




**REVIEW ARTICLE**

# Identifying and addressing pill aversion in adults without physiological-related dysphagia: A narrative review

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Solid oral dosage forms (SODFs) (often called pills by patients) are the default formulation to treat medical ailments. Beneficial therapeutic outcomes rely on patients taking them as directed. Up to 40% of the population experience difficulties swallowing SODFs, resulting in reduced adherence and impaired therapeutic efficacy. Often associated with children, this also presents in adults with dysphagia, and without any organic dysphagia (non-physiological-related or functional dysphagia). This review aims to identify and appraise current interventions used to screen for and overcome pill aversion in adults with functional dysphagia. A comprehensive search of the literature was conducted. Articles reporting pill aversion in adults aged  $\geq 18$  years with no underlying cause, history of, or existing dysphagia were included. Study quality was determined using the STROBE tool for observational studies. A narrative synthesis of the findings was prepared. We identified 18 relevant cohort studies, which demonstrate that pill aversion is a global problem. Perceived ease of and/or SODF swallowability appears to be influenced by female gender, younger age, co-morbidities (e.g., depression), and physical SODF properties. Patients often modify their medicines rather than raise this issue with their healthcare team. Screening for pill aversion is haphazard but controlled postural adjustments, coating SODFs and behavioural interventions appear to be successful solutions. SODF swallowing difficulties are a barrier to effective medication use. Healthcare professionals must recognise that pill aversion is a problem requiring identification through effective screening and resolution by training interventions, appropriate formulation selection or specialist referral.

**KEYWORDS**

adherence, drug information, medical education, medication safety, pharmacy

## 1 | INTRODUCTION

Medication acceptability refers to the patient or caregiver's ability to use a medicine as intended.<sup>1</sup> Medicines requiring specialist administration devices and/or techniques for administration often

present acceptability and adherence challenges. Solid oral dosage forms (SODFs) are the default formulations within research, industry and the clinic due to their low manufacturing costs, accurate dosing profiles, taste-masking potential, possibility of combining several active substances, ease of storage and portability, and

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patient acceptability. An ability to swallow these is essential for therapeutic efficacy but difficulties taking SODFs are well documented.<sup>2,3</sup>

Problems swallowing SODFs may present in individuals with no organic dysphagia who can easily swallow food or liquids, but experience difficulties with SODFs. These patients are considered to have non-physiological-related dysphagia and may be described as having “pill aversion”.<sup>4</sup> It is also important to note that changes in swallowing function are part of the natural ageing process.<sup>5</sup> These age-related asymptomatic anatomical and physiological changes in structure and swallowing tract function allow for functional swallow but prolonged reaction times. These changes are described as presbyphagia. Dysphagia, on the other hand, is a symptomatic disorder characterised by impaired swallowing safety and/or efficiency, resulting in impaired swallowing of solids or liquids often due to neurological disorders, muscular conditions or trauma (including stroke, head and neck cancers).

Studies have demonstrated that patients with physiologically related dysphagia have poor adherence to medication.<sup>6</sup> This leads to medicine wastage, poor treatment outcomes, increased hospitalisation, morbidity and mortality, and subsequent financial strains on already stretched healthcare systems.<sup>7</sup> Similar issues may arise in those with pill aversion and presbyphagia.

Whilst commonly recognised in children, it is estimated that up to 40% of adults also have difficulties swallowing SODFs.<sup>8</sup> Various studies have been conducted to identify risk factors in patients and characteristics of SODFs predisposing to problems.<sup>9,10</sup> With an increased focus on patient-centred care, it is possible that early recognition of pill aversion and intervention by healthcare professionals may improve adherence and health. Regulators and industry are also intervening by developing alternative dosage forms, such as mini-tablets and orodispersible tablets.

This review will collate the existing evidence to improve care for those with pill aversion and identify knowledge gaps. It will explore methods used to screen for and assist adult patients to overcome pill aversion, whether this be an intervention, a suitable alternative, or methods of safe and effective dosage form modification.

## 2 | AIM AND OBJECTIVES

The purpose of the review is to identify and appraise current interventions used to diagnose and overcome SODF/“pill” aversion in adults with functional dysphagia (i.e., no underlying physiological cause for dysphagia). This will involve: compiling the characteristics of medicines that contribute to aversion or difficulty swallowing; identifying methods used to screen for pill aversion; appraising interventions used in existing studies to assist patients with pill aversion; and reporting the impact of such interventions in terms of effectiveness and measurement of outcomes.

## 3 | METHOD

A systematic approach was adopted to identify and summarise relevant literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for the work was prospectively registered on PROSPERO (CRD42021227095).

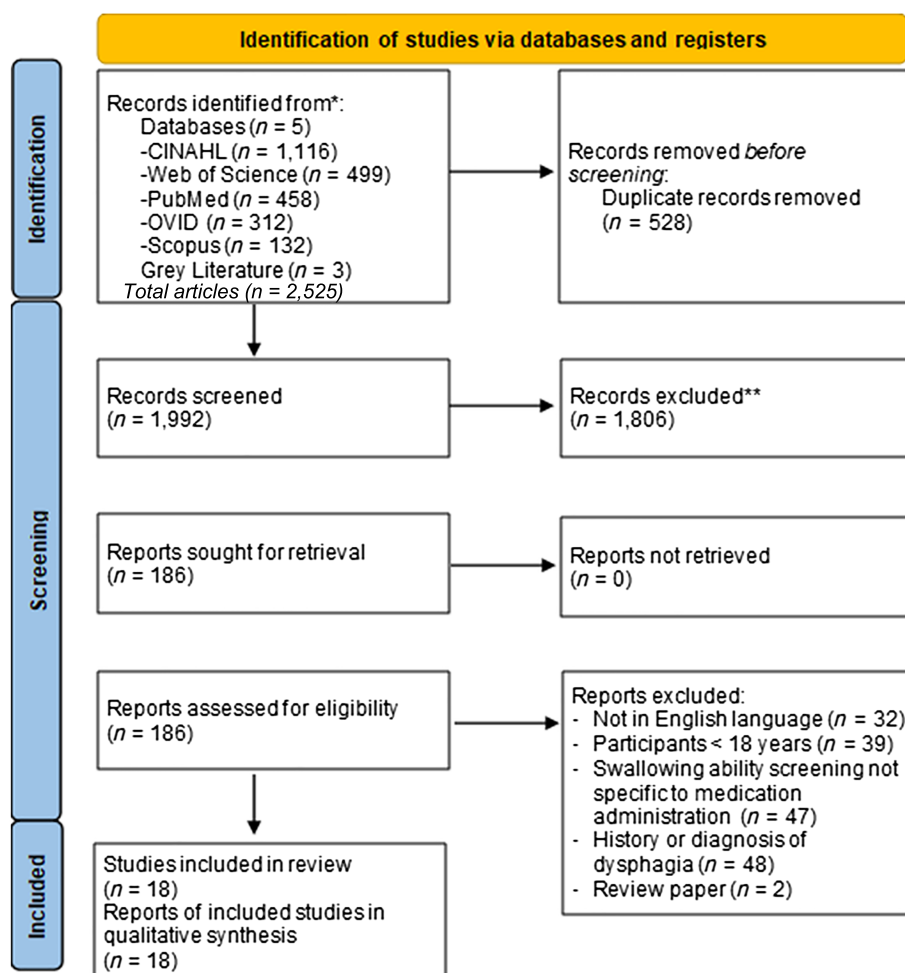
### 3.1 | Search strategy

A search strategy was developed using fundamental components of the research question: pill aversion, dysphagia, adults and interventions. Peer reviewed publications were identified by searching electronic databases: OVID, PUBMED, CINAHL, SCOPUS and Web of Science, in addition to grey literature searches by hand-searching reference lists and Google Scholar (as per Table S1 in the Supporting Information) (February–May 2021). Review papers were excluded but reference lists were hand-searched to ensure that any relevant studies presented in these were captured. The search strategy was tailored with the use of broader terms that considered variations in spelling and terminologies. Topic-specific Medical Subject Headings (MeSH) were employed: administration (oral), pharmaceutical preparations (administration and dosage), deglutition disorders and medication adherence, in addition to the following key words: dysphagia, swallowing difficulties, solid oral dosage forms, tablets, pills, pill-swallowing, adults, medication modification and health literacy.

### 3.2 | Eligibility/inclusion criteria

All studies published in the English language and relevant to the research question were included, with no restrictions on publication date. The Participant-Intervention-Comparison-Outcome (PICO) model was used to inform inclusion criteria as demonstrated in our protocol. Only articles reporting on participants aged 18 years or older (adults) without any physiological-related dysphagia were included. All interventions conducted in any healthcare setting were included: e.g., instrumental pill aversion assessments (questionnaires/interviews/screening tools, etc.), implementation and assessment of interventions to assist SODF swallowing in adults without underlying physiological causes of dysphagia. It was expected that primarily qualitative studies would be included without controls. Proposed comparators included: types of medications that patients have an aversion to, methods used to identify pill aversion and interventions used to overcome pill aversion from baseline to post-intervention.

Studies including mixed data from both paediatric and adults with no clear age stratifications were excluded. In addition, studies that captured those with diagnosed dysphagia/conditions associated with dysphagia, e.g. Alzheimer's and Parkinson's disease or stroke, were also excluded as per our protocol.



**FIGURE 1** PRISMA 2020 diagram of studies included in this review adapted from Page et al.<sup>14</sup>

An overview of the search strategy can be found in Table S1 in the Supporting Information (adapted from Jang et al.<sup>11</sup>).

### 3.3 | Study selection

Potentially eligible papers were exported to EndNote reference manager (version X9). This facilitated management of records and duplicate removal. Titles and abstracts of identified papers were independently screened against the eligibility criteria outlined in our protocol to determine whether they addressed the proposed research questions. If a paper met the inclusion criteria, it was reserved and underwent a single full-text review prior to confirmation for inclusion by a second reviewer with 10% of the final papers marked against the inclusion criteria by a third reviewer to resolve disagreements and reach a unanimous consensus for inclusion.

### 3.4 | Data extraction and synthesis

The primary outcomes of interest were to create a list of medicines that patients have an aversion to, identify and appraise interventions used to screen for and assist patients with pill aversion, and determine

the impact of these interventions on patient outcomes. It was expected that measures of effect would vary across included studies but were likely to include feelings of wellness/reassurance, improved medication use/adherence, improved carer and patient understanding around the taking and modification of SODFs, overall health outcomes (based on disease-specific targets) and continued SODF-swallowing success post-intervention.

Collaborative data extraction onto a pre-piloted table (Table S2 in the Supporting Information) was conducted by two team members with simultaneous assessment of quality using the STROBE tool for observational studies (Table S3) and conferment of quality by the remaining team members (who each looked at 25% of the included papers).<sup>12</sup> As per Zheng et al., studies that met the checklist with a score criteria of 80% or better were classed as high quality and those less than 80% low quality.<sup>13</sup> Key findings and emerging themes were collated to facilitate comparison of study design, intervention and outcome measures. A full systematic review and meta-analysis was not possible due to the heterogeneity of swallow measures and small number of studies.

The initial searches produced 2525 articles for review (Figure 1). Following removal of duplicates, screening of titles and abstracts and full-text reviews (186 articles), 18 met the protocol inclusion criteria and were reported in the final narrative analysis (Table 1 and Table S2

TABLE 1 Details of the 18 included articles based on PICO

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Overgaard 2001 Denmark	Patients at hospital pain centres aged 23–65+ years n = 331	Pill swallowing	No	No	No	Colour is important if taking >10 SODFs per day. Small arched tablets are acceptable. Medium and large tablets should be oblong or oval.	High
Kaplan 2010 Canada	University students aged 18–30 years n = 242	Pill swallowing	No	Postural adjustments —head position habituation	No	Changing to a new head position requires practice to develop habituation. No single head position was favoured among participants. Changing head position can result in improved comfort swallowing capsules.	High
Uloza 2010 Lithuania	Healthy hospital volunteers aged 18–64 years n = 41	Questionnaire	No	Pill swallowing	No	Coated tablets are easier to swallow than uncoated. Coating masks bitter tasting tablets.	High
Ibrahim 2012 Iraq	Community pharmacy patients over 18 years old n = 1000	Questionnaire	No	No	No	Capsules are the most favoured SODF (52.9%). Capsules are easiest to swallow and associated with a high perception of therapeutic benefits. Preference for capsules was significantly linked to gender, preferred by 61.6% of females.	High

(Continues)

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Marquis 2013 Switzerland	Community pharmacy patients over 18 years old n = 410	Semi-structured survey	Yes	No, but coping strategies were captured as part of the survey	22% reported past/ongoing difficulties	Tablet burden, gender or age were not definite triggers for swallowing difficulties. More women reported difficulties. Health professionals rarely enquired about pill swallowing. Formulation characteristics influence swallowability: large size, sticky coatings = unpalatability = poor swallowability. Analgesics, in particular paracetamol (19/104), are difficult to swallow. Strategies to overcome difficulties: Drink more water, switch formulation, cut/crush the SODF, mix the SODF with food, tilt the head backwards, intentional non-adherence and dosage form alteration.	High
Schiele 2014 Germany	Adults aged 18–85 years n = 151	No	No	Pill swallowing techniques: Pop-bottle method Lean forward technique	No	Pop-bottle method improved the ability to swallow tablets (59.7%) and the lean forward technique improved the ability to swallow capsules (88.6%). The unpleasant feeling in the throat was reduced and both	Low

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/ overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Yamamoto 2014 Japan	Healthy adult males aged 24–33 years n = 14	No	No	Pill properties to aid pill swallowing	No	<p>techniques showed relevant improvement in participant ability to swallow SODFs. 85.6% of participants would implement these techniques in their daily routine.</p> <p>Size, number of tablets and coating influence swallowability.</p> <p>The only study to view swallowing using videofluoroscopic images to quantitatively evaluate the physiological characteristics of tablet swallowing.</p> <p>Overall coated tablets were preferred to uncoated.</p>	High
Fields 2015 USA	Adults aged 23–77 years in tertiary centre waiting rooms and outpatient pharmacy n = 99	Structured interviews	No	No, but coping strategies were captured	54% answered yes to “Did you ever have to swallow a solid medication that was too difficult?”	<p>Formulation properties influence swallowability: size (too large, or too small &lt;4 mm loss of sense in the mouth), rough texture, sharp edges, taste.</p> <p>Coated SODFs are preferred and oval caplets ~6 mm length.</p> <p>Overcoming pill swallowing difficulties: plenty of liquids, forceful swallows, cut/crush the tablets, mix with food, open capsules</p>	High

(Continues)

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Lau 2015 Australia	Community pharmacy patients over 18 years old n = 369	Structured interviews	No	No, but medication modification was addressed	14.1% reported trouble swallowing medication	Difficulties swallowing medicines correlated with taking four or more doses per day. 10.6% modified their medicines, some unnecessarily. Over half of respondents recognised issues with modifying medicines but few could elaborate on this beyond changes in taste and pharmacokinetic/pharmacodynamic profile. Participants would seek advice from a healthcare professional if they were having difficulties swallowing medication (73.2%) and prior to modifying their medicines (55.8%).	High
Liu 2016 England	Community pharmacy patients over 65 years old n = 156	Questionnaire Sydney swallow and medicines acceptability	No, but real tablets used as models for different shapes and alternative oral formulations	No, acceptability of alternative dosage forms was discussed	11% Sydney swallow questionnaire 7.8% medicines acceptability questionnaire	Validation of the medicines acceptability questionnaire and no relationship seen between Sydney swallow score and age or gender. Alternative SODFs were not commonly used with the exception of dispersible tablets, which were preferred, followed by oral	High

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Dorman 2017 USA	Female HIV-infected patients under perinatal HIV medical care n = 140	Questionnaire	Yes	Psychological/behavioural	12%	<p>disintegrating and mini-tablets.</p> <p>Relationship between acceptability and swallowing difficulties: size and shape matter, with oblong and oval considered easiest to swallow.</p> <p>Pill training interventions used in children are inappropriate for pregnant females with HIV due to time constraints and priority to minimise risk of vertical transmission.</p> <p>It is important to address symptoms of pregnancy associated gastro-oesophageal reflux disease as this can be barrier to medication-taking.</p> <p>Counter-conditioning and cognitive restructuring facilitate overcoming association of first trimester feelings of nausea with pill taking and coming to terms with a new diagnosis eliminating negative thoughts about their diagnosis and medication-taking.</p>	High

(Continues)



TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Dorman 2019 USA	Adults over 18 years old living with HIV, prescribed antiretrovirals and attending an outpatient clinic n = 384	Questionnaire	Antiretroviral therapy regimen captured and formulation properties that make pills difficult to swallow	No	25.5% skipped pills due to pill aversion symptoms	Depression and anxiety, less education, unemployment, younger age, Hispanic patients and public insurance were associated with skipping pills due to pill aversion. This resulted in detectable viral loads. Emotions such as fear and negative feelings/negative stigma with diagnosis also precipitate pill aversion. Symptoms of pill aversion: gagging, nausea and heavy feeling in the stomach. Formulation factors influence pill aversion: taste, smell, size and texture.	High
Nativ-Zeltzer 2019 USA	Healthy community-based volunteers aged 30–67 years n = 226	Questionnaire PLL-5 & Pill swallowing	No	No	No	Validated tool to measure the extent of pill dysphagia with surgery results compared to barium tablet swallowing. Score < 6 = minimal/no pill dysphagia Mean score for healthy volunteers = 1.6 showing that there is some degree of pill dysphagia in the healthy population.	High

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Souza 2019 Brazil	Healthy community-based adults aged 20–84 years n = 439	Questionnaire EAT-10	No	No	17%	EAT-10 considers difficulties swallowing food, liquid and medication. Age and gender influence swallowing disabilities – more females and younger patients reported difficulties swallowing medication than males or older patients. Score < 3 = absence of dysphagia.	High
Seedat 2020 South Africa	Adults 18–95 years old n = 73	Questionnaire	Yes	No	33% found pill swallowing unpleasant	Link between female gender and difficulties swallowing medication. Emotional association with pill swallowing. Pill properties influence swallowability; size, texture, taste, shape and smell.	High
Arnet 2020 Ireland	Community pharmacy patients over 18 years old n = 66	Questionnaire SWallowing difficulties with MEDication intake and coping strategies (SWAMECO)	Yes	No, but coping strategies were captured	12.1%	All noted some level of discomfort on a visual analogue scale (0–10), mean score 6.9. No correlation observed between age, gender or number of medicines and difficulties swallowing food or liquids. Localisation of pills captured: primarily the pharynx and feeling of pills getting stuck/choking. Coping strategies included tablet	High

(Continues)

TABLE 1 (Continued)

Article details (author, year and country)	Population (age and participant number) (n)	Screening for pill aversion	List of medications patients have an aversion to	Interventions/overcoming pill aversion	Prevalence of pill aversion	Outcomes	Quality using STROBE checklist
Parraga Acosta 2021 USA	HIV adults over 18 years old n = 50	Pill swallowing	No	No	No	<p>splitting and opening capsules. Most held their head in a neutral position when taking tablets.</p> <p>Formulation properties influence swallowability, size, shape and texture. New smaller placebo 15.5 mm length preferred, oval shape and smoothness considered important factors for swallowability. Perceived ease of swallowability influences adherence.</p>	High
Radhakrishnan 2021 Australia	University students aged 18–30 years n = 152	Questionnaire & Pill swallowing	No	No, but coping strategies were captured	32%	<p>Smaller mouth cavity size significantly influences medication swallowing difficulty and higher density of case receptors on the tongue.</p> <p>Memories of swallowing difficulties, e.g. choking correlated with current difficulties.</p> <p>Coping strategies included modifying medicines crushing or cutting and changing head position.</p>	Low

in the Supporting Information). STROBE checklist analysis identified two studies as low quality (<80% score on STROBE checklist) (Table S3).<sup>15,16</sup> Several themes emerged as outlined below.

## 4 | PREVALENCE OF PILL AVERSION, PARTICIPANT DEMOGRAPHICS AND STUDY SETTINGS

Pill aversion is a global problem with studies produced from almost every continent: eight from Europe, six from North America, two from Asia and one each from South America and Africa. Most studies (67%,  $n = 12$ ) were conducted in community pharmacy or outpatient hospital clinics.<sup>1,15-31</sup> Participant numbers ranged from 14<sup>17</sup> to 1000,<sup>18</sup> with a median of 154 participants, aged 18–95 years. Two studies were gender specific, Yamamoto et al. (males) and Dorman et al. (pregnant females).<sup>17,19</sup>

The overall mean prevalence of pill aversion was 23.11% (10 studies, 2288 participants, range 11–54%). Risk factors for pill aversion identified and described in our included studies were: being female (five studies, total participants  $n = 2056$ , female  $n = 1061$ , odds ratio [OR] = 8.09]; Ibrahim et al. postulated gender-related disability but no statistical difference; [ $P = .1$ ] by Marquis et al.;  $P = .01$  by Souza et al.; in Seedat et al.'s study, 78% of participants who had difficulties were female)<sup>18,20-23</sup> and younger in age (two studies, total participants  $n = 574$ , mean age 48.4 years).<sup>24,25</sup> Dorman et al. (total participants  $n = 384$ ) also suggest that pill aversion may co-exist with mental health problems such as depression (28.4%) and anxiety (20.6%).<sup>24</sup>

## 5 | MEDICATIONS THAT PATIENTS HAVE AN AVERSION TO

Few studies provided a defined list of medicines that patients had an aversion to/difficulty swallowing, with a tendency to report medication classes rather than specific drug names. Marquis et al. noted 104 problematic medicines ( $n = 41$  analgesics), in particular paracetamol (19/104).<sup>21</sup> Seedat et al. describes medicines taken by participants including vitamins, medicines for long-term conditions such as cardiovascular disease, and antibiotics, but does not identify those causing swallowing difficulties.<sup>23</sup> Respondents to Arnet et al. specified painkillers, hyoscine butyl bromide, esomeprazole and antibiotics as associated with poor swallowability.<sup>26</sup> Fields et al. used a range of SODFs as models to determine perceived ease of swallow; these included “small SODFs”: e.g., thiazide diuretics and thyroid treatments, antibiotics to represent “very large” capsules, and calcium and potassium supplements to represent “jumbo” tablets.<sup>27</sup>

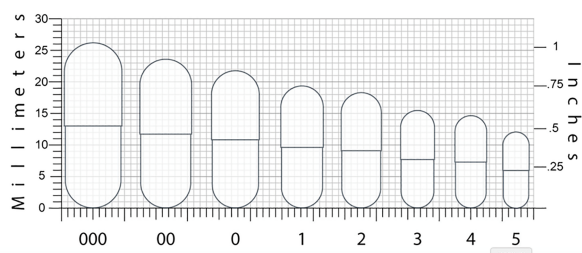
Formulation properties, e.g. size, shape, texture, taste and smell, were widely referred to as influential factors for ease of swallowability.<sup>1,15,18,20,22,26,29,31</sup> White colour was most preferred and purple/brown least in Overgaard et al.<sup>28</sup>

Capsules are considered preferable to tablets<sup>18,23,28</sup> with Ibrahim et al. demonstrating an association with gender (females) and age (<45 years).<sup>18</sup> Size matters and is demonstrated in Figures 2 and 3: larger capsules, e.g. #0 and above, are associated with reduced ease of swallowability, with Radhakrishnan et al. linking this to participants with a small mouth cavity.<sup>1,16</sup> Descriptions such as small, medium and large vary among the studies and defined measurements in terms of acceptable size also differs. Yamamoto et al. define small tablets as a diameter of 8 mm and large as of 9 mm.<sup>17</sup> Parraga Acosta et al.'s small tablet was 15.5 × 7.8 × 5.7 mm.<sup>29</sup> Fields et al. identifies medium-sized SODFs as 6–13 mm,<sup>27</sup> and Liu et al. identify difficulties over 11 mm.<sup>1</sup> Fields et al. indicate that SODFs can be too big but also too small, with those <4 mm causing handling difficulties, and a minimal sense of feeling when in the mouth.<sup>27</sup> Coated tablets are preferable to uncoated tablets<sup>17,18,28,30</sup> and Ibrahim et al. relate this preference also to gender (favoured by females),<sup>18</sup> and oblong or oval, over round shapes if tablets are medium–large in size.<sup>1,28,29</sup>

## 6 | SCREENING FOR SODF/PILL AVERSION

Most included studies ( $n = 13$ ) used self-reporting surveys or interviews to screen for pill aversion, with five studies asking participants to swallow SODFs to determine capability/feelings about ease of swallowability (further details can be found in Table S2 in the Supporting Information).<sup>15,20,21,24,26,28,29</sup> While most studies designed bespoke surveys, some utilised or adapted validated questionnaires: Liu et al. (Sydney Swallow and Medicines Acceptability questionnaires),<sup>1</sup> Marquis et al. determined participant perception of their state of health using a question from the General Health SF-36 questionnaire,<sup>21</sup> Souza et al. (EAT-10),<sup>22</sup> Nativ-Zeltzer et al. (PILL-5)<sup>25</sup> and Arnet et al. (SWAMECO questionnaire).<sup>26</sup> Dorman et al.'s two studies explored difficulties swallowing SODFs from a different angle, posing open questions to explore the psychological aspects of medicine-taking. Questions explored participants' thoughts about their SODFs and how they prepare to take them, images that they have of SODFs; along with SODF physical qualities that influence their swallowability and physical symptoms that they experience when taking SODFs.<sup>19,24</sup> Seedat et al. also acknowledge the psychology of medicine-taking and that there is not always a direct correlation between ease of swallowing and emotions.<sup>23</sup> Liu et al., Ibrahim et al. and Fields et al. used models/pictures of different SODFs to explore participant preferences and perceived ease of swallow.<sup>1,18,27</sup>

Participants' previous and current experiences of SODF swallowing were captured, with information such as history of medication-taking, number of daily SODFs, physical properties and specifics of difficult SODFs recorded.<sup>1,21,23,24,26,27,29,30</sup> Liu et al. and Marquis et al. also enquired about health status<sup>1,21</sup> and Dorman et al. about co-morbidities.<sup>24</sup> Two papers captured the impact of pill aversion on participants daily life.<sup>26,29</sup> Most studies focused on difficulties taking medicines; however, Lau et al., Fields et al., Souza et al. and Radhakrishnan et al. also explored difficulties swallowing food or liquids in



**FIGURE 2** Capsule sizes expressed in millimetres and inches. With permission from LFA Machines Oxford Ltd (<https://www.lfacapsulefillers.com/capsule-size-chart>).

addition to SODFs.<sup>16,22,27,31</sup> Lau et al. loosely linked difficulty swallowing medication in those taking four or more doses per day,<sup>31</sup> whilst Radhakrishnan et al. report that smaller mouth cavity size and high numbers of taste receptors may correlate to reduced confidence swallowing large capsules. They also state that aversion to certain foods, e.g. popcorn, granola bars or crisps/potato chips, may be associated with aversion to rough textured SODFs.<sup>16</sup>

Defining ease of swallowability varied: studies used Likert scales and visual analogue scales to determine participant comfort or perceived comfort of SODF swallowing. For example, Overgaard et al. utilised a verbal scale of very easy—easy—acceptable—difficult—very difficult.<sup>28</sup> Fields et al. enquired about perceived ease of swallowing of models defined on a 4-point scale as easy/no effort to hard or impossible to swallow,<sup>27</sup> whilst Parraga Acosta et al. used a 5-point Likert scale of very easy to very hard.<sup>29</sup>

Participants utilised a range of techniques to take their medicines or placebos during intervention studies. Techniques varied from the volume of liquid consumed, to head positioning and other adaptations to aid SODF swallowing. Overgaard et al. allowed participants to swallow SODFs with a minimum of 20 ml of water and a maximum of 250 ml.<sup>28</sup> and Schiele et al. and Uloza et al. similarly used 20 ml of water,<sup>15,30</sup> whilst Yamamoto et al. allowed participants 15 ml.<sup>17</sup> Radhakrishnan et al. reported that some participants chose to swallow placebo capsules without any liquid, whereas others used up to 150 ml.<sup>16</sup> Three questionnaire-based studies explored head position when taking SODFs.<sup>16,21,26</sup> Kaplan et al. asked participants to swallow capsules in five different head positions and feedback on each, selecting the most comfortable to practise at home.<sup>20</sup> A change in head position can facilitate better SODF swallowing but no conclusions were reached regarding a preferred head position. The PILL-5 questionnaire determines the degree of SODF dysphagia and localisation, e.g. pills stick in my throat/chest.<sup>25</sup> The SWAMECO questionnaire also captures this, asking participants to describe how SODF localisation feels.<sup>26</sup> Yamamoto et al. explored this with participants swallowing action, tablet location and transport evaluated using videofluoroscopic oesophagram (VFE): those where tablets localised under the tongue were unsuccessful at the tablet swallowing task in comparison to those with localisation at the dorsum of the tongue experiencing swallowing success.<sup>17</sup>

Lau et al., Marquis et al., Fields et al. and Arnet et al. explored the specifics around medicine-taking difficulties, its impact on daily lives,

and strategies to overcome these including coping strategies and medication modification.<sup>21,26,27,31</sup> Lau et al. asked about modification specifically, who had suggested this, and if participants knew of any problems associated with this approach.<sup>31</sup> In addition, Marquis et al. and Arnet et al. asked whether participants would seek advice from a healthcare professional prior to modifying their medicines.<sup>21,26</sup> Uloza et al. adopted use of a special coating to explore its impact on ease of swallowing.<sup>30</sup> A recurring theme established throughout the included articles was the level of self-perception and reflection required to identify pill aversion. Where there lacked a physiological reasoning behind an impaired ability to swallow medication, then diagnosis of pill aversion became less clear. This type of difficulty requires either the prescribing healthcare professional, or the patient themselves, to bring forth and discuss the issue. Without a clear process in place, pill aversion appears to go unnoticed and unresolved, resulting in some patients with difficulties swallowing oral medication modifying medication and skipping doses and therefore having poorer therapeutic outcomes.<sup>21,24,26,27</sup>

## 7 | INTERVENTIONS/OVERCOMING PILL AVERSION AND THE OUTCOME OF THESE

Few studies implemented and assessed the impact of interventions to assist those with SODF swallowing difficulties. All reported interventions proved successful, demonstrating that educational interventions are effective at improving patient experience with swallowing SODFs. Intervention studies are outlined below.

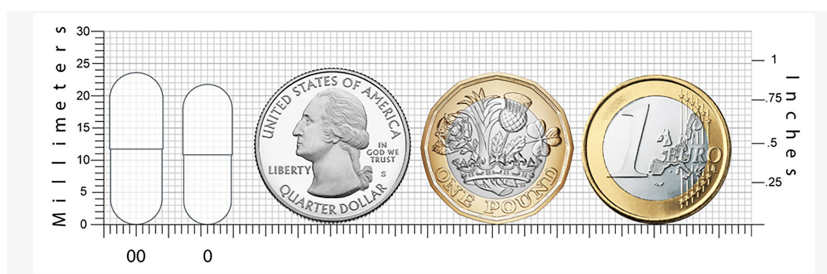
### 7.1 | Postural adjustment

Kaplan et al. taught participants to swallow gelatine capsules with the head to the centre, chin tilted up, chin tilted down, head rotated left and head rotated right.<sup>20</sup> They adopted the approach of daily practice and recording of comfort of each position for 14 days to ensure habituation and then reassessed participants. Preferred head position changed following training and habituation with 75% of participants preferring the new position. As detailed earlier, no clear consensus was reached as to the most comfortable position; however, 73% said that the study had changed the way they swallow SODFs for the future.

Schiele et al. also found improved swallowing ability following adoption of two postural methods: “pop-bottle method” and “lean forward technique”. The pop-bottle method is outlined well by Tse et al.<sup>32</sup> It involves holding the head in a neutral position, asking the person to place the placebo (starting with the smallest size) on the centre of their tongue sealing their lips around the pop-bottle (sports-topped bottle) and take three big gulps without putting the bottle down. If successful then the person moves to the next placebo size and repeats the steps. The lean forward technique is useful to prevent capsules floating in the mouth. Leaning forward whilst swallowing aids opening of the oesophagus and ease of capsule passage.

Schiele et al.'s study investigated administration of both placebo tablets and capsules. Participants swallowed SODFs of different sizes

**FIGURE 3** Comparison of size #0 and #00 capsules with common coins to show their scale. Used with permission from LFA Machines Oxford Ltd (<https://www.lfacapsulefillers.com/capsule-size-chart>).



and shapes with their eyes closed and 20 ml of water. After each administration they rated ease of swallow on an eight-point analogue scale (0 = very easy, 7 = very difficult). This scale allowed patients to quantify their difficulty via a visual artefact, thus reducing the use of subjective descriptions. The two dosage forms that caused most difficulty were recorded for each participant. They retook those specific dosage forms using either the “pop-bottle method” or “lean forward technique”. With both formulations there was improvement in participants' swallowing technique. The frequency of participants reporting an unpleasant feeling in the throat was reduced from  $n = 159$  to  $n = 82$  with tablet administration and from  $n = 10$  to  $n = 0$  with capsule administration. Overall, the use of those interventions reduced participant perception of troubled swallowing from  $n = 198$  to  $n = 103$  in tablet administration, and from  $n = 16$  to  $n = 0$  with capsule administration.

## 7.2 | Coating of SODFs

One study reported coating as a means to increase tablet smoothness and taste-masking.<sup>30</sup> Almost all participants  $n = 40/41$  (97.6%) found the coated tablets easier to swallow than uncoated equivalents, and 100% declared that coating masked the bitter taste of uncoated tablets. This demonstrates the potential of coating devices to counter SODF swallowing difficulties. These findings were also reflected in the study by Yamamoto et al.<sup>17</sup> Here, participants swallowed four types of tablet: small, large, coated and uncoated with 15 ml of water. Overall, participants preferred coated tablets.

## 7.3 | Behavioural interventions

Dorman et al. explored addressing the anxiety associated with SODF swallowing and recognised that pill aversion/ fear of taking SODFs is a significant barrier to antiretroviral regimen adherence and ultimately has detrimental consequences on viral load if not remedied.<sup>19</sup> Participants  $n = 17$  (12%) were offered behavioural interventions by a health psychologist. These included counter-conditioning to eliminate the association of antiretroviral treatment and early stages of pregnancy (nausea and vomiting) through relaxation techniques and counselling. Another approach was cognitive restructuring in the form of relaxation training to change the way participants felt about their diagnosis, associated SODF burden and fear around medication-taking.

## 7.4 | Patient adaptations

It is important to recognise that participants in many studies reported strategies that they adopted to aid SODF swallowing, many of which may bias the outcome, be inappropriate or risk compromising therapeutic activity. These included: drinking more water<sup>21,27</sup>; switching formulation<sup>21</sup> (although Liu et al. reported that not all alternative formulations were favourable, in particular, chewable tablets and granules<sup>1</sup>); cutting or crushing the SODF<sup>21,26,27</sup>; opening capsules<sup>26,27</sup>; mixing with food<sup>21,27</sup> and skipping doses.<sup>21,24,26</sup>

## 8 | DISCUSSION

Studies reporting the proportion of patients adherent to medicines state an average of 50% adherence. Perhaps some of these non-adherent individuals have pill aversion.<sup>27</sup> Regarding adherence interventions for SODFs, pill counts or medication event monitoring system pill caps are commonly used. In neither case can it be confirmed whether the patient actually took the medication or not.<sup>33</sup> Pill swallowing screening and interventions to assist paediatric patients are common. Although largely neglected in adults, these could help overcome some adherence issues.<sup>32,34,35</sup> Not all adult-focused pill aversion studies were eligible for inclusion in this review due to inclusion of participants with a history, or current diagnosis, of conditions that precipitate difficulty swallowing SODFs.<sup>6,36</sup> However, the included studies indicate that difficulties swallowing SODFs in adults without dysphagia is prevalent and often left unresolved, potentially resulting in negative therapeutic outcomes.

Study diversity was broad with several interventions reported to screen and overcome pill aversion, and various reporting methods used to determine their impact. We recognise the potential for bias in the review process as the literature specific to pill aversion is not well indexed in comparison to dysphagia. Therefore, despite our efforts, some suitable articles for inclusion may have been missed. Our exclusion criteria eliminated those living with dysphagia conditions potentially excluding some further high-quality evidence, but we suspect that due to the requirement for specialist intervention for these individuals, they are beyond the remit of this review. It is difficult to make direct comparisons between studies, and consistent evidence regarding the most effective interventions is somewhat lacking. However, we have, as far as possible, outlined the key findings of included studies.

The first point of action with individuals experiencing pill aversion should be restoring, and then maintaining, swallowing ability.<sup>8</sup> We are unable to provide a comprehensive and specific list of SODFs associated with pill aversion, but have reported characteristics that appear to influence SODF swallowability. These may help prescribers make appropriate formulation choices, and facilitate research and development of more patient-acceptable formulations of currently troublesome medicines. Further studies are required to capture this information and explore the reasons why specific medicines cause swallowing issues. If a patient requires a medicine, then emphasis should be on formulation choice within the medicine classes.<sup>3,21,26,36,37</sup> It is necessary to increase awareness of medicines that can directly affect swallowing function through impaired gastric motility, gastric mucosa irritation or that induce xerostomia.<sup>2</sup> In this era of patient-centred care, physicians and drug development teams must consider patient as individuals. This includes treatment choices informed by their suitability, product availability and, to a lesser extent, cost.

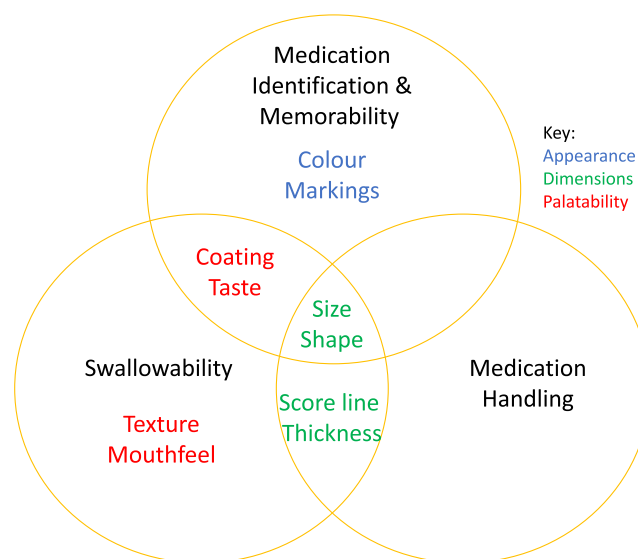
Although by 2050 an estimated one in six of the world's population will be over the age of 65, we must consider pill aversion as an ageless concern. Younger patients are as susceptible, if not more susceptible, to pill aversion. This is attributed to not being taught to swallow SODFs at a young age and perhaps having less experience swallowing SODFs.<sup>31</sup> Another aspect that may influence adherence for younger patients is pill burden/number of doses required during the day. Where possible, medicine-taking should not impact significantly on a patient's daily routine. Polypharmacy is often defined as regular use of five or more medicines and considered an older persons' burden resulting from treatment of multimorbidities associated with ageing.<sup>38</sup> However, polypharmacy is also a concern in younger patients with long-term conditions. There are numerous recommendations to minimise polypharmacy and tools to support deprescribing—e.g. The Choosing Wisely Campaign, STOPP (Screening Tool for Older People's Prescriptions) criteria,<sup>39</sup> and SIMPATHY (Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly)).<sup>40</sup> An alternative approach and increasing research area is formulation of poly-pills.<sup>41</sup> These fixed-dose combinations, where multiple drugs are combined into a single formulation, are proving useful for conditions such as cardiovascular disease and hypertension, but also type 2 diabetes mellitus and HIV. They eliminate the need to take multiple SODFs and evidence demonstrates that reduced pill burden significantly improves medication adherence.

The impact of physiological changes with age (presbyphagia) should be considered when older patients present with medication-taking difficulties. These include: changes in swallowing physiology, impaired oesophageal sphincter contractile reflexes, reduced salivary gland function, or prescribed medicines that precipitate this, e.g. opioids or diuretics, likelihood of developing disease that can precipitate swallowing issues, and reduced dexterity impairing medicine handling.<sup>2,42</sup> Gender may be another influential factor. Marquis et al. noted that anatomical differences in mouth cavity sizes, pharynx and larynx may explain higher levels of perceived female SODF swallowing disability.<sup>21</sup> This was also reported by Schiele et al. who noted that females had a stronger aversion to medicines than males, with female

gender indicated as a risk factor for pill aversion.<sup>36</sup> Although 16/18 studies captured participants of both genders, 27% of these found that more woman than men suffered from SODF swallowing difficulties. Not all findings were significant, thus further exploration around the influence of gender is necessary.

Co-morbidities such as depression, previous experience of medicine-taking, and demographics including educational level, influence to some extent beliefs about health conditions and medicines. This in turn determines the extent of medication adherence and, perhaps, where people seek help if they experience difficulties swallowing their medicines.<sup>18,24</sup> The influence of co-morbidities and demographics has been highlighted as being particularly influential on medication adherence and health outcomes for HIV patients.<sup>43</sup> The health belief model also should be considered. This has been widely reported and applied to a range of health topics including medication adherence and is referred to within the included studies of this review and wider literature. Mental health status has also been linked to gender, with females considered more prone to depression and anxiety disorders, and these alone serving as factors for pill aversion.<sup>36</sup> Educational status, employment status and the country patients live in also appear to influence views around certain medicines and medication-taking as discussed in detail by Tahaineh and Wazaify.<sup>6</sup> Addressing beliefs and concerns about medication must happen at the beginning of therapy.<sup>44</sup> This may be facilitated by a discussion about medication-taking and adherence when a new medicine has been prescribed, or at a medicines' use review. Healthcare professionals should therefore consider a patient's knowledge base, socioeconomic status and demographics when prescribing or counselling on medication use.<sup>45</sup>

The choice and properties of a pharmaceutical dosage form determine its acceptability and subsequent patient adherence. Shariff et al. summarise this by relating physical properties to the key stages of the medication-taking process as shown in Figure 4.<sup>42</sup>



**FIGURE 4** The relationship between SODF characteristics and medication-taking. Adapted from Shariff et al.<sup>42</sup>



Capsules appear preferable to tablets with ease of swallow attributable to their physical properties. MacLeod et al. identify capsules as being lighter than water and therefore able to float, often coated or gelatinous in nature and oblong in shape. This is in comparison to tablets, which, being heavier than capsules, do not float, are often uncoated and round, rendering them more difficult to swallow.<sup>46</sup>

## 8.1 | Appearance

Colour, markings and distinctive shapes aid with identification and memorability of SODFs, which is particularly useful for polypharmacy patients.<sup>28,47</sup> Certain colours are associated with particular tastes, e.g. pink with sweet flavours and yellow with salty.<sup>2</sup> Dimensions and palatability influence SODF swallowability profiles.

## 8.2 | Dimensions

Shape is the next memorable physical characteristic after colour.<sup>2</sup> Oblong or oval appears ideal for ease of swallowing, reflecting the preference for capsules, caplets or oblong tablets. It also influences ease of handling, as flat dosage forms are tricky for those with dexterity issues—diamond/raised shapes help overcome this.<sup>48</sup>

It is apparent that SODFs can be too big, but also too small. There is a balance between swallowability and handling. Studies state tablet size in diameter and capsules are often stated as sizes #000 to 5 rather than in millimetres. Sizes #000 to #0 are most likely to cause patients problems.<sup>1,16</sup>

It is not possible to compare studies fully as dimensions are not quoted in the same manner and how dimensions were calculated in the included studies of this review was not always clear. Overgaard et al., for example, stated dimensions as length × width × height for oblong or oval tablets and diameter × height for round tablets; others did not adopt this method.<sup>28</sup> Taking this into account, a recent Japanese study declares that the ideal indices for tablet/capsule size is to consider length + width + height with a cut-off acceptability of 21 mm. Some attempts have been made in paediatric studies such as that of Jones et al., who state the dimensions of placebos and Rashed et al. who used sweets and cake decorations of equivalent sizes to licensed medicines to aid “pill swallowing training”.<sup>35,49</sup> A reporting consensus needs to be reached in order to make valid comparisons and conclusions across studies.

Fields et al. reported a near-perfect swallow score for oval caplets of ~6 mm.<sup>27</sup> The Food and Drug Administration suggest SODFs of 8 mm or above are more likely to cause swallowing difficulties, but it is difficult to draw conclusions unless patients physically attempt to swallow SODFs of different sizes. Most included studies asked about patients' perceptions of swallowability only.<sup>3</sup> Further studies are required to determine the influence of thickness and how coating influences swallowability in physical swallow studies rather than participant perceptions.

## 8.3 | Palatability—taste and smell

The taste or smell of an SODF is also important for acceptability, with sweeter sugar coatings preferred.<sup>23,27</sup> Many drugs have a bitter taste and taste-masking may be executed during the manufacturing process, e.g. during granulation and coating of SODFs.<sup>2</sup> Uloza et al. demonstrated how special coating devices can be used to mask foul-tasting medicines immediately prior to administration.<sup>30</sup>

## 9 | SCREENING FOR PILL AVERSION

Questionnaires are a simple and effective method to communicate and screen patients regarding medication administration. There are, however, no “gold standard” protocols to detect and measure pill aversion, although some validated tools have been identified in this review.<sup>24</sup> It is important to develop or use screening tools that are relevant and suitable for adaptation to general clinical practice rather than simply meeting research questions.<sup>50</sup> The lack of standardisation in study design and pill aversion assessments for children and adults alike remains a concern.<sup>51</sup>

SODF swallowing problems may be the result of psychological (fear), physiological (dysphagia) or iatrogenic causes; thus, appropriate screening at an early stage, ideally at initial prescribing or dispensing, is essential to address difficulties from the outset.<sup>52</sup> Screening should inform and support treatment choices or signpost to specialists—e.g., psychologists or speech and language therapists—if further investigation is required.<sup>50</sup> Consideration of risk factors, as discussed earlier, may be useful for physicians to screen patients who have, or are at risk of, medication-swallowing difficulties. A similar approach to the framework suggested by Namasivayam-MacDonald and Riquelme may be used to screen at-risk patients, monitor or perform swallow assessments, implement interventions and monitor outcomes.<sup>5</sup>

The location of screening is important, with the included studies mainly taking place in healthcare settings. Mc Gillicuddy et al. and Lau et al. support GP surgeries and community pharmacies as screening sites due to good interpersonal relationships between these healthcare teams and their regular patients.<sup>31,53</sup>

How patients should be screened for pill aversion or indeed poor SODF adherence also remains inconclusive, but asking patients if they experience difficulties taking their medicines is essential.<sup>21</sup> Patients are reluctant to seek help from healthcare professionals regarding swallowing difficulties.<sup>31</sup> There is a need to educate patients around voicing their concerns on this subject as well as encouraging healthcare professionals to specifically ask about medicine-taking difficulties. Dorman et al. used open behavioural-focused questions—e.g., what thoughts do you have when you look at your pills? Further exploration of this approach may permit its generalisability to the wider population.<sup>19</sup>

A final challenge is how to interpret the findings once a screening tool has been used. With the PILL-5 method, a quantifiable result indicates the degree of SODF swallowing disability: a score of >6/20 indicates swallowing difficulties.<sup>25</sup> Similarly with the Sydney Swallow



Questionnaire, a score of >200 indicates risk of dysphagia.<sup>1</sup> Should screening tools just consider SODF swallowing disability or more widely look at difficulties swallowing food and liquids as per EAT-10, or SWAMECO, which explores other factors, e.g. tobacco, alcohol, history of pneumonia. Visual analogue scales are widely used to determine comfort/intensity of discomfort in paediatrics and adults. They are easy to use and interpret, and can be completed irrespective of language and health literacy; however, they do not provide a quantifiable level of swallowing disability.<sup>34</sup> Further work is required to determine which method is best for different patient cohorts. In addition to surveys, perhaps instrumentation should be used in those identified as having SODF swallowing disability, e.g. video fluoroscopic studies. This may aid understanding of the swallowing process, localisation of SODFs in the oesophagus, and monitoring swallowing efficiency with postural adjustment interventions.<sup>5</sup>

## 10 | METHODS TO OVERCOME PILL AVERSION/SODF SWALLOWING DIFFICULTIES

Patients experiencing medicine-taking difficulties often resort to unconventional and potentially dangerous self-management methods.<sup>54</sup> These primarily include modification of SODFs or non-adherence. Polypharmacy patients are more likely to experience swallowing difficulties and modify their medicines than those taking less than four doses per day.<sup>31</sup> The reasons for modification are broad ranging from halving medicines due to slight discomfort swallowing to fractional dosing and habitual modification of all medicines even when swallowing is not a problem.<sup>53</sup> This is particularly concerning in aged care facilities where sometimes all medicines are mixed together.<sup>55</sup> As detailed in the included papers, a number of approaches can be adopted to aid SODF swallowing. These should be tried prior to consideration of alternative dosage forms/routes of administration or de-prescribing, and as a last resort, medicine

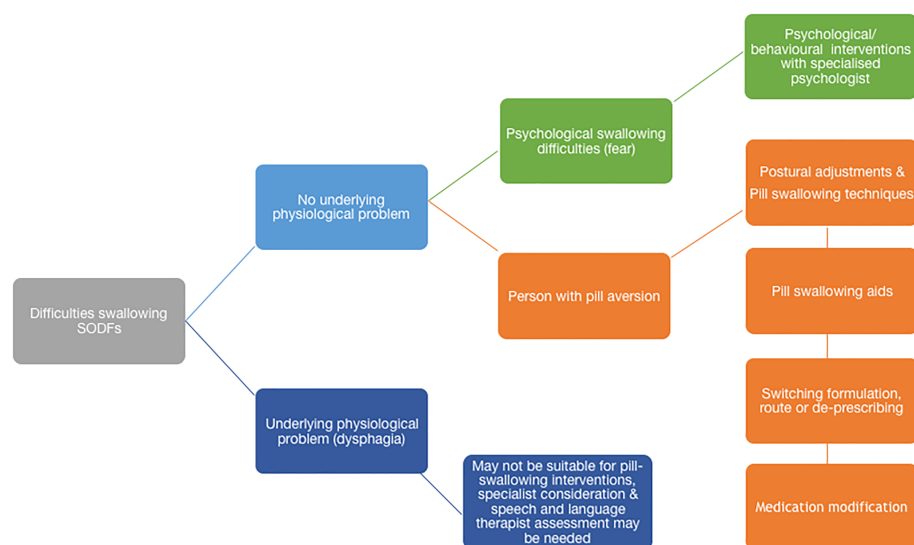
modification. Forough et al. summarise these approaches clearly in their review paper and as outlined in Figure 5.<sup>8</sup> There is an evident unmet need to educate not only patients, but healthcare professionals alike, regarding suitable medicine modification. This is highlighted in a scoping review by Masilamoney and Dowse, which indicates gaps in healthcare professionals' knowledge regarding medication modification, limited evidence as to its long-term effectiveness on adherence and therapeutic outcomes, the need for accessible guidance on modification, and a multi-disciplinary team approach with pharmacist-led training.<sup>56</sup>

Forough et al. consider behavioural interventions a specialist area, and the included work of Dorman et al. also used health psychologists to conduct interventions of counter-conditioning and cognitive restructuring.<sup>8,19</sup> Positive reinforcement through rewarding, praising and repetition may be adopted and aid success of postural adjustments and instructional techniques as demonstrated by Tse et al.<sup>32</sup>

Postural adjustments—e.g., central head position—are easy to implement, regulate the direction and flow of SODFs and protect the airway from aspiration.<sup>15,20</sup> Further work is required to determine the optimal head position and instructional technique.<sup>32</sup> Successful instructional techniques confirm that SODF swallowing is a learnt skill and can be taught like any life skill such as people being taught to tie their shoe laces.<sup>31</sup> Although these interventions use placebo tablets or candy, which may not be representative of SODFs in terms of texture, they serve as useful representatives of “real” SODF sizes.<sup>35</sup>

Coating increases SODF smoothness and taste-masking with negligible impact on drug pharmacokinetics. Lubricant gels and sprays have also proven effective in paediatric populations—e.g., Pill Glide flavoured spray.<sup>57,58</sup> Flavour compatibility remains an issue with these, and further work is required in larger child cohorts and adults.

Use of special drinking receptacles—i.e. pill swallowing cups—have helped small cohorts of children<sup>59</sup> but not all.<sup>35</sup> Evidence is weak and there are concerns that such devices promote a head back position and risk of aspiration, adding to the anxiety of medication-taking, and there is the practicality regarding cup portability. Pill swallowing



**FIGURE 5** A summary of approaches to manage SODF swallowing difficulties. Adapted from Forough et al.<sup>8</sup>

straws may avoid this with promotion of a head neutral or chin-down position; however, evidence on their effectiveness is lacking.<sup>8</sup>

If postural adjustments or training techniques prove unsuccessful, consideration should be given to the formulation and therapy-related determinants of non-adherence.<sup>42,52</sup> When a medicine is initiated, it must be implemented as intended and treatment continued for the required duration of time as per the taxonomy of medication adherence.<sup>52</sup> Therapy requirements differ between adults and children. Drug companies should involve the end-user (patients/carers/health-care providers) from the beginning of the design process.<sup>52</sup> The European Medicines Agency has issued guidelines for the development of age-appropriate medicines, initially prioritising paediatrics. This has been expanded to include therapies tailored for older adults who often have similar cohort needs to paediatrics.<sup>60</sup> Capsules are largely favoured among adult patients over alternative formulations of SODFs (outlined briefly below).<sup>1,18,27</sup>

Multi-particulate systems offer flexible dosing solutions with granules or pellets in defined dosing units although not many medicines on the market are available in this form and there is the issue of food–drug interactions and potentially heat–drug interactions. Oro-dispersible tablets avoid the need for swallowing the tablet as a whole and for administration with water. However, not all medicines are suitable for delivery this way, so product availability in this type of formulation is limited and controlled-release and taste-masking remains a challenge.<sup>61</sup> Mini-tablets may prove useful for children and in cases where tablet splitting would occur. Madathilethu et al. demonstrated the benefits of uniform dosing of hydrocortisone mini-tablets over quartered hydrocortisone tablets.<sup>62</sup> There is, however, the issue of mouthfeel and dexterity considerations, especially for older adults.<sup>2,42,48</sup> A balance must therefore be achieved between appearance, dimensions, palatability, ease of handling, frequency of dosing swallowability and therapeutic benefits of SODFs.<sup>42,52</sup>

If necessary, a liquid preparation or alternative route—e.g., buccal, rectal, transdermal—should be considered; however, not all preparations are formulated for all routes and each come with their own advantages and disadvantages.<sup>63</sup> An alternative is to de-prescribe, rationalising therapy and reducing pill burden. Medicine use reviews could be used as an opportunity to identify and address pill aversion/overburden. Modification of formulations is considered a last resort if alternative formulations cannot be found and must be implemented under the guidance of a healthcare professional. Not all medicines are suitable for modification as discussed, and there are unmet educational needs around appropriate practices. As with screening, the location and frequency of interventions must also be considered, and support for patients and healthcare professionals should be provided regularly, at the normal site of their regular healthcare/work.<sup>53</sup>

## 10.1 | Limitations and assumptions of this study

A multitude of papers that were screened did not specifically outline the medical history of participants, e.g. a past/present diagnosis of physiological dysphagia contributing to the swallowing difficulties

experienced. As a result, the researchers did not include any articles where there was uncertainty around this, to avoid drawing misleading conclusions. Bias is never completely avoidable; the advantage of having multiple researchers meant that bias regarding the decision to include or exclude studies could be minimised. The inclusion and exclusion criteria from the predesigned protocol enabled elimination of any queries or discrepancies via discussion between the researchers and a unanimous decision was reached. The STROBE tool allowed the identification of any bias within studies during the data collection period.<sup>12</sup> The number of papers suitable for inclusion was limited, and only texts available in English were included as no facilities for translation were available. The relative subjectivity of swallowing difficulties/pill aversion and heterogeneity of the literature meant a full systematic review and meta-analysis of papers could not be performed.

## 11 | CONCLUSION

Research to date has focused primarily on dysphagia rather than pill aversion, thus highlighting the need for more studies in this area. Pill aversion is an issue that many patients face, regardless of age, gender or health status, although there appears to be a positive association with younger age, female gender and poor mental health status and pill aversion. It can often go undiscussed between the prescriber and the patient. The literature presented shows that if training and educational interventions are implemented, there is potential for pill aversion symptoms to be identified, reduced and overcome. Evidence varies as to which method is best to overcome pill aversion: perhaps a combination of methods is the optimal approach but instructional methods—e.g. pop-bottle technique—may be most effective when considering success rate, convenience, ease of implementation and likelihood of prolonged success. From the current data, it appears that for swallowability and handling, the ideal SODF is white, oblong in shape but convex, coated if a tablet and size up to 11 mm diameter, or maximum size #0 capsule. This review identifies and appraises current knowledge regarding pill aversion but also highlights gaps in current knowledge for future studies to investigate.

### 11.1 | Gaps and weaknesses in the literature for consideration in the design of future studies

We identified several gaps in the literature which merit further investigation, and common weaknesses which should be considered by investigators in future studies.

There is a lack of standardisation in study design and assessment, which must be addressed in order to reach strong conclusions regarding the ideal screening and intervention methods.<sup>51</sup> Surveys are quick and easy tools to obtain information from a large study population. They have proven efficacious at capturing the severity of pill aversion within the general population and highlight the need for validated screening methods and interventions suitable for implementation in healthcare

settings. Currently there is no approved and widely used screening tool for pill aversion, and no consensus on how to define success following screening and intervention. Exploration of formulations that people have an aversion to is currently limited and requires further work to both inform prescribing and drug design. Several validated tools may be utilised for overcoming pill aversion, both educational approaches and pill swallowing aids. Implementation of reported methods (e.g., “pop-bottle” and “lean forward” technique), requires exploration in widespread practice, before an alternative formulation is prescribed, or the dosage form is modified. Comparing and contrasting screening and interventions adequately will facilitate more conclusive findings of their impact and usefulness in identifying and overcoming pill aversion.

## COMPETING INTERESTS

All authors have declared that they do not have any conflicts of interest to disclose.

## CONTRIBUTORS

Literature searching and screening for inclusion was shared equally by all authors, with full text review and removal of duplicates by E.L. and Y.T. M.A., S.A., A.M. and P.P. determined assessment of quality with simultaneous extraction of data. All authors contributed equally to manuscript generation.

## DATA AVAILABILITY STATEMENT

The authors will readily provide further data if requested.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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