Review Article

Systematic Review of the Effectiveness of Botulinum Toxin or Radiotherapy for Sialorrhea in Patients with Amyotrophic Lateral Sclerosis

Carol A. Stone, MBChB, MRCP, and Norma O’Leary, MBBCHBAO, BMedSc
Our Lady’s Hospice (C.A.S.) and Blackrock Hospice (N.O.), Dublin, Ireland

Abstract
Fifty percent of patients with amyotrophic lateral sclerosis (ALS) experience problems handling serous saliva and 20% fail to achieve adequate control of sialorrhea with anticholinergic medications, or experience intolerable adverse effects from these drugs. Both botulinum and radiotherapy have been suggested in the literature as treatments for intractable sialorrhea. In this review, we assess the evidence for the effectiveness and toxicity of botulinum toxin and radiotherapy for sialorrhea in patients with ALS. Relevant studies were retrieved from Medline, Embase and Cochrane Databases. Handsearching of Neurology, Journal of Pain and Symptom Management, and Palliative Medicine and of reference lists, was carried out. Five studies (28 patients) were included in the analysis of botulinum. Of the four studies using an intraglandular method of injection, no adverse effects occurred. Two of these had positive findings of the effect of botulinum in salivary secretion rate and quality of life. In contrast, significant adverse effects were experienced by two patients in a study of retrograde injections into the salivary ducts. Two studies were included in the analysis of radiotherapy (27 patients). Both demonstrated a positive effect of radiotherapy on salivary secretion rate. Some patients experienced mild acute side effects. Because of the small numbers of studies, small sample sizes, and poor quality of reporting, it is not possible to draw firm conclusions. There is some evidence indicating that both botulinum and radiotherapy are well tolerated, effective treatments for persistent sialorrhea in patients with ALS and that the duration of action is up to three months with botulinum and six months with radiotherapy.

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Key Words
Amyotrophic lateral sclerosis, motor neurone disease, sialorrhea, drooling, botulinum, radiotherapy

Background
Amyotrophic lateral sclerosis (ALS) is a disease of both upper and lower motor neurons. Its prevalence is 4–6 per 100,000 population. The mean age of onset is 56 years and it is
more common in males than females. In early stage disease, features of either bulbar or spinal disease predominate, but as the disease progresses, typically both become evident. Median survival in the bulbar form of the disease is 20 months and in the spinal form 29 months. The only specific treatment that may modestly improve survival is riluzole, a glutamate antagonist. Patients with ALS should receive regular support from a multidisciplinary team, with the goal of maintaining nutritional status and respiratory function, and symptomatic management of pain, emotional lability, depression, spasticity, cramps, and sialorrhea.

Patients with bulbar palsy experience problems handling serous saliva and mucous nasal and bronchial secretions as a result of poor lip closure, head position, and weakness of bulbar muscles. The management of mucous bronchial secretions differs from that of serous salivary secretions. Approximately 1.5 L of saliva is produced per day. In the fasting state, the paired submandibular glands produce 70% of saliva; the sublingual glands produce 5%; and the parotid glands produce 20%. Stimulated salivary production is mainly by the parotid glands. Inability to swallow saliva causes drooling or sialorrhea, which can lead to maceration of skin, soaking of clothes, and exacerbation of dysarthria. It can also cause psychosocial distress and social embarrassment.

Secretory innervation to the salivary glands is mainly via parasympathetic nerves. The mainstay of management of sialorrhea in ALS is use of anticholinergic medications. However, some patients have an inadequate response to these medications or experience intolerable adverse effects. Alternative treatments, namely injections of botulinum toxin and radiotherapy, have been suggested in the literature. Botulinum blocks presynaptic release of acetylcholine at parasympathetic ganglia, in addition to its better known action at the neuromuscular junction. Its effect on the presynaptic vesicles is irreversible, with recovery occurring over a period of three months by re-sprouting of the axons. The effect of external beam radiotherapy in reducing salivary production in patients treated for salivary gland tumors is well recognized. As the mean survival of patients newly diagnosed with ALS is 20–29 months, the risk of inducing cancer in this population is negligible.

This systematic review was conducted to 1) assess the evidence for the effectiveness and toxicity of botulinum for sialorrhea in patients with ALS, and 2) assess the evidence for the effectiveness and toxicity of radiotherapy for sialorrhea in patients with ALS.

Criteria for Selecting Studies for This Review

Experimental and quasi-experimental studies and observational studies, both controlled and uncontrolled, were sought. Single case reports, expert opinions, and studies of retrospective design were excluded. Studies of patients with a diagnosis of ALS and sialorrhea in any health care setting were selected. Studies of patients with sialorrhea as a result of other etiologies were not included.

Reviewed studies included clinical trials of botulinum toxin of any subtype. Trials including any injection technique, frequency of administration, or dose were eligible for inclusion. Eligible trials of radiotherapy could include any modality, dose, or fractionation to salivary glands.

Data were extracted from trials to evaluate efficacy and safety. Specifically, studies were reviewed for the effect of botulinum toxin or radiotherapy on 1) saliva production, 2) quality of life (QOL), and 3) potential adverse effects.

Search Strategy

Databases

The electronic databases Medline (from 1966 to Week 1, April 2006) and Embase (from 1988 to week 15, 2006) were searched via Ovid. The “find similar articles” function was used for all retrieved relevant articles. The final searches of these databases were carried out on April 16, 2006.

From the Cochrane Library (Issue 2, 2006), the Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the Central Register of Controlled Trials (CENTRAL) were searched via Wiley Interscience. The final search of these databases was carried out on April 17, 2006.

Medline and Embase searches were restricted to studies of humans and publication in English.
Medline was searched using the Medical Subject Headings (MeSH terms) motor neurone disease, sialorrhea, parotid gland, radiotherapy, and botulinum toxins. The MeSH terms were exploded and all subheadings were included.

Embase was searched using the MeSH terms (terms exploded and all subheadings included) motor neurone disease, salivation, hypersalivation, salivary gland, radiotherapy, botulinum toxin, and botulinum toxin A. A free text search of “drooling” was also carried out.

CDSR, DARE and CENTRAL were searched using free text (motor neuron* disease, amyotrophic lateral sclerosis, sialorrhea*, drooling and saliva*).

Reference Lists, Handsearching, and Unpublished Studies

Handsearching of the reference lists of articles retrieved by electronic searches was carried out. Although review articles were not eligible for inclusion, reference lists of review articles for which the full text was available electronically were handsearched at this stage.

The contents pages of Neurology, Journal of Pain and Symptom Management, and Palliative Medicine from January 1996 until April 2006 were searched.

Contact was made with specialists in radiotherapy and otolaryngology in Ireland with the purpose of identifying any national unpublished data.

Methods of the Review

Study Selection

A single reviewer (CS) examined the titles of all retrieved articles and subsequently the abstracts of potentially relevant articles. In the next step, the full texts of all relevant articles were obtained. These were reviewed by both the authors. Articles were excluded if they did not meet the criteria for selection of studies (see above). See Fig. 1 for more detail of the results of search strategy and study selection.

Data Extraction

Data were extracted from the reports of included studies into two separate tables according to the intervention studied, botulinum toxin or radiotherapy. Using these standardized tables, information from the studies was reported under the headings: participants, intervention, measured outcomes, results, and study quality (Tables 1 and 2). The study design was described plus the level of the study on the hierarchy of study designs for studies of effectiveness was recorded. This was carried out by CS and verified by NO.

Study quality was assessed using a checklist that has been designed and successfully validated for assessment of both randomized controlled trials and nonrandomized studies. This tool was selected as it incorporates subscales within it, thus providing the reader with a profile of the methodological strengths and weaknesses of each study. There are 27 items on this checklist, two of which were customized by the authors to more specifically address the principal confounders and power of the studies (Table 3). The item relating to study power was altered to reflect if study size was adequate to power the study to 80%, setting \( P < 0.05 \), to detect a clinically significant outcome using the Altman nomogram. This was answered as “yes” if it was stated in the report that the reported outcome was significant with \( P < 0.05 \). If it was stated in the report that the reported outcome was significant with \( P > 0.05 \), the author (CS) calculated the sample size required to power the study to show that the reported outcome was significant with \( P < 0.05 \) and answered the item accordingly. If a report did not clearly state the outcome, to calculate the standard difference, a 33.3% reduction in mean daily tissue use was used as a clinically significant outcome for the purpose of the power calculation.

Power calculation was only possible in studies that provided the data required to calculate the standard deviation (SD) of the variable (pretreatment). The checklist was otherwise applied according to the guidelines of its authors. The maximum score possible on the customized Quality Index Scale is 28. CS and NO independently assessed the quality of the included studies using the Quality Index Scale. The results were then compared and disagreements were resolved by consensus.

Data Analysis

The studies of radiotherapy were analyzed separately from those of botulinum toxin. It was not appropriate to stratify the analyses according to study quality as there were
minimally significant differences in quality between studies and the number of included studies was low. Meta-analyses were not possible because of the heterogeneity of studies with respect to the studied intervention and measurement of outcomes. Data analysis was descriptive.

**Description of Studies**

A total of five studies of botulinum for management of sialorrhea in patients with ALS were included, the first of which was published in 2000 and the most recent in 2006. The cumulative number of patients was 28. Only two studies of radiotherapy for management of sialorrhea in patients with ALS, both published in 2001, were eligible for inclusion. The cumulative number of patients was 27. All were uncontrolled observational studies of “before and after” design and level 4 on the hierarchy of study designs for studies of effectiveness.

**Studies of Botulinum Toxin for Management of Sialorrhea in Patients with ALS**

Participants: The studies differed regarding selection criteria. Two clarified that included
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Measured Outcomes</th>
<th>Results</th>
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<tbody>
<tr>
<td>Giess et al.,16 Germany</td>
<td>Patients with ALS (n = 5)</td>
<td>Botulinum toxin A/Botox® 6–20 MU into each parotid gland using 27-gauge needle</td>
<td>1. Salivary gland scintigraphy prior to and 2 weeks after last injection 2. Number of tissues used daily—before and after intervention 3. QOL using modified DLQI 4. Bulbar function monitored weekly</td>
<td>1. Reduction in radiotracer uptake post last injection but $P &gt; 0.05$ 2. Reduction in no. of tissues used daily but $P &gt; 0.05$. Maximum response at 4 weeks, effect sustained at 3 months in three of four responders 3. Improved QOL in four of five patients 4. No adverse effects Study lacked power</td>
</tr>
<tr>
<td>Winterholler et al.,12 Germany</td>
<td>Patients with ALS meeting El Escorial criteria (definite) (n = 2)</td>
<td>Botulinum toxin A/Botox® 12.5 MU into each parotid and sublingual gland retrogradely via catheter into salivary duct</td>
<td>1 and 2. Reduction in mean weight of expectorated saliva by 67% and reduced radiotracer uptake 2. Weight of tissue onto which patient had expectorated as much saliva as possible over 10 minutes (MESP) measured before and on day 7 postintervention 3. QOL measured by questionnaire 4. Bulbar function monitored weekly</td>
<td>Adverse effects: Both found the procedure painful. Patient 1: severe swelling of sublingual gland and base of tongue, requiring treatment. Patient 2: reported impairment of swallow from day 4–21</td>
</tr>
<tr>
<td>Scott et al.,13 USA</td>
<td>Patients with ALS meeting El Escorial criteria (definite) n = 6</td>
<td>Botulinum toxin A/Botox® 10 MU into each parotid gland using 27-gauge needle Repeated injection with 20 MU into each parotid after 12 weeks</td>
<td>1. Patient log book of daily tissue use 2. Single item from ALSFRS assessing salivation 3. Single item from MQOL regarding overall QOL 4. Patient impression questions 5. Physical examination before and at 1, 2, 4, 8, and 12 weeks postintervention</td>
<td>1. No change in mean daily tissue use in three of six patients after 10 MU injection 2 and 3. No subjective clear effect on drooling using ALSFRS or on QOL using MQOL No adverse effects Study lacked power</td>
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</table>

<table>
<thead>
<tr>
<th>Quality Score (max score = 28)</th>
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<tbody>
<tr>
<td>Study lacked power</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>11</td>
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<tr>
<td>Authors</td>
<td>Country</td>
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<td>---------</td>
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</tr>
<tr>
<td>Manrique, 15</td>
<td>Brazil</td>
</tr>
<tr>
<td>Verma and Steel, 14</td>
<td>USA</td>
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</table>

**Notes:**
- MU = mouse units; MQOL = McGill quality-of-life questionnaire; DLQI = dermatology life quality index; VAS = visual analogue scale.
- Mean duration of bulbar symptoms: 22.8 ± 14.6 months
- Mean age: 45–59 years
- Mean time since diagnosis: 33.6 months
- Four of five patients had a response that fulfilled these criteria, lasting 4 months in three patients and 3 months in one patient.
- Mean age: 69.5 years
- Mean duration of bulbar symptoms: 22.8 ± 14.6 months
- Mean age: 69.5 years
- Verma and Steel, 14 USA
- Patients with ALS (n = 10) sialorrhea refractory to anticholinergic medications
- Local anesthesia with prilocaine into each parotid and submandibular gland 30 minutes before the procedure
- Sialorrhea refractory to tolerated doses of anticholinergic medications
- Mean time since diagnosis: 33.6 months
- Age range: 45–59 years
- Mean duration of bulbar symptoms: 22.8 ± 14.6 months
- Mean age: 45–59 years
- Mean time since diagnosis: 33.6 months
- Age range: 45–59 years
- No adverse effects
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Measured Outcomes</th>
<th>Results</th>
<th>Quality Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al., 17 Sweden</td>
<td>ALS meeting El Escorial criteria (probable or definite) $n = 18$</td>
<td>7 Gy or 7.5 Gy bilaterally to middle and caudal lobes of parotid and posterior submandibular glands Linear accelerator 4–6 MV photons</td>
<td>1. Salivary secretion rate (SSR) measured at days 0, 2, and 14 2. Subjective response via interview 3. Single question regarding effect of treatment 4. Quantification of anticholinergic drugs before and after treatment 5. Oral cavity examination</td>
<td>1. Mean reduction in SSR of 43% at day 1 and 5 and 7% at day 14 2. All caregivers reported diminished salivation 3. Anticholinergics discontinued in all patients 4. None had evidence of radiation-induced mucositis</td>
<td>14</td>
<td></td>
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<tr>
<td>Refractory sialorrhea</td>
<td>Estimated prognosis of less than 2 years  Mean age 62.3 years</td>
<td>Mean duration of disease 22 months</td>
<td>Study lacked power</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Harriman et al., 18 Canada</td>
<td>Patients referred from an ALS clinic $n = 9$</td>
<td>8 Gy in single fraction or 12.5 Gy in two equal fractions to a single field encompassing submandibular and sublingual glands and the caudal lobes of the parotid glands</td>
<td>1. SSR measured pretreatment and at 2 and 6 months 2. Subjective assessment of patients’ perception of percentage of reduction in saliva production at 2 weeks 3. “Degree of drooling” six-point Likert scale pretreatment, at 2 and 6 months 4. Questionnaire to assess adverse effects at 2 weeks</td>
<td>1. SSR at 2 months had reduced in all five surviving patients. SSR at 6 months was less than baseline in two of three surviving patients 2. See main text 3. Four of five patients at 2 months and two of the three at 6 months reported improvement using “Degree of Drooling” scale 4. “Minor” adverse effects (see main text)</td>
<td>16</td>
<td></td>
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</table>
Table 3
Quality Index Scale Scoring of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reporting</th>
<th>External Validity</th>
<th>Internal Validity Bias</th>
<th>Power</th>
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<tbody>
<tr>
<td></td>
<td>Quality Index</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Giess et al.¹⁶</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Winterholler et al.¹²</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Scott et al.¹³</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Manrique¹⁵</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Verma and Steel¹⁴</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Andersen et al.¹⁷</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Harriman et al.¹⁸</td>
<td>Yes</td>
<td>UTD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total score (maximum possible score = 28)</td>
<td>14</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

UTD = unable to determine.

*Sample size of 85 would have been required to detect reduction in mean daily tissue use of 33.3% at significance level P < 0.05 and at 80% power. The mean daily tissue use in this study, however, was reduced by 76.4%. A sample size of 15 would have been required for this to have a significance level of P < 0.05 and at 80% power.

*Sample size of 260 would have been required to detect a reduction in mean daily tissue use of 33.3% at significance level P < 0.05 and at 80% power. The mean daily tissue use in this study was reduced by 29%. Authors quote significance level P < 0.02.

*The mean reduction in saliva secretion rate at 14 days was by 0.62 mL/5 min (57%). A sample size of 140 would have been required for this to have significance of P < 0.05 at 80% power.

*Sample size of 25 would have been required to detect reduction in salivary secretion rate by 33.3% at significance level P < 0.05 and 80% power.
patients met El Escorial criteria for a definite diagnosis of ALS. Three of the five studies stated that patients had failed to achieve adequate control of drooling with anticholinergic medications. The other studies reported that sialorrhea was “disabling” or “uncontrolled.”

Mean duration in months of bulbar symptoms, as reported in three of the studies, was comparable. The mean age of study participants in these three studies were similar, whereas those in the study carried out by Manrique were younger.

**Intervention:** Injection technique, dose of botulinum toxin used, and whether the intervention was repeated were the main variations between studies. All the studies used botulinum toxin type A, marketed as Botox (Allergan, Inc., Irvine, CA).

In all but one study, in which the botulinum was delivered retrogradely via a small catheter into the salivary duct, the botulinum was injected directly into the salivary glands. The dose administered and the treatment protocol differed between studies as detailed in Table 1.

**Outcomes Measured:** Saliva production was measured using a reliable and valid objective measure (Technetium scintigraphy) in only two of the studies. Of the three other studies, two recorded the number of paper tissues used daily as a measure of salivary production, whereas the methods used by Manrique did not include a quantitative assessment of saliva production.

Two studies used tools to measure overall QOL, whereas the other three used tools to specifically assess the impact of drooling on QOL. All but one of the studies assessed patients for evidence of adverse effects at regular intervals, either by assessment of specified bulbar functions, or by an unspecified examination.

Patients were followed up for at least three months in all the studies.

**Results:** In the study by Winterholler et al. using a transducal method of administration, there was a mean reduction of saliva production, as measured by maximum expectorated sputum production (MESP) of 67% at seven days. Unfortunately, the results of the Technetium scintigraphy were not reported for both patients. This pilot study was discontinued after the occurrence of parotitis in one patient and subjective worsening of swallowing in the other.

Of the studies using injections of botulinum into the salivary glands, the study by Geiss et al. used a mean of 46 MU (SD 16.9 MU) botulinum per person. Although there was a reduction in Technetium-99 uptake at two weeks and daily paper handkerchief use at four weeks, the study lacked power. Maximum response was seen at four weeks. The effect was sustained at three months in three of the four responders. The QOL of four of five patients improved.

In the study by Verma and Steel, two of the 10 patients reported no improvement and had inadequate follow-up, five received and responded to 7.5 MU botulinum per parotid gland, and three went on to require a second injection at four weeks of 15 MU per parotid gland. Subgroup analysis by treatment received was not reported and it was not clear if the participants who had inadequate follow-up were included in the analysis, in combination with a sensitivity analysis. They report a 30% reduction in mean daily handkerchief use \( (P < 0.02) \) and a mean reduction of 10 points in the “Drooling Impact Score” \( (P < 0.001) \) at four weeks. This tool, which was devised by the authors, has not yet been validated. The maximum possible score is 40. Maximum response occurred at 2–4 weeks.

In the study conducted by Manrique \( (n = 5) \), all patients received 20 MU botulinum to the parotid glands and 30 MU to each submandibular gland. Quantitative analysis of saliva production was not conducted. A four-item questionnaire was designed to assess the impact of the intervention on QOL by measuring the change in social interactions and the need to eliminate saliva from the mouth. A significant improvement in three of the four domains occurred in four of the five patients for up to four months. However, evidence of the validity of this questionnaire for this purpose was not given.

In the two-phase study by Scott et al. \( (n = 6) \) using 10 MU and 20 MU botulinum, the variance in the number of tissues used per day before treatment was large (mean 35.56, SD 33.49), and as a result, the study lacked power. The mean daily paper handkerchief use of three of the six patients who received 10 MU botulinum per parotid gland did not change, and of the four patients who went on to receive 20 MU botulinum, one used more
handkerchiefs after the intervention. There was no clear effect of the intervention on overall QOL or subjective rating of drooling using the related item from the ALS functional rating score (ALSFRS). In their report, the authors do not clearly state how long the given outcomes were measured after the intervention.

No adverse effects were detected in the four studies of botulinum injections into the parotid gland.

Studies of Radiotherapy for Management of Sialorrhea in Patients with ALS

Participants: In one study, all patients fulfilled El Escorial criteria for a probable or definite diagnosis of ALS, whereas in the other, patients had a clinical diagnosis. In both trials, all patients had been treated with anticholinergic medication with unsatisfactory results. Patients who had previously had surgery or radiotherapy to the salivary glands were excluded from one study, whereas the participants in the other included two people who had previously had surgical procedures aimed at reducing sialorrhea. Patient demographics were reported in only one of the studies (see Table 2).

Intervention: The radiation field differed between the studies and the dose and fractionation differed both between and within studies. In one study, 7 Gy or 7.5 Gy was administered bilaterally to the middle and caudal lobes of the parotid glands and posterior submandibular glands. In the other, they administered 8 Gy in single fraction or 12.5 Gy in two equal fractions to a single field encompassing submandibular and sublingual glands and the caudal lobes of the parotid glands.

Outcomes Measured: In both the studies, salivary secretion rate was measured by weighing cotton rolls placed in the mouth for 5 minutes. The measures used to assess subjective response in both studies focused on perception of effectiveness of the intervention or change in severity of drooling rather than QOL. The studies varied in the methods used to assess adverse effects. In one, the oral cavity was examined at days two and 14 for signs of radiation-induced damage, and in the other, a questionnaire on side effects was completed by the patient at two weeks. The details of the questionnaire were not given.

Results: In the study by Andersen et al. (n = 18), the salivary secretion rate pretreatment, and at one and 14 days post-treatment, was described for 15 patients only. They reported that the mean reduction in salivary secretion rate was 43% at day 1 and 57% at day 14. However, the variance in salivary secretion rate was large (mean 1.44, SD 1.31), and as a result, the study lacked power. Anticholinergic medications were discontinued in all patients after radiotherapy. All caregivers reported diminished salivation after the intervention. The response rate to the question regarding the effectiveness of the treatment was low. Anticholinergic medications were recommenced at 4–6 months in six patients. One patient experienced persistent xerostomia and a “few” had transient aching in their cheeks in the 24 hours post-treatment.

In the study by Harriman et al., the effect of radiotherapy on salivary secretion rate was measured at two and six months. However, four of the nine patients had died at two months. Salivary secretion rate had reduced in the five surviving patients (P-values not given). At six months, six patients had died. Salivary secretion was less than baseline in two of the three surviving patients at this time (data not available for the third patient). Subjective assessments of response were carried out at two weeks. Three patients reported no reduction in saliva production, one patient had died and five reported a reduction in drooling, ranging from 40–80% in magnitude. Four of the five patients at two months and two of the three patients at six months reported subjective improvement, as recorded in change in the “Degree of Drooling” scale. It was not possible to discern a benefit from the increased dose of 12.5 Gy over the 8 Gy dose.

In the study by Andersen et al., one patient experienced persistent xerostomia and some patients complained of aching of their cheeks within the first 24 hours. In the study by Harriman et al., four patients reported erythema and burning of skin, two reported a sore throat, and one complained of nausea.

Details of studies that did not meet the inclusion criteria are recorded in Table 4.

Discussion

The mode of administration used by Winterholler et al. differed significantly from the
other studies using botulinum toxin. Both patients experienced adverse effects compared with none in the other four studies of intraglandular injections. Two of the four other studies had positive findings, both in the objective measures used to assess salivary production rate and in measures of QOL or impact of drooling on QOL. 14,16 A shortcoming of both studies is that they did not present subgroup analysis by treatment received. Although the results reported by Verma and Steel reached statistical significance, it is not clear if data for the two patients who were lost to follow-up were included in the analysis.

In the study by Scott et al., however, they failed to demonstrate a clear improvement in saliva production rate or QOL. A potential reason for this is the outcome measures used. Using the number of paper handkerchiefs used daily as an objective outcome measure is inherently flawed, as it is subject to bias. The item from the ALSFRS assessing salivation on a five-point scale may not be adequately sensitive, and measures of overall QOL have the potential to be biased by unrelated changes in the patients’ conditions or circumstances.

Of the reviewed studies of the effectiveness of botulinum toxin, none reported having conducted adequately comprehensive assessments of adverse effects; two reported that they measured bulbar function weekly,14,16 one that patients had regular neurological examinations,12 and another that patients had “focused physical examinations.”13 Studies using single fiber electromyography on distal skeletal muscles of patients receiving local injections of 20–165 MU of botulinum toxin for focal dystonias have demonstrated altered neuromuscular transmission for up to 12 weeks postinjection.26,27 The proposed mechanism of this observed effect on distant sites is the circulation of botulinum in blood after local administration.28 No patient experienced objective weakness in muscles distant from the injection site in the double-blind, randomized, controlled trial conducted by Lange et al.28 However, concerns that botulinum-induced altered neuromuscular transmission in patients with already impaired neuromuscular function, such as those with ALS, may have a clinical impact have not been addressed by these studies.

In both studies of radiotherapy, patients had failed pharmacotherapy but it was not possible to determine if the sample populations were otherwise comparable. Although the radiation field differed between studies, both regimens targeted a limited proportion of the salivary glands to avoid causing xerostomia. Although the dose and fractionation differed between and within the studies, it is not clear whether this significantly affected the outcome. Both studies lacked power. In the study by Harriman et al., this was further reduced by the high attrition rate in two months. However, both studies have positive objective findings, albeit not reaching statistical significance. With the exception of persistent xerostomia in one patient, adverse effects from radiotherapy were minor and short-lived. However, neither study conducted a comprehensive evaluation of adverse effects, with one study examining the oral cavity of patients and the other using a questionnaire. The effects of radiotherapy persisted for 4–6 months.

Because of the small number of studies, small sample sizes compounded by high attrition rates, poor quality in reporting of results and use of unreliable outcome measures, it is not possible to draw firm conclusions regarding the effectiveness, safety, or duration of action of either botulinum toxin or radiotherapy in management of sialorrhea as a result of ALS. However, we can generate the following hypotheses:

1. Injections of botulinum into the parotid gland are effective at reducing sialorrhea

<table>
<thead>
<tr>
<th>Table 4 Excluded Studies*</th>
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<tbody>
<tr>
<td>Study</td>
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<tr>
<td>Lipp et al.19</td>
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<tr>
<td>Ellies et al.20</td>
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<td>Tan et al.21</td>
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<td>Porta et al.22</td>
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<tr>
<td>Bhatia et al.23</td>
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<td>Stalpers24</td>
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<td>Borg and Hirst25</td>
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*Studies did not meet inclusion criteria upon evaluation of the full text article.
and improving QOL for up to four months (with a maximum response at four weeks) in patients with sialorrhea as a result of ALS.

2. Injections of botulinum into the salivary ducts are associated with significant adverse effects and should be avoided.

3. Radiotherapy to a proportion of the salivary glands is effective at reducing sialorrhea at doses of 7–12.5 Gy and may be effective for up to six months.

As the incidence of ALS is relatively low and the incidence of refractory sialorrhea inherently less, it remains a challenge to conduct studies that are adequately powered. The timing and mode of outcome measurement must be appropriate to this population of patients with advanced disease and short prognosis, and outcome measures must be reliable and valid, and include both objective and subjective assessments. Inclusion of measures which specifically address the impact of drooling on QOL, rather than overall QOL, may be less likely to be affected by confounding variables. Of the measures used in included studies, the “Drooling Impact Score,” as devised by Verma and Steel appears to have face and content validity, and to be responsive to change, although further validation is desirable. The design of studies of the effectiveness of botulinum toxin in patients with ALS should incorporate the evaluation of distant muscle strength. This could be achieved using an interrupted time series design to measure the decline of the ALSFRS or muscle strength before and after the intervention.

Limitations of this review include incompleteness of the search for gray literature and language restriction.

Both injections of botulinum into the parotid glands and radiotherapy to a proportion of the salivary glands appear to be useful techniques for patients with sialorrhea refractory to anticholinergic medications. Choice of intervention should take into consideration ease of accessibility and risk of adverse effects; the findings in this review suggest that radiotherapy is associated with a mild acute illness.

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References
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