Effectiveness of adjunctive analgesics in head and neck cancer patients receiving curative (chemo-) radiotherapy: A systematic review.

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Effectiveness of adjunctive analgesics in head and neck cancer patients receiving curative (chemo)radiotherapy: a systematic review

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ABSTRACT

Introduction: Radiotherapy with or without systemic therapy is the main treatment for locally advanced head neck cancer (HNC) patients. This treatment can cause mucositis, dysphagia and severe (neuropathic) pain. Adjunctive analgesics could play a significant role in the treatment of neuropathic pain in cancer patients. Our aim was to give an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo)-radiotherapy.

Methods: This systematic review was conducted following the PRISMA guidelines. PubMed, Embase, Web of Science, The Cochrane Library and Clinicaltrials.gov were searched for studies concerning “head neck cancer”, “adjunctive analgesics”, “pain” and “radiotherapy”.

Results: Nine studies were included in our synthesis. Most studies were of low quality and had a high risk of bias on several domains of the Cochrane Collaboration tool. Only two studies comprised high quality randomised controlled trials in which pregabalin and a doxepin rinse respectively showed their effectiveness in HNC patients receiving (chemo-)radiotherapy.

Conclusion: More high quality trials (randomised controlled trials, using standardised pain scales) are necessary to provide clear evidence on the effectiveness of adjunctive analgesics, (besides pregabalin and a doxepin rinse) in the treatment of HNC (chemo-)radiation induced pain.

INTRODUCTION

Head and neck cancer (HNC) incidence is rising. In Belgium, there were 2694 new diagnoses in 2016 [1]. It is speculated that by 2020, there will be 151.000 new diagnoses in Europe and 833.000 worldwide [2]. Treatment modalities for HNC include surgery, radiotherapy, chemotherapy, biotherapy, immunotherapy, targeted therapy and brachytherapy. In most cases~~,~~ ~~or~~ combinations of these are used [3–5]. Systemic therapy combined with radiation is the main treatment for locally advanced HNC patients [6]. However, this treatment may cause severe pain and other complications.

Cancer pain can be classified ~~as following~~in three categories: tumour induced pain, iatrogenic pain (induced by ~~the therapies~~treatment) and incidental pain (caused by co-existing conditions) [3]. In HNC patients, pain is often a serious complication and is present in a high proportion of patients [3,6–8], before (50%), during (81%) and after treatment (70%) [6]. This may be acute pain caused by inflammation of the mucosa (mucositis) and of the skin (dermatitis), or late pain caused by radiation-induced fibrosis [6]. Post-operative pain is another possibility [3]. Neuropathic pain is also often reported [9,10]. Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a primary lesion or dysfunction in the nervous systems, resulting in debilitating pain [11]. This can be caused by tumour infiltration or by therapy [9,10]. In case of neuropathic pain due to tumour infiltration, nociceptive and neuropathic components are involved, therefore referred to as mixed pain. In case of neuropathic pain by cancer therapy, it can be considered as pure neuropathic pain, therefore referred to as purely neuropathic pain [10]. Pain may have a substantial impact on the patients' quality of life (QOL) [6] and could lead to social isolation, functional impairment and emotional and spiritual distress [8]. Moreover, it could lead to reduced treatment compliance, dose modifications or treatment interruption and in that way, causing a lower patient survival [6,8]. Therefore, optimal pain control is essential.

The World Health Organisation (WHO) developed pain guidelines, including the WHO pain ladder consisting of three steps that should be followed in case of pain: first oral administration of non-opioids, then mild opioids and ~~afterwards~~ finally strong opioids (e.g. morphine) until pain relief is obtained [3]. These WHO guidelines for pain relief ~~were~~ have been validated for both cancer pain in general a~~n~~d for HNC pain specifically. In these guidelines, the WHO advises to use adjuvant pain medications too for pain treatment in HNC, as these treatments are highly effective and relatively safe [3]. For mixed pain, adjuvant analgesics could be used next to opioids. For purely neuropathic pain, the WHO suggests the use of adjuvant analgesics as first line treatment [10].

In the past, opioids (e.g. morphine) were considered as standard treatment for cancer pain management and radiation-induced pain in HNC patients [6,12]. However, its use is impeded ~~because of th~~bye multiple side effects such as nausea, vomiting, depression, sedation, drowsiness, hallucinations, cognitive impairment, pruritus, constipation, and respiratory depression [6,7,12]. Opioids are narcotic ~~medications~~ drugs and have addictive properties [13]. Moreover, certain types of pain, such as neuropathic pain, respond poorly to opioids alone [6,12]. ~~As a~~By consequence, escalating doses are required [11,12]. Adjuvant analgesics could be a possible alternative.

Adjuvant analgesics can be defined as drugs with a primary indication other than pain, but with analgesic properties under certain circumstances [8,14]. They~~It~~ can also be defined as drugs that do not contain acetaminophen and those not classified as non-steroidal anti-inflammatory or opioid agents, but play a role in the management of chronic pain [15]. Another term is adjunctive

Comment [TB1]: This is not clear from what follows, which are static figures or not comparable to the Belgian figures

Comment [TB2]: The classification is not fully clear: you start with these three, but then add in other types (acute, late, post-operative, neuropathic etc. without explaining to which category they belong. Make this more clear by explaining which classfication you use: cause, type, according to time etc.

Comment [TB3]: Do you have an idea about the incidence of the different types? I would expect that tumour-induced pain is at least as important.

Comment [TB4]: Define the difference between adjuvant and adjunctive

analgesics, which may be better fit, as these drugs are often already used as first-line therapy [8,15]. Therefore, in this systematic review, we will use the term adjunctive analgesics.

Adjunctive analgesics could play an important role in the treatment of neuropathic pain in cancer patients [16]. There are different classes of adjunctive analgesics ~~comprising~~ including anticonvulsants, tricyclic antidepressants (TCA), selective serotonin and norepinephrine reuptake inhibitors (SSNRI), NMDA receptor antagonists, topical agents and others (cannabinoids, clonidine, corticosteroids, etc.) [8,9,14]. Anticonvulsants include gabapentin and pregabalin and are suggested to help relieve neuropathic cancer pain [8,9,14]. Other anticonvulsants investigated are lamotrigine, oxcarbazepine, topiramate, levetiracetam [14]. TCAs include amitriptyline, imipramine, clomipramine, doxepin, nortriptyline and desipramine and have been prescribed for years to treat neuropathic pain [9,14]. SSNRI, also antidepressants, have shown efficacious analgesic effects in the treatment of neuropathic pain and include venlafaxine and duloxetine [8,9,14]. Concerning NMDA receptor antagonists, ketamine may be a possible treatment for chronic cancer pain [8,9,14]. Cannabinoids also have analgesic properties and could be used for the management of neuropathic cancer pain [8,9,14]. Alpha-2 (α-2) adrenergic agonists, such as clonidine and tizanidine have been used for neuropathic cancer pain, but their specific role has not been established [9,14]. Further, corticosteroids, such as dexamethasone and methylprednisolone, could be effective for cancer pain relief [8]. Last, local anaesthetics, such as lidocaine and mexiletine can decrease pain intensity [8,14].

Oral mucositis is one of the most commonly reported adverse events in HNC patients receiving (chemo-)radiotherapy, which causes pain that can range from mild to severe and can persist up to 6 months after the completion of radiotherapy, or more [5]. Therefore, benzydamine or other mouthwashes can be used as treatment for this mucositis which could result into pain relief as well [17].

In this systematic review, we give an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo-)radiotherapy.

Comment [TB5]: For what?

Comment [TB6]: explain

Comment [TB7]: explain

Comment [TB8]: it is somewhat surprising to find this statement in an introduction without further explanation

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews [18]. The protocol was registered in the International Prospective Register of Systematic Reviews-PROSPERO (CRD42018085632).

Eligibility criteria

We aimed to identify all types of studies (cohort studies, randomised controlled trials, etc.) that included head neck cancer patients receiving curative (chemo-or bio-) radiotherapy and that investigated the effectiveness of adjunctive analgesics. All articles reporting pain or pain management as outcome were included. Only articles in English were included. Papers reporting on pain prevention were excluded.

Literature search method

The following databases were searched: PubMed, Embase, Web of Science and The Cochrane Library. Clinicaltrials.gov was consulted for ongoing clinical trials. Studies published ~~up~~ until February 2019 were included. The search terms that were used are listed in table 1.

Table 1: Search terms

Head and neck cancer	Head neck cancer; Head neck tumor; Head neck tumour; Head neck neoplasm; Head neck malign; Head neck carcinoma
Pain	Pain; Pain medication; Pain management ; Pain measurement; Pain assessment; Analgesia
Radiotherapy	Radiotherapy; Radiation
Adjunctive medication	Adjunctive medication/analgesia; Adjuvant medication/analgesia; Co-analgesic; Off-label; Off label; Anticonvulsant; Antiepileptic; Gabapentin; Pregabalin; Topiramate; Lamotrigin*: Carbamazepine; Levetiracetam; Oxcarbazepine; Tiagabine; Zonisamide; Phenytoin; Valproate; Antidepressant; Anti-depressant; Tricyclic antidepressant; TCA; Amitriptyline; Nortriptyline Desipramine; Selective serotonin reuptake inhibitor; SSRI; Serotonin inhibitor; Noradrenaline inhibitor; SNRI; Paroxetine; Citalopram; Venlafaxine; Duloxetine; Imipramine; Doxepin*; Bupropion; Clomipramine; Fluoxetine; Mirtazapin; Sertraline; N methylaspartate antagonist*; N-methylaspartate inhibitor; Ketamine; Memantine; Dextromethorphan; Methadone; Amantadine; Antipsychotic; Neuroleptic; Antipsychotic agents; Chlorpromazine; Clozapine; Olanzapine; Haloperidol; Pimozide; Quetiapine; Risperidon*; Sulpiride; Tiaprid*; Zuclopenthixol; Zoledronic*; Pamidronate*; Clodronate; APD; Lidocaine*; Capsaicin*; BTX-A; Botulinum toxin; Corticosteroid*; Dexamethasone; Prednisone; Denosumab; Bisphosphonate; Biphosphonate; Cannabinoid; Local anaesthetic; Local anesthetic; Clonidine; Tizanidine; *Adrenergic agonists; Mexiletine; Mouth wash

The search in PubMed was narrowed by filtering studies concerning humans. At the Cochrane Library, the search was limited to title, abstract and keywords. At clinicaltrials.gov, the condition

described was “head and neck cancer”, the intervention “pain medication” and “radiotherapy” was completed under the category “other”.

All studies were gathered in a self-constructed database. After removal of duplicates, title and abstract were screened by two individual reviewers (TL and PDB). The remaining studies were screened for eligibility by the two reviewers independently. On the selected studies, a snowballing approach was applied: reference lists were screened for additional eligible studies.

Quality assessment

The included studies were subjected to a critical quality assessment, using The Cochrane’s Collaboration Tool, by two individual reviewers (TL and LT). In this way, studies were judged based on selection, performance, detection, attrition and reporting or other forms of bias [19].

Data extraction

The following data was extracted from the articles: study characteristics (first author, country, article type, drug, comparison, sample size, primary site of disease and chemotherapy received), study therapy characteristics (dose, indication, comparison, number of patients) and outcome (pain outcome, adverse events and toxicity and other reported outcomes e.g. mucositis, quality of life, depression, etc.).

Due to the high heterogeneity in the reported data from the studies, performing a meta-analysies was not possible.

RESULTS

Search results

We obtained 264 records from our database search and after removal of duplicates, 216 articles were left. After screening on title and abstract, we maintained 74 articles. The main reasons for exclusion ~~was because~~were that the articles did not concern adjunctive analgesics or~~and~~ did not concern HNC patients. After full-text screening and quality analysis, nine articles were included for analysis in this review. No additional studies were identified through snowballing (Figure 1).

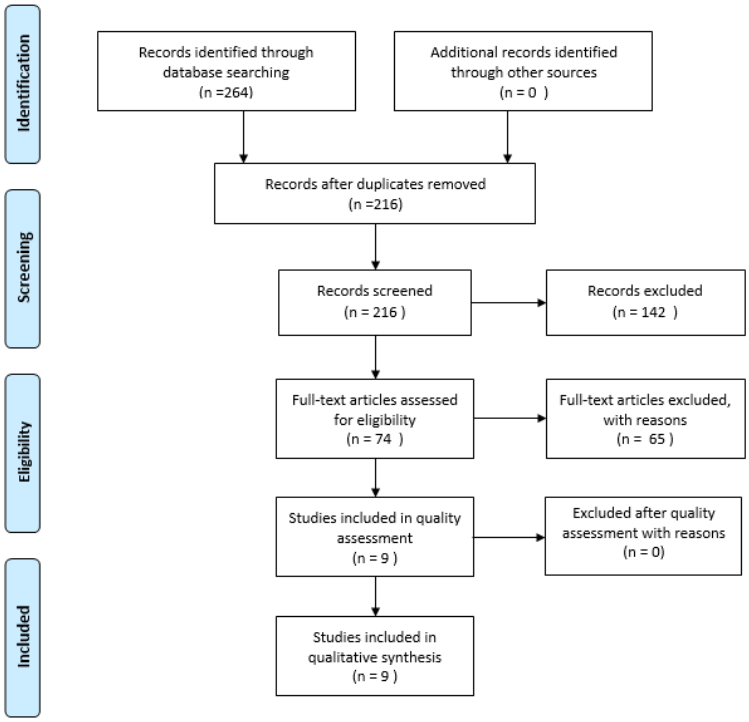

Figure 1: PRISMA flowchart of the search

Risk of Bias assessment

The six domains of the Cochrane Collaboration tool for risk of bias were assessed for each of the included studies (Figure 2). On the first domain (random sequence generation), four of the nine studies had a low risk of bias and five had a high risk of bias. For the next domain, allocation concealment, three studies had a low risk of bias, five had a high risk of bias and for one study, the risk of bias was unclear. There was a high risk of bias for the domain "blinding of participants and personnel" in six studies, a low risk in two studies and an unclear risk in one study. On the domain "blinding of outcome assessment", two studies had a low risk of bias, five had a high risk of bias and two an unclear risk of bias. In the next domain (incomplete outcome data), a low risk of bias was judged in eight studies and an unclear risk of bias in one study. On the last domain (selective reporting), eight studies were judged to have a low risk of bias and one to have a high risk of bias. Six studies had a high risk of bias due to a low sample size and the

lack of a power calculation. This bias was categorised under "other bias". Three studies did include a power calculation and had an acceptable sample size, resulting into a low risk of bias. A summary of the bias assessment is presented in figure 2. The extensive judgement can be found in appendix F.

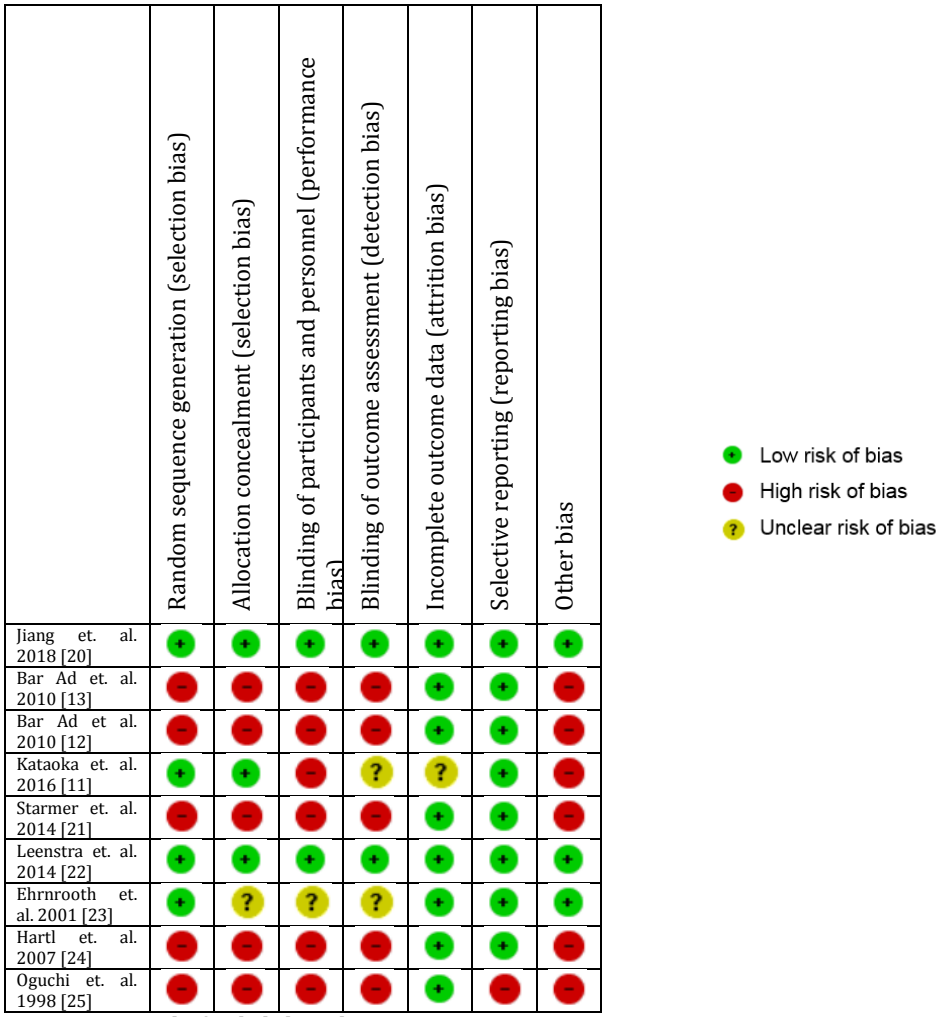

Figure 2: Bias risk of included articles

Study and study therapy characteristics

A summary of the study and study therapy characteristics can be found in Appendix A and B respectively. Four studies were performed in the United Stated of America (USA) [12,13,21,22], one in China [20], one in Denmark [23], one in France [24] and two in Japan [11,25]. Four studies were randomized trials [11,20,22,23], two were retrospective cohort studies [12,13], one was a prospective cohort study [24] and two were historically controlled studies [21,25]. Four studies investigated the effect of gabapentin [11–13,21], one of pregabalin [20], one of a doxepin rinse [22], one of nortriptyline [23], one of botulinum toxin [24] and one investigated a polymer film containing tetracaine [25]. Study medication was indicated for neuropathic pain in

one study [20], for painful mucositis in six studies [11–13,22,23,25], for pain in general in one study [21] and for radiation induced pain, trismus and masticator spasm in one study [24].

Pain outcomes

Different methods were used to measure the effectiveness of the adjunctive analgesic on pain. Most studies utilised patient reported measures, such as the numeric rating scale (NRS) [20], the Brief Pain Inventory-Short Form (BPI-SF) [20], a visual analogue scale (VAS) [11,23], an 11-point numerical analogue pain scale [22], the Pain Likert Scale [23], the McGill Pain Questionnaire (Danish version) [23], or patient reported pain (not specified) [21,24,25]. However, some studies also looked at the use of pain medications e.g. the use of adjunctive pain medication [12,13], or additional pain medication such as acetaminophen [11], opioids [11–13,23], or other analgesics [21–23,25]. Because of this variety, we could not perform a meta-analysis to obtain an overall result of all studies included. An overview of the reported pain outcomes can be found in Appendix C and are described below.

Pregabalin

Jiang et. al. [20] conducted a randomized, double-blind, placebo-controlled trial including 64 patients in each group (pregabalin and placebo) and found a decreased pain intensity of 2.44 on the NRS at week 16 in the pregabalin group compared to the placebo group ($p=0.003$). 19 out of 64 patients receiving pregabalin achieved pain relief of 50% or more at week 16 compared to only five out of 64 patients receiving placebo ($p=0.003$). Moreover, pain intensity decreased gradually from week 1, but more in the pregabalin group than in the placebo group ($p<0.001$).

Also, at week 16, a significantly decreased pain severity, measured by the BPI-SF, was observed in the pregabalin group compared to the placebo group ($p=0.047$).

Gabapentin

Four studies explored the effectiveness of gabapentin in HNC patients receiving radiotherapy [11–13,21] of which two were retrospective cohort studies [12,13], one was a historically controlled study [21] and one a randomised trial [11].

Bar Ad et. al. [13] performed a retrospective cohort study in 29 patients and observed that 28 patients used the median dose of gabapentin of 2700 mg/day at week 3, 4, 5 and 6 and that at week 3 and 4, only three of the 29 patients required low doses of narcotics (15-30 mg/day Roxicodone). At week 5 and 6, ten patients required additional low doses of narcotics (15-40 mg/day Roxicodone).

In a consequent retrospective cohort study in 42 patients, Bar Ad et. al. [12] observed that at week 2, 3, 4 and the last week of radiotherapy, 38 patients used gabapentin. Only five patients required an additional median dose of 10 mg/day oxycodone-equivalent at week 2. At week 3, 4, and the last week of radiotherapy, 14 patients required 10 mg/day oxycodone equivalent, 23 patients required 30 mg/day oxycodone equivalent and 30 patients required 60 mg/day oxycodone-equivalent respectively.

Kataoka et. al. [11] compared gabapentin plus standard pain control (SPC) to SPC alone in a randomised trial in 20 patients (9 in gabapentin group; 11 in SPC group). They established a significant difference in maximum VAS score in the gabapentin group compared to the SPC group (74 vs. 47 resp., $p=0.552$). However, no difference in VAS score was detected between groups at each time point from baseline till week 4. No significant difference was found in the number of days until use of additional analgesics acetaminophen and opioids between groups.

Starmer et. al. [21] compared gabapentin to standard treatment (including use of narcotic pain medications) of historical controls in a cohort of 46 patients. They observed significantly lower maximal pain scores in the gabapentin group compared to the control group (p=0.038). Moreover, in the gabapentin group, 13% of the patients did not require additional pain medication compared to the control group, in which all patients required narcotics and 70% required multiple narcotics analgesics.

Doxepin rinse

Leenstra et. al. [22] compared a doxepin oral rinse to a placebo rinse in a randomised double blind trial including 140 patients. The area under the curve (AUC) for mean mouth and throat pain reduction was greater in the doxepin group (-9.1) compared to the placebo group (-4.7) ($p<0.001$). The treatment difference after cross-over analysis was -3.5 ($p<0.001$). After 30 minutes, the average mouth and throat pain score reduction was -2.0 in the doxepin group compared to -1.0 in the placebo group (p=0.0032). A significant difference in pain reduction was observed 1, 2, 3 and 4 hours after study initiation. No significant difference in use of additional analgesics was found after 2 and 4 hours between groups (8.8% vs. 2.9% and 16.9% vs. 14.5% respectively).

Nortriptyline

Ehrnrooth et. al. [23] analysed nortriptyline versus oral morphine in a randomised trial (19 patients in the nortriptyline group, 20 in the morphine group) and found significant lower VAS scores in the opioid group compared to the nortriptyline group one and two weeks after randomisation (p=0.007 and p=0.04 respectively). However, no significant changes in pain were observed between groups from baseline to one and two weeks post-randomisation. There was a trend to higher pain scores on the Pain Likert scale in the nortriptyline group compared to the opioid group at baseline and one week post-randomisation (not significant). According to the McGill Pain Questionnaire, there we no significant differences between groups in sensory, affective or miscellaneous pain at the four time points.

Botulinum toxin

Hartl et. al. [24] performed a prospective cohort study to observe the effect of botulinum toxin on pain in 19 patients. They found pain being reported on average 5.6 years after radiotherapy and a significant pain improvement after one month of botulinum toxin therapy (p=0.002). However, painful muscle cramps recurred in 11 patients 3.5 months after injection.

Polymer film containing tetracaine

Oguchi et. al. [25] used a historically controlled design to compare the effect of a polymer film containing tetracaine (AD film; 25 patients) and topical anaesthetics (27 patients). A significantly higher complete pain relief was obtained at rest and while eating in the AD film group compared to the control group (82% vs. 44% and 68% vs. 22% respectively). No significant difference was observed ~~between both groups~~ in duration of complete pain relief (30' vs. 30'-2h). Partial and complete pain relief was comparable in both groups. In the AD film group, median duration of grade 3-4 oral pain was 10 days compared to 15 days in the control group. Only four patients in the AD film group needed systemic analgesics due to grade 3-4 oral pain compared to 21 patients in the control group.

Reported adverse events and toxicity

An overview of the reported adverse events and toxicities is~~are~~ described below and is~~are~~ summarised in Appendix D.

Pregabalin

In the study of Jiang et. al. [20], 35 patients (54.7%) in the pregabalin group and 29 patients (45.3%) in the placebo group experienced at least one adverse event (p=0.29). Adverse events described were dizziness, somnolence, facial oedema and increased pain.

Gabapentin

A small number of patients experienced mild side effects or gabapentin related toxicities: four patients (13%) in the study of Bar Ad et. al. [13], two patients (5%) in the other study of Bar Ad et. al. [12], three of the 9 patients (33%) in the study of Kataoka et. al. [11] and three of the 23 patients (13%) in the study of Starmer et. al. [21]. The toxicities described comprised dizziness, nausea, vomiting, follicular skin rash/ allergic skin reaction, somnolence, vertigo, headaches and fatigue.

Doxepin rinse

In the study of Leenstra et. al. [22], stinging and burning, bad taste and drowsiness were reported following ~~toxicities concerning~~use of the doxepin rinse~~ were reported: stinging and burning, bad taste and drowsiness~~.

Nortriptyline

Ehrnrooth et. al. [23] reported minor side effects in 14 patients in both the nortriptyline (74%) and control group (70%): nausea, vomiting, constipation, cardial arrhythmia and neurocortical symptoms.

Botulinum toxin

Hartl et. al. [24] only reported the painful injections of the botulinum toxin as toxicity (37%).

Polymer film containing tetracaine

Oguchi et. al. [25] did not have any toxicities or side effects to report. There were no acute or chronic adverse effects on the oral mucosa or gastrointestinal tracts, no allergic dermal reactions, no cases of haematological toxicity and no cases of aspiration pneumonia or bronchitis.

Other reported outcomes

The focus of this systematic review was the effect of adjunctive analgesics on pain in HNC patients receiving (chemo-)radiotherapy. However, adjunctive analgesic could have other beneficial effects that should be taken into account, such as improvements in psychological distress, in quality of life (QoL), lower depression, better functionality and less cramps, improvements in radiation induced mucositis, better nutritional management and less weight loss, less secondary infections and a better tumour control and better survival. These are described below and are summarised in Appendix E.

Comment [TB9]: Why would this be the case?

Pregabalin

Jiang et. al. [20] investigated **psychological distress** and observed a significant improvement in all subscales of the Profile of Mood States-Short Form (POMS-SF), but not on the Vigor-Activity and Confusion-Bewilderment subscales in the pregabalin group compared to the control group.

Looking at the **QoL**, significant improvements could be observed in the physiology and psychology domains of the WHO Quality of Life – BREF (WHOQOL-BREF) scores in the pregabalin group compared to placebo (p=0.004 and p=0.01 resp.).

The Patients Global Impression of Change (PGIC) and the Clinical Global Impression of Change (CGIC) were used to follow up on the **improvement and satisfaction of patients with treatment.** The PGIC scale showed 30 patients (47.6%) that reported treatment success in the pregabalin group, as opposed to eight patients (12.9%) in the placebo group ($p<0.001$). The CGIC showed 36 patients (57.1%) with treatment success in the pregabalin group, compared to ten patients (16.1%) in the placebo group ($p<0.001$).

12.5% of the patients in the pregabalin group used **rescue medication**, while this number was 40.6% in the placebo group ($p<0.001$).

Compliance was comparable in both groups: 80.5% of patients took 80% or more of their prescribed medication.

Gabapentin

Bar Ad et. al. followed in both studies [12,13] up on **radiation induced mucositis and radiation induced dysphagia**. In their first study [13], all patients developed mucositis. During the first two weeks of treatment, grade 1 and 2 mucositis occurred in 80% of the patients. By week 2, 3 and 4, grade 2 mucositis occurred in 13%, 53% and 73% of the patients respectively. By week 5 and 6, grade 2 or 3 occurred in 80% of the patients. Grade 3 mucositis occurred in 6% of the patients and no grade 4 mucositis was reported.

Comment [TB10]: This seems to be related to radiotherapy (and chemotherapy), it is not clear to me why this would be related to gabapentin? I think Fréderic Duprez also commented on this. You may prefer to comment on this in the discussion section.

During week one of treatment, one patient (3%) reported dysphagia. By week 4 and 6, 53% and 60% of the patients respectively reported grade 1 dysphagia. Grade 2 dysphagia was reported by one patient (3%) during this trial, starting at week 3. Grade 3 dysphagia was reported by two patients (6%) during week 3 and by one patient (3%) by week 6. 33% of patients did not report any swallowing difficulty. No grade 4 dysphagia was reported.

In their subsequent study [12], all patients developed mucositis. Grade 1 and 2 mucositis occurred in 88% of the patients during the first 2 weeks of treatment. Grade 2 mucositis occurred in 44% of the patients during week 2. Grade 3 mucositis was not reported by week 2, but occurred in 17%, 45%, 60% and 81% of the patients by week 3, 4, 5 and 6 respectively. Grade 2 mucositis or higher occurred in 71%, 86%, 95% and 100% of the patients by week 3, 4, 5 and 6 and again, no grade 4 mucositis was reported.

During week one of treatment, two patients (5%) reported grade 1 dysphagia. By week 2 and 3, grade 1 or 2 dysphagia was reported by 38% and 52% of the patients respectively. By week 4, 76% of the patients reported dysphagia with 36% grade 2 or 3. By week 5 and 6, 95% of the patients reported dysphagia with 48% grade 2 or 3. No grade 4 dysphagia was reported.

Kataoka et. al. [11] also followed up on **oral mucositis** and reported that all patients experienced oral mucositis. Grade 3 or 4 mucositis occurred in 45.5% of the patients in the control group compared to 63.6% in the gabapentin group.

Concerning **QoL**, no significant decrease was observed in most domains over four weeks of radiotherapy between both groups. **Weight gain** was significantly higher in the gabapentin group compared to the control group ($p=0.0062$).

Starmer et. al. [26] focussed on **percutaneous endoscopic gastrostomy (PEG) use** and **physiological outcomes**. PEG use was later in the gabapentin group compared to the historic control group (3.7 vs. 2.29 weeks; $p=0.013$) and the PEG tube was removed earlier ~~removed~~ (7.29 and 32.56 weeks; $p=0.039$). 21.7% of patients in the gabapentin group never used their PEG tube compared to 4.3% in the control group ($p=0.038$). Patients in the gabapentin group lost ~~on average~~ 7.45% weight~~,~~ on average, while this was 11% in the control group ($p=0.037$).

Velopharyngeal closure, tongue base retraction, laryngeal elevation, epiglottic tilt and pharyngeal constriction were less affected in the gabapentin group. Significantly lower penetration-aspiration scale (PAS) scores were found in the gabapentin group compared to the control group (1.89 vs. 4.0; p=0.052), indicating better airway protection. Significantly higher functional oral intake scale (FOIS) scores were found in the gabapentin group compared to the control group (5.4 vs. 3.21; p=0.0003) indicating more advanced diet levels.

Doxepin rinse

No other outcomes were reported by Leenstra et. al [22].

Comment [TB11]: Other than?

Nortriptyline

Ehrnrooth et. al. [23] used the Beck's Depression Inventory (BDI) to assess the degree of **depression**. A significant reduction in BDI scores was observed in the nortriptyline group compared to the oral morphine group (p=0.02).

Botulinum toxin

Hartl et. al. [24] determined the **functionality and cramps** of the patients included and observed a significant improvement in overall functional score (p=0.04) and muscular cramps (p=0.04) after botulinum toxin injection. There was no significant improvement in jaw opening.

Polymer film containing tetracaine

Oguchi et. al. [25] observed **mucositis** in 88% of the patients in the AD film group compared to 92% in the control group.

17 patients in the AD film group did not require intra—venous (IV) infusions or **hyperalimentation** compared to nine patients in the control group. In the AD film group, less **weight loss** and a better weight recovery was observed compared to the control group (not significant).

No **secondary bacterial or fungal infection** of the oral cavity and/or oropharynx was observed in the AD film group compared to 4 cases of oral infection and 2 cases of aspiration pneumonia in the control group.

No significant difference in **3-year local control rate** was found between both groups (96% vs. 92%) ~~and no~~nor any difference in **3-year disease free survival rate** (87% vs 85%).

DISCUSSION

In this systematic review, our aim was to provide an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo-)radiotherapy. Out of the 216 articles obtained through our database search, we could select and include nine studies relevant to this topic and meeting the inclusion criteria. Four studies concerned research into gabapentin, an anticonvulsant [11–13,21]. Another anticonvulsant, pregabalin, was investigated in a study by Jiang et. al [20]. The four remaining studies investigated the effect of a doxepin rinse [22], nortriptyline [23], botulinum toxin [24] and a polymer film containing tetracaine [25] respectively.

Pregabalin, originally an anticonvulsant, is recommended by several guidelines for ~~the~~ use in several chronic neuropathic pain conditions, including diabetic neuropathy and postherpetic neuralgia. Jiang et. al. could demonstrate a significant decrease in pain intensity and severity, improved mood states and a higher quality of life in patients treated with pregabalin compared to placebo. Some patients experienced dizziness, somnolence, facial oedema and increased pain, but overall, pregabalin therapy was well tolerated. This was a high quality trial with a ~~-~~low risk of bias on all domains of the Cochrane Collaboration tool, meaning these results are highly reliable [20].

Gabapentin, similar to pregabalin, has been used to treat several neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, chronic pain, post-operative pain and trigeminal neuralgia. Bar Ad et. al. proposed in both included studies that gabapentin could be a promising treatment to avoid or reduce the need for narcotic pain medication in HNC patients receiving radiotherapy [12,13]. Furthermore, Starmer et. al. ~~could~~ demonstrated other positive results of gabapentin: ~~lower~~ less pain, shorter pain duration and less use of narcotics. PEG use was also later, the PEG tube ~~was~~ could be ~~earlier~~ removed earlier and less patients actually used their PEG tube. Swallowing function was better maintained too [21]. However, these studies had a high risk of bias on several domains of the Cochrane Collaboration tool, due to the low sample size and the design of the studies as it were two retrospective cohort studies and one historically controlled study. Kataoka et. al. performed a randomised trial comparing gabapentin to standard treatment. They could not demonstrate a beneficial effect of gabapentin [11]. Two domains of the Cochrane Collaboration tool comprised a high risk of bias and two domains comprised an unclear risk of bias. Therefore, further research is necessary to provide evidence on the effectiveness of gabapentin.

Comment [TB12]: Was this in patients who got a "prophylactic PEG"?

Doxepin hydrochloride is a tricyclic antidepressant and when administered topically, it has anaesthetic and analgesic properties. This doxepin rinse was shown to be statistically significantly superior to a placebo rinse in the treatment of oral mucositis pain caused by HNC radiotherapy. Pain reduction was significantly higher [22]. This comprised a highly qualitative trial with a low risk of bias, therefore contributing to reliable results.

Nortriptyline, also a tricyclic antidepressant, is proved to have analgesic properties. Nortriptyline was shown to provide sufficient pain control in some HNC patients, but opioids generally provided better pain relief. As expected, depression scores were lower in patients receiving nortriptyline [23]. Despite the randomised trial design of this study, an uncertain risk of bias was present for three domains of the Cochrane Collaboration tool. More trials are necessary to determine the effectiveness of nortriptyline in HNC (chemo-)radiation induced pain. It should be noted that in trials investigating pain outcome, the experimental medication is often compared to morphine, while it would be of more interest to perform a comparison between the experimental medication in combination with morphine versus placebo in combination with morphine instead.

Botulinum toxin has mainly been used for the treatment of muscle stiffness, spasticity and dystonia, but also for various types of neuropathic pain. In a study of Oguchi et. al., the injection of botulinum toxin significantly improved pain scores and masticator spasms in HNC patients with radiation induced pain. However pain recurred in 11 of 19 included patients 3.5 months after injection [24]. The study had a high risk of bias on five of the seven domains of the Cochrane Collaboration tool, suggesting more research is needed to prove its usefulness in HNC (chemo-) radiation pain.

A polymer film containing tetracaine was developed to treat acute radiation-induced oral mucositis. It comprised tetracaine, ofloxacine, miconazole, guaiazulene and triacetin. A study of Oguchi et. al. proved the usefulness of this polymer film to relieve radiation-induced mucositis pain, to maintain a good nutritional management and to prevent secondary oral infections [25]. However, this study had a high risk of bias on almost all domains of the Cochrane Collaboration tool. Moreover, ~~study~~ it dates from 1998 and results could be outdated. After more than 20 years, no more recent study was found investigating this polymer film into more detail. Therefore, the actual effectiveness of this polymer film in reducing HNC pain has not been established.

Next to the adjunctive analgesics discussed above, there are many other adjunctive analgesics that have been suggested to be beneficial for cancer pain, including antidepressants e.g. amitriptyline, venlafaxine, duloxetine imipramine, but also NMDA receptor antagonists e.g. ketamine, or others like cannabinoids [8]. However, in our literature search, no evidence was found of the effectiveness of these agents for HNC radiation induced pain.

As pain in HNC patients is often caused by radiation induced mucositis, in addition to pain caused by the tumour itself, in our search we also included mouth washes that ~~perhaps would~~may contain adjunctive analgesic agents. However, most mouthwashes are used in the prevention of oral mucositis and not as treatment of pain, which was beyond the scope of this systematic review. Therefore, no studies with e.g. magic mouthwash were included. Yet, we would like to emphasise the importance of prophylaxis and maintenance of oral hygiene with help of mouth washes such as chlorhexidine mouth washes and others [17,27,28]. Nevertheless, research into mouth washes e.g. granulocyte-colony-stimulating factor mouthwashes has also shown contrary results, so more investigations would be necessary to provide clear evidence on the role of~~f~~ these mouthwashes [29–32]. Low-level laser therapy (LLLT) is another option for the prevention and treatment of oral mucositis [33]. This treatment option lies beyond the scope of this systematic review, but is definitely worth mentioning.

As referred to before, the WHO guidelines support the use of adjunctive analgesics for HNC pain. Following the three step pain ladder, acetaminophen, NSAIDs and opioids play also a significant role [3,5,10]. An optimal management guideline for HNC pain has not been developed yet, as for this, more high quality trials are necessary [3,6].

There are some limitations to~~of~~ this systematic review. First, because of the high heterogeneity of parameters reported in the trials, we were not able to perform a meta-analysis to obtain a clear comparison between trials. The included studies used different tools to evaluate pain and other outcomes, making this impossible. Next, two of the included studies [20,24] investigated the effect of the adjunctive analgesic *after* radiotherapy, which is a different approach compared to the other studies investigating the effect *during* radiotherapy. Yet, in our opinion, these studies were of too high value to be excluded from our analysis. Last, due to the low quality of most of the included studies, it is hard to provide clear evidence of the reported outcomes.

Comment [TB13]: These are not recommended as a standard: chlorhexidine can be rather irritating for the mucosa, especially if it has been irradiated. Even after radiotherapy we do usually not recommend it due to its aggressiveness towards the mucosa.

Comment [TB14]: There are also some drawback and worries regarding its effect on the tumour itself, which may be mitochondria-mediated.

Comment [TB15]: How can there be evidence of reported outcomes? The outcomes are the evidence (or not).

At the moment, there is only evidence of the effectiveness of pregabalin and a doxepin rinse for the treatment of HNC (chemo-)radiation induced pain. We ~~can~~ therefor conclude that more research ~~would be~~is necessary to provide clear evidence o~~f~~n the effectiveness of other adjunctive analgesics. More randomised trials, using standardised pain scales, would be a great contribution to this research question.

Comment [TB16]: Why don't you mention that you will try to address this in a trial?

REFERENCES

Comment [TB17]: Check formatting of some references (use of capitals for 13 and 30, missing DOI for some (unless too old)

[1] Belgian Cancer Registry. Cancer Fact Sheet Head & Neck Cancer. 2016.

[2] Boscolo-Rizzo P, Zorzi M, Mistro A Del, Mosto MC Da, Tirelli G, Buzzoni C, et al. The evolution of the epidemiological landscape of head and neck cancer in Italy: Is there evidence for an increase in the incidence of potentially HPV-related carcinomas? PLoS One 2018;13. doi:10.1371/JOURNAL.PONE.0192621.

[3] Trotter PB, Norton LA, Loo AS, Munn JI, Voge E, Ah-See KW, et al. Pharmacological and Other Interventions for Head and Neck Cancer Pain: a Systematic Review. J Oral Maxillofac Res 2012;3. doi:10.5037/JOMR.2012.3401.

[4] Milazzo-Kiedaisch CA, Itano J, Dutta PR. Role of gabapentin in managing mucositis pain in patients undergoing radiation therapy to the head and neck. Clin J Oncol Nurs 2016;20:623–8. doi:10.1188/16.CJON.623-628.

[5] Ling IS, Larsson B. Individualized pharmacological treatment of oral mucositis pain in patients with head and neck cancer receiving radiotherapy. Support Care Cancer 2011;19:1343–50. doi:10.1007/s00520-010-0955-1.

[6] Mirabile A, Airoldi M, Ripamonti C, Bolner A, Murphy B, Russi E, et al. Pain management in head and neck cancer patients undergoing chemo-radiotherapy: Clinical practical recommendations. Crit Rev Oncol Hematol 2016;99:100–6. doi:10.1016/j.critrevonc.2015.11.010.

[7] Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol 2012;23. doi:10.1093/annonc/mds233.

[8] van den Beuken-van Everdingen MHJ, de Graeff A, Jongen JLM, Dijkstra D, Mostovaya I, Vissers KC, et al. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. Pain Pract 2017;17:409–19. doi:10.1111/papr.12459.

[9] Connolly I, Zaleon C, Montagnini M. Management of Severe Neuropathic Cancer Pain. Am J Hosp Palliat Med 2012;30:83–90. doi:10.1177/1049909112443586.

[10] Jongen JLM, Huijsman ML, Jessurun J, Ogenio K, Schipper D, Verkouteren DRC, et al. The Evidence for Pharmacologic Treatment of Neuropathic Cancer Pain: Beneficial and Adverse Effects. J Pain Symptom Manage 2013;46:581–590.e1. doi:10.1016/j.jpainsymman.2012.10.230.

[11] Kataoka T, Kiyota N, Shimada T, Funakoshi Y, Chayahara N, Toyoda M, et al. Randomized trial of standard pain control with or without gabapentin for pain related to radiation-induced mucositis in head and neck cancer. Auris Nasus Larynx 2016;43:677–84. doi:10.1016/j.anl.2016.02.012.

[12] Bar Ad V, Weinstein G, Dutta PR, Dosoretz A, Chalian A, Both S, et al. Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy. Cancer 2010;116:4206–13. doi:10.1002/cncr.25274.

[13] Ad VB, Weinstein G, Dutta PR, Chalian A, Both S, Quon H. GABAPENTIN FOR THE TREATMENT OF PAIN RELATED TO RADIATION-INDUCED MUCOSITIS IN

PATIENTS WITH HEAD AND NECK TUMORS TREATED WITH INTENSITY-MODULATED RADIATION THERAPY. Head Neck 2010;32:173–7. doi:10.1002/hed.

[14] Lussier D, Huskey AG, Portenoy RK. Adjuvant Analgesics in Cancer Pain Management. Oncologist 2004;9:571–91.

[15] Guay DR. Adjunctive agents in the management of chronic pain. Pharmacotherapy 2001;21:1070–81.

[16] Bonomi M, Batt K. Supportive management of mucositis and metabolic derangements in head and neck cancer patients. Cancers (Basel) 2015;7:1743–57. doi:10.3390/cancers7030862.

[17] Mallick S, Benson R, Rath GK. Radiation induced oral mucositis: a review of current literature on prevention and management. Eur Arch Oto-Rhino-Laryngology 2016;273:2285–93. doi:10.1007/s00405-015-3694-6.

[18] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement (Chinese edition). J Chinese Integr Med 2009;7:889–96. doi:10.3736/jcim20090918.

[19] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi:10.1136/BMJ.D5928.

[20] Jiang J, Li Y, Shen Q, Rong X, Huang X, Li H, et al. Effect of Pregabalin on Radiotherapy-Related Neuropathic Pain in Patients With Head and Neck Cancer: A Randomized Controlled Trial. J Clin Oncol 2019;37:135–43. doi:10.1200/JCO.18.00896.

[21] Starmer HM, Yang W, Raval R, Gourin CG, Richardson M, Kumar R, et al. Effect of gabapentin on swallowing during and after chemoradiation for oropharyngeal squamous cell cancer. Dysphagia 2014;29:396–402. doi:10.1007/s00455-014-9521-1.

[22] Leenstra JL, Miller RC, Qin R, Martenson JA, Dornfeld KJ, Bearden JD, et al. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: A phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32:1571–7. doi:10.1200/JCO.2013.53.2630.

[23] Ehrnrooth E, Grau C, Zachariae R, Andersen J. Randomized trial of opioids versus tricyclic antidepressants for radiation-induced mucositis pain in head and neck cancer. Acta Oncol (Madr) 2001;40:745–50. doi:10.1080/02841860152619179.

[24] Hartl DM, Cohen M, Juliéron M, Marandas P, Janot F, Bourhis J. Botulinum toxin for radiation-induced facial pain and trismus. Otolaryngol - Head Neck Surg 2008;138:459–63. doi:10.1016/j.otohns.2007.12.021.

[25] Oguchi M, Shikama N, Sasaki S, Gomi K, Katsuyama Y, Ohta S, et al. Mucosa-adhesive water-soluble polymer film for treatment of acute radiation-induced oral mucositis. Int J Radiat Oncol Biol Phys 1998;40:1033–7. doi:10.1016/S0360-

3016(97)00903-6.

[26] Starmer HM, Yang WY, Gourin CG, Kumar R, Jones B, McNutt T, et al. One-Year Swallowing Outcomes in Patients Treated with Prophylactic Gabapentin During Radiation-Based Treatment for Oropharyngeal Cancer. Dysphagia 2017;32:437–42. doi:10.1007/s00455-017-9783-5.

[27] Saunders DP, Epstein JB, Elad S, Allemano J, Bossi P, van de Wetering MD, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21:3191–207. doi:10.1007/s00520-014-2542-3.

[28] Saarilathti K, Kajanti M, Joensuu T, Kouri M, Joensuu H. Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: A double-blind prospective randomized phase III study. Int J Radiat Oncol Biol Phys 2002;54:479–85. doi:10.1016/S0360-3016(02)02935-8.

[29] LIANG G, DU W, KE Q, HUANG B, YANG J. The effects of recombinant human granulocyte colony-stimulating factor mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients. Adv Clin Exp Med 2017;26:409–13. doi:10.17219/acem/61913.

[30] Rovirosa A, Ferre J, Biete A. GRANULOCYTE MACROPHAGE–COLONY–STIMULATING FACTOR MOUTHWASHES HEAL ORAL ULCERS DURING HEAD AND NECK RADIOTHERAPY. Int J Radiat Oncol Biol Phys 1998;41:747–54.

[31] Sprinzl G, Galvan O, de Vries A, Ulmer H, Gunkel A, Lukas P, et al. Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. Eur J Cancer 2001;37:2003–9. doi:10.1016/s0959-8049(01)00170-8.

[32] Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H. Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: A prospective randomized study. Int J Radiat Oncol Biol Phys 2000;46:525–34. doi:10.1016/S0360-3016(99)00452-6.

[33] Peralta-Mamani M, da Silva BM, da Silva Pinto AC, Rubira-Bullen IRF, Honório HM, Rubira CMF, et al. Low-level laser therapy dosimetry most used for oral mucositis due to radiotherapy for head and neck cancer: A systematic review. Crit Rev Oncol Hematol 2019;138:14–23. doi:10.1016/j.critrevonc.2019.03.009.

APPENDICES

Appendix A: Study characteristics

Author	Country	Article type	Drug	Comparison	Sample size	Primary site of disease	Chemotherapy received
Jiang et. al. 2018 [20]	China	Randomised controlled trial	Pregabalin	Placebo	N = 128	nasopharynx, lip and oral cavity, larynx, oropharynx, paranasal sinus, other	50 (78,1%) in the pregabalin group; 47 (73,4%) in the placebo group
Bar Ad et. al. 2010 [13]	USA	Retrospective cohort study	Gabapentin	No comparison	N = 30	Salivary gland tumours, thyroid cancer, skin cancer, oropharyngeal squamous cell carcinoma, oral cavity squamous cell carcinoma, unknown primary squamous cell carcinoma, paragangliomas, laryngeal squamous cell carcinoma	No chemotherapy, only 2 pts cetuximab
Bar Ad et. al. 2010 [12]	USA	Retrospective cohort study	Gabapentin	No comparison	N = 42	Oropharyngeal squamous cell carcinoma, oral cavity squamous cell carcinoma; laryngeal and hypopharyngeal squamous cell carcinoma; paranasal sinuses carcinoma; sinonasal undifferentiated carcinoma; nasopharyngeal squamous cell carcinoma	all pts; 21 pts platinum-based chemo every 3 weeks (cisplatin + etoposide, cisplatin + cetuximab); 18 pts weekly systemic therapy (carboplatin + paclitaxel); 3 pts unknown chemo
Kataoka et. al. 2016 [11]	Japan	Randomised trial	Gabapentin + Standard pain control	Standard pain control (acetominophen + opioids)	N = 22	Oral cavity, nasopharynx, oropharynx, hypopharynx, oropharynx and hypopharynx, larynx	all pts: cisplatin
Starmer et. al. 2014 [26]	USA	Historically controlled study	Gabapentin	Standard treatment (including narcotic pain medication)	N = 46	~~tongue~~ base of tongue, tonsil, soft palate	all pts
Leenstra et. al. 2014 [22]	USA	Randomised double blind trial	Doxepin rinse	Placebo rinse	N = 155	Oropharyngeal, oral cavity, laryngeal, nasopharyngeal, salivary, hypopharyngeal, not specified	110 from 140 pts received chemotherapy
Ehrnrooth et. al. 2001 [23]	Denmark	Randomised trial	Nortriptyline	Oral morphine	N = 43	Larynx, pharynx, oral cavity	not reported
Hartl et al. 2007 [24]	France	Prospective cohort study	Botulinum toxin	No comparison	N = 19	nasopharynx, oropharynx, oral cavity, oral cavity and oropharynx, larynx, parotid gland	11 pts chemotherapy
Oguchi et al. 1998 [25]	Japan	Historically controlled study	Film containing tetracaine	Topical anaesthetics	N = 52	squamous cell carcinoma or oral cavity	7 pts in AD film group and 5 in comparison group (peplomycine 5 mg iv twice a week for 1-3 weeks or UFT 200 mg/day for 2-3 weeks

Appendix B: Study therapy characteristics

Author	Drug	Dose	Indication	Comparison	Number of patients
Jiang et. al. 2018 [20]	Pregabalin	max 600 mg daily (p.o.)	neuropathic pain	Placebo	N = 128 64 in pregabalin group, 64 in placebo group
Bar Ad et. al. 2010 [13]	Gabapentin	median dose of 2700 mg/day (p.o.)	pain control, mucositis	No comparison	N = 30 29 included in analyses
Bar Ad et al. 2010 [12]	Gabapentin	median dose of 2700 mg/day (p.o.)	mucositis, dysphagia, pain	No comparison	N = 42
Kataoka et. al. 2016 [11]	Gabapentin	start at 300 mg from the initiation of RT, escalated every 3 days by 300mg/day up to 900 mg/day (maintained till 4 weeks after RT) (p.o.)	pain related to radiation induced mucositis	Standard pain control (SPC) (acetominophen + opioids)	N = 22 20 included in analyses 11 in SPC group, 9 in gabapentin group
Starmer et. al. 2014 [21]	Gabapentin	2700 mg/day (p.o.)	pain	Standard treatment (including narcotic pain medication)	N = 46
Leenstra et. al. 2014 [22]	Doxepin rinse	10mg/mL+2,5mL, diluted to 5mL with 2,5mL of sterile or distilled water (oral rinse)	oral mucositis pain	placebo rinse (prepared in similar manner: Ora-Sweet SF = alcohol-free flavoured sugerfree syrup vehicle = placebo base solution	N = 155 140 included in primary endpoint analyses, 129 included in crossover analyses
Ehrnrooth et. al. 2001 [23]	Nortriptyline	start with 25 mg x 2, increased by 25 mg every second day, until pain relief or intolerable side effects or until max of 150 mg/day (pts older than 60y received 50% of all doses) (p.o.)	painful mucositis	oral morphine (morphine chloride: start with 5mg x6, and additional doses per 5 mg; titration to acquire pain relief without intolerable side effects; steady state pts converted to morphine sulphate	N = 43 39 included in analyses 19 in nortriptyline group, 20 in morphine group
Hartl et. al. 2007 [24]	Botulinum toxin	50 units of Botox, 250 units of Dysport per muscle (transcutaneous injection)	radiation induced pain, trismus and masticator spasm	No comparison	N = 19
Oguchi et. al. 1998 [25]	Film containing tetracaine	(p.o.)	oral mucositis pain	topical anaesthetics (viscous lidocaine, Xylocaine) and/or general systemic analgesics	N = 52 25 in AD film group, 27 in comparison group

Appendix C: Reported pain outcome

Author	Drug	Comparison	Number of patients	Method of pain assessment	Results
Jiang et. al. 2018	Pregabalin	Placebo	N = 128 64 in pregabalin group, 64 in placebo group	NRS BPI-SF	At week 16, pain intensity was decreased by 2.44 (SD, 1.52) in the pregabalin group vs. 1.58 (SD, 1.25) in the placebo group (p=0.003). 19/64 pts in the pregablin group vs 5/64 in the placebo group achieved pain relief of 50% or more at week 16 (p=0.003). Pain intensity decreased gradually from week 1, more in the pregabalin group vs placebo group (p<0.001). Significantly decreased pain severity in pregabalin group compared to placebo (p=0.047) at week 16.
Bar Ad et. al. 2010	Gabapentin	No comparison	N = 30 29 included in analyses	Gabapentin use Narcotics use	At week 3, 4, 5 and 6, 28 pts used gabapentin median dose 2700 mg/day. At week 3 and 4, 3 pts required additional low doses of narcotics (15-30mg/day Roxicodone). At week 5 and 6, 10 pts required additional low doses of narcotics (15-40 mg/day Roxicodone).
Bar Ad et. al. 2010	Gabapentin	No comparison	N = 42	Gabapentin use Opioid use	At the 2nd, 3rd, 4th and last week of RT, 38 pts used gabapentin. At the 2nd week of RT, 5 pts required additional median dose of 10 mg/day oxycodone-equivalent. At the 3rd week of RT, 14 pts required 10 mg/day oxycodone-equivalent, at the 4th week of RT, 23 pts required 30mg/day oxycodone-equivalent and at the last week of RT, 30 pts required 60 mg/day oxycodone-equivalent.
Kataoka et. al. 2016	Gabapentin	Standard pain control (acetominophen + opioids)	N = 22 20 included in analyses 11 in SPC group, 9 in gabapentin group	VAS Acetaminophen or opioid use	Maximum VAS score in the gabapentin group was 74 vs 47 in standard of care group (p=0.552). From baseline to week 4, no difference in VAS score was detected between groups at each time point. 13 days till starting acetaminophen in the gabapentin group vs 15 days in the standard of care group (p=0.7898). 22.5 days till starting opioids in the gabapentin group vs 21.5 days in the standard of care group (p=0.9646).
Starmer et. al. 2014	Gabapentin	Standard treatment (including narcotic pain medication)	N = 46	Patient-reported pain Additional pain medication	Significantly lower maximal pain scores between gabapentin and control group (p=0.0003). Pain duration was shorter in the gabapentin group vs control group (p=0.038). In the gabapentin group, 13% required no additional pain medication. In the control group, all pts required narcotics, 70% required multiple narcotic analgesics.
Leenstra et. al. 2014	Doxepin rinse	placebo rinse (prepared in similar manner: Ora-Sweet SF = alcohol-free flavoured sugaer-free syrup vehicle = placebo base solution	N = 155 140 included in primary endpoint analyses, 129 included in crossover analyses	11-point numerical analog pain scale Additional analgesics	AUC for mean mouth and throat pain reduction was greater in the doxepin group (-9.1) compared to the placebo group (-4.7) (p<0.001). Treatment difference after cross-over analyses was -3.5 (p<0.001). Average mouth and throat pain score reduction of -2.0 in the doxepin group compared to -1.0 in the placebo group after 30 minutes (p=0.0032). Significant pain reduction after 1, 2, 3 and four hours since study initiation. No significant difference in use of additional analgesic agents after 2-hours and 4-hours (8.8% vs 2.9% and 16.9% vs 14.5% respectively).
Ehrnrooth et. al. 2001	Nortriptyline	oral morphine (morphine chloride: start with 5mg x6, and additional doses per 5 mg; titration to acquire pain relief without intolerable side effects; steady state pts converted to morphine	N = 43 39 included in analyses 19 in nortriptyline group, 20 in morphine group	VAS Pain Likert scale McGill Pain	Significant lower VAS scores in opioid group compared to nortriptyline one and two weeks after randomisation (p=0.007 and p=0.04 respectively). No significant changes in pain between groups from baseline to one and two weeks post-randomisation. Trend to higher pain scores in nortriptyline group versus opioid group at baseline and one week post-randomisation (not significant). No significant difference between groups in sensory, affective or miscellaneous pain at the four time points.

		sulphate		Questionnaire (Danish version) Additional morphine Concomitant analgesics	11 pts in the nortriptyline group needed additional morphine versus zero in the opioid group, on average 13.4 days (+-8.4) since the start of nortriptyline. None of the pts needed concomitant analgesics.
Hartl et. al. 2007	Botulinum toxin	No comparison	N = 19	Reported pain	Pain reported on average 5.6 years after radiotherapy. Significant pain improvement after one month (p=0.002). Painful muscle spasms recurred in 11 pts 3.5 months after injection.
Oguchi et. al. 1998	Film containing tetracaine	topical anaesthetics (viscous lidocaine, Xylocaine) and/or general systemic analgesics	N = 52 25 in AD film group, 27 in comparison group	Patient-reported pain Systemic analgesics	Significantly higher complete pain relief at rest and while eating in the AD film group versus topical anaesthetics group (82% vs 44% and 68% vs 22% respectively) No significant difference between AD film group vs topical anaesthetics group in duration of complete pain relief (30' vs 30'-2h). Partial and complete pain relief was comparable in both groups. In the AD film group, median duration of grade 3-4 oral pain was 10 days versus 15 days in the topical anaesthetics group. Only 4 pts in the AD film group needed systemic analgesics due to grade 3-4 oral pain versus 21 pts in the topical anaesthetics group.

Appendix D: Reported adverse events and toxicity

Author	Drug	Comparison	Number of patients	Adverse event or toxicity	Frequency	Description
Jiang et. al. 2018	Pregabalin	Placebo	N = 128 64 in pregabalin group, 64 in placebo group	SAE or AE	35 pts (54.7%) in the pregabalin group and 29 pts (45.3%) in the placebo group experienced at least one AE (p=0.29).	• Dizziness: 12 in pregabalin group, 4 in placebo group • Somnolence: 13 in pregabalin group, 3 in placebo group • Facial oedema: one patient in pregabalin group discontinued the trial • Increased pain: two pts in the placebo group discontinued the trial
Bar Ad et. al. 2010	Gabapentin	No comparison	N = 30 29 included in analyses	Toxicity	4 pts (13%) experienced mild side effects	• Dizziness • Nausea • Vomiting • Follicular skin rash: one patient
Bar Ad et. al. 2010	Gabapentin	No comparison	N = 42	Gabapentin related toxicity	2 pts (5%) experienced mild side effects	• Dizziness
Kataoka et. al. 2016	Gabapentin	Standard pain control (acetominophen +	N = 22 20 included in	Adverse events specific to	3 pts with gabapentin related toxicities	• Somnolence: two pts in gabapentin group • Allergic skin reaction: one patient in gabapentin

		opioids)	analyses 11 in SPC group, 9 in gabapentin group	gabapentin		group
Starmer et. al. 2014	Gabapentin	Standard treatment (including narcotic pain medication)	N = 46	NR	3 pts with gabapentin related toxicities	• Vertigo and headaches: one patient • Fatigue: two pts
Leenstra et. al. 2014	Doxepin rinse	placebo rinse (prepared in similar manner: Ora-Sweet SF = alcohol-free flavoured sugar-erfree syrup vehicle = placebo base solution	N = 155 140 included in primary endpoint analyses, 129 included in crossover analyses	Oral rinse side effects	NR	• Stinging and burning (numeric scale): mean of 9.6 vs 4.0 (p<0.001), maximal at 5 minutes • Taste (numeric scale): mean AUC of 7.7 vs 5.1 (p<0.018) • Drowsiness: AUC of -.2.4 in placebo vs -0.7 in doxepin rinse (p=0.0297)
Ehrnrooth et. al. 2001	Nortriptyline	oral morphine (morphine chloride: start with 5mg x6, and additional doses of 5 mg each; titration to acquire pain relief without intolerable side effects; steady state pts converted to morphine sulphate	N = 43 39 included in analyses 19 in nortriptyline group, 20 in morphine group	Side effects	14 pts experienced minor side effects in both groups	• Nausea: 11 pts in nortriptyline group vs 8 in opioid group • Vomiting: 4 pts in nortriptyline group vs 1 patient in opioid group • Constipation: 5 pts in nortriptyline group vs 8 pts in opioid group • Cardial arrhythmia: 1 patient in nortripyline group vs none in opioid group • Neurocortical: 4 pts in nortriptyline group vs 3 pts in opioid group
Hartl et. al. 2007	Botulinum toxin	No comparison	N = 19	Toxicity	7 pts	• Painful injections
Oguchi et. al. 1998	Film containing tetracaine	topical anaesthetics (viscous lidocaine, Xylocaine) and/or general systemic analgesics	N = 52 25 in AD film group, 27 in comparison group	Toxicity and adverse events	No toxicity	• No acute or chronic adverse effects on the oral mucosa or gastrointestinal tracts • No allergic dermal reactions • No cases of haematological toxicity • No cases of aspiration pneumonia or bronchitis

Appendix E: Other reported outcomes

Author	Drug	Comparison	Number of patients	Outcome	Results
Jiang et. al. 2018	Pregabalin	Placebo	N = 128 64 in pregabalin group, 64 in placebo group	Psychological distress Quality of Life	Significant improvements in all subscales of POMS-SF, but not in Vigor-Activity and Confusion-Bewilderment subscales in pregabalin vs placebo. Significant improvements in physiology and psychology domains of WHOQOL-BREF scores in pregabalin vs placebo (p=0.004 and p=0.01 resp.). PGIC scale showed 30 pts (47.6%) with treatment success in pregabalin group vs 8 pts (12.9%) in placebo

				Improvement and satisfaction with treatment Rescue medication Patient compliance	group (p<0.001). CGIC scale showed 36 pts (57.1%) with treatment success in pregabalin group vs 10 pts (16.1%) in placebo group (p<0.001). 12.5% of pts took rescue medication in the pregabalin group vs 40.6% in the placebo group (p<0.001). Compliance was comparable in both groups: 80.5% of pts took 80% or more of their prescribed medication.
Bar Ad et. al. 2010	Gabapentin	No comparison	N = 30 29 included in analyses	Radiation induced mucositis Radiation induced dysphagia	All pts developed mucositis. During the first 2 weeks of treatment, grade 1 and 2 mucositis occurred in 80% of the pts. By week 2, 3 and 4, grade 2 mucositis occurred in 13%, 53% and 73% of the pts respectively. By week 5 and 6, grade 2 or 3 occurred in 80% of the pts. Grade 3 mucositis occurred in 6% of the pts. No grade 4 mucositis was reported. During week one of treatment, one patient (3%) reported dysphagia. By week 4 and 6, 53% of the pts and 60% reported grade 1 dysphagia respectively. Grade 2 dysphagia was reported by one patient (3%) during this trial, starting at week 3. Grade 3 dysphagia was reported by two pts (6%) during week 3 and by one patient (3%) by week 6. 33% of pts did not report any swallowing difficulty. No grade 4 dysphagia was reported.
Bart Ad et. al. 2010	Gabapentin	No comparison	N = 42	Radiation induced mucositis Radiation induced dysphagia	All pts developed mucositis. Grade 1 and 2 mucositis occurred in 88% of the pts during the first 2 weeks of treatment. Grade 2 mucositis occurred in 44% of the pts during week 2. Grade 3 mucositis was not reported by week 2, but occurred in 17%, 45%, 60% and 81% of the pts by week 3, 4, 5 and 6 respectively. Grade 2 mucositis or higher occurred in 71%, 86%, 95% and 100% of the pts by week 3, 5, 5 and 6. No grade 4 mucositis was reported. During week one of treatment, 2 pts (5%) reported grade 1 dysphagia. By week 2 and 3, grade 1 or 2 dysphagia was reported by 38% and 52% of the pts respectively. By week 4, 76% of the pts reported dysphagia with 36% grade 2 or 3. By week 5 and 6, 95% of the pts reported dysphagia with 48% grade 2 or 3. No grade 4 dysphagia was reported.
Kataoka et. al. 2016	Gabapentin	Standard pain control (acetominophen + opioids)	N = 22 20 included in analyses 11 in SPC group, 9 in gabapentin group	Quality of life Oral mucositis	No significant decrease was observed in most QOL domains over 4 weeks radiotherapy between both groups. Weight gain was significantly higher in in the gabapentin group vs SPC group (p=0.0062). All pts experienced oral mucositis: grade 3 or 4 mucositis occurred in 45.5% of the pts in SPC group vs 63.6% in gabapentin group.
Starmer et. al. 2014	Gabapentin	Standard treatment (including narcotic pain medication)	N = 46	PEG use Physiological outcomes	Later PEG use in gabapentin group vs control group (3.7 vs 2.29 weeks; p=0.013), earlier PEG removal in gabapentin vs control group (7.29 vs 32.56 weeks; 0.039). 21.7% of pts in the gabapentin group never used their PEG tube vs 4.3% in the control group (p=0.038). Pts in the gabapentin group lost on average 7.45% weight vs 11% weight loss in the control group (p=0.037). Velopharyngeal closure, tongue base retraction, laryngeal elevation, epiglottic tilt, and pharyngeal constriction was less effected in the gabapentin group.

					Significant lower PAS scores were found (1.89 vs 4; p=0.0052) in the gabapentin group, indicating better airway protection. Significant higher FOIS scores were found (5.4 vs 3.21; p=0.0003) in the gabapentin group, indicating more advanced diet levels.
Leenstra et. al. 2014	Doxepin rinse	placebo rinse (prepared in similar manner: Ora-Sweet SF = alcohol-free flavored sugar-~~er~~free syrup vehicle = placebo base solution	N = 155 140 included in primary endpoint analyses, 129 included in crossover analyses	NA	NA
Ehrnrooth et. al. 2001	Nortriptyline	oral morphine (morphine chloride: start with 5mg x6, and additional doses of 5 mg each; titration to acquire pain relief without int~~r~~olerable side effects; steady state pts converted to morphine sulphate	N = 43 39 included in analyses 19 in nortriptyline group, 20 in morphine group	Depression	Significant reduction in BDI scores in nortriptyline group vs oral morphine group (p=0.02).
Hartl et. al. 2007	Botulinum toxin	No comparison	N = 19	Functionality and cramps	Significant improvement in overall functional score (p=0.004) and muscular cramps (p=0.004). No significant improvement in jaw opening.
Oguchi et. al. 1998	Film containing tetracaine	topical anesthetics (viscous lidocaine, Xylocaine) and/or general systemic analgesics	N = 52 25 in AD film group, 27 in comparison group	Radiation induced oral mucositis Nutritional management and weight loss Secondary infections Tumour control and survival	Mucositis was observed in 88% of the pts in the AD film group vs 92% in the comparison group. 17 pts in the AD film group did not require IV infusions or hyperalimentation vs 9 in the comparison group. Less weight loss and better weight recovery were observed in the AD film group vs the comparison group (not significant). No secondary bacterial or fungal infection of the oral cavity and/or oropharynx was observed in the AD film group vs 4 cases of oral infection and 2 cases of aspiration pneumonia in the comparison group. No significant difference in 3-year local control rate was found between both groups (96% vs 92%) and no difference in 3-year disease free survival rate (87% vs 85%).

Appendix F: Quality assessment

Jiang et. al. 2017		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	LOW RISK	Quote: "This trial was a randomized, double blind, placebo-controlled multicenter trial..."
		Comment: Probably done
Allocation concealment	LOW RISK	Quote: "The 1:1 random allocation, stratified by age (≤ 60 years or > 60 years) and participating center, was centralized using a computer-generated pseudorandom code with block size of four or six."
		Comment: Probably done
Performance bias		
Blinding of participants and personnel	LOW RISK	Quote: "Non-transparent envelopes with the allotted sequences inside were prepared and kept sealed to avoid revealing the sequences during the trial." "To ensure the double-blind principle, randomization was performed by an independent investigator who did not participate in enrolment. Assessors and patients were blinded to group allocation."
		Comment: Probably done
Detection bias		
Blinding of outcome assessment	LOW RISK	Quote: "To ensure the double-blind principle, randomization was performed by an independent investigator who did not participate in enrolment"
		Comment: Probably done
Attrition bias		
Incomplete outcome data	LOW RISK	4/68 patients in the pregabalin group did not receive pregabalin due to pregnancy (n=1) or missed baseline data (n=3). 5/69 patients in the placebo group did not receive placebo because of migration to another city (n=2) or because of refusal to participate (n=3). 7/64 in the pregabalin group discontinued treatment because of adverse events, protocol violation, withdrawal of consent, lost to follow up or unable to contact. 8/64 in the placebo group discontinued treatment because of adverse events, protocol violation, withdrawal of consent, lost to follow-up or unable to contact.

Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other souces of bias	LOW RISK	No other sources of bias detected

Bar Ad et. al. 2010		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	HIGH RISK	Non-randomised trial
Allocation concealment	HIGH RISK	Non-randomised trial
Performance bias		
Blinding of participants and personnel	HIGH RISK	All patients received gabapentin, there was no blinding
Detection bias		
Blinding of outcome assessment	HIGH RISK	Retrospective trial, all patients received gabapentin, there was no control group
Attrition bias		
Incomplete outcome data	LOW RISK	No incomplete outcome data, 30 cases were included and analysed in this retrospective trial
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		

Other sources of bias	HIGH RISK	No power calculation and low sample size

Bar Ad et. al. 2010		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	HIGH RISK	Non-randomised trial
Allocation concealment	HIGH RISK	Non-randomised trial
Performance bias		
Blinding of participants and personnel	HIGH RISK	All patients received gabapentin, there was no blinding
Detection bias		
Blinding of outcome assessment	HIGH RISK	Retrospective trial, all patients received gabapentin, there was no control group
Attrition bias		
Incomplete outcome data	LOW RISK	No incomplete outcome data, 42 cases were included and analysed in this retrospective trial
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other sources of bias	HIGH RISK	No power calculation and low sample size

Kataoka et al		
Domain	**Judgement**	**Support for judgement**
Selection bias		

Random sequence generation	LOW RISK	Quote: "Patients were randomly assigned…"
		Comment: Probably done
Allocation concealment	LOW RISK	Quote: "… at a 1:1 ratio. Computer-assisted randomization without stratification was used."
		Comment: Probably done
Performance bias		
Blinding of participants and personnel	UNCLEAR	No information concerning blinding can be found
Detection bias		
Blinding of outcome assessment	UNCLEAR	No information on blinding of outcome assessors was reported
Attrition bias		
Incomplete outcome data	UNCLEAR	2 from the 11 patients in the intervention group were excluded, one due to termination because of total laryngectomy and 1 because of insufficient VAS and QOL questionnaire
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other souces of bias	LOW RISK	No other sources of bias detected

Starmer et al 2014		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	HIGH RISK	Non-randomised trial
Allocation concealment	HIGH RISK	Non-randomised trial

Performance bias		
Blinding of participants and personnel	HIGH RISK	Non randomised trial, partially retrospective study
Detection bias		
Blinding of outcome assessment	HIGH RISK	Non randomised trial, partially retrospective study
Attrition bias		
Incomplete outcome data	LOW RISK	No incomplete outcome data, all patients were included and analysed in this trial
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other souces of bias	LOW RISK	No other sources of bias detected

Leenstra et. al. 2014		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	LOW RISK	Quote: "Randomization was performed…"
		Comment: Probably done
Allocation concealment	LOW RISK	Quote: "Patients were assigned to eighter doxepin-placebo (arm 1) or placebo-doxepin (arm 2) in a 1:1 ratio using the Pocock and Simon dynamic allocation procedure, which balances the marginal distributions of the stratification factors."
		Comment: Probably done
Performance bias		
Blinding of participants and personnel	LOW RISK	Quote: "… and then blinded study personnel administered the rinse…"

		Comment: Probably done
Detection bias		
Blinding of outcome assessment	LOW RISK	Quote: "After completion of the questionnaires from the blinded second dose, patients were unblinded…"
		Comment: Probably done
Attrition bias		
Incomplete outcome data	LOW RISK	14 patients withdrew before start of study; 1 patient was ineligible; 6 pts refused further treatment after primary endpoint analyses, 1 patient stopped because of adverse events and 4 pts stopped because of other reasons. However, missing outcome data is balanced in numbers across intervention groups
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section were reported as outcome
Other bias		
Other sources of bias	LOW RISK	No other sources of bias detected

Ehrnrooth et. al. 2009		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	LOW RISK	Quote: "… in a randomized design.."
		Comment: Probably done
Allocation concealment	UNCLEAR	No information on allocation concealment was reported
Performance bias		
Blinding of participants and personnel	UNCLEAR	No information concerning blinding was reported

Detection bias		
Blinding of outcome assessment	UNCLEAR	No information on blinding of outcome assessors was reported
Attrition bias		
Incomplete outcome data	LOW RISK	2/20 patients in opioid group and 2/21 in TCA group non evaluable. One patient from the TCA group refused further participation because of dryness of the mouth, one patient in TCA group and 2 patients in opioid group did not complete the questionnaires
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other sources of bias	LOW RISK	No other sources of bias detected

Hartl et. al. 2007		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	HIGH RISK	Non-randomised trial
Allocation concealment	HIGH RISK	Non-randomised trial
Performance bias		
Blinding of participants and personnel	HIGH RISK	No comparison group
Detection bias		
Blinding of outcome assessment	HIGH RISK	No comparison group
Attrition bias		

Incomplete outcome data	LOW RISK	No incomplete outcome data; all 19 included patients were analysed in this study
Reporting bias		
Selective reporting	LOW RISK	All aspects described in the method section are reported as outcome
Other bias		
Other sources of bias	HIGH RISK	No power calculation and low sample size

Oguchi et. al. 1998		
Domain	**Judgement**	**Support for judgement**
Selection bias		
Random sequence generation	HIGH RISK	Non randomised trial
Allocation concealment	HIGH RISK	Non randomised trial
Performance bias		
Blinding of participants and personnel	HIGH RISK	Non randomised trial, partially retrospective study
Detection bias		
Blinding of outcome assessment	HIGH RISK	Non randomised trial, partially retrospective study
Attrition bias		
Incomplete outcome data	LOW RISK	No incomplete outcome data, all patients were included and analysed in this trial
Reporting bias		
Selective reporting	HIGH RISK	Not defined in advance what outcome would be reported
Other bias		
Other sources of bias	HIGH RISK	No power calculation and low sample size