial variability in the bolus head location at the trigger of swallow and such variability may be related to the sex and race of an individual.[10] A number of physiological mechanisms take place during the pharyngeal stage of swallowing: soft palate elevates to seal the opening of nasopharynx; vocal cords and arytenoids abduct to seal the opening of trachea; epiglottis inverts to cover the laryngeal vestibule; and hyoid bone and larynx move superiorly and anteriorly which widens and elevates the pharynx and the upper esophageal sphincter (UES).[1]

The esophagus is a muscular tube that connects the pharynx with the stomach and has specialized muscular tissue acting as sphincters at either end (UES; and lower esophageal sphincter, LES). The esophageal neural control is dependent on whether the muscle is striated or smooth. The esophageal phase of swallowing is dominated by peristaltic waves which are coordinated by the enteric and central nervous systems.[11] The enteric ganglia in the esophageal walls facilitate peristalsis, communicate with and are influenced by the brain stem and the cortex.[12] The nerves in the esophagus which lead to peristalsis are excitatory utilizing muscarinic cholinergic receptors or inhibitory using nitric oxide.[11] Nitric oxide appears to be important for the precise timing of peristaltic activity descending in the smooth muscle, while cholinergic innervation generates the motor response. The esophageal phase of swallowing depends upon the relaxation of its two sphincters, and the coordinated action of striated and smooth muscles composing the longitudinal and circular muscles of the esophagus.[6]

Dysphagia may be considered as any disruption in the process of swallowing. Its classical definition is that of difficult and/or disordered swallowing.[1] Patients with anatomical or physiologic deficits in the mouth, pharynx, larynx, and esophagus may demonstrate signs and symptoms of dysphagia.[13] Dysphagia can be categorized in terms of the location and type of pathology, for example, mechanical or inflammatory processes leading to changes in bolus transit.[2] The primary approach may be focused on the anatomical region, ie, oropharyngeal or upper esophageal pathology. Oropharyngeal dysphagia is essentially difficult swallowing due to pathology affecting the oropharynx whereas esophageal dysphagia is caused by pathology affecting that organ. Oropharyngeal dysphagia and esophageal dysphagia may be distinguished on the basis of a careful focused history with an emphasis on the presence of immediate aspiration or cough with swallowing and other symptoms, such as nasopharyngeal regurgitation, voice changes, or the perception that there is an uncoordinated swallow at initiation.[13]

Many conditions may lead to a disruption in the normal process of swallowing eventually causing some degree of dysphagia. Moreover, dysphagia can occur at any age and is known to affect around 4% of the population; with greater prevalence (approximately 15%) in the elderly.[14] Some studies suggest that around 30% of older patients in hospital and up to 68% of those in nursing homes have some form of disordered swallowing.[15] Recent literature has identified sarcopenia as a major cause of dysphagia in the elderly.[14] Apart from old age, it is also known that dysphagia may be associated with neurological disorders such as stroke. Current literature shows that dysfunctional swallowing may be found in at least 50% of all patients with stroke.[16] A patient with dysphagia may consequently suffer from malnutrition, dehydration and aspiration pneumonia.[16]

Diagnosis of dysphagia is the first and most important step in the recovery journey of patients with dysphagia associated with neurological diseases. An accurate diagnosis requires an approach focused on motility and imaging techniques. The use of videofluoroscopic swallow study (VFSS) has been studied extensively, but it is not without cost restraints, is non-transportable and exposes patients to ionizing radiation. Video-endoscopic study (Flexible Endoscopic Swallowing Study, FEES) provides the ability to directly observe oropharyngeal structures as they move during swallowing but it requires expertise and the capital equipment can be costly, but the technique can be done at the bedside. More recently, some studies have used ultrasound to study the swallow, and although it has mainly been used in research, there is the plausible promise that it could be used as an adjunct in the assessment of swallowing.[17,18]

Establishing an accurate diagnosis of the underlying dysphagia-causing pathology is important in determining the probable natural evolution of dysphagia, the ultimate aim of treatment and which treatment modality is best placed to address the underlying deficit. Providing the right treatment should aid recovery but such rehabilitation does require a multidisciplinary approach. Beyond conventional approaches such as texture modification and behavioural therapies, recent literature has seen some progress on the pharmacological front albeit with few options. Neuromodulation has also shown some promising results over the past few years. Furthermore, the use of soft robotics has opened a new arena for the study of dysphagia and the development of novel treatments for this cohort of patients.

An example of designing treatment based on the etiopathology, through the medium of neuromodulation, is by contrasting the disease of stroke with Parkinson's disease (PD). Both commonly cause dysphagia but stroke causes dysphagia after a single insult that damages cortical or brainstem structures associated with swallowing. Depending on the location of the insult, different treatment modalities may be more or less applicable. Should the stroke have predominantly damaged the sensory cortices, a peripherally acting neuromodulation technique may be selected due to its effects at increasing sensory inflow into the swallowing sensorimotor system. By contrast, should the stroke have affected the brainstem, a directly acting neuromodulation technique may be best placed to effect beneficial neuroplastic change. Furthermore, although more studies are needed in this area, a short course of neuromodulation may be sufficient to reverse the damage from a single stroke-related insult. On the other hand, PD is a progressive neurodegenerative disease where dysphagia arises as a result of loss of neuronal function over a long period of time. Therefore, a prolonged course of regular neuromodulation interventions may be required with the aim to prevent further decline rather than fully normalize swallowing function. Table 1 provides some suggestions of potential treatment options for each stage of swallowing based on the treatments that we have discussed in this review.

Compensatory Strategies

Compensatory strategies for dysphagia were first described in the late 1970s with the aim to improve swallowing safety through modifications of food texture, liquid consistency and/or feeding posture.[19] Studies have shown that bolus volume and viscosity alter swallow biomechanics in various ways, including changing the duration, extent and timing of movements of oropharyngeal structures during swallowing, as well as the dynamics of bolus flow.[19] As such, early studies proposed that modification of bolus texture may reduce the risk of misdirection of bolus during swallowing. Indeed, several systematic reviews have found that increasing bolus viscosity can reduce the risk of airway penetration in patients with dysphagia.[20–22] However, such changes in the physical properties of the bolus are also associated with lowered palatability and increased pharyngeal residue, which may subsequently increase the risk of post-swallow aspiration. To date, there is insufficient literature to depict the effects of different bolus viscosities on swallowing physiology and clinical outcomes.

Apart from bolus modifications, changing body posture while swallowing has been proposed to improve swallowing safety. For example, chin tuck posture has been found to narrow airway entrance[23] and increase the duration of laryngeal vestibule closure during swallowing,[24] hence providing a better airway protection compared to head neutral posture. A large scale randomized controlled trial (RCT) study with 515 patients with dementia or PD who aspirated on thin liquids found that the effects of two compensatory strategies, chin tuck posture and thickened fluid, on the 3-month cumulative incidence of pneumonia were comparable.[25] However, patients who received thickened fluid intervention had higher incidence of dehydration, urinary tract infection and fever than those who received with chin-tuck posture intervention.

Taken together, modifications of bolus texture and feeding posture may improve swallowing safety, but these strategies may be accompanied by drawbacks including increased pharyngeal residue and risk of dehydration and associated complications. The latest European Stroke Organization and European Society for Swallowing Disorders guideline recommended that, in patients with post-stroke dysphagia, texture-modified diets and/or thickened liquids should be prescribed only based on an appropriate assessment of swallowing, and with constant monitoring of fluid balance and nutritional intake.[22]

Rehabilitative Exercises

Rehabilitative exercise is one of the most common treatment options recommended by speech therapists for patients with dysphagia. The aim of these exercises is to improve swallowing efficiency and safety through improving the strength, coordination and/or motility of structures that are involved in swallowing, such as lips, tongue, pharynx and UES, based on the patient's impairments.[26] For example, lingual strengthening and range of motion exercises may be recommended to patients with difficulties in bolus clearance from the oral cavity or food propulsion. However, it remains unclear whether improvements in strength or motility of specific structures translate into improvements in swallowing function.[27] A Cochrane review suggested that although behavioral treatments may improve swallowing and reduce dysphagia severity and the risk of penetration and aspiration, the positive findings may be due to chance given the lack of differences when compared with other dysphagia treatments.[28] Several systematic reviews also found that the evidence in support of these techniques predominantly originates from small exploratory studies with a relative dearth of good quality RCTs.[26–30]

Recently, a number of new rehabilitative exercise programs supported by a relatively high level of evidence, such as RCTs, have been introduced. One example is expiratory muscle strengthening training (EMST). EMST is a device-facilitated rehabilitative exercise that aims to increase the force generation capacity of expiratory and submental muscles by forcibly blowing into a handheld device with built-in resistance.[31,32] The strength of resistance is adjustable through a one-way spring-loaded valve. In patients with dysphagia secondary to PD, studies showed that 4 weeks of EMST reduced dysphagia severity and improved UES function[33,34] with the improvement sustained for at least 8 weeks post-training.[34] Importantly, it was found that the functional improvement following EMST was not driven by modulation of the central cortical swallowing network, but rather by peripheral neuromuscular strengthening mechanisms.[34] Similar benefits in improving swallowing safety have also been reported in patients with post-stroke dysphagia in stroke patients.[35,36] In addition to improvement in swallowing function, Park et al also reported improvement in suprahyoid muscle activity following EMST.[36] A recent systematic review suggested that EMST may be effective in improving airway protection in patients with dysphagia associated with stroke or PD.[37] However, this finding was based on the results from only 4 RCTs. Therefore, the evidence for the clinical efficacy of EMST remains weak and insufficient.

Chin-tuck against resistance (CTAR) exercise is another rehabilitative exercise that has received growing interest. It was first introduced by Yoon et al in 2014 and is developed from the Shaker (head-lift) exercise. It aims to strengthen suprahyoid muscles by inducing patients to flex them against resistance.[38] The resistance originates from an inflatable rubber ball, which is placed between the chin and the sternum, as the chin press against it.[38] Other variations of CTAR with the use of a flexible resistance bar and other elastic resistant tools have also been described.[39] Yoon et al found that the effects of CTAR on suprahyoid muscle activation were comparable to that of the Shaker exercise in healthy subjects, but they noted that the pressure from the ball may have contributed to the increase in muscle activation during the task.[38] A few RCTs have been conducted in patients with post-stroke dysphagia.[40–43] A systematic review suggested that CTAR had similar effects in improving swallowing function to the Shaker exercise.[39] The quality of published RCTs is considered "good", with a Physiotherapy Evidence Database (PEDro) Scale of 6 to 7.[40,44,45] The meta-analysis evaluated the effects of 3 RCTs[40,41,43] and revealed a large pooled treatment effect.[46] However, it should be noted that the small number of published RCTs are heterogeneous with respect to their CTAR treatment regimens which makes comparisons between studies challenging and their amalgamation as part of a meta-analysis imperfect.

A growing number of clinicians across the globe have adopted the use of neuromuscular electrical stimulation (NMES) for dysphagia rehabilitation in recent years. The aim of NMES is to improve the effectiveness of swallowing therapy by strengthening the muscles involved in swallowing.[47] NMES involves the application of electrical stimuli to the skin around the face and neck through surface electrodes. Stimulation intensity can be varied depending on the treatment goals. Low intensity sensory NMES allows patients to feel the tingling sensation on the skin, whereas high-intensity motor NMES can trigger muscle contractions. Several RCTs have reported the positive effects of NMES in improving swallowing function in patients with dysphagia associated with stroke and other neurological conditions.[48–53] Meta-analyses on the effects of NMES revealed an overall potential treatment benefit for dysphagia.[28,54,55] However, despite these positive clinical outcomes, the scientific evidence on the underlying mechanisms of NMES is lacking. Little work has been done on its neurological and physiological effects on the central swallowing motor system. The National Institute for Health and Care Excellence (NICE) guideline published in 2018 suggested that NMES may have potential benefit for post-stroke oropharyngeal dysphagia, but the evidence is limited in quality and quantity, and the evidence for dysphagia associated with other etiology is insufficient.[47] Therefore, it is recommended that NMES should be used with special arrangements for clinical governance in patients with post-stroke dysphagia and only in the context of research for other dysphagic patients. Future studies should aim at a better understanding of the underlying mechanisms of NMES to fully elucidate its observed clinical benefits.

Taken together, the quality of evidence for the clinical efficacy of rehabilitative exercises has improved in recent years as there is an increasing number of RCTs conducted in dysphagic patients. EMST, CTAR and NMES are the most studied rehabilitation treatments and they showed preliminary benefits for dysphagia. While it is encouraging to see the improved quality of evidence in this area, several critical issues, including heterogeneity in treatment regimens, treatment effects over longer periods of time and in pathological populations other than stroke, and the underlying mechanisms of action, need to be addressed in future well-designed RCTs.

Biofeedback as an Adjunct to Rehabilitative Treatments

Biofeedback refers to the feedback information based on biokinematic measures that are used to assist adaptation learning of motor skills through the acknowledgement of errors.[56] Through biofeedback, patients are made aware (typically visually) of their errors during training so that they may adjust their performance accordingly. Recent dysphagia treatments have attempted to incorporate biofeedback into treatment regimens while several biofeedback software programs have been introduced in the market in recent years. Examples of such biofeedback techniques include surface electromyography (sEMG), accelerometry and tongue manometry.[57] Among these techniques, sEMG biofeedback is the most studied. SEMG biofeedback is typically performed by placing surface electrodes over the anterior neck or submental muscles of a patient to monitor the changes in muscle activities during swallowing. The recorded signals are then processed and transformed into a visual display or auditory prompt such that the patient can understand the biomechanical properties of their swallow and adjust their swallow efforts according to instructions from therapists. Several early non-RCT studies showed that behavioral swallowing therapy augmented by sEMG biofeedback improved swallowing function, biomechanics and swallowing-related quality of life in patients with PD,[58] stroke[59–61] and head and neck cancer.[59] However, a recent systematic review and meta-analysis by Benfield et al found that although biofeedback combined with dysphagia therapy had significant beneficial effects in improving hyoid displacement, there were no significant effects on swallowing function or nasogastric extubation.[57] Given the limited number of studies comparing the effects of dysphagia treatments with and without biofeedback, definitive conclusions on its effectiveness cannot currently be drawn.

Pharmacological Treatments

The use of pharmacological treatments for dysphagia is an understudied area but has received growing interest recently. While some drugs are known to be associated with dysphagia, for example, neuroleptic medication which has the potential of inducing extrapyramidal symptoms,[62] other drugs may potentially alleviate dysphagia.[63] Transient receptor potential (TRP) channel agonists (mainly capsaicin) are the most extensively studied pharmacological treatment for dysphagia. More than half of the RCTs on the clinical effects of these agents (62.5%, 5 out of 8 studies) were published in the last five years.[63] These studies suggested that TRP channel agonists reduce the latency of swallowing response and severity of dysphagia. The mechanisms underlying these functional changes remain speculative, but it is thought to be related to the enhanced sensory input to the swallowing system. TRP channel agonists activate the TRP receptors which are distributed throughout the swallowing tract and trigger sensory impulses to the nucleus tractus solitarius (NTS) of the medulla and the sensorimotor cortex. Several studies have reported that these agonists have neurophysiological and biochemical effects on the swallowing system. These effects include enhanced cortical activation in the cingulate gyrus and medial frontal gyrus during swallowing,[64] cerebral blood flow in the insula,[65] altered excitability of the swallowing motor cortex,[66] and the changes in the serum levels of substance P, a neuropeptide closely related to the cough or swallowing reflex.[65,67] Importantly, some changes are associated with functional improvements in elderly patients with dysphagia.[64] Furthermore, the effects of TRP channel agonists appear to be dose-dependent.[68] These findings suggested that TRP agonists may have direct effects on the human swallowing system. While the evidence of clinical benefits of these agonists remains limited, recent progress appears promising. Future studies should explore their underlying mechanisms, long-term effects and their effects in patients with dysphagia associated with other neurological conditions.

Neuromodulation Treatments

The therapeutic application of neuromodulation techniques for neurogenic dysphagia has gained a lot of attention over the past two decades. These techniques modulate the neurological control of swallowing and aim to promote neuroplasticity, which is the ability of the nervous system to adapt to extrinsic or intrinsic stimuli and is crucial for functional recovery following neurological damage. These techniques can be classified into peripherally or centrally driven neuromodulation, based on their routes of administration. Peripheral neuromodulation stimulates peripheral nerves or muscles that are involved in swallowing. Pharyngeal electrical stimulation (PES) is an example of a peripheral neuromodulation technique that has received the Conformitè Europëenne (CE) mark approval as a dysphagia treatment. PES delivers electrical stimuli to the pharyngeal mucosa through electrodes that are housed in an intraluminal catheter.[69] Physiological studies have shown that even a short period (10 minutes) of PES can induce persistent (30 minutes) cortical excitation in the human swallowing system.[69,70] Other studies found that PES can induce neurophysiological,[71,72] biochemical[73,74] and behavioral changes[75] in the human swallowing system. It can also reverse the temporary disruptions induced by a cortical "virtual lesion", a technique used in the field as a virtual stroke model.[75] Despite the promising evidence with healthy subjects, results with patients are mixed. Some studies suggest that PES is beneficial for patients with dysphagia,[70,75] while other studies have not shown significant effects compared to sham stimulation.[76,77] However, a recent meta-analysis revealed PES has a beneficial effect in improving swallowing function in patients with post-stroke dysphagia.[78] An ongoing large-scale, multi-center study (clinical trial registration reference: ISRCTN98886991) that involves 50 sites over 4 countries (United Kingdom, Austria, Denmark and Germany) with a target sample size of 800 patients with post-stroke dysphagia will provide further clarity on its clinical efficacy.

Central neuromodulation targets modulating the swallowing system through either electromagnetic (repetitive transcranial magnetic stimulation; rTMS) or electrical (transcranial direct current stimulation; tDCS) stimulation of the brain.[79] Both rTMS and tDCS are considered non-invasive brain stimulation (NIBS) because these techniques can stimulate the brain without the need for surgical procedures. These two techniques operate based on different working principles (Table 2). RTMS indirectly induces electrical current within the brain and can either upregulate or down-regulate synaptic efficiency depending on the stimulation frequency.[80] On the other hand, tDCS delivers relatively weak electrical impulses into the brain through surface electrodes attached to the skull and modulates the firing threshold of the neurons.[81] Both techniques can induce long-term changes in neuroplasticity that last longer than the duration of stimulation, making them a potentially viable tool for dysphagia rehabilitation. A simple comparison on the characteristics, including the working principles, physical properties, and costs, of the two techniques is presented in Table 2.

Several safety guidelines have been published for both rTMS[82–84] and tDCS.[85] In general, both rTMS and tDCS are considered safe. The most undesirable adverse effect of rTMS is its ability to induce seizures, but the risk is extremely low (less than 0.03%) when the safety guidelines are followed and there is no reported permanent

Table 2 Comparison Between the Characteristics of Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS)

		rTMS and tDCS	
Similarities		• No surgical procedures involved • Capable of inducing neuroplasticity in the human swallowing system • Induced neuroplasticity is associated with changes in swallowing behaviour • Capable of reversing "virtual lesion" in the swallowing motor cortex • Showed preliminary treatment benefits for patients with post-stroke dysphagia	
		rTMS	**tDCS**
Differences	**Proposed mechanism of action**	Electromagnetic induction High intensity of induced current causes depolarization of nerve cells and triggers action potential	Direct electric current Low intensity current alters the threshold of membrane polarization
	Safety	May induce seizure, but the risk is extremely low (< 0.03%) with no permanent damage	Transient adverse effects such as itchiness on scalp, burning sensation and headache
	Size of equipment	Bulky	Small and portable
	Cost	Relatively expensive (Approximately USD 35,000)	Relatively cheap (Approximately USD 1500)

damage.[83] The latest rTMS safety guidelines suggested that rTMS using figure-of-eight coil is considered safe in individuals who are taking drugs that lower seizure thresholds, and individuals with cardiac pacemakers, vagus nerve stimulators, and spinal cord stimulators, as long as it is applied at least 10 cm away from electronic components.[83] TDCS is considered a safer technique compared to rTMS due to the use of weak electric current. The adverse effects associated with tDCS such as itchiness at the scalp, burning sensation and headache are transient and usually resolved after stimulation is ceased.[85,86]

Regarding their effects on the human swallowing system, physiological studies with healthy volunteers suggest both rTMS and tDCS can alter the excitability of the swallowing (pharyngeal) motor cortex,[87–89] swallowing behavior,[88,90,91] and reverse the effects of a pharyngeal motor cortical "virtual lesion".[92,93] In dysphagic patients, particularly stroke patients, a large number of RCTs on the effects of these NIBS techniques on swallowing have been published in the last decade.[78,94] Overall, although there is substantial variability in stimulation parameters and no consensus has been reached as regards the optimal stimulation protocol, NIBS techniques have shown preliminary treatment benefits for patients with post-stroke dysphagia. Importantly, Cheng et al analysed the effects of neuromodulation treatments based on the timing of follow-ups.[78] They found that the treatment effects of PES, rTMS and tDCS were most prominent within the first 2 weeks after treatment, but the treatment effects became insignificant by the third month post-treatment. However, they also noted that only a few studies have investigated longer-term (beyond 2 months) effects of neuromodulation such that the findings between immediate and long-term treatment effects may not be directly comparable. Nonetheless, this study highlighted our lack of knowledge regarding the long-term effects of neuromodulation treatments. Apart from stroke patients, some studies have also suggested that NIBS may also be beneficial to patients with multiple sclerosis (MS)[95] and PD.[96] Moreover, application of NIBS in the cerebellum has received increasing attention in recent years. Some studies suggested that cerebellar rTMS may be beneficial for patients with post-stroke dysphagia.[97,98]

Recently, the German Society of Neurology,[99] the European Stroke Organization and European Society for Swallowing Disorders[22] have published some guidelines on the use of neuromodulation for dysphagia. Clinicians should refer to these guidelines and recommendations when making clinical decisions of using neuromodulation treatments for dysphagia.

Soft Robotics

Soft robotics is a new and exciting development in the field of medical research. The definition of soft robots varies across engineering fields.[100] The term "soft" can refer to the incorporation of living biological components, or the use of elastomeric and deformable materials.[101] The first type of soft robot is typically built with soft materials that are biologically compatible such that they can be used as implants.[102] Such an approach shows potential in the management of swallowing and voice impairments in patients following total laryngectomies, which is a surgical procedure that removes the entire larynx. A fully automated tissue-engineered larynx with a valve that allows respiration and phonation and avoids aspiration during swallowing may help tracheotomized patients restore long-term swallowing and voice function.[102]

The second type of soft robot has been built to mimic human swallowing. Such robots allow investigation of the effects of different management strategies on swallowing without putting patients at risk of complications. Dirven et al built a bioinspired esophagus to investigate the relationship between bolus rheological properties and esophageal transport behavior.[103] Without the intra- and inter-individual variability in human swallowing, the rheological properties of boluses can be tested in a controlled and repeatable environment, providing information valuable for treatment planning.

A further application is the testing of esophageal endoprosthetic stents. Placement of these stents (esophageal stenting) is a treatment for esophageal cancer patients with esophageal strictures to expand the esophagus such that adequate oral nutrition can be maintained. These implanted stents may become displaced over time due to prolonged esophageal peristalsis. Due to ethical concerns, it is challenging to test different properties of stents in humans. Therefore, a soft robotic esophagus has been developed to overcome this challenge. Using a robotic soft esophagus (RoSE), which mimics human swallowing action, Bhattacharya et al were able to identify certain radial stiffness characteristics that can minimize stent displacement under prolonged peristaltic contractions.[104]

Conclusions

In this review, we have discussed both traditional and more novel dysphagia treatments that have been introduced in the past two decades. In general, the quality of evidence that supports the use of these newer treatments is at least comparable if not better than traditional treatments as their clinical efficacy is evaluated by randomized controlled trials in patients with neurogenic (mainly stroke) dysphagia. Nonetheless, there are several critical issues, including heterogeneity in treatment regimens, long-term treatment effects, underlying mechanisms of some neuromodulation treatments, and the effects of these techniques in non-stroke dysphagia, that remain to be addressed in future well-designed clinical trials.

Abbreviations

CE, Conformitè Europëenne; CTAR, chin-tuck against resistance; EMST, expiratory muscle strengthening training; FEES, Flexible Endoscopic Swallowing Study; fMRI, functional magnetic resonance imaging; LES, lower esophageal sphincter; MS, multiple sclerosis; NIBS, non-invasive brain stimulation; NICE, National Institute for Health and Care Excellence; NMES, neuromuscular electrical stimulation; NTS, nucleus tractus solitarius; PD, Parkinson's disease; PEDro, Physiotherapy Evidence Database Scale; PES, pharyngeal electrical stimulation; RCT, randomized controlled trial; RoSE, robotic soft esophagus; rTMS, repetitive transcranial magnetic stimulation; sEMG, surface electromyography; tDCS, transcranial direct current stimulation; TRP, transient receptor potential; UES, upper esophageal sphincter; VFSS, videofluoroscopic swallow study.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosure

SH is a board director, stock holder and chief scientific officer of Phagenesis Ltd., a company that is involved in dysphagia treatment; also reports grants from MRC/UKRI, and non-financial support from ESSD. Other authors declare that there are no conflicts of interest.

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