A Review of Options for Treating Sialorrhea in Amyotrophic Lateral Sclerosis

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Introduction

Purpose of This Review
Search Strategy and Selection Criteria
Anticholinergic Drugs
BoNT (Botox)
Radiotherapy
Surgical Treatment

Sialorrhea or drooling represents quite a common problem in patients with amyotrophic lateral sclerosis (ALS). In this review, we describe the possible treatments for this issue. Current medical management is not always effective: anticholinergic drugs (atropine, glycopyrrolate, amitriptyline, hyoscyamine, and transdermal scopolamine) are often used, but there is very little evidence of their effectiveness in patients with ALS. More invasive treatments, such as botulinum toxin injections and/or radiation therapy in the salivary glands, can be considered when anticholinergic drugs are not effective. In this review, we also explore the possible surgical options for treatment of sialorrhea. Although no specific studies have been conducted on patients with ALS, surgical therapies might represent a valid option for treatment of sialorrhea since there is no tachyphylaxis or need for repeated therapeutic sessions. Key words: amyotrophic lateral sclerosis; salivary glands; sialorrhea; drooling; aspiration pneumonia; botulinum toxin; radiotherapy; surgical intervention; quality of life.

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volvement of upper motor neurons causes a set of symptoms known as pseudobulbar palsy, which is characterized by spasticity of the bulbar muscles (which control speech, chewing, and swallowing) and emotional lability (pathologic laughing and crying). In addition, loss of motor neurons in the spinal cord causes muscular weakness and atrophy, leading in turn to progressive respiratory dysfunction, labored communication, and decreased voluntary as well as reflexive coughing.5-8

In ALS, sialorrhea is caused mostly by a decreased ability to swallow secretions (not by increased saliva production) due to tongue spasticity, orofacial and palatino-lungual muscle control failure, facial weakness, and inability to maintain oral and buccal competence.9,10 The progressive weakness of facial muscles and difficulty in swallowing saliva leads to drooling.11-13 About half of all patients affected by ALS report significant sialorrhea or drooling at some point during the course of the disease, and ~20% of them have moderate-to-severe symptoms.14 There are different scales for the assessment of sialorrhea. The revised Amyotrophic Lateral Sclerosis Functional Rating Scale, a widely used and validated instrument to monitor disease progression in ALS, contains 3 items assessing the function of bulbar muscles, including one evaluating sialorrhea.15

In 2013, Abdelnour-Mallet et al16 attempted to evaluate the effectiveness of 2 other scales: the Oral Secretion Scale (designed for the evaluation of hypersialorrhea in ALS) and the Sialorrhea Scoring Scale (initially developed for Parkinson’s disease). Although both scales have a high inter-rater and intra-rater reliability, there are some limitations. The Oral Secretion Scale is not designed to evaluate the effectiveness of invasive treatments for hypersialorrhea, whereas the Sialorrhea Scoring Scale does not predict tolerance to noninvasive ventilation (NIV) in ALS patients. Salivary secretion in healthy adults is ~1.2 L/d. During unstimulated salivation, 69% of saliva is contributed by the submandibular glands, 26% by the parotid gland, and 5% by the sublingual glands. During stimulated salivation, the parotid gland contribute 66% of the total flow.17 The submandibular gland, a mixed but mostly serous gland, is responsible for stimulated and unstimulated saliva production, whereas the parotid gland, a purely serous gland, secretes saliva mainly during mastication. The sublingual gland is purely mucous. Excessive amounts of saliva significantly decrease quality of life by impairing speech production and lung function. Patients may also experience difficulties with NIV and in sleeping in a reclined position because of saliva aspiration.

The increase in mucous secretions in the throat and lungs, the inability to swallow saliva, and the cough impairment due to progressive weakness and diaphragm and respiratory muscle fatigue usually lead to an increased risk of aspiration pneumonia.5,18-21 Drooling also causes dermatologic problems, such as facial irritation and skin exoriation.5 Although pulmonary aspiration syndromes are often misdiagnosed in patients with ALS, they are associated with a high mortality.8 In a cohort of 40 consecutive patients with ALS, Sorenson et al18 observed the occurrence of aspiration pneumonia in 5 cases (13%). In an autopsy cohort of patients with ALS, Kurian et al22 found a similar number of occurrences, with aspiration pneumonia being listed as the cause of death in 11% of cases, bronchopneumonia in 41%, and respiratory failure in 9%. Death was directly attributable to motor neuron disease in 11% of cases, cardiac causes in 14%, malignancies in 5%, and other causes in the remaining 9% of patients.22 Excessive drooling also limits tolerance of NIV, which has been consistently shown to increase the life expectancy and quality of life of patients with ALS.23-33 Thus, a successful management of sialorrhea may prolong NIV tolerance in ALS,34 resulting in enhanced survival.35

Table 1. Inclusion Criteria for the Four Key Questions

<table>
<thead>
<tr>
<th>Study design</th>
<th>Question 1</th>
<th>Question 2</th>
<th>Question 3</th>
<th>Question 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Retrospective case control</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prospective cohort or clinical trial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical characteristics of range of symptoms</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Duration of symptom relief</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Did the studies cited answer the following questions? Question 1: Which area was treated? Question 2: What therapy was used (and at which dosage level)? Question 3: How long did the effect last? Question 4: Have side effects been reported?

Purpose of This Review

We present a systematic review of studies describing the various possible treatments for sialorrhea in subjects with ALS, attempting to assess the effectiveness of these therapies in improving quality of life and diminishing the risks due to excessive drooling and to evaluate their side effects and long-term efficacy.

Search Strategy and Selection Criteria

After defining criteria for study selection (Table 1) and for validity assessment, we searched MEDLINE for studies published from January 1994 through November 2013 using the following MeSH terms: sialorrhea, drooling, ptalism, anticholinergic drug, neuromuscular agents, botulinum toxin (BoNT), radiotherapy, surgical intervention.
AND parotid, submandibular glands, salivary glands, amyotrophic lateral sclerosis, motor neuron disease, and spinal cord disease. Only studies on human subjects with ALS published in English were included. Case reports, reviews, editorials, and letters were excluded.

The literature review was focused on answering the following key questions: anatomic targets and therapeutic doses of treatments for sialorrhea, long-term efficacy of treatments, and reported side effects of treatments. AN, NT and GAG independently reviewed the full texts of articles meeting eligibility criteria based on their abstracts (see Table 1).

### Anticholinergic Drugs

Self-reported data from the ALS CARE Program (www.outcomes-umassmed.org/als, accessed March 21, 2014) suggest that > 70% of patients with ALS may benefit from treatment with anticholinergic medications (atropine eye drops [1–2 drops 4 or 6 times/d], glycopyrrolate [1–2 mg 3 times/d], amitriptyline [25–50 mg at bedtime], scopolamine transdermal patch [0.5 mg every 3 d], hyoscyamine sulfate [0.125–0.25 mg 2–4 times/d], diphenhydramine [25–50 mg 3 times/d], and/or oxitropium bromide [0.5 mg every 3 d]) (Table 2). There are very few clinical studies evaluating the effectiveness of these drugs on patients with ALS in a systematic fashion. A recent study by McGeachan et al suggests that scopolamine patches are the most effective anticholinergic drugs for management of sialorrhea in ALS, reporting a positive response in 85% of treated subjects. However, the authors noticed that about half of these subjects also required additional therapies and that 20% had to discontinue the scopolamine patches, mostly because of skin reactions. Orally administered anticholinergic drugs are often interrupted due to systemic side effects, such as sedation and delirium, which are especially common in elderly patients. Anticholinergic drugs can also cause thickening of mucous secretions in the throat and lungs, which is a far worse and more severe complication than drooling. Pulmonary aspiration is a far worse and more severe complication than drooling. However, this version may differ from the final published version in the online and print editions of RESPIRATORY CARE.

<table>
<thead>
<tr>
<th>Anticholinergic Drug</th>
<th>Mode of Administration</th>
<th>Recommended Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Eye drops</td>
<td>1–2 drops 4 or 6 times/d</td>
<td>Sensitivity to bright light, dry mouth, blurred vision, irregular heartbeat, mental confusion, difficulty urinating</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tablet</td>
<td>25–450 mg at bedtime</td>
<td>Constipation, drowsiness, dry mouth, dizziness, tiredness or sleepiness, feeling faint when getting up, increased blood pressure, fast/racing heart, palpitations, heart attack, stroke, irregular or slow heart beats, very low blood pressure, feeling or being sick, diarrhea, increased need to urinate</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Transdermal patch</td>
<td>0.5 mg every 3 d</td>
<td>Pupillary dilatation, skin reaction, urinary retention</td>
</tr>
<tr>
<td>Hyoscyamine sulfate</td>
<td>Tablet or elixir</td>
<td>Tablet or elixir 4 or 6 times/d</td>
<td>Diarrhea, confusion, hallucinations, tachycardia or uneven heart rate, drowsiness, blurred vision, nausea, constipation, problems with urination, dry mouth</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Tablet</td>
<td>25–50 mg 3 times/d</td>
<td>Sleepiness, fatigue, dizziness, dry mouth, difficulty urinating</td>
</tr>
<tr>
<td>Oxitropium bromide</td>
<td>Aerosol</td>
<td>1.5 mg twice daily</td>
<td>Dry mouth, cough, hoarseness, urinating less than usual or not at all, stuffy nose, nosebleed, fast heart rate</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>Tablet</td>
<td>1–2 mg 3 times/d</td>
<td>Blurred vision, constipation, decreased sweating, dizziness, drowsiness, dry mouth, pupillary dilatation, nausea</td>
</tr>
</tbody>
</table>

**BoNT (Botox)**

Patients with ALS or other neurodegenerative disorders (such as Parkinson’s disease) who do not improve and/or have serious side effects with anticholinergic drugs may benefit from injections of BoNT under ultrasound guidance into the parotid and submandibular glands. BoNT, commonly known as Botox, improves sialorrhea by reduc-
ing the release of acetylcholine at the neurosecretory junction. In Table 3, we present the most relevant studies concerning the use of BoNT in the treatment of sialorrhea in ALS.39,41-50 These studies used different BoNT serotypes (A39,42,43,45-47,49-54 and B23,41,44-46,48), treatment regimens, and routes of administration (direct or transductal approach) with varying outcome measures. A typical regimen is the administration of a total dose of 250 U of BoNT-A: 100 U diluted in 0.4 mL of saline injected into 2 sites of each parotid gland and 25 U diluted in 0.1 mL of saline injected into a single site of each submandibular gland. Another common approach is the injection of total dose of 2,500 U of BoNT-B, again subdivided into 2 sites of injection for each parotid gland (1,000 U in 0.4 mL of saline) and a single site of injection for each submandibular gland (250 U in 0.1 mL of saline). Sialorrhea is reduced 3–7 d after the injections, and maximum reduction occurs ~2–4 weeks after treatment. The mean duration of the beneficial effect is usually three and half months,39 although the relapse time is extremely variable, and inhibition of saliva production may last up to 6 months after injection.44 BoNT serotypes A and B are considered to be equally efficacious and safe. In a study evaluating the differences between the 2 serotypes, Guidubaldi et al46 found that BoNT-B has a shorter latency and the same duration of efficacy compared with BoNT-A. However, the costs of the 2 treatments are significantly different: at the doses used in the study, a treatment with BoNT-B costs approximately half that with BoNT-A. In the vast majority of cases, BoNT injection has no side effects.55-57 Uncommon adverse events are increased viscosity of saliva, local pain, chewing weakness, and respiratory infections. Anaphylactic reactions are rare but often serious. In 2005, Li et al58 reported the first case of death connected with administration of a Botox-lidocaine mixture in a patient with chronic neck and back pain. Another study reported a case of deterioration of bulbar function after botulinum treatment in a patient with ALS.50 Four days after injection, the patient suffered rapid onset of bulbar dysfunction, resulting in severe aphagia and anarthria. A progressive cervical kyphosis connected with BoNT injection has also been reported by Hogan et al.56

### Radiotherapy

Radiotherapy of the salivary gland has also been proposed as an effective method to reduce excessive drooling in patients with ALS.59 Several studies on radiotherapy for the treatment of sialorrhea in ALS adopted different techniques (electron-based therapy vs photon-based therapy) and doses (Table 4). Electron-based therapy appears to be well tolerated and induces a sustained improvement compared with photon-based therapy, with no serious side effects. In a retrospective study by Guy et al,60 a good response to radiotherapy was observed in 65% of subjects. However, 4 of 13 subjects treated with photon-based therapy experienced acute toxicity symptoms (oral pain and mucositis during or immediately after irradiation) or delayed reactions (edema or xerostomia 1 month after irradiation or oral pain 3 months after irradiation). Conversely, none of the 8 subjects treated with electron-based therapy reported side effects. The authors suggested an optimum total dose of 20 Gy administered in 5 fractions, encompassing the whole of the submandibular gland and sparing the upper part of the parotid gland. The benefits of radiation treatment persisted for 4–6 months.19 Another study

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**Table 3.** Summary of Studies Concerning Botulinum Toxin Use in Subjects With Amyotrophic Lateral Sclerosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>No. of Cases</th>
<th>Botox Type</th>
<th>Total Dose (U)</th>
<th>Parotid (U)</th>
<th>Submandibular (U)</th>
<th>Duration of Effect (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al36,41</td>
<td>Prospective randomized double-blind placebo-controlled</td>
<td>18</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
<td>500</td>
<td>750</td>
<td>3</td>
</tr>
<tr>
<td>Verma and Steele39</td>
<td>Prospective open-label</td>
<td>8</td>
<td>A</td>
<td>Botox, 15–45</td>
<td>7.5–22.5</td>
<td>None</td>
<td>2.5</td>
</tr>
<tr>
<td>Gilio et al43</td>
<td>Prospective open-label</td>
<td>26</td>
<td>A</td>
<td>Botox, 20–40</td>
<td>10–20</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td>Contarino et al44</td>
<td>Prospective open-label</td>
<td>9</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
<td>1,000</td>
<td>250</td>
<td>3</td>
</tr>
<tr>
<td>Guidubaldi et al46</td>
<td>Prospective randomized cross-over double-blind</td>
<td>7</td>
<td>A/B</td>
<td>Dysport, 250</td>
<td>100</td>
<td>25</td>
<td>2.5–3</td>
</tr>
<tr>
<td>Anagnostou et al47</td>
<td>Prospective randomized double-blind</td>
<td>10</td>
<td>A</td>
<td>Botox, 40</td>
<td>20</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Costa et al48</td>
<td>Prospective open-label</td>
<td>15</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
<td>1,000</td>
<td>250</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Scott et al49</td>
<td>Prospective open-label</td>
<td>6</td>
<td>A</td>
<td>Botox, 20–60</td>
<td>10–30</td>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Giess et al50</td>
<td>Prospective open-label</td>
<td>5</td>
<td>A</td>
<td>Botox, 30–82</td>
<td>30–72</td>
<td>5</td>
<td>&gt; 2.5</td>
</tr>
<tr>
<td>Møller et al51</td>
<td>Prospective open-label</td>
<td>7</td>
<td>A</td>
<td>Botox, 80–140</td>
<td>25–40</td>
<td>15–30</td>
<td>–</td>
</tr>
<tr>
<td>Manrique52</td>
<td>Prospective open-label</td>
<td>5</td>
<td>A</td>
<td>Botox, 100</td>
<td>20</td>
<td>30</td>
<td>3–4</td>
</tr>
<tr>
<td>Lipp et al53</td>
<td>Prospective double-blind placebo-controlled</td>
<td>12</td>
<td>A</td>
<td>Dysport, 37.5–150</td>
<td>18.75–75</td>
<td>None</td>
<td>3</td>
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<tr>
<td>Porta et al54</td>
<td>Prospective open-label</td>
<td>4</td>
<td>A</td>
<td>Botox, 50–100</td>
<td>15–40</td>
<td>10–15</td>
<td>4–7</td>
</tr>
</tbody>
</table>

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**References:**

1. Anagnostou et al. (2005) [Reference]
2. Costa et al. (2014) [Reference]
3. Scott et al. (2015) [Reference]
4. Giess et al. (2016) [Reference]
5. Møller et al. (2017) [Reference]
7. Lipp et al. (2019) [Reference]
8. Porta et al. (2020) [Reference]

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**Table 4.** Summary of Radiotherapy Treatment Options for Sialorrhea in ALS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Total Dose (U)</th>
<th>Parotid (U)</th>
<th>Submandibular (U)</th>
<th>Duration of Effect (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al36,41</td>
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<td>18</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
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<td>Verma and Steele39</td>
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<td>8</td>
<td>A</td>
<td>Botox, 15–45</td>
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<tr>
<td>Gilio et al43</td>
<td>Prospective open-label</td>
<td>26</td>
<td>A</td>
<td>Botox, 20–40</td>
<td>10–20</td>
</tr>
<tr>
<td>Contarino et al44</td>
<td>Prospective open-label</td>
<td>9</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
<td>1,000</td>
</tr>
<tr>
<td>Guidubaldi et al46</td>
<td>Prospective randomized cross-over</td>
<td>7</td>
<td>A/B</td>
<td>Dysport, 250</td>
<td>100</td>
</tr>
<tr>
<td>Anagnostou et al47</td>
<td>Prospective randomized double-blind</td>
<td>10</td>
<td>A</td>
<td>Botox, 40</td>
<td>20</td>
</tr>
<tr>
<td>Costa et al48</td>
<td>Prospective open-label</td>
<td>15</td>
<td>B</td>
<td>NeuroBloc, 2,500</td>
<td>1,000</td>
</tr>
<tr>
<td>Scott et al49</td>
<td>Prospective open-label</td>
<td>6</td>
<td>A</td>
<td>Botox, 20–60</td>
<td>10–30</td>
</tr>
<tr>
<td>Giess et al50</td>
<td>Prospective open-label</td>
<td>5</td>
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<td>Botox, 30–82</td>
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<td>Møller et al51</td>
<td>Prospective open-label</td>
<td>7</td>
<td>A</td>
<td>Botox, 80–140</td>
<td>25–40</td>
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<tr>
<td>Manrique52</td>
<td>Prospective open-label</td>
<td>5</td>
<td>A</td>
<td>Botox, 100</td>
<td>20</td>
</tr>
<tr>
<td>Lipp et al53</td>
<td>Prospective double-blind placebo</td>
<td>12</td>
<td>A</td>
<td>Dysport, 37.5–150</td>
<td>18.75–75</td>
</tr>
<tr>
<td>Porta et al54</td>
<td>Prospective open-label</td>
<td>4</td>
<td>A</td>
<td>Botox, 50–100</td>
<td>15–40</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>No. of Cases</td>
<td>Anti-cholinergic Drugs</td>
<td>Radiated Gland</td>
<td>Doses</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Bourry et al</td>
<td>Retrospective</td>
<td>21</td>
<td>Yes</td>
<td>18 subjects, parotid/ submandibular; one subject, submandibular/ one parotid; 2 subjects, both parotid glands</td>
<td>In 17 d, 19.1 Gy × 5 fractions (mean dose)</td>
</tr>
<tr>
<td>Kasarskis et al</td>
<td>Retrospective case series</td>
<td>10</td>
<td>9 subjects</td>
<td>One parotid gland unilaterally; one subject, both parotid glands</td>
<td>In 3 d, 15 Gy × 3 fractions</td>
</tr>
<tr>
<td>Neppelberg et al</td>
<td>12</td>
<td>12 Submandibular and lower part of parotid glands</td>
<td>Single fraction of 7.5 Gy</td>
<td>4- or 6-MV photons</td>
<td>One subject developed a slight redness of the skin in the irradiated area 3–7 d after treatment. Nine of 14 subjects felt more viscous saliva after treatment. Two subjects complained about xerostomia during meals, and one subject had the feeling of a lump in the throat. One subject reported a slight temporary swelling in front of the ears 3 d post-radiotherapy.</td>
</tr>
<tr>
<td>Harriman et al</td>
<td>Retrospective</td>
<td>9</td>
<td>Single-field compassing submandibular and sublingual glands and caudal lobes of parotid glands</td>
<td>Single fraction of 8 Gy or double equal fractions of 12.5 Gy</td>
<td>Subjects experienced only minor side effects: in 4 subjects, erythema and burning of skin from a few hours to 2 wk; in 2 subjects, sore throat for a few hours to 4 d; and in one subject, nausea for a few days. One subject felt that the saliva had become thicker post-treatment.</td>
</tr>
<tr>
<td>Andersen et al</td>
<td>Prospective</td>
<td>18</td>
<td>Yes</td>
<td>Parotid glands</td>
<td>13 subjects, 7.0 Gy as a single dose on each side; 5 subjects, 7.5 Gy as a single dose on each side</td>
</tr>
</tbody>
</table>
found similar beneficial effects by targeting under-computed tomography guidance a single parotid gland unilaterally with a total dose 15 Gy delivered in 3 equal fractions.\textsuperscript{10} Single-dose radiotherapy has also been proven to be beneficial in reducing excessive drooling in ALS. In 14 subjects treated with a single fraction of 7.5 Gy, Neppelberg et al\textsuperscript{60} observed a 50% reduction in salivary secretion after 2 weeks and a 20% reduction after 3 months. It has been suggested that a dose of 8 Gy delivered in a single fraction may be as effective and safe as higher fractionated doses,\textsuperscript{14} and increasing the dose did not improve initial achievement.\textsuperscript{61} A review of published studies on BoNT and radiotherapy for sialorrhea in ALS attempted to evaluate and compare the effectiveness and side effects of the 2 treatments. However, because of the small number of published studies, the small sample sizes, and the poor quality of reporting, it was not possible to draw firm conclusions recommending one treatment over the other.\textsuperscript{42}

Surgical Treatment

Another therapeutic option for the management of excessive drooling is surgical intervention. To our knowledge, however, there are no clinical studies focused on patients with ALS in the literature, and most of the published studies were performed on children with cerebral palsy.\textsuperscript{63} In these particular patients, salivary duct or gland surgery is considered to be the best established treatment, especially in the most severe cases of sialorrhea. In 1996, Strauss et al\textsuperscript{63} defined Wilkie’s original operation (1967) as “the main surgical procedure” for controlling sialorrhea. The procedure consists of the retropositioning of the parotid ducts into the tonsillar fossa region along with unilateral submandibular gland resection. Several variants of the Wilkie procedure have been described: transposition, instead of resection, of the submandibular gland duct into the tonsillar fossa; ligation, instead of repositioning, of the parotid ducts, along with the usual submandibular gland resection; deviation of both submandibular and parotid ducts behind the anterior pillar of the soft palate (4-duct diversion); bilateral submandibular duct relocation with or without sublingual gland excision; a combination of ipsilaterally parotid duct ligation and contralateral parotid duct repositioning; and ligation of both parotid and submandibular ducts (4-duct ligation).

Submandibular duct relocation with or without excision of the sublingual gland is currently the most common approach. By relocating the papillae of the submandibular ducts from the anterior oral cavity to the base of the tongue, saliva from the submandibular glands can flow directly into the oropharynx.\textsuperscript{64} However, this procedure cannot be performed in patients with a history of recurrent aspiration pneumonia, as it may increase aspiration risk because it directs the saliva posteriorly.\textsuperscript{65} The average postoperative stay in a hospital for this kind of procedure is \( \sim 2 \) d. In 2007, Glynn and O’Dwyer\textsuperscript{66} studied whether the combination of sublingual gland excision and submandibular duct relocation gives better overall results in controlling drooling. They concluded that both procedures were equally effective, but the combination increased the morbidity of the procedure while not providing any better control of drooling. However, this more extensive intervention may prevent ranula formation.\textsuperscript{66}

Studies on the efficacy of the 4-duct ligation procedure had contrasting results. In 2008, Stamataki et al\textsuperscript{67} showed that the long-term effectiveness of the 4-duct ligation procedure in controlling anterior drooling is questionable as measured by caregiver satisfaction and need for additional medical and surgical therapies. Martin and Conley\textsuperscript{68} reached similar conclusions. However, Chanu et al\textsuperscript{69} obtained very different results. In fact, in their study, 4-duct ligation seemed to be a simple procedure and caused significant reduction in drooling and improved quality of life. Additionally, the procedure had few complications, which could be managed effectively. The authors concluded that 4-duct ligation is effective in controlling moderate-to-severe sialorrhea in children.\textsuperscript{69} Three-duct ligation procedures have also been described in the literature.\textsuperscript{47} Unfortunately, duct ligation is not a permanent solution. In 2006, Osailan et al\textsuperscript{70,71} published 2 works about ligation of the submandibular duct in rats. In the first study, they evaluated submandibular gland atrophy with or without chorda-lingual nerve resection and observed that, in the absence of chorda-lingual ligation, the extent of glandular atrophy was reduced.\textsuperscript{70} In the second study, their goal was to investigate the recovery of submandibular gland function after the removal of an obstruction.\textsuperscript{71} They ligated the submandibular glands of rats with micro-clips for 1, 4, and 8 weeks. The glands were then allowed to recover after removal of the micro-clips for 8, 16, and 26 weeks under stimulation with autonomimetic drugs. The authors concluded that following severe atrophy, the rat submandibular glands regenerated after 24 weeks and secreted normal quantities of saliva. This is true for acinar cells, but not for ductal ones.\textsuperscript{71} In 1989, Grant et al\textsuperscript{72} studied the effect of resection of the chorda tympani nerve on ipsilateral and contralateral salivary secretion. They studied 20 subjects undergoing exploratory ear surgery for mastoidectomy, stapledectomy, or tympanoplasty. Chorda tympani resection did not reduce salivary flow in 35% of the subjects, whereas in the remaining 65%, the submandibular flow was reduced by \( \sim 54\% \). These results strongly suggest that the morbidity of bilateral chorda tympani section alone outweighs the expected benefit in individuals with sialorrhea and a limited lifespan, such as patients with ALS. Therefore, it can be considered a poor method for reducing stimulated salivary flow.\textsuperscript{72}
Treatment Options for Sialorrhea in ALS

In conclusion, although a surgical approach to sialorrhea is possible in children affected by cerebral palsy, nothing similar has been tested in patients with ALS. Indeed, there is currently no safe and effective surgical therapy for these patients; however, we believe that surgery may represent a valid option for the treatment of excessive drooling in ALS because there is no tachyphylaxis or need for repeated therapeutic sessions.

Conclusions

In our experience, the first-line treatment for excessive drooling in patients with ALS is represented by anticholinergic medications. Among the different possibilities, we believe the use of a scopolamine transdermal patch (1.5 mg/d) or sublingual amitriptyline (25 drops at bedtime) to be the most effective and best tolerated option. We have no personal experience with glycopyrrolate because it has not been approved for human use in Italy. In non-responders, we also used oxtropium bromide via nasal aerosol (1.5 mg twice daily) with some success. However, anticholinergic drugs are not a definitive solution for excessive drooling in ALS. For this reason, many patients have to deal with other more invasive therapies, such as botulinum injection and radiotherapy. The available data do not permit us to determine with certainty which is the better option. Radiotherapy has fewer side effects but a shorter duration of effect. Conversely, botulinum presents more side effects, but its action lasts longer. To date, there are no evidence-based guidelines for the management of sialorrhea in patients with ALS, and application of the different techniques is based on experience of only a few specialized centers. The goal of this review was to highlight the advantages and disadvantages of each method and to represent a practical tool for all physicians involved in the symptomatic treatment of sialorrhea in ALS.

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