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# ARIX: A randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer

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**Background:** Radiation treatment of head and neck cancer can cause chronic xerostomia which impairs patients' quality of life. The study reported here examined the efficacy of acupuncture in alleviating xerostomia symptoms especially dry mouth.

**Patients and methods:** A total of 145 patients with chronic radiation-induced xerostomia >18 months after treatments were recruited from seven UK cancer centres. The study employed a randomised crossover design with

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participants receiving two group sessions of oral care education and eight of acupuncture using standardised methods. Patient-reported outcome (PROs) measures were completed at baseline and weeks 5, 9, 13, 17, and 21. The primary outcome was improvement in dry mouth. Objective saliva measurements were also carried out.

**Results:** Acupuncture compared with oral care, produced significant reductions in patient reports of severe dry mouth (OR = 2.01, $P = 0.031$) sticky saliva (OR = 1.67, $P = 0.048$), needing to sip fluids to swallow food (OR = 2.08, $P = 0.011$) and in waking up at night to drink (OR = 1.71, $P = 0.013$). There were no significant changes in either stimulated or unstimulated saliva measurements over time.

**Conclusion:** Eight sessions of weekly group acupuncture compared with group oral care education provide significantly better relief of symptoms in patients suffering from chronic radiation-induced xerostomia.

**Key words:** acupuncture, head and neck cancer, quality of life, xerostomia

## introduction

Patients treated for head and neck cancer may develop unpleasant sequelae such as radiation-induced dry mouth (xerostomia), a common side-effect following radical or adjuvant radiotherapy. Although parotid function may recover within 18 months of treatment, prevalence of persistent xerostomia can be as high as 41% 5 years after radiotherapy [1].

Chronic xerostomia impairs quality of life; interfering with taste, chewing, swallowing, speaking, and sleeping [2]. Management options providing short-term help include mouthwashes, gels and toothpastes. Pilocarpine taken regularly can offer relief; however, muscarinic receptors stimulation may cause sweating, rhinitis, and urinary frequency [3]. In a survey of UK oncologists, only 36% prescribed pilocarpine; lack of evidence or unwanted side-effects were reasons given for not using it [4]. Parotid-sparing intensity-modulated radiotherapy (IMRT) can reduce the incidence of xerostomia [5] but involves resource-intensive complex planning, which is neither universally available nor appropriate for every patient.

Complementary and alternative medicine (CAM) use is common. One survey reported that 20% of head and neck cancer patients had tried CAM, the most popular being herbal remedies, vitamin supplements, and relaxation techniques. [6]. Acupuncture is an increasingly accepted means for controlling pain, chemotherapy-induced nausea, and hot flushes [7–9]. Studies suggest that it may also be beneficial in relieving symptoms of xerostomia [10, 11]. In a recent phase II study of acupuncture-like transcutaneous electrical nerve stimulation, 47 patients with xerostomia received 24 sessions over 12 weeks. Positive treatment responses were achieved in 30 (86%) patients at 6 months [12]. Another study randomised patients with nasopharyngeal cancer to acupuncture and standard care during radiotherapy treatment to determine whether acupuncture helped prevent xerostomia [13]. The results showed significant differences favouring acupuncture in PROs and salivary flow rate.

We have also reported encouraging results from a pilot study [14]. Patients with chronic xerostomia were treated in a group setting using an acupuncture protocol developed in the United States [15]. We postulated that our group intervention provided an additional level of peer support and shared experience contributing to the beneficial effects observed. This pilot informed the design of the phase III trial, namely two interventions: (i) group sessions of oral care education led by a clinical specialist and (ii) group acupuncture.

We now report results from this randomised crossover trial examining the efficacy of acupuncture in ameliorating patients' self-report of severe dry mouth symptoms, and any relationships with objective salivary measurements.

## patients and methods

Brighton and Sussex Medical School sponsored the study; it was approved by Brighton East Research Ethics Committee (09/H1107/81) and registered with the International Standard Randomised Controlled trial register (ISRCTN13130687). The trial was carried out according to STRICTA standards [16].

### patients

Seven oncology centres in England, UK, participated in the Acupuncture in the treatment of Radiation-Induced Xerostomia (ARIX) trial. Patients treated with radical radiotherapy (at least one parotid gland in the irradiated field) and recurrence free ≥18 months later were eligible; they received invitation letters and information leaflets with an 'expression of interest' form to return to the coordinating centre. Exclusion criteria included: history of heart valve disease, bleeding disorders, problems with frequent infections and needle phobias. All needle sites were confirmed as accessible (i.e. no reconstructive prosthesis or surgical scar at any points).

Potential participants attended a trial introduction meeting at their local centre to learn more about the study, following which written, informed consent was obtained [17].

### randomisation

Randomisation was conducted by an independent statistician who assigned the order of interventions through a mixed randomisation method [18]. This uses a combination of simple randomisation in uneven blocks and standard permuted blocks of varying size, to avoid predictability of allocations while keeping the balance between groups close to equal throughout the trial. Crossover occurred 4 weeks after the end of the first intervention. (Figure 1 trial schema).

### interventions

#### oral care sessions

Specialist nurses and radiographers were trained by the investigators to deliver two oral care educational sessions lasting 1 h, given 1 month apart. Standardised slide presentations with accompanying guidance notes ensured consistency of delivery. Session one covered the aetiology of xerostomia, its effects on daily living and current preventative research; session two covered dietary advice, symptomatic relief products available (artificial saliva etc.), and oral hygiene advice. This ensured that all patients had a clear and shared understanding of the lifestyle and dietary

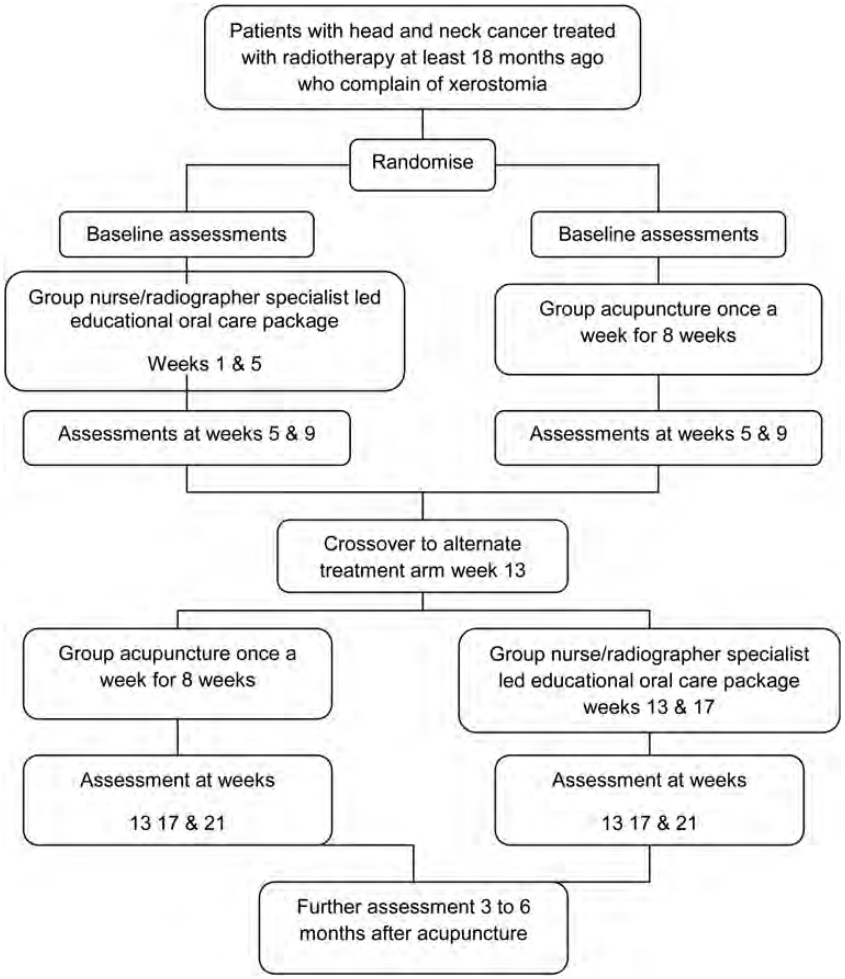


**Figure 1.** Trial schema.

modifications possible to improve xerostomia. Patients also shared their experiences of xerostomia and its impact on daily life, and discussed their own lifestyle modifications and use of dry mouth products.

### acupuncture sessions

Group acupuncture sessions lasted 20 min and occurred weekly for eight consecutive weeks. Therapists were all registered members of the British Acupuncture Council or equivalent bodies and attended workshops to learn the standardised trial protocol. The technique was based on one previously reported [15] but included LI20, an additional facial point based on advice from British Medical Acupuncture Society members.

Needles, (0.2 × 7 mm) were inserted in both ears at the following points: Salivary Gland 2, Modified Point Zero, and Shen Men. Distally 0.16 × 25 mm needles were used bilaterally in LI2 (index finger) and LI20 (nasolabial groove at the level of the most prominent part of the ala nasi). Needles were inserted to dermis, retained for 20 min, and manually rotated at 10 min to increase the likelihood of de qui. Electro stimulation and other co-interventions (moxibustion etc.) were not permitted.

## assessment tools

### subjective

PRO data were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQC30) [19] and the Head and Neck subscale (H&N-35) [20]. These standardised measures require Likert-type responses, 'not at all', 'a little' 'quite a bit,' and 'very much'. Ratings are obtained for individual items, for subscale scores, and for a global score. Subjects completed four additional questions, addressing key xerostomia symptoms reported in our pilot study [14].

### objective measure

Saliva (stimulated and non-stimulated) production was measured using Schirmer strips. The modified Schirmer test is an objective, well-tolerated test for measuring mouth dryness [21]. Unstimulated saliva was measured by inserting a test strip to the floor of the mouth for 2 min. Measurements were recorded in millimetres. Lemon juice was applied to the tongue to stimulate saliva and the procedure repeated. Subjects refrained from eating, drinking, or smoking for 1 h before the test.

Questionnaire data were collected at baseline and weeks 5, 9, 13, 17, and 21. Saliva was measured immediately before treatment sessions. There was a follow-up assessment 3–6 months after completion of acupuncture, examination of patients' expectations before treatment, and subsequent experience.

## primary and secondary end points

The primary end point was patient-reported change in severity of dry mouth ('not at all/a little' and 'quite a bit/very much'). Secondary end points were patient-reported change in other key xerostomia symptoms (sticky saliva, dry lips, need to sip water to relieve dry mouth, need to sip

water to help swallow food, and waking at night to sip water) and changes in saliva production.

### statistical analysis

The primary outcome was analysed using longitudinal analyses based on logistic regression models estimated using generalised estimating equations [22] with an exchangeable correlation structure (supplementary Information S1, available at *Annals* of Oncology online).

The secondary outcome responses were dichotomised to 'not at all/a little' (positive outcome) and 'quite a bit/very much' (negative outcome) and analysed using logistic regression models with estimation by generalised estimating equations, as above.

In addition, the data collected for all EORTC QLQ C-30 items and H&N-35 questionnaires were transformed to a 0–100 scale following EORTC guidelines.

## results

Figure 2 shows the trial consort diagram. 144/145 patients participated (109 male and 35 female). Seventy-five patients were randomised to oral care followed by acupuncture (group 1) and 70 to acupuncture followed by oral care (group 2). Table 1 displays the demographics of the patients allocated by treatment group. The extent of parotid radiation was comparable on both arms. Five patients left the study from group 1 by week 9 and 7 from group 2. The mean attendance rate to the acupuncture sessions was 89% and to the oral care sessions 80%. Six-month assessments were only available for 68 participants due to the trial being delayed due to unresolvable administrative problems.

### patient-reported outcomes

Improvements for five of the six symptoms were noted following acupuncture (see Table 2). Of those in group 2 who had severe dry mouth at baseline, 14 patients (26%) improved 9 weeks later, compared with 8 (14%) in group 1 who received oral care during this period. Twelve (24%) of those in group 1 who had severe dry mouth at week 9 showed improvement 8 weeks later following acupuncture, compared with seven (19%) patients who crossed over to oral care. The estimated odds

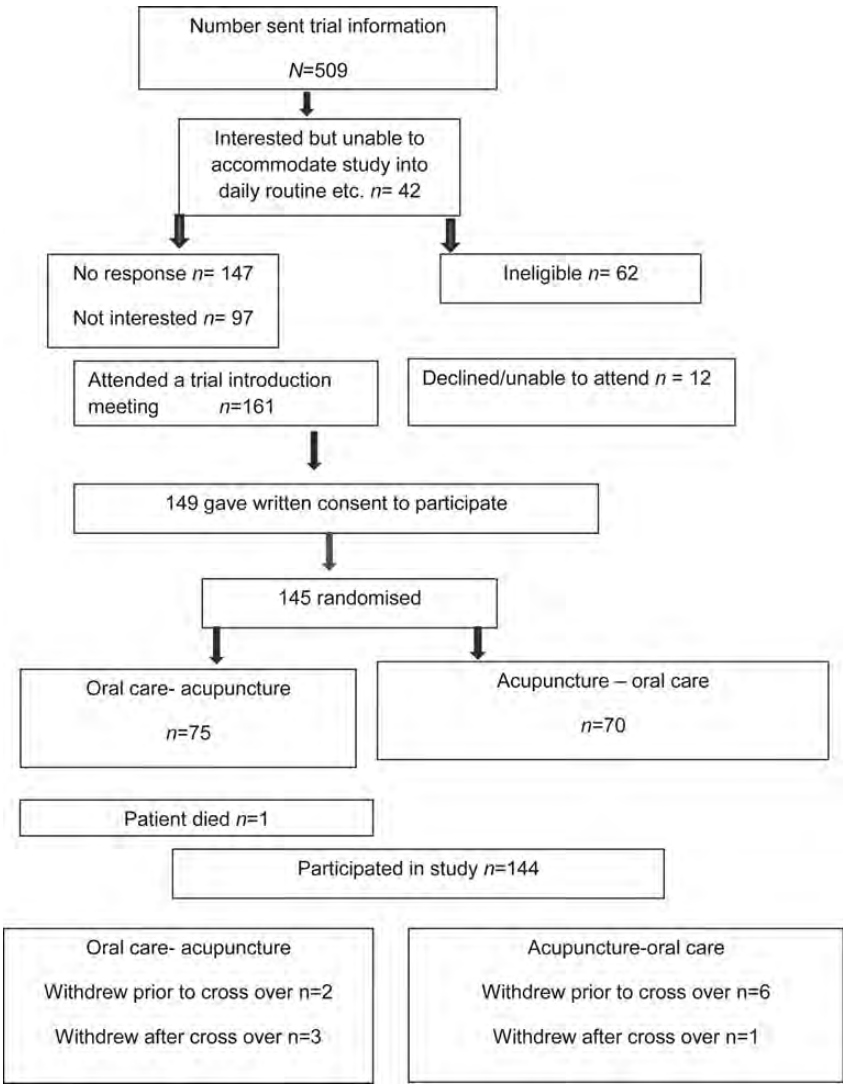


**Figure 2.** Recruitment consort diagram.

**Table 1.** ARIX patient demographics grouped by treatment arm

| | Group 1; O-A ($n = 74$) | Group 2; A-O ($n = 70$) | Total ($n = 144$) |
|---|---|---|---|
| Age (years) | | | |
| Mean | 60.3 | 58.6 | 59.4 |
| Median | 60 | 57 | 58 |
| Range | 43–79 | 41–83 | 41–83 |
| Tumour site | | | |
| Larynx | 4 | 5 | 9 |
| Oral cavity | 8 | 3 | 11 |
| Oropharynx | 52 | 48 | 100 |
| Nasopharynx | 3 | 3 | 6 |
| Hypopharynx | 3 | 3 | 6 |
| Parotid gland | 2 | 0 | 2 |
| Occult/unknown | 2 | 8 | 10 |
| T stage | | | |
| 1 | 18 | 12 | 30 |
| 2 | 25 | 27 | 52 |
| 3 | 17 | 13 | 30 |
| 4 | 7 | 9 | 16 |
| Unknown/cannot be measured | 5 | 9 | 14 |
| Missing (1x non-hodgkins lymphoma, 1x not recorded) | 2 | 0 | 2 |
| N stage | | | |
| 0 | 16 | 15 | 31 |
| 1 | 16 | 12 | 28 |
| 2 | 36 | 38 | 74 |
| 3 | 4 | 5 | 9 |
| Missing | 2 | 0 | 2 |
| Surgery to tumour | | | |
| None | 42 | 39 | 81 |
| Primary tumour only | 4 | 6 | 10 |
| Primary tumour + lymph nodes | 16 | 9 | 25 |
| Neck dissection only | 12 | 16 | 28 |
| Surgery to parotid glands | | | |
| None | 72 | 69 | 141 |
| Partial parotidectomy (1 gland) | 2 | 0 | 2 |
| Complete parotidectomy (1 gland) | 0 | 1 | 1 |
| Chemotherapy | | | |
| Yes | 46 | 48 | 94 |
| No | 28 | 22 | 50 |
| Radiotherapy technique | | | |
| 2D orthogonal fields | 11 | 15 | 26 |
| Conformal 3D | 61 | 54 | 115 |
| IMRT | 1 | 0 | 1 |
| Not recorded | 1 | 1 | 2 |
| Dose prescribed to primary tumour (Gy) | | | |
| Mean | 63.5 | 65.6 | 64.6 |
| Range | 50–70 | 55–70 | 50–70 |
| Not recorded | 2 | 0 | |
| Time from RT completion to randomisation (months) | | | |
| Mean | 41.5 | 44.6 | 43.0 |
| Median | 39.5 | 42.0 | 41.0 |
| Range | 18–75 | 18–104 | 18–104 |

O-A, oral care followed by acupuncture; A-O acupuncture followed by oral care.

ratio of improved dry mouth 9 weeks after acupuncture compared with oral care was 2 ($P = 0.031$), after adjusting for the effect of time, residual effects, treating cancer centre, and patient characteristics (Table 3). Female participants were twice as likely to report severe dry mouth as men ($P = 0.03$).

The estimated odds ratios of improvement in severity of symptoms for acupuncture compared with oral care were sticky saliva (OR = 1.67, $P = 0.048$), needing to sip to swallow food (OR = 2.08, $P = 0.011$), and waking up at night needing to drink (OR = 1.71, $P = 0.013$). Also, we found moderate evidence (OR = 1.65, $P = 0.065$) that acupuncture was more likely to relieve dry lips than oral care. We found no demonstrable difference between acupuncture and oral care at reducing patients' need to sip liquids to relieve their dry mouth.

Supplementary Figure S3, available at *Annals of Oncology* online, shows the odds of presenting severe symptoms over time for each outcome. Time had an important effect on key symptoms. The odds of reporting dry mouth decreased significantly at the rate of 28% per week at baseline and less markedly at the rate of 8% per week at week 5. Similarly, the odds of reporting dry lips and sticky saliva decreased at the rates of 24% and 21% per week at baseline but only 7% and 6% at week 5, respectively. The decline in the odds of reporting the need to sip liquids to relieve dry mouth was estimated to be at the rate of 18% per week at baseline and 5% at week 5. The odds of reporting the need to sip liquids for food and waking at night to drink declined at a rate 15% per week at baseline and 4% at week 5. The absence of a difference in the effect of time between groups suggests that carryover effects were not present.

Most items from the EORTC QLQ C-30 and H&N-35 questionnaires (excluding the items above) had scores reflecting high levels of functioning and low rates of other symptoms. There was very little variability over the length of the trial, precluding further analysis. Mean global QoL score did not change significantly over time either within or between groups. Ranges were 70.3–74 and 74.8–77.6 for groups 1 and 2, respectively. Mean scores of the scales and single items are presented in supplementary online S3, available at *Annals of Oncology* online.

## saliva measurements

There were no significant changes in either stimulated or unstimulated saliva over time or by intervention. Supplementary Figure S4, available at *Annals of Oncology* online, shows median saliva measur ements over time by group order. Female participants had significantly lower saliva measurements ($P = 0{\cdot}02$) than men (both stimulated and unstimulated).

## relationship between subjective and objective measures

We found strong evidence for an inverse relationship between having a dry mouth and stimulated saliva level

**Table 2.** Data from patients who reported severe symptoms at baseline and at crossover

| Period | Baseline to week 9 | | Total | Crossover to week 21 | | Total |
|---|---|---|---|---|---|---|
| Group | Symptoms remain | Improve | | Symptoms remain | Improve | |
| H&N35 Q.41: Dry mouth | | | | | | |
| Oral, acupuncture | 50 | 8 | 58 | 39 | 12 | 51 |
| Acupuncture, oral | 40 | 14 | 54 | 29 | 7 | 36 |
| H&N35 Q.42: Sticky saliva | | | | | | |
| Oral, acupuncture | 38 | 11 | 49 | 31 | 11 | 42 |
| Acupuncture, oral | 24 | 19 | 43 | 17 | 3 | 20 |
| Extra question 1: Sipped liquids | | | | | | |
| Oral, acupuncture | 51 | 8 | 59 | 41 | 10 | 51 |
| Acupuncture, oral | 41 | 11 | 52 | 33 | 7 | 40 |
| Extra question 2: Sipped to swallow | | | | | | |
| Oral, acupuncture | 54 | 2 | 56 | 41 | 8 | 49 |
| Acupuncture, oral | 43 | 11 | 54 | 34 | 3 | 37 |
| Extra question 3: Dry lips | | | | | | |
| Oral, acupuncture | 36 | 13 | 49 | 25 | 16 | 41 |
| Acupuncture, oral | 35 | 13 | 48 | 23 | 7 | 30 |
| Extra question 4: Woken up at night | | | | | | |
| Oral, acupuncture | 32 | 5 | 37 | 21 | 13 | 34 |
| Acupuncture, oral | 26 | 12 | 38 | 22 | 5 | 27 |

'Improvement' reflects reduced symptoms at the end of treatment and 'symptoms remain' refers to persistent severe symptoms at the end of treatment.

**Table 3.** Estimated odds ratios of reduced symptoms following acupuncture compared with oral care, based on a generalised estimating equations logistic regression model adjusted for logarithm of time in weeks, order group, contrast variable between treatments, centre, patient's gender and age

| Outcome | Odds ratio | 95% CI | | *P* |
|---|---|---|---|---|
| H&N35 Q.41: Dry mouth | 2.01 | 1.38 | 2.64 | 0.031 |
| H&N35 Q.42: Sticky saliva | 1.67 | 1.16 | 2.17 | 0.048 |
| Extra question 1: Sipped liquids | 1.59 | 0.99 | 2.18 | 0.129 |
| Extra question 2: Sipped to swallow | 2.08 | 1.52 | 2.64 | 0.011 |
| Extra question 3: Dry lips | 1.65 | 1.12 | 2.18 | 0.065 |
| Extra question 4: Woken up at night | 1.71 | 1.29 | 2.13 | 0.013 |

Significant effect of gender on dry mouth ($P = 0.03$, female patients more likely to have severe dry mouth OR = 2.2); we found no evidence for the presence of carryover effects on any of the outcomes.

($P = 0.001$), needing to sip liquids to relieve dry mouth and stimulated saliva ($P < 0.001$), and feeling dry lips and stimulated saliva ($P = 0.03$). These relationships were present over and above the effects of time, patient characteristics, and treatment effects.

### participants' expectations of the benefits of acupuncture

We related participants' expectations of benefit from acupuncture to actual outcome in 68 participants for whom data were available 3–6 months later. A majority (29/68 = 43%) thought they would 'feel better' although only 9/29 (31%) had their expectations met. A small number (9/68 = 13%) thought that they would feel 'much better', 4/9 (44%) felt 'better' after treatment. About 3/11 (27%) participants who had no expectation of benefit, reported an improvement at the end of the study. Nineteen participants did not know what to expect; this group contained the only respondent to report feeling much better alongside four others 'feeling better'. None of the participants expected to feel worse and none reported feeling worse as a consequence of participation.

### adverse events

Two patients were treated for coronary syndromes during the 8 weeks of acupuncture. On review both had multiple risk factors for cardiac disease, and therefore, the events were not likely to be acupuncture treatment related. During the oral care time period, one patient suffered a traumatic hip fracture and another was hospitalised for aspiration pneumonia.

## discussion

This study is the largest reported randomised trial of acupuncture for the amelioration of radiation induced xerostomia in patients treated for head and neck cancer. Results show that a course of group acupuncture was useful in relieving symptoms of dry mouth, and provided greater benefit than oral care alone. There were significant reductions in patients' reporting of severe dry mouth, sticky saliva, needing to sip to swallow food, and in waking up at night to drink. There was very little variability in overall quality of life in these patients, who functioned well over the length of the trial. We did not demonstrate a link between subjective improvements in dry mouth and rates of saliva. The basal and stimulated salivary flow rates vary significantly between individuals and subjective sensations of oral dryness are not reliable indicators of measurable flow rate.

Long-term care of patients treated for head and neck cancer presents new challenges, and amelioration of treatment-related side-effects is an essential component of survivorship. The American Head and Neck Society follow the NCCN guidelines for the management of radiation-induced xerostomia, which, similar to the UK, recommend the use of IMRT and drug therapy (e.g. pilocarpine, cevimeline) [23, 24]. In the absence of other useful treatments, it is reasonable to test acupuncture particularly in the context of studies suggesting benefit in pilocarpine-resistant xerostomia [25].

The mechanisms underpinning the benefits of acupuncture are not clear. Needling inevitably causes brain activity, and this may alter brain biochemistry inducing neurotransmitters and neurohormone release in a different way. This in turn may affect parts of the central nervous system related to sensation and involuntary body functions, such as immune reactions and autonomic processes including regulation of blood pressure, blood flow, and body temperature.

In the case of xerostomia, acupuncture may produce autonomic stimulation of any residual salivary gland tissue directly or by increasing blood supply to it or the multiple minor salivary glands that line the upper aerodigestive tract. Imaging studies using functional MRI (fMRI) have shown that unilateral use of the acu-point LI-2 led to bilateral activation of the insula and adjacent operculum in 20 healthy volunteers [26]. The significance of this activation is not known but illustrates that the point has a biological effect. Also, other studies have shown increased fMRI activity with needle rotation [27]. Our choice of acupuncture points was based on a desire to use a standardised technique. We chose a schedule which had the support of acupuncture therapists and had shown some success in previous work, we added the facial point after discussion with acupuncture therapists, some of whom use very little auricular acupuncture. Other studies have used a wide variety of points or highly individualised treatment strategies making comparisons between subjects and trials much more difficult. The efficacy of individual acu-points is unknown and may be the subject of further study.

Our results together with those recently published [11, 12] show benefits from acupuncture, but the putative role of a placebo effect needs discussion. Studies require good control groups so that any apparent effects from acupuncture are not attributable to the therapeutic relationship with the practitioner, a Hawthorne effect, or subjects' expectations of benefit from the procedure. Determining a good control group is difficult. Sham acupuncture using non-penetrative needles or the use of 'non-active' neutral points may control for therapist interaction but may have unintended consequences due to 'neutral' points having real but unintended effects [28]. In addition, functional imaging studies of sham techniques have demonstrated brain activity similar to that seen with real needling further supporting the view that this may not be an appropriate control [29]. We did not employ sham acupuncture for this reason. We controlled for a 'peer support' effect by giving both interventions in groups, yet participants reported an increase in their xerostomia related quality of life when having an active procedure (acupuncture) more than when attending an educational session. It is feasible that, when the groups met for the eight weekly acupuncture sessions, they gained more emotional support from each other than when they met for the two educational sessions. However, there was no difference between groups for social and emotional QoL, only the specific xerostomia question—severity of dry mouth.

It is a well-known phenomenon in theories of social cognition that the expectation of benefit may have a role in 'priming' an intervention group to report better subjective outcomes. In our study, only 13% of respondents expected to feel much better as the result of the intervention, and there was no clear correlation between expectation and outcome for participants.

A strength of our study was that it was a randomised trial of a reproducible and standardised protocol, conducted within strict clinical governance guidelines. In many acupuncture studies, adverse events are rarely captured but to be able to compare acupuncture with conventional therapies, safety data are required. In our study, two serious coronary events occurred but were deemed unrelated to acupuncture. Treatment was otherwise entirely non-toxic.

Acupuncture benefits may be subject to attrition over time, and we do not know how enduring the effects were beyond 3 months. However, the trial appears to establish the effectiveness of the technique, and group sessions offer a pragmatic and affordable system of delivering the intervention. Future studies may be warranted to refine the technique further, establish the duration of benefit and length of treatment, or booster sessions needed to improve and maintain efficacy.

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## disclosure

The authors have declared no conflicts of interest.

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