

## Review

# Management of oral drug therapy in elderly patients with dysphagia

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We aimed at summarizing current evidence on age-related changes in swallowing, the impact of selected medications on swallowing, and the management of oral drug therapy in older patients with dysphagia. The risk for oropharyngeal swallowing disorders increases with age. Though increasing age facilitates subtle physiologic changes in swallow function, age-related diseases are most significant factors in the onset and severity of dysphagia. In older people, dysphagia can also occur as a side effect of some medications. Drug-induced dysphagia can appear as a drug side effect or as a complication of the therapeutic action of the drug, mainly through induction of xerostomia, impaired swallowing muscle function or esophageal injury. Whatever the mechanism leading to dysphagia, the administration of drugs to dysphagic patients is a really challenging issue. Manipulations of solid oral drugs frequently occur in geriatric settings, leading to potential medication errors and changes in drug performance. The implementation of guidelines for management of oral drug therapy in dysphagic patients may contribute to improve the quality of care provided to this very frail population.

**Key words:** Swallowing disorders, Dysphagia, Elderly, Functional status, Polypharmacy, Medication-induced dysphagia

## INTRODUCTION

Dysphagia refers to the loss of swallowing function <sup>1</sup>, and is a growing health concern in aging populations. Its incidence in acute care settings has been reported as high as 33%, and affects up to 68% of elderly nursing home residents <sup>2</sup>, resulting in a high incidence of respiratory complications <sup>3</sup>.

Age-related changes in swallowing functions place older adults at risk for dysphagia for two major reasons. First, healthy aging takes its toll on head and neck anatomy, as well as physiologic and neural mechanisms underpinning swallowing function. Such mechanisms of naturally diminishing functional reserve

contribute to swallowing alterations in healthy older adults which are known as *presbyphagia*. Second, age-related diseases, including neurological (e.g. stroke, Parkinson's and Alzheimer's disease) and non-neurological diseases (e.g. gastro-oesophageal reflux disease) <sup>4 5</sup> may be associated with swallowing disorders. Finally, older patients with multiple chronic diseases are often treated with complex polypharmacy regimens, and selected medications may contribute to the onset of swallowing disorders by several different mechanisms.

The clinical implications of dysphagia are complex and potentially dangerous. Indeed, besides increasing the risk of aspiration pneumonia, swallowing disorders

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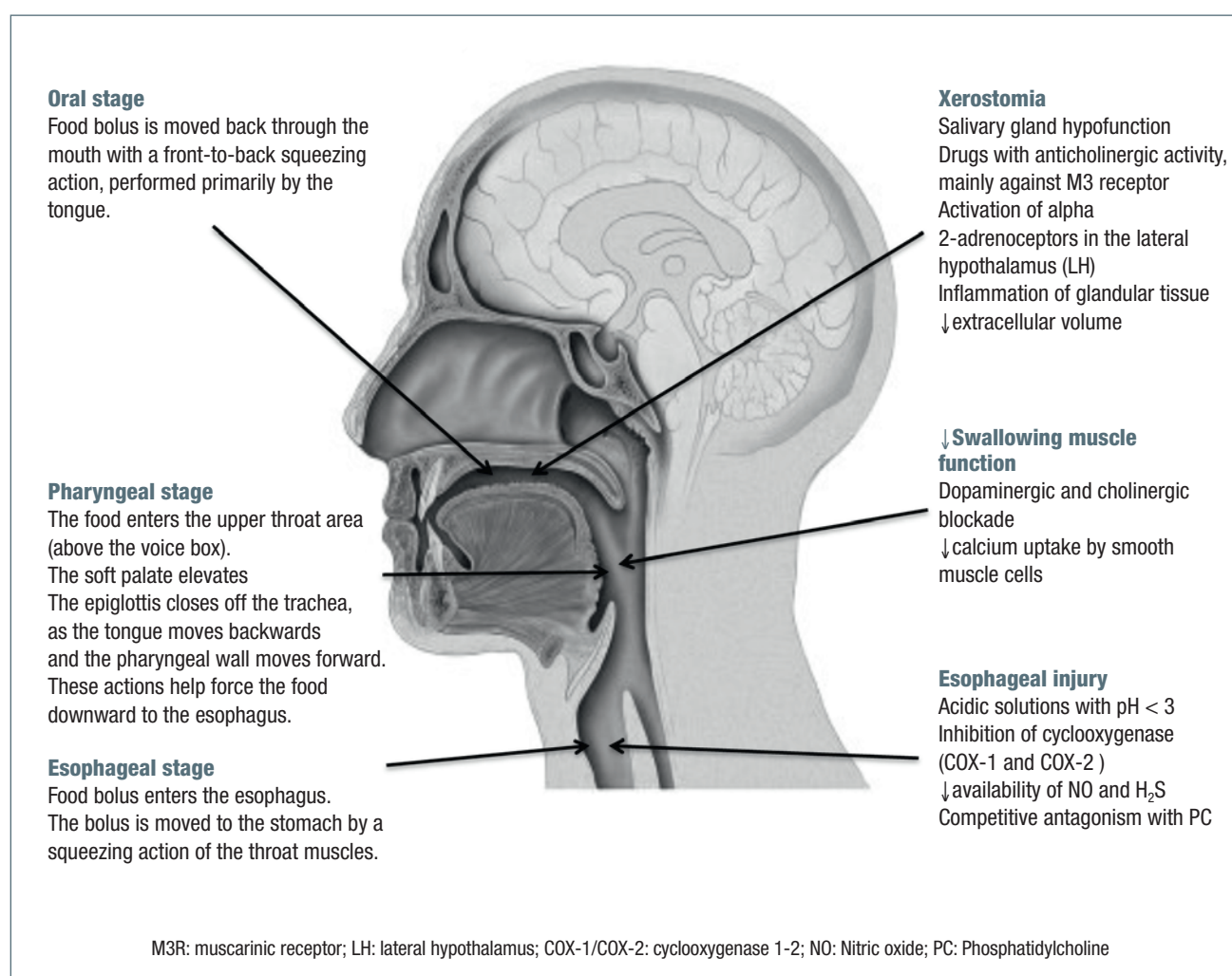
could compromise medication adherence and therapeutic outcomes. Big size and poor quality of tablet coatings are among reasons to withdraw oral medications<sup>6</sup>, and older age is associated with increasing prevalence of oral drug administration problems<sup>7</sup>. Despite this bulk of evidence, swallowing problems often remain concealed in older adults, leading to dehydration/malnutrition<sup>8</sup> and pneumonia<sup>9,10</sup>. Therefore, the aim of this review is to summarize current evidence on age-related changes in swallowing, the impact of selected medications on swallowing, and the management of oral drug therapy in older patients with dysphagia.

## AGING AND PRESBYPHAGIA

The physiologic process of swallowing requires a complex series of psychological, sensory, and motor

functions, that are both voluntary and involuntary. Swallowing process is divided in three stages: 1) *Oral stage* (voluntary); 2) *Pharyngeal stage*; 3) *Esophageal stage* as reported in figure 1.

During the oral stage, the food is manipulated (masticated if a solid) into a cohesive unit (referred to as bolus) in preparation for the remaining phases of the swallowing process. Food is chewed and mixed with saliva to form a bolus and it is positioned on the tongue for transport. Once the bolus is prepared, the tongue begins the anterior to posterior propulsion of the bolus for passage to the pharynx. Sensory receptors in the oropharynx and tongue itself are stimulated and pharyngeal swallow is triggered. The food enters the upper throat area, the soft palate elevates and the epiglottis closes off the trachea, as the tongue moves backwards and the pharyngeal wall moves forward. These actions help force the food downward to the esophagus. Finally, the food bolus enters the esophagus and it is moved



**Figure 1.** The main stages in the swallowing process, (left) and the main mechanism of drug induced dysphagia (right).

to the stomach by a peristaltic action of the throat muscles (esophageal stage). Bolus transport in the thoracic esophagus is quite different from that in the pharynx, because it is driven by true peristalsis regulated by the autonomic nervous system. Once the food bolus enters the esophagus passing the upper esophageal sphincter (UES), a peristalsis wave carries the bolus down to stomach through the lower esophageal sphincter (LES). Gravity assists peristalsis in upright position.

Aging is characterized by changes occurring in the structure, motility, coordination, and sensitivity of the swallowing process<sup>11</sup>, and it has been estimated that 35-68% of people aged 65 or more have some degree of swallowing dysfunction<sup>12-13</sup>. Declining muscle strength, receptor density and sensory receptor responsiveness are associated with a reduced lingual pressure leading to slow bolus velocity<sup>14</sup>. Periventricular white matter lesions and cerebral atrophy are usually associated with longer duration of swallowing and prolonged swallowing response time<sup>15</sup>. A desynchronization of the swallowing response of glossopalatal junction, velopharyngeal junction, laryngeal vestibule and UES<sup>16</sup> can lead to intra-esophageal stasis (bolus retention) and reflux from the lower pharyngo-UES<sup>17</sup>. Effortful swallowing has shown to impact the swallowing response in young and older adults. While effortful swallowing can increase the oral pressure and the swallow response durations at various levels in both age groups, there were significant differences between young and older volunteers whereby the older achieved a lower maximum pressure and higher residues in the pyriform sinuses upon effortful swallowing<sup>18</sup>. Swallowing might also be affected by a decline of saliva production, which in turn impairs

bolus formation. Even if the saliva secretion, which is triggered by cholinergic stimulation of the muscarinic receptors within the saliva glands, remains stable over the life span, the decreasing number of saliva-producing acinar cells might decrease the salivary reserve. Additionally, the composition of saliva also changes with age. The saliva is composed of water, mucin, and various bactericidal components like proteolytic enzymes, antibodies, amylases and lipases. Density and viscosity of saliva increases with aging, also contributing to impaired swallowing function among older people<sup>19</sup>. Finally, sarcopenia, defined as the loss of skeletal muscle mass and strength with increased risk of adverse outcomes<sup>20</sup>, contributes to presbyphagia. Indeed, it affects the muscles of the upper aero-digestive tract involved in the swallowing process, thus reducing the strength and function of the swallowing response<sup>19</sup>.

## CAUSES AND CONSEQUENCES OF DYSPHAGIA

Stages of swallowing (i.e. oropharyngeal and esophageal) may be differentially affected by several diseases (Tab. I). Among these, neurologic disorders are the most frequent cause of swallowing impairment in elderly patients. Dysphagia occurs commonly after stroke, with prevalence estimates ranging between 40%-60% in the acute phase of stroke<sup>21-22</sup>, mainly due to the interruption of voluntary control of the oral phase<sup>23</sup>. Dysphagia is often observed among patients with Parkinson's disease (PD), where swallowing problems affect over 80% of diseased population, reflecting the underlying motor impairments and the extent of

**Table I.** Causes of dysphagia.

<b>A. Causes of oropharyngeal dysphagia</b> <sup>106-107</sup>	
Neurologic	Stroke, Dementia, Traumatic brain injury, Cerebral palsy, Guillain-Barré syndrome, Poliomyelitis, Myopathy, Coma
Myopathic	Connective tissue disease, Dermatomyositis, Myasthenia gravis, Myotonic dystrophy, Oculopharyngeal dystrophy, Sarcoidosis, Paraneoplastic syndromes
Neoplastic	Any tumor involving the aerodigestive tract
Geriatric	Age-related changes
Iatrogenic	Drugs (chemotherapy, neuroleptics etc.), Radiation therapy
Infective	Diphtheria, botulism, Lyme disease, Syphilis, Mucositis (herpes, cytomegalovirus, Candida etc.)
Metabolic	Amyloidosis, Cushing's syndrome, Thyrotoxicosis, Wilson's Disease
Dysfunctional	Gastroesophageal Reflux Disease
<b>B. Causes of esophageal dysphagia</b> <sup>106-107</sup>	
Mechanical (intrinsic and extrinsic)	Pyloric stenosis, Tumors, Thoracic aorta aneurysm, Muscleskeletal problems
Neuromuscular (primary and secondary)	Achalasia, Diffuse esophageal spasm, Scleroderma, Collagen diseases
Anatomical	Cricopharyngeal Bar, Zenker's diverticulum, Osteophytes, Congenital malformations, Cervical scars

the disease's progression<sup>24</sup>. The swallowing disorders most frequently observed in PD patients are related to the oral and pharyngeal phase, resulting in abnormal bolus formation, delayed swallowing response, and prolonged pharyngeal transit time, with repetitive swallows to clear the throat. Dementia is frequently associated with dysphagia, and it has been estimated that up to 45% of institutionalized patients with dementia have some degree of swallowing difficulty<sup>25</sup>. These difficulties may relate to cognitive impairment, motor deficits such as weakness or apraxia, loss of appetite, and/or food avoidance. As a result, patients with dementia may experience weight loss and increased dependency for feeding.

Moreover, swallowing disorders can be caused by combinations of several underlying conditions or comorbidities whose impact on risk of dysphagia is not always as obvious as for neurological diseases. Gastroesophageal reflux disease may lead to esophageal motility disturbances due to the reflux of acidic gastric contents into the esophagus and symptomatic chronic irritation or injury to the esophageal mucosa<sup>26</sup>. The gastrointestinal complications of diabetes mellitus are the outward forms of the diabetic visceral neuropathy, which can affect tonus and motility of the esophagus, especially in late stages of diabetes<sup>27</sup>. Recently, the association between chronic obstructive pulmonary disease (COPD) and swallowing disorders has been investigated<sup>28</sup>. Limited laryngeal elevation, decreased tongue strength and movements, and delayed swallowing response are the most frequent alterations of swallowing in COPD patients<sup>29</sup>. Preiksaitis et al. suggested that patients with COPD may be prone to disrupted breathing/swallowing pattern because of the combined effects of deglutition apnea and reduced ventilatory capacity<sup>30</sup>. Dysphagia of cardiac origin is yet rarely diagnosed symptom<sup>31</sup>. The position of the esophagus relative to the spine seems to be an important factor in determining whether or not an enlarged left atrium can cause compression of the esophagus. If the esophagus is displaced to the left, its lateral movement is limited by the descending aorta and it can then be compressed against the spine by the enlarged heart<sup>32</sup>. Finally, esophagus motor dysfunction has been reported in patients with chronic renal failure (CKD) in uremic stage. Though uremic neuropathy and/or myopathy are likely involved in esophageal motor dysfunction<sup>33</sup>, the pathogenesis of CKD-related dysphagia is still unclear<sup>34</sup>.

As for consequences of dysphagia, swallowing difficulties may contribute to malnutrition and dehydration. Up to 30% of neurological patients and up to 55% of frail older patients with dysphagia present or are at risk of malnutrition with a strong relationship between

severity of dysphagia and incidence of malnutrition<sup>35,36</sup>. In a recent study in older patients with dysphagia the prevalence of malnutrition (36.8%) and risk of malnutrition (55.3%) was significantly higher compared older patients without dysphagia<sup>37</sup>. A recent resolution of the Council of Europe on food and nutritional care in hospitals identified functional oropharyngeal dysphagia as a major contributor to malnutrition and its consequences, including prolonged hospital stay, impaired quality of life, and unnecessary health care costs<sup>38</sup>. Dehydration also is an important concern among dysphagic patients<sup>39</sup>. About 75% of individuals in long-term care have been reported to be dehydrated when relying on thickened liquids for oral hydration<sup>40</sup>. Moreover, dehydration increases the risk of falls, kidney failure, constipation, urinary tract infections, delirium, respiratory infections, loss of muscle strength and pressure sores among bedridden patients<sup>41</sup>. Thus, nutritional and hydration status should be carefully scrutinized among older people with swallowing disorders.

Aspiration pneumonia is among leading causes of mortality after stroke, accounting for nearly 35% of post-stroke deaths<sup>42</sup>. Additionally, aspiration pneumonia is associated with worsening nutritional status during hospitalization<sup>37</sup>, increased costs due to longer hospital stay<sup>43</sup>, and more severe disability after stroke<sup>37</sup>. Swallowing problems increase the risk of aspiration (inhaling fluid or stomach contents into the lungs) and pneumonia<sup>19</sup>. Altered mental status, esophageal motility disorders and vomiting, oropharyngeal colonization, and enteral feeding also represent important risk factors which need to be taken into account when assessing a dysphagic patient<sup>44</sup>. Oral care, and among patients with tube feeding, postpyloric feeds may reduce the risk of aspiration pneumonia<sup>45,46</sup>.

Finally, another important consequence of dysphagia is the difficulty in the administration of oral medications. Indeed, difficulty swallowing pills is often the first sign of dysphagia among older patients, and select medications themselves can cause swallowing problems<sup>31</sup>. Current evidence about these important issues will be summarized in the following sections.

## MEDICATION-INDUCED DYSPHAGIA

Adverse drug reactions might cause swallowing dysfunction, mainly through induction of xerostomia, impaired swallowing muscle function or esophageal injury (Tab. II).

Xerostomia (dry mouth), is often observed among users of selected medications<sup>10</sup>, especially in patients treated with complex polypharmacy regimens<sup>47</sup>. More than 400 pharmaceutical products have been

**Table II.** Drugs that may contribute to swallowing disorders (from Stegemann et al., 2012<sup>10</sup>, mod.).

Drugs that may contribute to esophageal injury	Drugs that may contribute to xerostomia	Drugs that may contribute to dysphagia
Antibiotics <ul style="list-style-type: none"> <li>• Tetracycline</li> <li>• Macrolids</li> <li>• Penicilline</li> </ul> NSAID <ul style="list-style-type: none"> <li>• Acetilsalicylic Acid</li> <li>• Piroxicam</li> <li>• Indometacin</li> </ul> Bisphosphonate <ul style="list-style-type: none"> <li>• Alendronate</li> </ul>	<ul style="list-style-type: none"> <li>• Antipsychotics</li> <li>• Antidepressants</li> <li>• Antiemetics</li> <li>• Anxiolytics</li> <li>• Antihistamines</li> <li>• Diuretics</li> <li>• Anticholinergics</li> <li>• Antihypertensive</li> <li>• Bronchodilators</li> </ul>	Antipsychotics <ul style="list-style-type: none"> <li>• Haloperidol</li> <li>• Olanzapine</li> <li>• Clozapine</li> <li>• Paliperidone</li> <li>• Risperidone</li> </ul> Anticholinergics <ul style="list-style-type: none"> <li>• Nitrazepam</li> <li>• Clonazepam</li> </ul> Chemotherapy <ul style="list-style-type: none"> <li>• Vincristine</li> </ul>

considered to have adverse effects on the mechanisms responsible for salivary output, although experimental support for this evidence is available only for some medications<sup>48</sup>. Probably the most common mechanism of medication-induced salivary gland hypofunction (SGH) is an impairment of the signaling pathway in salivary tissue reducing the saliva production or release from the salivary glands. Drugs with anticholinergic activity, mainly against the muscarinic receptor (M3R) are the most reported cause of reduced salivation. The M3R mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands. Tricyclic antidepressants present anticholinergic effects in a variety of degrees<sup>49</sup>. They block the effects of acetylcholine on the muscarinic receptors, resulting in a decreased salivary flow rate. Therefore, sympathetic stimulation predominates, which leads to more viscous saliva production<sup>50</sup>. Anticholinergic bronchodilators, including the most recent glycopyrronium<sup>51</sup> and acridinium bromide<sup>52</sup>, also diminish salivary production and secretion, with a reduction in flow rates of whole and parotid saliva<sup>53</sup>. Select antihypertensive agents that act on central alpha 2-adrenergic receptors, such as clonidine, usually cause dry mouth. The study of Takakura et al.<sup>54</sup> demonstrated that activation of alpha 2-adrenoceptors in the lateral hypothalamus (LH) inhibits salivation, suggesting that LH is one of the possible central sites involved in anti-salivatory effects. Selected chemotherapy treatments also causes transient xerostomia: cyclophosphamide, epirubicin or methotrexate, and 5-fluorouracil appear to affect the function of acinar and ductal cells, by inducing dilation of the excretory duct<sup>55</sup>, acinar degeneration and inflammation of glandular tissue<sup>56</sup>, with recovery of salivary function after the end of treatment cycles. Finally, some medications may cause xerostomia without affecting salivary flow. Diuretics cause an overall decrease extracellular volume or electrolyte loss secondary

to the increased urine output. As a consequence, there is a decrease on the salivary flow rate<sup>57 58</sup>.

Selected drugs may affect swallowing by impairment of muscle function. Psychotropic medications may depress bulbar centres and result into inhibition of the cough, gag and swallow reflex. The well known extrapyramidal effects of antipsychotics and neuroleptics may lead to dysphagia by reducing the tonus of the pharyngeal muscles<sup>59</sup>. Psychotropic drugs may also produce dopaminergic and cholinergic blockade producing peripheral and central effects on swallowing and potential impairment of oesophagus motility and the gag reflex<sup>60</sup>. A number of drugs act directly on the smooth muscle of the lower oesophageal sphincter to reduce resting sphincter pressure. Several experience has been reported with isosorbide dinitrate and the calcium antagonists, particularly nifedipine<sup>61</sup>. The sublingual use of isosorbide dinitrate before meals has been shown to decrease mean resting lower oesophageal sphincter pressures, with relaxation usually lasting at least 90 minutes<sup>62</sup>. Calcium antagonists interfere with calcium uptake by smooth muscle cells, producing relaxation of the lower oesophageal sphincter as well as reducing the amplitude of peristaltic contractions in the body of the oesophagus.

Medication-induced esophageal injury has been reported with many medications. In some cases, it is a class effect and can be caused by a direct dose-dependent erosive effect on the esophageal mucosa or an indirect effect mediated by changes in the esophageal pH. Patients may experience a sudden onset of burning and retro-sternal pain aggravated upon swallowing<sup>63</sup>. These injuries, including esophageal ulceration, perforation, strictures, and esophagitis, often present as a perception that food or a pill is stuck in the throat<sup>64</sup>. The majority of cases are attributed to anti-microbial medications, including penicillines, macrolides and tetracyclines (doxycycline generates strongly acidic solutions with



pH < 3)<sup>65</sup>. Other drug classes prone to induce esophageal disorders are nonsteroidal anti-inflammatory drugs (NSAID), such as acetylsalicylic acid, indomethacin and piroxicam. NSAIDs cause gastroduodenal damage by 2 main mechanisms: a physiochemical disruption of the gastric mucosal barrier and systemic inhibition of gastric mucosal protection, through inhibition of cyclooxygenase (COX) and prostaglandin-endoperoxide synthase 2 (PG G/H synthase) activity of the gastrointestinal mucosa<sup>66</sup>. A reduced synthesis of mucus and bicarbonate, an impairment of mucosal blood flow, and an increase in acid secretion are the main consequences of NSAID-induced PG deficiency<sup>67</sup>. There is mounting evidence to suggest that gastric damage induced by ns-NSAIDs does not occur because of COX-1 inhibition; dual suppression of COX-1 and COX-2 is necessary for damage. However, against a background of COX inhibition by antiinflammatory doses of NSAIDs, their physicochemical properties, in particular their acidity, underlie the topical effect, leading to short-term damage<sup>68</sup>. Additional mechanisms may contribute to damage, including uncoupling of oxidative phosphorylation leading to ATP depletion, reduced mucosal cell proliferation and DNA synthesis, as well as neutrophil activation. Evidence suggests that NSAIDs may also induce GI damage by interference with mucosal synthesis and availability of Nitric oxide (NO)<sup>69</sup> and hydrogen sulfide (H<sub>2</sub>S)<sup>70</sup>. These mediators are endogenously generated gaseous mediators, important in maintaining gastric mucosal integrity, which share many biologic effects with PGs.

Even bisphosphonates may cause mucosal injury. Bisphosphonates act as topical irritants to the GI lining resulting in chemical esophagitis. It is hypothesized that bisphosphonates compromise the protective, hydrophobic mucosal barrier of the GI tract allowing gastric acid to agitate the epithelial lining. The chronic irritation and inflammation leads to erosions and/or ulcerations. Phosphatidylcholine (PC) is one of the phospholipids responsible for the hydrophobic properties of the bilayer<sup>71</sup>. Phosphatidylcholine has demonstrated an ability to create a protective environment on both inert and biological surfaces and protect GI cells from irritating agents. Both bisphosphonates and PC are similar in size and molecular structures – with a negatively charged phosphate group and a positively charged nitrogen group connected by a 2-carbon chain. The comparable molecular composition of bisphosphonates and phospholipids creates competitive binding on the mucosal layer. When bisphosphonates bind, this prevents PC or other protective phospholipids from binding and producing the hydrophobic barrier that protects the epithelial lining from gastric acid<sup>71</sup>. Gastrointestinal toxicity seems to be less relevant with risedronate<sup>72</sup>. In many

cases of upper gastrointestinal ulcers caused by bisphosphonates, patients failed to take their medications correctly. In these cases, alendronate in the stomach was likely refluxed back into the esophagus, causing esophageal ulcers, erosive esophagitis, odynophagia, dysphagia, esophageal hemorrhage, and esophageal stricture<sup>73</sup>. Finally, mucoadhesive substances able to adhere to mucosal wall, e.g. gelatine in capsule pharmaceutical formulations<sup>74</sup>, can cause oesophageal injury, which can be severe if the medicinal agent has corrosive properties<sup>75</sup>. Whatever is the mechanism by which a given drug adversely affect the gastrointestinal system, these adverse effects are clinically important even when are not severe. Indeed, prolonged gastrointestinal symptoms can ultimately cause medication non-adherence and its inherent negative outcomes.

In conclusion, drugs may affect swallowing thorough several different mechanisms. Drug-induced swallowing disorders are usually reversible and might be resolved by changing the medication regimen<sup>47 59</sup>. Thus, healthcare professionals can play an important role in reducing the burden of drug-induced swallowing disorders by alerting patients and caregivers to early warning signs and providing education to help patients prevent these effects.

## MEDICATION ADHERENCE

The oral route of administration of medications is the most preferred one, but swallowing oral medications in the form of pills, tablets, or capsules also represents a really challenging task for many individuals with dysphagia. Indeed, medication non-adherence is among the most relevant clinical issues among patients with swallowing disorders.

Medication adherence is directly affected by dysphagia, as it increases the risk for omissions in general practice population<sup>6</sup> as well as in nursing home residents<sup>76</sup>. For example, 15% of all residents in long-term care facilities reported difficulty swallowing tablets and capsules. Of them, 5% regularly expectorated, while 27% did not even attempt to swallow the medication<sup>76</sup>. Consequences of non-adherence may be more serious, and less easily detected and resolved in older compared to younger patients<sup>77</sup>. Patients with dysphagia who fail to comply with prescribed medications are likely to encounter increased morbidity and mortality. In addition to worse medical treatment outcomes, medication non-adherence leads to higher hospitalization rates and healthcare costs<sup>78-80</sup>.

Thus, awareness of dysphagia-related non-adherence is of paramount importance for correct management of pharmacological therapy.

## MANAGEMENT OF ORAL MEDICATIONS IN DYSPHAGIC PATIENTS

Problems related to enteral feeding and drug administration to patients with swallowing issues is a growing concern for physicians, pharmacists and nurses<sup>81</sup>, and this issue is even more complex when patients are treated at home with or without the assistance of a caregiver.

### RISK OF TABLET CRUSHING

Crushing tablets and opening capsules are the main alterations of dosage forms in patients with swallowing difficulty and account for up to one third of oral drug administrations in nursing homes<sup>82</sup>. This practice may alter the rate and extent to which the active ingredient is absorbed<sup>83 84</sup>, leading to overdosing or underdosing. Overdosing is particularly dangerous when the drug has a narrow therapeutic index, because a small difference in plasma concentration can cause serious adverse effects<sup>85</sup>. This evidence should be applied for products containing carbamazepine, digoxin, lithium, theophylline, phenytoin, phenobarbital, and others. For example, crushing tablets of digoxin exposes patients to the risk of clinically relevant arrhythmias<sup>86</sup>. Opening a capsule of the oral anticoagulant dabigatran increases the drug's bioavailability by about 75%, thus exposing patients to the risk of haemorrhage<sup>87</sup>. Thus, these medications should never be chewed or opened.

As regards the risk of underdosing, gastro-resistant (or enteric-coated) tablets and capsules containing gastro-resistant granules are designed to release the active ingredient beyond the stomach. The purpose is usually to protect the active ingredient from gastric acid. When a gastro-resistant layer is destroyed by crushing, underdosing is very likely, as for example with gastro-resistant tablets of sulfasalazine or proton pump inhibitors<sup>88</sup>.

Besides causing overdosing or under dosing, tablet crushing raise several other issues. For example, crushing products with carcinogenic or teratogenic potential may expose carers or healthcare professionals to health risks through powder aerosolisation. Similarly, preparations containing hormones (oral contraceptives, hormonal replacement therapy), corticosteroids (such as dexamethasone) and some other drugs (finasteride, mycophenolate) should not be crushed due to the risks associated with powder aerosolisation<sup>89</sup>. In addition several drug substances may also cause irritation if the powder is aerosolised and inhaled or contact with eyes, skin, or other mucosal membranes (e.g. alendronate, piroxicam, ganciclovir, hydroxycarbamide)<sup>90</sup>. Finally, for drugs which have a particularly bitter taste, a coating (sugar/film) is often used to help mask the taste of the

active substance. A sugar coating provides a thick hard coat to a tablet and is traditionally used to mask the taste of particularly unpleasant tasting drugs such as ibuprofen or quinine. Crushing tablets containing bitter or unpleasant tasting drug substances may produce a preparation which is unpleasant to taste and which a patient may refuse to take unless the taste can be masked using a suitable food or liquid<sup>91</sup>.

### DRUG THERAPY WITH ENTERAL TUBES

Crushing of tablets and opening of capsules were used by 85.5% of the nurses to convert them into an applicable form for enteral tubing<sup>92</sup>. However, several issues must be considered with concurrent administration of oral medications and enteral formulas, especially during continuous tube feeding, because incorrect administration methods may result in clogged feeding tubes, decreased drug effectiveness, increased risk adverse effects or drug-enteral formula incompatibilities<sup>93</sup>.

Liquid formulations should be preferred because they are readily absorbed and are less likely to cause tube occlusions. Since syrups are more likely to cause clumping when exposed to enteral nutrition, elixirs or suspensions should be favored<sup>94</sup>. However, also oral liquid medications may potentially cause adverse effects. Many liquid preparations are extremely hyperosmolar or contain large amounts of sorbitol, increasing the risk of GI intolerance. This is particularly troublesome when a large volume of drug is dispensed per dose. Hypertonic medications may not be well tolerated when delivered into the small intestine. Additionally, when hypertonic medications are rapidly administered into the stomach, they may easily reach the small bowel resulting in osmotic diarrhea<sup>95</sup>. In this case, it may be necessary to change the medication with a therapeutically equivalent agent not containing sorbitol or carrying lower osmolality. Switching the administrative route may also be helpful. Changing the medication formulation (e.g., from a liquid to a crushed tablet or opened capsule when it can be safely done) may be another option.

The addition of medication directly to the enteral formula should be avoided. Although it may be convenient to mix drugs with enteral feedings, this practice can result in physical incompatibilities, decreased drug absorption, increased risk of tube occlusions, and potential microbial contamination<sup>96</sup>. Various medications may cause drug-formula incompatibilities and result in tube occlusions. For example, mixing certain acidic syrups and elixirs with enteral formulas may produce clumping or thickening because the acidic liquid preparations cause protein denaturation in the enteral formula. Formulas containing intact proteins are more affected than those that contain free amino acids or hydrolyzed protein. To avoid these potential interactions

and incompatibilities, medications should be given as a bolus and separated from enteral nutrition, and feeding tubes should be flushed with 15-30 mL of water before and after medication administration <sup>97</sup>.

While it should be reminded that product licence of each clearly states the conditions for which the medication may be suitably administered, the above issues raised the need for algorithms for medication management to be applied in different settings in order to improve medication adherence and reduce drugs manipulation in patients with dysphagia.

Recently, guidelines for the management of oral therapy in patients with swallowing problems have been developed in order to ensure that the most appropriate formulation is prescribed for each patient <sup>88</sup>. Guidelines strategies are summarized in Table III.

#### LEGAL IMPLICATIONS OF CRUSHING TABLETS

Besides the pharmacological aspects of crushing tablets, there are also legal implications <sup>98</sup>. Indeed, the administration of medications outside their product licence, as well as mixing medication inappropriately with food or drink before administration takes on a degree of liability for any adverse effects and this practice can be judged as unlawful according to the civil law.

In Italy, the Italian Medicines Agency (AIFA) grant the Marketing Authorisation to the pharmaceutical companies based on some declared parameters that include product characteristics related to: i) therapeutic indications; ii) contraindications and adverse reactions; iii) dosage, pharmaceutical form, route for drug administration. The pharmacological activity of an oral medication depends on its molecular structure, ionization, lipid

solubility and binding to plasma protein and tissue <sup>99</sup>, and inappropriate manipulations can lead to mucosal damage and to significant changes in efficacy and safety profile of the drug <sup>100 101</sup>. Liability can be minimized through an improved communication and proper assessment of the swallowing difficulty and a clear documentation of the reason for drug manipulations. In this context, following guidelines and recommendations reported in the summaries of product will improve the quality of pharmacological treatment provided to dysphagic patients.

## CONCLUSIONS

Swallowing disorders are multifactorial in nature and affects a significant number of older patients. Age-related changes in swallowing functions are attributed to physiological, anatomical, motor and sensory alterations. Swallowing disorders are highly prevalent among older patients with neurological diseases, but less obvious non-neurological causes should not be ignored. Some medications may increase the risk of dysphagia. People with swallowing disorders tend to refrain from food and beverages which leads to increased risk of malnutrition and dehydration. Manipulation of drug products is a significant source for medication errors and harmful outcomes, as well as it might have some legal implications <sup>102</sup>. Oral drug prescription to patients with dysphagia should be limited to medications that can be administered without manipulation or for which the manipulation is clearly described in the summary of product. Medication adherence is directly affected by

**Table III.** Summary of guidelines strategies and practice suggestions for the management of oral medications in dysphagic patients.

Guideline strategy	Suggestions
Switching to liquid or dispersible oral formulations	<ul style="list-style-type: none"> <li>• Check dose equivalence</li> <li>• Evaluate efficacy and side effects frequently</li> </ul>
Alternative routes of administration	<ul style="list-style-type: none"> <li>• Transdermal</li> <li>• Parenteral/injectable</li> <li>• Buccal</li> <li>• Rectal</li> <li>• Intranasal</li> <li>• Sublingual</li> </ul>
Altering a solid-dose oral medication	<ul style="list-style-type: none"> <li>• Consider how stable the product is once opened to the environment</li> <li>• Drug manipulation may impact efficacy and the potential for side effects (e.g. phenytoin, digoxin, carbamazepine) – Check summary of product for informations.</li> </ul>
Administering medications via enteral tube	<ul style="list-style-type: none"> <li>• Ensure that there is a functional and accessible gastrointestinal tract</li> <li>• Check for risk of tube blockage and drug-tube interactions</li> <li>• Check for drug-enteral feed interactions</li> <li>• Flush the tube before and after giving medications (with ≥ 30 ml water)</li> <li>• If more than one drug is required, give drugs separately and flush between administrations (with ≥ 10 ml water)</li> </ul>



difficulties of swallowing or administration of solid oral dosage forms to the patient as it increases the risk for drug omissions<sup>103</sup>.

Dysphagia management should be considered a 'team event', in which many professionals may contribute<sup>104</sup>. Furthermore, no single strategy is appropriate for all elderly patients with dysphagia. Guidelines for the management of oral therapy in patients with swallowing problems provide some useful information to be implemented into clinical practice. Additionally, in many countries long-term care continues to shift from institutional care to an array of home- and community-based options. Thus, informal or family caregivers that are being expected to share increasingly complex care for dependent elderly persons, should be adequately trained before being involved in the management of dysphagia<sup>105</sup>. Finally, healthcare professionals involved in treating patients with swallowing disorders should also consider to alert the industry to provide suitable dosage forms where they do not exist yet.

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