

Management of Dysgeusia related to Cancer: A Systematic Review

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ABSTRACT:

Introduction: Taste change due to cancer is a notorious side effect, adversely affecting appetite and weight. Even though taste change or dysgeusia is one of the major causes of poor nutritional status in cancer survivors, it is not addressed as a significant problem and is often left untreated. The main purpose of this review is to explore current knowledge of pharmacological and behavioral interventions for the treatment of cancer related taste change. **Methods:** This systematic review was conducted in accordance with PRISMA guidelines to identify original articles on taste change. Multiple databases including; Scopus, Medline, EMBASE, CINAHL, and all databases via Pro quest were searched for original articles or studies related to taste change caused by cancer or its treatment. Relevant articles were subjected to a full text evaluation and assessed by Critical appraisal skills program (CASP) guidelines and the Effective public health practice project (EPHPP) instrument. **Results:** The search revealed 12 eligible studies, six of which were randomized controlled trials. Most of the studies used a standardized validated tool to measure taste change. Dysgeusia is common in cancer, 14 to 100% cancer patient report it. Pharmacological management with zinc remains inconclusive as one study reports it as beneficial and two other studies reported null effect. Few studies suggested dietary modifications such as use of sugary, salty foods that are helpful to reduce the effect of dysgeusia. **Conclusion:** Dietary counseling and informing the patient well about self-care strategies before treatment has consistently shown positive results on taste change, with strong statistical power. Other potential treatments for dysgeusia such as zinc, amifostine, and megestrol acetate gave inconsistent results.

Keywords: cancer • dysgeusia • taste disorders • treatment • zinc

INTRODUCTION:

Change in taste perception in people with cancer is a common problem and could be due to malignancy or to the treatment regimes.[1-3] It has been estimated that between one quarter and one half of all cancer patients experience changes in their taste and smell perception.[4-6] Gustatory changes, particularly dysgeusia (abnormal or impaired sense of taste), is also caused by the physiological changes of cancer but often it is effect of cancer treatment.

[7,8] Even though it is not life limiting, impaired taste is associated with poor nutritional intake, weight loss and consequently decreased quality of life.[8] Taste disorders are the major cause of malnutrition in the cancer patient, but it has been understudied and poorly addressed by health care professionals in the oncology setting.[1,9,10] Taste is an important sensation that serves to evaluate the nutritious content of food, supports oral intake and prevents ingestion of potentially toxic substances. [2] Research suggests that patients with taste loss had a worse outcome than those that did not lose their sense of taste and were able to maintain their food intake and nutritional support.[4,7,11,12,13]

Due to the high prevalence in advanced cancer patients, it may be stipulated that this chemosensory disturbance limits the efficacy of therapeutic food supplements or dietary intervention.[11] The main reason not to consider dysgeusia just as an expected side effect is because it causes poor compliance to chemotherapy and consequently weaker outcomes

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or failure of any treatment.[4,14,15]

There are few treatments available that are scientifically proven to prevent Dysgeusia.[16] The 1989 NIH (National Institute of Health) Development consensus conference on the oral complications of cancer therapies and the publication of the National Cancer Institute monograph in 1990 has provided some clinical recommendations based on the evidence and expert opinion.[15] There is some counseling for patient experiencing taste change but this is not consistent for every subject.[17] On the other hand some of vitamins and minerals have been tried to decrease the onset of dysgeusia but they need to be verified with a larger study. Attempts to prevent dysgeusia through the prophylactic use of zinc sulfate and amifostine have been of limited benefit. [18-20] Some studies on clonazepam, megestrol acetate (MA), and miracle fruit has been tried but the studies are not strong enough to generalize the outcome. Some drugs have been effective to treat the dysgeusia in idiopathic dysgeusia, but there is a lack of data for cancer patients. The dose of treatments such as radiotherapy or chemotherapy has an apparent role in occurrence of dysgeusia. The dose of these treatments has to be well evaluated and kept to a minimal effective dose to avoid the side effects. [1,10,18]

Sporadic research has been carried out to investigate the prevention and treatment of the taste changes related to cancer and its treatment. The aim of this review is to investigate pharmacological and behavioral management strategies for the prevention and management of taste alteration caused by cancer and its treatment in adult cancer survivors. In particular, it will focus on common cancers and treatments affecting taste, and estimate the occurrence of taste change in cancer. Furthermore, this research will indicate pharmacological interventions to reduce taste change and behavioral modification helpful to reduce the effect of taste change, and unveil understudied research question.

METHODS:

A thorough systematic search of the literature was conducted in multiple databases; Scopus, Medline via Ovid, and Pubmed, web of science, Cochrane library, Google scholar. Further, an in depth search was done via EMBASE, CINAHL and all databases via Pro quest. Search terms included: (cancer OR neoplasm OR hyperplasia OR chemotherapy OR radiotherapy) AND (taste OR taste alteration OR taste change OR taste disorder OR gustatory disorder OR dysgeusia OR ageusia) AND (treatment OR coping strategies). The search was restricted to title, key words, and abstract and limited to human studies of adults, published

between the years 2000 to 2015. The studies were sorted by relevance, cross matched with inclusion and exclusion criteria, and excluded if needed after abstract review. The relevant papers were studied, tested, and critically analyzed for their contribution towards the objective of current research. The studies were evaluated against Critical appraisal skills program (CASP) guidelines. In addition, the Effective public health practice project (EPHPP) instrument has been applied for a crude rating of evidence.[21,22] Research papers were judged for many criteria, including sample size, possibility of bias, appropriateness of methodology. For the purpose of including a broader area of relevant literature, a manual search of viable papers' reference list was carried out. To augment the knowledge of the researcher in the given topic, Google search, previous reviews, conference paper, related websites, and text books were studied.

Inclusion and exclusion criteria:

The primary search revealed that there are ample studies which assessed cancer and its treatment related to taste change, but there are limited studies which actually investigated its prevention and management. On that ground, broad inclusion criteria were applied and all original research papers that examined treatment for taste change in cancer as primary outcome were incorporated. In addition, articles concerning the efficacy of certain drugs in taste change irrespective of cause were studied to weigh the worth of that drug. Intervention studies which were done in cancer and its treatment related to taste change only were included in review. Studies in adults and only in the English language, or translated in English were considered for the review. Also, studies which did not investigate the treatment for taste change, reviews, meta analysis, and letters editorials, reviews based on expert opinion and personal opinion paper, narrative review were excluded. Studies with different types of cancer, and different treatments including radiotherapy, chemotherapy were included in the review. Qualitative studies and scarcely studied treatment were also included, for example, vitamin-D, miracle fruit, and change of chemotherapy. Due to the scarcity of literature in this field, small scale studies with potential expansion and studies considered weak but may have significant impact on treatment of taste change and were included in the review. Therefore, case studies were also included in current review; in clinical management their contribution is important and cannot be denied, they might provide a basis for further studies.

Data extraction based on previous reviews and capable to cover the research question were

developed and used to record the details of each study. They are refined to match the availability of information and objective of the review. Different studies had varied research design and different way to measure their outcome so it was not possible to carry out the meta-analysis.

RESULTS:

The search found 156 papers in the relevant subject from different databases. Duplicates ($n=57$) were deducted, seven of which were the same paper which the author had published in different journals with a slightly different running title.[23,24] Many of the studies focused on the relationship of taste change and cancer related treatments but did not suggest any treatment therefore these ($n=20$) were also excluded. Moreover, studies suggesting treatment and care strategies based on the expert opinion or previous case report or studies but not tested or not the primary part of their research were not included in review. Thus, the articles were screened only to be on the treatment for the taste change not limited to suggestion, reporting previous finding, or showing the relationship between taste change and cancer. After the initial screening, 20 papers were selected for the review which narrowed down to 12 after excluding the papers before 2000 and not testing the actual treatment (Fig: 1).[5,25]

The study characteristics of reviewed papers are given in the Table 1. Since there was no any restriction in study design, it ranged from double blind placebo controlled trial to case study report. Out of the 12 reviewed papers half of them were randomized control trials,[3,20,26-29] with four of them double blinded, placebo control.[3,20,26,27] Two studies were cross sectional studies,[30,31] and there were three prospective longitudinal studies,[32-34] one was a case study,[34] and another one quasi experimental study.[35] Sample size ranged from two to 531, with commonest diagnosis of head and neck cancer followed by breast cancer, lung cancer, gastrointestinal (GI) cancer, and a wide range of other cancer diagnosis. Seven out of 12 studies used previously studied, validated standardized tool to find out the taste change and improvement; four of them used objective, close ended questions to find out the improvement with a given treatment or strategy. Most of the studies included patients with chemotherapy,[20,26,30-35] some of the studies were confined to radiotherapy,[3,24,28] and a few studied the patients receiving a combination of treatment.[29] Amongst these, the most common chemotherapeutic agent was carboplatin and oxyplatin but, most of them used various chemotherapeutic agents.

Importantly, the treatment modality and diagnoses were not uniform in all studies. Some of the

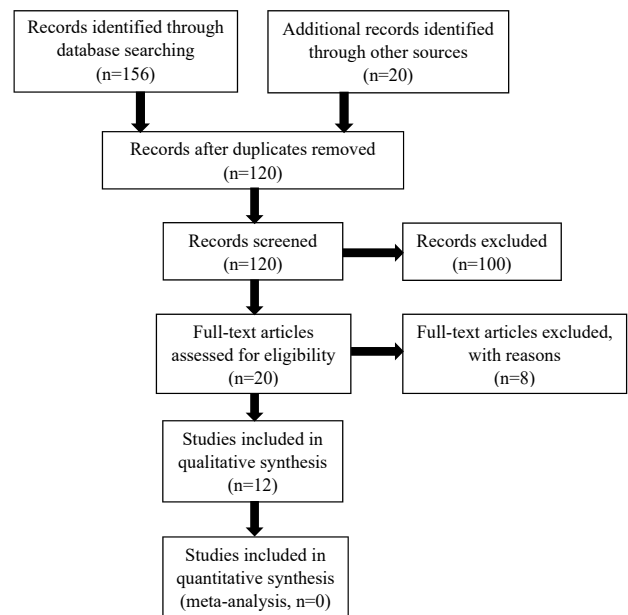


Fig 1: Flow diagram of selected studies for systematic review

studies enrolled just head and neck cancer whereas some excluded them. Moreover, some of the studies included the patient getting chemotherapy and other studied patient getting radiotherapy and some of them both methods. Not all of the studies measured the taste change before the treatment and continued to measure it for a longer period. The studies which measured taste used subjective and objective method and the outcome measure also differ; therefore it was impossible to unify the result in a single platform.

The studies which randomized double blinded and placebo control trial are scored high in CASP checklist and many strong results in EPHPP was considered more powerful than the observational studies. However, six out of 12 of the reviewed papers are randomized double blinded control trial. The findings of this review resembles previous work done in this discipline as all of them concluded that the use of zinc and other drugs are controversial and show different result in different studies.[2,18,36,37] But this review has covered a wider range of treatment and trials in given subject.

Prevalence of Dysgeusia:

Prevalence of dysgeusia or taste change was reported by all of the studies; however they differ in widely with respect to the percentage of prevalence. All the Sample of the reviewed papers reported change in taste perception to some extent ranging from 14 to 100%. The degree of taste change depended upon the type of cancer and its treatment.[11,35,38-40] The prevalence among the patient receiving a combination of both radiotherapy and chemotherapy was 76%, radiotherapy only

was 66.5%, radiotherapy of head and neck cancer was 55 to 88%, after completion of radiotherapy continue dysgeusia was 15% and chemotherapy only was 56.3%. [10,18,41-44] Most of the studies were done in head and neck cancer and breast cancer but it is not possible from this review to conclude which cancer or treatment

regimen has more effect on taste. Some of the papers suggests that the dose of radiotherapy and choice of drug for chemotherapy might have negative effect on taste change. However, these papers have not discussed the role of chemotherapy in changing taste perception nor the dose of radiotherapy and its impact on taste change.

Table 1: Summary, characteristics and findings of studies included in the review (Table continued to next page)

Author/Year	Design	N	Type of Cancer	Place	Treatment	Chemotherapeutic substance	Intervention	Tool to assess taste change	Possible bias	EPHPP Quality Rating
Bernhardson et al. 2009	Cross-sectional	518	Various/ form oncology and gynecology outpatient	Sweden	Chemotherapy	Cyclophosphamide, fluorouracil, epirubicin, Paclitaxel, folic acid, oxaliplatin, carboplatin, irinotecan, vinorelbine, gemcitabine, cisplatin	Behavioral modification dietary modification	Based on previous qualitative interview study, pilot tested, revised many times.	Possibility of recall bias	Strong
Boltong et al 2012	Cross-sectional	10	Colorectal cancer	Germany	Radiochemotherapy tumor resecting surgery	Carboplatin	Dietary behavioral modification	Patient's subjective reporting	Confined to colorectal cancer only, small sample size, use of non standardised tool	Moderate
Buntzel et al 2002	Randomised placebo control trial	531	Head and Neck Cancer	United states	Chemotherapy	Doxorubicin, carboplatin, cisplatin, cyclophosphamide, topotecan, bevacizumab, gemcitabine, rituximab, folic acid, ifosfamide	Drug: Amifostine	Prepared questionnaire for this study, use of RTOG (Radiation Therapy Oncology Group) classification to evaluate the level of toxicities		Moderate
Cusnir et al 2012	Non randomised crossover design	47	GI cancer, breast cancer, and other cancer	United states	Chemotherapy	cyclophosphamide, doxorubicin, carboplatin, cisplatin, gemcitabine, methotrexate, 5-fluorouracil, paclitaxel, docetaxel	Miracle fruit (Synsepalum dulcificum)	Patient's subjective reporting	Mostly advanced disease, self reported taste change only, no use of validated taste, small sample size, very short duration of study	Moderate
Ekurt et al 2015	Randomised placebo control trial	100	Non small cell carcinoma and other several primary malignant cancers	Turkey	Radiochemotherapy	Cisplatin, etoposide	Drug: Magesrol acetate	Brief questionnaire based on scoring from 1 to 5 according to the degree of loss of change, developed by authors	Non validated tool, high drop-out, diagnosis and chemotherapeutic agent not clear, conclusive for advanced cancer and weight losing patients only	Strong
Fink M. 2011	Case report	2	Breast Carcinoma and pancreatic cancer	Germany	Chemotherapy	Docetaxel 75 mg/m ² , carboplatin. Infusional fluorouracil, leucovorin, and oxaliplatin	2000 U vitamin D3	None	Case selection	Moderate
Halyard M Y et al 2006	Randomised double blind placebo controlled trial	169	Head and Neck Cancer	United states	Radiation	None	Drug: Zinc	The linear analogue self assessment scale, transformed to 0-100 scale, taste alteration incidence was compared by using Fisher's exact test for both patient and physician reported taste change		Strong

Lyckholm et al 2012	Randomised placebo control trial	58	Leukemia, bladder, breast, cervix, colon, lung cancer and other cancer	United states	Chemotherapy	Actinomycin, adriamycin, bevacizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, docetaxel, etopodide and other s	Drug: Zinc	0-100 scale to describe taste loss where 100 is no loss and 0 is worst distortion (patient reported outcome)	high dropout, initial taste change was not recorded	Strong
Maureen et al. 2009	Quasi experimental	42	Breast, Lung or ovarian cancer	United states	Chemotherapy	Doxorubicin, carboplatin, cisplatin, cyclophosphamide	Behavioral and dietary modification, use of taste change suggestion sheet	two section test change survey based on results of previous large study of patients undergoing chemotherapy, checked for content validity and pilot tested, modified as necessary		Moderate
Najafzade, N 2013	Randomised double blind placebo control trial	35	Head and Neck Cancer	Iran	Radiation	None	Drug: Zinc	Measuring detection and recognition threshold for four taste qualities , taste acuity was evaluated by 3 drop method induced by Henkin	Supported by a grant from Isfahan University of Medical Sciences	Strong
Strasser et al 2008	Randomised placebo control double blind study	52	Prostate, lung, Breast cancer and other cancers	Switzerland	Chemotherapy	Taxane based/ Docetaxel or Paclitaxel	Drug: Glutamine	Use of a Visual Analogue Scale (VAS) tested for test retest reliability in a pilot study with r=0.52; P=0.006	Used Glutamine manufactured by Baxter company only. Glutamine was tested for prevention not for treatment. sample size was small, power <80%	Strong
Wilken et al 2012	Non randomised crossover design	8	Breast cancer, ovarian cancer, pancreatic, endometrial cancer and carcinomatosis and other cancer	United states	Chemotherapy	Doxorubicin, carboplatin, cisplatin, cyclophosphamide, topotecan, bevacizumab, gemcitabine, rituximab, folinic acid, ifosfamide	Miracle fruit (Synsepalum dulcificum)	Patient's subjective reporting	Case selection, only one male, very short duration and small sample size	Moderate

Behavioral and dietary modification:

All the three observational studies (Table 2) suggested that information on self-management strategies such as changes in meal patterns or modifications of food was helpful to combat dysgeusia, supporting previous studies.[45,46] Most of the strategies were applied by patient but a study by Boltong Anna included the strategies applied by the carer as well, as they are most commonly altering the foods offered to patients.[31] Boltong revealed some of the strategies used by patient which include "just get on with things", "seeking specific food or ingredient for example ginger, high salt", "adding more seasoning to food".[31] Rewaldt et al. suggested providing a suggestion sheet that helped 91% of the patients.[35] Amongst nineteen suggested strategies, the most useful with 100% efficacy was avoiding strong smell or taste, followed by eating blander food, drinking more water with food, oral care before eating, and eating smaller amount frequently. Least useful, with an efficacy of

Table 2: Summary of studies examining behavioral modification

Author/Year	Suggested strategies
Bernhardson et al. 2009	<ol style="list-style-type: none"> Strategies related to food and eating e.g., avoid specific food Focusing on mouth e.g., use chewing gum Avoiding odors e.g., staying away from smoke, increased cleanliness Other strategies e.g., going out for fresh air, relaxation
Maureen et al 2009	<ol style="list-style-type: none"> Avoiding strong smell Eating blander food Drinking more water with food Oral care before eating Eating smaller more frequent meals
Boltong et al 2012	<p>A. Patient's strategies:</p> <ol style="list-style-type: none"> Just go on with things Seeking specific food such as ginger, soy sauce, Worcestershire sauce Adding more seasoning to food seeking highly salty food <p>B. Carer strategies:</p> <ol style="list-style-type: none"> Buying patient's favorite food

71%, was to 'Eat cold food'.[35] In contrast another study on patients with breast cancer found the most

useful strategy to 'Eat strongly flavored food' and eating candy before food and to use plastic utensils. [47] Bernhardson et al. suggested similar strategies to Boltong and Rewaldt, mainly altering the routine of meal, avoiding smell and smoke, maintain oral hygiene, but has controversial finding on use of salt and sweet.[30] Almost one third of patient who reported taste change experienced high levels of distress and impact on daily life. The strategies were categorized into three; strategies related to food and eating, strategies focusing on mouth, strategies to avoid odor, and other strategies, the first category was considered most helpful.[30]

Zinc supplementation:

The most common intervention tried to treat dysgeusia was use of zinc (Table 3). Although closely associated with taste, zinc has yet been proven to be an effective intervention for taste alteration.[20,24] Three randomized placebo control trial investigated the use of zinc to prevent cancer related dysgeusia.[3,19,20] The study of Najafizade et al., with a sample size of 35, concluded that zinc is helpful to prevent radiation induced taste change in patient with head and neck cancer.[3] This finding is conflicting with the study done by Jatoi et al. (2009) with sample size 169 and another study done by Lyckholm et al. with sample size 58.[19,20] Both of these studies concluded that zinc has no preventive role for taste change related to cancer; rather it might have some negative effects if used for longer period.

Other supplementation:

Other substances like glutamine, amifostine, megestrol acetate, and miracle fruit were tried for the treatment of dysgeusia, nevertheless it is not possible for this review to draw a conclusion to say which of the intervention is best and can be recommended (Table 4). Most of the treatment show very limited effect on dysgeusia; also it was not replicated in subsequent researches. Glutamine was used to prevent dysgeusia caused by taxane based chemotherapy by Strasser et al. The study was well designed and used subjective taste sensation, confounders were managed accordingly, but the study fails to show any association between use of glutamine and dysgeusia.[26] Other study by Buntzel et al. suggests that amifostine is successful to protect against the acute and late toxicities, including taste alteration, of radiochemotherapy in advanced head and neck cancer.[29] A case study on use of vitamin D was successful to reveal the relationship of impaired taste and serum vitamin D level, however the result has to be interpreted cautiously as it was based on two cases.[34] Megestrol Acetate (MA) was associated with improved taste with $p < 0.001$ in a randomized control trial, but it's hard to interpret the result as the information about the validity of the tool used is lacking, also the dropout rate is high. [28] Wilken et al. studied the use of miracle fruit in 2012 with eight patients of various cancers treated with chemotherapy.[42] Miracle fruit is found to be helpful to prevent cancer related dysgeusia but cannot be generalized due to small sample size and weak study design.[33]

Table 3: Summary of studies investigating use of zinc to prevent taste alteration related to cancer and its treatment

Author Year	Dose	Treated with zinc (n)	Placebo (n)	Period of the study	Main findings	Conclusions
Halyard M Y et al 2006	45 mg orally three times a day	84	85	May 2002 to October 2005	<ol style="list-style-type: none"> 1. Zinc sulfate did not significantly increase the interval to taste alterations 2. It did not decrease the incidence of taste alteration 3. Zinc sulfate should not be prescribed to cancer patient for the purpose to prevent taste alteration. 	Zinc sulfate was not helpful to prevent taste loss
Najafizade, N 2013	50 mg orally three times a day	20	15	2009 and 2010	<ol style="list-style-type: none"> 1. Zinc sulfate 150mg/day during radiotherapy and continuing for one month later can prevent or decrease the effects of radiotherapy on taste perception 2. Study cannot reveal whether the beneficial effect of zinc on taste perception continue in long term 	Zinc sulfate was successful to prevent taste loss due to radiotherapy
Lyckholm et al 2012	50 mg orally twice a day	29	29	2002 to 2005	<ol style="list-style-type: none"> 1. No significant difference in taste loss between the use of oral zinc supplement group and placebo group 2. Sense of smell diminished over time with the zinc supplement 	Zinc has no effect on preventing taste loss

Table 4: Summary of studies investigating use of other supplement to prevent taste alteration related to cancer and its treatment

Author/ Year	Dose	Period of the study	Main findings	Conclusions
Fink M 2011	2000U vitamin D3	2010	<ol style="list-style-type: none"> 1. With vitamin D substitution, there was no more stomatitis, most of the taste disorders were receding 2. Reported a clear improvement of dysgeusia after treatment with 2,000 U vitamin D3 for 1 week during continued chemotherapy 	Vitamin D was helpful to treat dysgeusia
Strasser et al 2008	Glutamine 30gm/day	March 2004 to march 2006	<ol style="list-style-type: none"> 1. Oral glutamine at the dose given did not result in a lower incidence of subjective taste disturbances associated with taxane based chemotherapy 2. However, it can be hypothesized that the use of glutamine a treatment can be efficient. 	Glutamine was not helpful to prevent taste loss related to chemotherapy
Wilken et al 2012	Six Miracle fruit/day for 14 day	N/A	<ol style="list-style-type: none"> 1. All participant reported positive taste change, the supplement affected the level of sweetness in several different food groups, the supplement increased food intake for some. 	Miracle fruit was successful to improve the taste in cancer patient
Buntzel et al 2002	amifostine 500 mg before each chemotherapy	1999 to 2000	<ol style="list-style-type: none"> 1. Amifostine treated patient did not develop mucositis, and developed less severe type of xerostomia only. 2. Patient treated with amifostine experienced decreased level of loss of taste compared to control 3. Amifostine had a significant influence on taste alteration during the first 12 months of follow up. 4. Amifostine was well tolerated and offered significant protection from toxicities related to RCT used alone. 	Amifostine treated patient had lower rate of taste loss
Ekurt et al 2000	Megestrol acetate 480 mg once a day	1997 to 1998	<ol style="list-style-type: none"> 1. No adverse effect of MA was noted 2. Statistically significant weight gain in patient group receiving MA 3. Significance difference in loss of taste between MA group and control groups (p value 0.000, 80% vs 25% in control group) 	Improvement in taste was noted in MA treated patient

DISCUSSION:

The presence of dysgeusia in patients with cancer due to various reasons is well established with the prevalence of 14 to 100% in this review; many studies suggested the consequence of it on the compliance of treatment, weight loss, and quality of life. There are very few studies which explored treatments for cancer related taste change, which are inconclusive till the period of this review. From the current available literature around this topic some coping strategies and pharmacological management can be considered.[30,31,35] This review contained more interventional studies like randomized controlled trial, but their results were not replicated to each other. Nonetheless, the behavioral modification has more or less similar outcome, other suggestion about drug for example, zinc, amifostine, megestrol acetate, and use of miracle fruit is not convincing.

Studies focusing on counseling, behavioral and dietary modification concluded that using more sweetened drinks, use of candy and use of more salt has been very effective strategies to overcome the dysgeusia.[47] Additionally, there are few reliable methods available for measuring taste pose a bigger challenge and few of the studies mention about the reliability and rationale of instrument they used. The

reviewed paper concluded the avoidance of strong flavors to be effective, but the previous study in different setting opposes this finding.[47] Because of different study design and different method to assess taste improvement, there is not a concrete method to combat taste change. But importantly, all the paper suggests counseling the client and providing information is helpful to try different strategies.

Zinc was most commonly used to treat taste alteration which has established evidence to treat dysgeusia of various causes including cancer. [5,20,48-51] This finding was supported in the research done by Najafizade et al.[3,5] However it is important to notice at this point that both of the study had some limitations including smaller sample size, it used recognition threshold to measure taste acuity and studied only on head and neck cancer survivors. In contrast to the study of Najafizade et al, there are statistically robust studies in this review which high lights its side effects and ineffectiveness to prevent dysgeusia in cancer patients.[19,20] Even though the use of zinc is well established for wound repair and maintenance of immunity,[26] long-term and excessive consumption of zinc may have a negative impact on the immune system in cancer patients, zinc supplementation should be used cautiously by

cancer patients.[19,20] The later studies are larger in sample size and better in their methodology as one of them used validated, patient completed questionnaire and other covered a wide range of cancer diagnosis.[19,20] In addition they are done in different treatment modalities so it reflected the futility of zinc to improve the taste alteration. The available literature to date is not evidentially robust to advocate the use of zinc sulfate or zinc gluconate to prevent or treat cancer related dysgeusia.

Some of the studies have suggested the use of miracle fruit as being helpful in treatment and prevention of cancer related dysgeusia.[32,33] The entire participant reported positive change in taste with miracle fruit, however it was a subjective judgment as patient said that the metallic taste disappeared and improved taste. The generality of the study remains questionable as the author did not disclose the method of assessing taste change and the sample size was too small, the author has conducted the study systematically and captured the qualitative aspect.[33] Further study on miracle fruit was conducted by Cusnir et al. in 2014 in a larger sample size with 47 patients almost equal no of male and female and in randomized fashion which suggests the similar finding of Wilken. Again the outcome is questionable as the dropout rate was too high (only 23 completed the trial) and it is not clear about the view of rest 15 participants. Since the author was expecting for a larger confirmatory trial it might be wisdom to cautiously think on the result of the upcoming trial.[32]

Some drugs like glutamine and amifostine have been examined to prevent and treat dysgeusia, but they did not exhibit positive results.[26,29] The study by Strasser et al. suggested no benefits from glutamine on taste change; however, the study was well designed with subjective and objective record of taste change. It is not easy to consider the finding of this study as the author did study on taxane based chemotherapy only, the glutamine used for trial was from specific manufacturer, there was no dose gradient, was done in mixed cancer population, glutamine was tested for prevention only and the dropout rate from the study was high.[26] Use of amifostine as a cytoprotective agent has been studied well but the results are different in studies. The reviewed paper of Buntzel et al favors the use of amifostine before chemotherapeutics on the ground of its successful use to protect against various toxicities induced radiation and simultaneous chemotherapy used in other cancers.[29] This finding does not parallel to the author's previous finding and opposes the finding of another study by Komaki et al. Former one suggested amifostine reduced the incidence and severity of acute and late toxicities in general but

specifically for dysgeusia were not very striking; later one showed the dysgeusia was more frequent among patients given amifostine.[52,53] Other studies were not clear on the effect on dysgeusia.[54]

Use of megestrol acetate (MA) is not frequently studied, the presented study by Erkurt et al. supports the positive outcome on dysgeusia, but the study has several limitations to prevent it from generalisation. Most importantly it was done for short time period so it is unclear about the long term effect, its effectiveness is limited to advanced cancer and weight loosing cancer, use of validated tool is not demonstrated in the study, along with this aggressive supportive treatment is sought.[26] A case study showed a subjective improvement in taste change in breast cancer and pancreatic cancer patient with vitamin D supplementation, the result is yet to be examined systematically for more reliable result.[34]

Strengths and limitation of current review:

The most important part of this review is that it has excavated a wide range of potential treatment for the dysgeusia related to cancer. Every paper meeting the inclusion criteria is reviewed and the papers beyond the criteria but still under the topic were consulted. Despite the application of a systematic methodology, this review cannot make firm recommendations for clinical practice because of the heterogeneity of the reviewed studies. [22,55-57] Degree of taste change and comparison to different kinds of cancer and its treatment are beyond the scope of this article. The research papers not available from library access, Athens account and inter library loan services was not able to be included in this review. Furthermore, studies not providing enough information to check for the quality were not chased forward to contact the author because of the lack of time and design of the review. In opposition to guidelines which recommend that data extraction and quality analysis should be done in duplicate to mitigate the possibility of bias by a single person, the current review is a compilation by a single author. The available literature only draws a fragmented picture of experimental treatments for cancer related taste change. It might be worthwhile to invest in patient education on behavioral and dietary modification, conducting larger prospective trials on scarce interventions like vitamin D, miracle fruit, megestrol acetate.

CONCLUSION:

The most effective management for the dysgeusia which shows consistent results is

dietary counseling and informing the patient well about self-care strategies before treatment. Other potential treatments for dysgeusia such as zinc, amifostine, megestrol acetate have inconsistent and unsatisfactory results. This systematic review did not therefore succeed in presenting any conclusive pharmacological treatment for cancer related taste changes.

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