R E V I E W

Sialorrhea in Parkinson's disease: prevalence, impact and management strategies

Nick Miller[1]
Margaret Walshe[2]
Richard W Walker[3]

[1]Newcastle University Institute for Ageing, Speech and Language Sciences, Newcastle University, Newcastle-Tyne NE1 7RU, Great Britain; [2]Clinical Speech and Language Studies, Trinity College Dublin, University of Dublin, Dublin 2, Ireland; [3]Department of Medicine, North Tyneside General Hospital, North Shields, NE29 8NH, Great Britain

Abstract: Saliva plays an important part in oral health maintenance, mastication, deglutition and the start of the digestive process. It supports clear speech. Alterations to the composition and flow of saliva through hyper- or hyposecretion or anterior loss through the lips thus have potentially significant consequences. This article reviews the metrics, possible age and gender differences and diurnal variability of flow in healthy individuals. It then focuses on the ways in which this is altered in Parkinson's disease (PD) and the possible mechanisms for why people with PD drool. It reviews procedures for clinical assessment and management. Many studies report drooling prevalence >50% of people with PD, though in the early stages the impact may not yet be great. In PD, saliva flow is normal or even decreased compared to people without PD. Motorically sialorrhea arises from an interaction between oro-facial rigidity, lingual bradykinesia and aspects of oro-pharyngeal dysphagia. Postural, cognitive, attentional and pharmacological factors may also contribute. Objective evaluation of sialorrhea looks at the rate and variability of flow (milliliters or milligrams per unit time; swallow intervals; consistency). Since objective measures seldom reflect patient-reported lived experience, assessment includes rating scales that capture subjective concerns. Because altered salivary function impacts on (peri)oral health, assessment and monitoring of this is strongly advocated. Methods in each of these assessment domains are introduced. Clinical guidelines recommend behavioral interventions in the first instance, with pharmacological treatments, including botulinum injection, as follow-up possibilities. Surgical procedures are reserved for severe or intractable cases. High-quality evidence for the efficacy of behavioral interventions is lacking. Drug therapy efficacy is also under-studied, apart from botulinum toxin management. Few studies have examined surgical interventions in PD, though principles are well established from other populations. Strands of enquiry for improving our knowledge of behavioral interventions are suggested.

Keywords: drooling, Parkinson's, management, review

Introduction

Saliva plays a vital role in health and well-being. Impairment of production and/or control of saliva may lead to a range of negative effects ranging from mild annoyance at perceived lack or excess of saliva to major health and social issues. Saliva control is affected by Parkinson's disease (PD). Key guidelines for PD management emphasize the importance of attending to saliva.[1,2]

The target readership of the review are people familiar with PD who are seeking an up-to-date exposition of the issues and findings around sialorrhoea in people with Parkinson's. To set the context, the opening section summarizes some principal points around production and control of saliva in unaffected individuals and its

Correspondence: Nick Miller
Newcastle University Institute for Ageing, Speech and Language Sciences, George VI Building, Newcastle University, Newcastle-Tyne NE1 7RU, Great Britain
Tel +441 912 085 603
Email Nicholas.Miller@ncl.ac.uk

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role in health maintenance. It then examines recent literature on how PD disrupts this and possible health and psycho-social consequences of overlooking changes. Subsequent sections consider assessment of saliva flow, with an emphasis on clinical methods. It concludes by reviewing options for management, including behavioral, pharmacological and surgical possibilities. Excessive saliva flow is also termed sialorrhea, ptyalism or drooling. These terms are used interchangeably in this article. Difficulties with saliva control may lead to unintended loss posteriorly into the pharynx and anteriorly from the lips. The former has considerable implications in assessment of swallowing, swallowing safety and airway health.[3] Whilst posterior and anterior loss are not unrelated, the focus here is on anterior loss.

Role of saliva in health and well-being

Two primary functions of saliva concern its role in maintaining oral pH and microbiotic homeostasis, and facilitating swallowing and speaking.[4–6] Saliva possesses antimicrobial, anti-viral and anti-fungal properties which aid oral cleansing, protect against infection and support tissue repair; it dilutes sugars and helps stabilize acidity; it contributes to remineralization of dental enamel. It serves as a buffer for extremes of temperature or against noxious substances. It lubricates the oral cavity, thereby supporting formation and transport of the bolus to the pharynx. It acts as a first stage in digestion and stimulates interaction with chemosensory receptors to aid taste and smell perception. It supports smooth and accurate movement of the tongue and lips for speech.

Healthy salivation

Healthy saliva flow produces around 0.75–1.5 liters per day.[4,5,7,8] Unstimulated (also called "resting state") flow estimates range around 0.10–2.9 mL/min.[8,9] As the wide estimates illustrate, there exists considerable inter- and intra-individual variation. There is a circadian rhythm to flow, peaking mid-late afternoon and lowest during sleep.[5,10,11] Flink et al[10] showed significant increases in flow between 07.30 and 11.30, with proportionately comparable increases in flow across subgroups defined as having very low, low and normal flow rates. Using visual analog scales to estimate subjective sensation of dry lips, dry throat, ease of speaking and swallowing and saliva consistency, the very low flow group showed significant improvements between testing points, with smaller changes for the low group and none for the "normal"

group. There is therefore a risk of misdiagnoses if testing time variables and baseline status are ignored;[10] Flink et al recommended early morning testing as an optimally informative time.

Secretion is heightened by stimulation (gustatory, olfactory and possibly visual), with magnitude of response decreasing across sour, salt, bitter, sweet, umami/savory stimulants.[5,12,13] Although the overall estimate is 30% of secretion from the parotids, 60% from the submandibular and 10% from the sublingual and minor glands,[4,5] a shift in contribution occurs between unstimulated and stimulated mode. In unstimulated conditions, ca 65% of saliva secretion emanates from the submandibular glands and is rich in mucin,[5,12] which forms a viscoelastic lubricating and protective covering for the oral mucosa. In stimulated conditions, around 50% (higher during mastication) of flow originates from the parotids, leading to high concentrations of alpha-amylase (ptyalin) and other enzymes with a function in decomposing starches.

Possible gender differences in saliva production have been debated. Males produce significantly greater flow. Not all studies corroborate this.[13,14] In other research,[15,16] males produced significantly greater absolute volumes of saliva, but once relative size of glands, body height and body mass index/surface area were controlled, gender differences disappeared. Hence, in judging normality individuals should be compared to data from the same gender.[15]

Some studies claim decreases in flow with age.[9,14] Others have not replicated these differences.[13,17,18] Diminution with age of olfactory and gustatory sensitivity may exercise some influence on stimulated flow. Age-related tissue changes in the salivary glands may influence mucin secretion.[5,18,19] Also, secretion may be affected by medications.[20] Older people are more likely to be on long-term (multi)drug regimes.[12,21]

Frequency of swallowing (and therefore clearing of saliva) varies. Frequency is greatest during meals.[6] Highest flow rates are associated with shortest swallowing intervals.[8] Least swallows occur during sleep. Twenty-four hour total swallows is around mean 580, range 200–1000.[7] Mean interval between swallows is around 60 secs but with large ranges (9–200).[8] During sleep, periods of mean 30.3 mins without a swallow happen.[7,11] Sleeping deglutition frequency ranged between 2.1 and 9.1 swallows per hour in ten adults, 20–25 years, with swallows most prevalent in REM sleep.[11]

Disruption to saliva flow in PD

Impaired flow or consistency of saliva exposes to risks of lowered resistance to infection, depressed oral health, impaired bolus formation and transportation and implications for digestion. Consequences include dry mouth, ulceration, tooth decay, gingivitis, candidiasis, halitosis and perioral dermatological issues.[12,19,22] Actual and perceived xerostomia (sensation of dry mouth) or (sensation of) excess saliva in the mouth can influence voice quality and intelligibility beyond problems that stem from the underlying PD. Hyposalivation linked to medication or dysautonomia,[12,20] or loss of saliva through drooling can affect bolus formation and exacerbate an already compromised swallowing mechanism. As the secondary effects from drooling (eg odor, stained clothes, constant wiping) are socially undesirable in many societies, presence of sialorrhea may bring repercussions for psycho-social health of the person who drools and added burden for the carer (eg washing clothes; restricted social life).

Prevalence figures suggest ca 10–70% of people with PD are affected by drooling,[23–32] with no significant variation across ethnic groups.[33] In investigations that report control data, drooling occurred in ca 6–15% of people unaffected by PD.[25,28,30,34] Divergences in estimations reflect composition of populations studied, assessment methods and condition (stimulated or/and unstimulated condition), patient vs clinician evaluation, as well as examination time (of day; in progression of PD).[35]

In an analysis of autonomic and sensory symptoms in 207 people with very early and untreated PD,[25] 42% recorded drooling, but for 90%, the influence of all autonomic dysfunction symptoms was only mild. In another,[30] drooling occurred in 50% of 119 people at early stage PD; 37% felt it a significant problem. Kalf et al[26] evaluated 104 pwPD (person/people with PD) and found 71% drooled – 43% with a sensation of excessive saliva or night time drooling ("pre-droolers") and 28% who drooled through the day (only two were observed drooling at examination). Impact was greater with more advanced PD. Feresttehnejad et al[31] found significant drooling for only 11.7% of 314 people with PD at or around initial referral. This proportion rose to 55.3% at approximately 4-year follow-up, demonstrating the likelihood that drooling becomes a significant problem if left unchecked.

People with PD often report xerostomia. Some medications influence actual and perceived dryness.[20,21,36] Anterior saliva loss can be a contributory factor. The relationship between dysphagia, drooling and xerostomia, though often observed, is complex.[22,37–39] Barbe et al[19] ascertained subjective dysphagia was associated with drooling and xerostomia, but drooling prevalence or intensity did not influence xerostomia symptoms. Xerostomia peaked at 09.00 and 21.00 but there appeared no significant association of this with drooling intensity levels.

Drooling can impact quality of life for pwPD and carers.[22–24,28,40–42] Karakoc et al[43] reported drooling in 65% of 63 people with PD, but no independent significant correlation of drooling severity with quality of life. However, they measured the latter from the total PDQ-39 score,[44] rather than with a tool that measures drooling impact. Further, 89% of their cohort evidenced only night-time symptoms when one might expect little psycho-social impact.

Mechanisms for drooling disturbance in PD

Patient reports of "too much saliva in my mouth" suggest hypersalivation as a cause. However, saliva production appears unchanged or even depressed in PD, indicating excessive salivation is not a crucial factor.[26,38–40,45–47]

Decreased salivary flow may relate to dysautonomia in PD. Hyposecretion may arise from medications common in PD.[20,21,36] Altered reaction to stimulation, from reduced olfactory and other sensory triggers, may also play a role.[48] Hou et al[49] conducted a fMRI investigation to examine basal ganglia functional connectivity in drug-naïve people with PD who did or did not drool. Those with sialorrhea showed significantly reduced functional connectivity of putamen within bilateral sensorimotor cortices, superior and inferior parietal lobules and areas in the right occipital and temporal lobes.

Risk factors for drooling in PD

If susceptibility to anterior drooling is not related to hypersalivation, other factors must be at work. Suggested candidates have been dysphagia, oro-facial rigidity/hypomimia, lingual bradykinesia, cognitive status, male gender and more advanced disease stage.[23,24,28,31,39,43,50,51] Individuals with non-tremor dominant PD phenotypes were at higher risk of drooling.[31,52] The precise contribution of these factors remains unsettled. The uncertainty rests partly on general issues above regarding why estimates of drooling prevalence and flow rates exist, but variability in individual profiles of impairment and disability also contributes.

Susceptibility of males probably relates to greater absolute flow rate when body mass and gland sizes are not controlled for – though not all studies have found a male predominance.[23,24,29] Relationship to greater disease severity likely reflects increased rigidity, poorer cognitive status and more marked dysphagia of later stages, and, in as far as medications may alter the picture, higher medication dependency.[21]

Dysphagia in PD arises from a range of factors.[3] Those most pertinent to anterior drooling relate to reduced tongue motility and depressed initiation of swallow reflexes. This leads to failure to swallow saliva regularly and/or efficiently, leaving excess saliva in the mouth and the (mistaken) impression of hypersalivation. However, as noted above, whilst some have noted a strong association of dysphagia with sialorrhea others found the relationship not so straightforward.

Facial muscle rigidity can impair lip control and depress swallowing efficiency, as well as render individuals prone to anterior loss of saliva.[31,39] Any combination of stooped body posture, flexed neck and open lips/lowered mandible may aggravate attempts to retain saliva in the mouth, hinder directing saliva posteriorly and reduce the likelihood of initiating a swallow reflex. Germane to this, there was greater propensity for drooling in pwPD and camptocormia.[53]

Cognitive impairment can influence drooling likelihood and severity.[30,50] The relationship may not be directly with cognitive status so much as associated changes to attention, especially during competing or dual task situations.[54] Reynolds et al[55] measured drooling severity and frequency at rest and during a distracting computer task in 18 people with PD reporting day-time drooling. There was no significant difference between drooling severity at rest and during distraction, but participants swallowed significantly less frequently and drooled significantly more often during the distraction task.

The question of possible consequences of l-dopa medication and deep brain stimulation (DBS) for drooling arises in PD. The effects of l-dopa (negative or positive) on sialorrhoea remain unclear. The question has not been a prime focus of investigations, so inferences are indirect at best. Drooling is linked to higher l-dopa daily dosage equivalents (LDDE),[23,24] but this likely reflects greater prevalence of drooling in more severe PD of greater duration. When motor, age and duration variables are controlled, LDDE appears no longer associated with drooling severity.[23,24,52] Proulx et al[38] found an association of l-dopa and hyposalivation, but Persson et al[56] observed no differences in salivary

secretion rate between pwPD and controls, nor between subgroups of pwPD taking versus not taking dopaminergic medication. Bagheri et al[45] established no difference in salivary flow rates between treated and de novo pwPD. Barbe et al[19] linked higher LDDE to drier mouth. In so far as dopamine modulates salivary secretion,[57] an association of LDDE and drooling might be expected, but clear causal evidence in humans is lacking.

L-dopa can influence variables in swallowing efficiency,[3,58] and thus indirectly change drooling. Currently, dysphagia study outcomes do not afford sufficient evidence to conclude a positive, neutral or negative effect of possible swallowing changes on sialorrhoea.

Similar conclusions apply to the effects of DBS in PD. No studies have tested drooling directly. In one study, increased drooling was an adverse effect of DBS reported by one of 18 patients.[59] Positive, neutral and negative influences of DBS on aspects of swallowing are reported,[3,60–63] which potentially could have repercussions for drooling. However, in the absence of direct data pertaining to impacts on sialorrhoea, the issue remains open.

Assessment of saliva flow

Evaluation of saliva flow is challenged by a range of issues, including: difficulty obtaining objective measures in naturalistic settings (though[64] found no differences in unstimulated flow rate between laboratory and clinic settings); time and place variability that exists in respect of natural variation in flow rates; fluctuations in motor function experienced by pwPD that can impact on swallowing and saliva control; the variety of situations across pwPD concerning where they experience difficulties or not; and the subjective nature of whether an individual perceives there to be a problem present or not. Similar to other activity limitations in PD such as dysphagia and dysarthria, perceived magnitude of psychosocial impact of drooling, dry mouth and excess saliva does not necessarily correlate significantly with objective measures of saliva flow and loss.[3,19,65–67]

These factors underline that no single assessment captures all dimensions important for establishing baseline and outcome measures of salivation/drooling. Accordingly, outcome evaluation covers a range of measurements, with a focus on key variables that encompass the patient's own chosen concerns and goals.

Objective measures of flow/volume

Objective measurements of milliliters or milligrams secretion per minute typically center around gathering saliva at

regular intervals over given time periods.[68,69] Sampling methods include collecting saliva from cups placed over salivary ducts, expectoration into pots or tubes, weighing of gauze or cotton rolls held at given loci in the mouth, use of centrifuges to extract saliva from the gauze to quantify the volume of saliva absorbed or allowing saliva to dribble from the mouth with the head held forwards over receptacles.

As secretion is sensitive to a number of influences, gathering ideally occurs under controlled conditions. Posture is controlled; the environment is quiet, with absence or minimization of visual, olfactory or gustatory stimuli known to prompt increased flow. Comparability of stimulated flow across patients and time demands use of standard stimulatory material and doses (eg citric acid volume and concentration; gum consistency and flavor control for chewing). To assure inter- and intra-individual comparability, evaluations ideally happen at the same time of day; at the same point in the drug cycle (or with patients in a pragmatically defined off state); in the same relationship to meal times (eg 2 hrs absence of eating before testing, in the morning having fasted overnight). On–off status and fluctuations need to be monitored as well as presence and severity of dyskinesias that may affect measurements.[70]

Van Hulst et al[71] devised a drooling severity quotient to assess severity in children with cerebral palsy that could be adapted to people with PD. Before observations began, all food was cleared from the child's mouth and the lips and chin wiped clean. Appearance of a new drop or string of saliva at the lips was counted as a drooling event. The presence or absence of drooling was recorded by the observer at 15-second intervals across 10 mins of observation. The drooling quotient is the number of drooling events observed expressed as a percentage of total observation points. Since saliva volume may be influenced by swallowing behavior, saliva measures can be gainfully supplemented by parallel swallow frequency metrics – eg from live visual counts or palpation of larynx raising associated with swallows, or counts based on accelerometer detected movements or swallow sound acoustics.[72]

The time costs involved probably preclude above methods representing routine clinical procedures. They are more aptly confined to research investigations or individual cases that strongly warrant such investment of time and effort. Day-to-day clinical practice is more likely to rely on rating scales.

Rating scales

Many tools are unstandardized and unvalidated scales restricted to use in one center. Some are scales developed for any etiology of (suspected) drooling, acquired or developmental. The number that have undergone psychometric evaluation is low; those devised or adapted specifically for PD even lower.

One partially validated tool is the Sialorrhea Clinical Scale for PD (SCS-PD).[73] It has seven items employing 4-point ordinal rating scales for the pwPD to determine their impression of drooling over the previous week. Items cover severity and frequency when asleep and awake, impact in relation to speaking and eating, and impact on social situations.

The Radboud Oral Motor Inventory for PD subscale for saliva (ROMP-S)[74] is the only other tool currently validated on pwPD. It is derived from the unvalidated Drooling Frequency and Severity Scale (DFSS),[75] originally drawn up for children with cerebral palsy, but employed in several other populations. It was slightly modified for ROMP-S, in particular by adding the option to score that one is troubled by (perceived) accumulation of saliva without actually drooling. The nine items, rated on 5-point ordinal scales, cover day and night-time frequency and severity, effects on speech and eating and drinking, how frequently one has to wipe away saliva, limitations on daily activity and social participation and overall impact.

Reid et al (2009)[76] devised and produced a psychometric validation of a tool to evaluate the impact of drooling in children with developmental disability, which shows potential for adaptation to people with PD. The child version uses 10-point equal appearing interval scales to chart overall severity, frequency and disruption in relation to need to wipe the face/furniture/toys and wash clothes, effects on perioral skin, embarrassment socially and in relation to smell of the saliva, and impact on the child and their family.

Another approach entails diaries completed at specific times/places over given periods by the pwPD to look at severity and frequency of symptoms and other variables of importance to them. Hauser et al (2004)[77] validated this method in relation to effects of motor fluctuations and dyskinesias but the technique has been used with other symptoms, including drooling.[78] Diary information is supplemented with five questions related to symptoms of interest, scored on visual analog scales.

Some studies have employed the drooling item in UPDRS II.[79] This has been criticized as a coarse scale: suggested severity levels are not spread evenly across scale-points; while it is presented as an ordinal progression, the combination of asking about three variables that may vary independently of one another (perceived amount of saliva in mouth; night-time drooling; daytime drooling) makes it difficult to classify responses accurately. The UPDRS sub-scales on facial rigidity/lip opening and motor fluctuations and their impact may provide useful supplementary diagnostic information.

The Movement Disorder Society reviewed dysautonomia rating scales pertinent to PD,[80] including for sialorrhea. They recommended further psychometric work on visual analog scales and classed the SCS-PD,[73] as a suggested tool pending further validation. ROMP-S[74] was unavailable at the time. They considered two broader scales – the Nonmotor Symptom Assessment Scale, Non-motor Symptoms Questionnaire,[81] and the Scales for Outcomes in PD-Autonomic,[82] as suitable for recording presence–absence of sialorrhea but not finer quantification.

Measurement of related variables

In as far as ptyalism in PD may be linked to other symptoms, other assessments may be pertinent to place real and perceived drooling in its broader context. These cover assessment of swallowing, speech and voice.[3,65] Detailed dental examination and monitoring of oral health may be indicated for some individuals, over and above routine dental supervision.[22,83]

People with PD may experience dry mouth/xerostomia.[21] Perceived dryness does not necessarily reflect objective levels of dryness defined by salivary flow rate/volume, mucosal wetness and saliva consistency.[84] The Clinical Oral Dryness Score (CODS)[85] is a validated clinician-administered semi-quantitative tool. The score comes from observing the presence/absence of ten symptoms and signs characteristic of dry mouth. It is combined with a 0–10 rating by the patient on how far they are bothered by xerostomia. Perceived impact has also been gauged using five questions related to possible activity and participation restrictions commonly reported by people with xerostomia.[85]

The PDQ39[44] contains items on avoiding eating and drinking in public and speech/communication problems, but has nothing specific to drooling, despite several studies employing it as a sialorrhea rehabilitation outcome measure.

Drooling does not easily lend itself to blanket rating scales or general questions. Some tools above include subscales that endeavor to capture situational variability in severity, frequency and impact. When and where drooling poses a problem for pwPD can be highly individual, related to their lifestyle and own perceived impact of saliva loss. To deliver tailored support case history taking can extend rating scales by identifying times and places where the person considers drooling exercises a strong impact. This can lead to evaluation of what contributors to impact appear particularly pertinent to the circumstances – eg (attention to) posture, fatigue, cognition, during or soon after meal times, in relation to speaking, eating in public. This in turn facilitates targeted intervention activities that address the main concerns of the individual. It also enables specific goal-oriented outcome measures to monitor clinical and social success.

Management of saliva flow

The British NICE (National Institute for Health and Care Excellence) guidelines for PD[2] recommend referral to a speech-language clinician for assessment and treatment of drooling, though overall management is multidisciplinary. The guidelines advocate behavioral methods of intervention in the first instance, followed by consideration of pharmacological or surgical options if/when these are ineffective.

Behavioral

Behavioral interventions seek compensatory strategies to minimize or remove the problem with drooling and/or entail more active intervention to modify what appears to be the culprit underlying dysfunction, such as reduced swallowing frequency or efficiency, or oro-facial rigidity.

Attention to posture is a frequently employed compensatory route. Intervention aims to achieve and maintain a head and trunk position that minimizes or prevents anterior saliva loss. If assessment has identified key contexts where drooling is most bothersome – eg rising from a chair, reading, working at the computer, eating, lying down – then focusing on strategies that work for those circumstances should arguably be more successful than general (re)training of posture. Management may couple posture procedures with other strategies, such as remembering to swallow as much saliva as possible before attempting to rise from the chair, avoiding particular foodstuffs at certain times, raising the eyelevel of reading material or computer screen. Having prompt words/signals that companions use to discreetly remind the pwPD to apply their strategy in target situations is a common addendum.

If ptyalism is linked to (especially oral phase) dysphagia, then therapies that foster safer and more efficient swallowing should potentially result in less saliva loss. Few dysphagia interventions have been tested out on pwPD,[3] and have generally neglected drooling changes in favor of measuring swallow safety and airway health. Hence, further work is awaited regarding the logic of applying swallowing therapy to alleviate drooling in PD.

Several dysphagia therapies involve oro-facial exercises aimed at better bolus management and initiation of patterned swallow reflexes, whilst other therapies have sought to counteract hypomimia.[3,86–89] If oro-facial rigidity contributes to anterior saliva loss and these techniques improve oro-facial control, then drooling should be ameliorated. To date, no large-scale treatment trials have examined this.

If the problem with drooling is not so much the inability of the person to swallow voluntary and safely but the frequency with which saliva is cleared, methods to cue the person to swallow at regular intervals may be effective. Preliminary demonstrations of this principle exist.[78,90] Initial studies employed auditory cues. These may not be the most favorable – the person with PD may not hear them and they may attract unwanted attention of others in the environment. To circumvent this, others have employed tactile cues. In a proof of concept and feasibility pilot,[78] employing a wrist-worn tactile cue to increase swallowing regularity twenty-two from twenty-eight participants found positive benefits, with significant overall group differences on visual analog scale self-rating of drooling frequency and severity pre-post the 4-week intervention. Early indications are that devices prove highly successful for many people with PD, but not everyone. Longer term follow-up has not yet been detailed. Future work is required to test out on larger populations which person, situation, cue type and frequency variables lead to more successful outcomes.

Since drooling and dysphagia are linked to poorer oral hygiene, management should encompass daily care routines and regular dentist supervision.[22,83] For pwPD who experience dry mouth, artificial saliva products are available.[91–93] Whilst largely successful in ameliorating certain aspects of real and perceived dry mouth, they are not substitutes for all the roles of saliva. Many efficacy studies have been criticized for the level of (potential) commercial bias involved. The specific needs of pwPD have not been a focus. Firmer indications for short- and long-term xerostomia management for pwPD is therefore needed.

Use of gum, salivation stimulus strips and saliva stimulation agents[21,94,95] have been suggested as means to overcome xerostomia. However, whether they might thereby exacerbate perceptions of over-accumulated saliva has not been investigated, and risks of increased dental caries arise with some agents.

Pharmacological

A range of pharmacological interventions have been used to treat drooling in pwPD.[21,57,96] Anticholinergic drugs block cholinergic receptors, thereby depressing salivary secretion. Botulinum toxin inhibits acetylcholine release, in turn leading to hyposecretion of saliva by inhibiting cholinergic parasympathetic and postganglionic sympathetic activity. Both avenues can be contraindicated if there is already significant dry mouth.

The British PD NICE guidelines 2017[2] recommend consideration of pharmacological management for drooling only if non-pharmacological management is unavailable or has been ineffective. The anticholinergic glycopyrrolate bromide is considered first line. If this is ineffective, not tolerated or contraindicated, referral to a specialist service for botulinum toxin A* is an option. Anticholinergic medicines other than glycopyrrolate bromide should only be applied if the person's risk of cognitive adverse effects is thought to be minimal.

Glycopyrronium was effective in a small (n 23) randomized control trial in PD,[97] with no evidence that it worsened motor symptoms. It shows fewer central nervous system side-effects than other anticholinergics as it is not centrally acting. It should be used with care in pwPD with significant cognitive decline, or who experience hallucinations. It is poorly absorbed and therefore has relatively few systemic side-effects, but these can include bladder outflow obstruction, cough, nausea, headache and dizziness. Glycopyrrolate should be given as 1-2 mg 2 or 3 times daily orally. Other anticholinergic medicines are only considered if there are no concerns about potential cognitive side-effects.

Sublingual atropine was used in an open-labeled pilot study in 6 pwPD and 1 progressive supranuclear palsy patient with drooling at a dose of 1 drop of 1% atropine solution twice daily for 1 week.[98] It reduced salivary production, measured objectively and subjectively, but one patient experienced delirium and two experienced hallucinations. In a study with 17 pwPD with drooling,[99] there was no significant difference in objective measures after two weeks when comparing Ipratropium bromide to placebo, but there was a mild subjective improvement in

the Ipratropium group and no significant differences in adverse events. However, there was insufficient evidence on safety and efficacy to recommend Ipratropium bromide spray for the treatment of drooling in PD.[96] Systematic reviews[57,100] have reported Clonidine to significantly improve long term the number of times that saliva had to be cleared from the mouth, and Modafinil, an α-1 receptor agonist, has been reported to improve drooling most likely by improving dysphagia.

Botulinum toxin (BoNT) is recognized as beneficial for drooling control in the majority of pwPD, with relative lack of adverse side-effects.[101,102] Of existing subtypes, Botulinum toxin A and B (BoNT-A and BoNT-B) are most common in PD, with BoNT-A more widespread. All therapeutic doses of BoNT are considered safe for management of drooling in PD, with evidence for the efficacy of ona-A; abo-A, inco-A and BoNT-B.[103–110]

Which formulation to choose varies.[111,112] Evidence for abo-A, ona-A and Rima-B to manage drooling in PD is stronger, with lower level recommendation for inco-A, mainly due to lack of strong research evidence.[112] Inco-A has the advantage that, unlike some other formulations, it can be stored at room temperature making it more suited for community care settings.

Dosage of BoNT varies by subtype involved, with a lack of agreement on the optimum dosage.[101,113] Lack of effect of some formulations has been attributed to the low dosage employed rather than the formulation itself.[114] Further research is needed on this. Therapeutic effects of BoNT commonly appear within a week after injection, although there is variability. Effects are temporary, lasting from ca 2.5–5 months before further injections are required.

BoNT is usually injected into the parotid or submandibular glands or both. Studies differ as to whether unilateral or bilateral injections prove more effective. Injection site is typically located by using ultrasound, electromyography or by manual palpation of the gland. Many clinicians suggest ultrasound guidance is essential for locating precise injection site, giving lower risk of adverse events, but there remains no clear consensus on this.[102,106,113] A risk is that BoNT diffuses into surrounding muscles and soft tissue resulting in muscle weakness and possible (increased) dysarthria, dysphagia and/or mastication difficulty.[103,110,115] Therefore, techniques that increase injection accuracy are important. Other possible side-effects include xerostomia, thickening of saliva,

diarrhea, gait disturbance, neck pain and an increased risk of poor oral hygiene.[101,107,108,116]

Despite widespread use, there exists a lack of clear consensus on the safest and most effective formulation, dosage and method of treatment.[21,113] Clinical guidelines or recommendations specific to BoNT for drooling in PD are not definitively established. As a result, clinicians working with pwPD continue to encounter difficulty determining the candidacy, efficacy and safety of BoNT in this context.

Surgical

Following NICE Guidelines,[2] surgical interventions are reserved for cases where other approaches proved unsuccessful or are no longer effective (eg resistance to pharmacological agents developed; too severe to overcome by behavioral compensation). Several surgical procedures are available, alone or in combination, uni- or bilaterally applied. These include radiotherapy, neurectomy, salivary gland excision, duct ligation and duct rerouting or relocation. None is 100% successful for all pwPD. Options present a range of possible adverse effects, covering harmful radiation exposure, short or long-term toxicity, more severe xerostomia, impact on swallowing, loss of taste perception and hearing loss (when neurectomy involves the chorda tympani nerve). Trials have predominantly involved children with cerebral palsy, with fewer studies directed at adults.[117–119] Very few specifically involve pwPD.[120] Consideration for surgery and choice of technique remains a highly individualized case by case affair.

Conclusion

Sialorrhea is a frequent in pwPD. Whilst for most individuals it may not exercise a perceived impact comparable to other features of motor and non-motor change in PD, especially in the early stages, for those who are affected it represents a challenging and distressing symptom. Even when drooling does not unduly bother the individual, its potential consequences for swallowing, speech, oral and general health mean it should be attended to as a strategy to prevent other possible complications. Interventions are available but there remains a serious need for more definitive studies, especially in relation to pwPD.

Disclosure

The authors declare no conflicts of interest in this work.

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