Review Article

Coming to Your Senses: Detecting Taste and Smell Alterations in Chemotherapy Patients. A Systematic Review

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Abstract

Context. Taste alterations (TAs) and smell alterations (SAs) are frequently observed, yet understudied side effects in chemotherapy patients, considerably affecting patients' quality of life.

Objectives. This review provides a systematic evaluation of the literature on TAs and SAs in cancer chemotherapy patients and discloses understudied research questions.

Methods. A systematic methodology based on the PRISMA guidelines was applied to identify original research articles with TAs and SAs as primary outcomes in chemotherapy patients. MEDLINE and Embase were searched using Medical Subject Heading and free-text terms. Study extraction and evaluation were done by three reviewers using predefined criteria.

Results. The search revealed 22 eligible studies, including three randomized controlled trials. Different measurement approaches were identified, with a clear trend toward self-report measures during the past decade. The methodological quality of the included studies varied, especially reports on SAs, which were inconsistent and hard to interpret. Regarding TAs, there is evidence that taste thresholds increase during chemotherapy. Qualitative changes, for example, metallic taste, are frequent but cannot be attributed to specific chemotherapy regimens. There are large research gaps regarding TAs and SAs in different patient populations and the impact of different chemotherapy regimens. Adequate management strategies are rare.

Conclusion. Current research results do not allow firm conclusions concerning the occurrence, severity, and quality of TAs and SAs under different chemotherapy regimens. Patient information on TAs and SAs, therefore, largely is based on the clinician's experience. In the palliative care setting, TAs and SAs need further

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investigation in the light of their importance in preventing food-related problems and maintaining a reasonable quality of life. J Pain Symptom Manage 2012;44:880–895.

Key Words
Cancer, chemotherapy, taste disorders, olfaction disorders, quality of life

Introduction

Many health care providers dealing with cancer patients frequently observe altered sensations of taste and smell, not only as disease symptoms in head and neck cancer patients but also as side effects of antineoplastic therapy. Such alterations play an important role in the patients' health and health-related quality of life by affecting food intake and appetite[1–5] and by their association with the development of food aversions and weight loss.[6,7] Yet, research on these side effects is scarce. Studies focusing on head and neck cancer patients undergoing radiotherapy provide evidence for the impact of radiation on taste and smell sensation.[8,9] Knowledge of such effects of chemotherapy is less extensive. Prevalence data on chemotherapy-related altered taste sensations range very broadly from 38% to 84%,[3,10,11] and studies on altered smell sensations in the context of chemotherapy are rare and report conflicting results.[2,12]

The mechanisms by which chemotherapeutic substances cause altered taste and smell sensations are not entirely known. Distortion of receptor activity[13] as well as saliva and mucus production[14] have been discussed. Furthermore, cytostatic agents might be secreted in saliva or diffuse from plasma into the oral cavity.[15] One important etiology seems to be the inhibitory effect of cytostatic agents on mitosis in replicating receptor cells[16] as in many patients, altered taste sensations resolve shortly after the end of chemotherapy when cell turnover is restored. Further suggestions about underlying mechanisms include damage to cranial nerves (e.g., demyelination of nerve fibers), tissue necrosis or infection, blockage of the nostrils,[17] modification of afferent pathways as a result of penetration of the blood-brain barrier by cytostatics, and neurotoxic effects of cytostatics, such as chemotherapy-induced neuropathy.[6]

The complex character of the senses of taste and smell, such as their interaction, as well as interaction with the sensations of texture and temperature, makes it difficult to subject them to investigations. Further complicating the academic discussion is an inconsistent terminology, especially regarding taste. When discussing alterations of taste and smell, chemosensory dysfunctions and changes in the perception of flavors and odors are referred. A viable and commonly applied classification for taste and smell changes as chemosensory dysfunction is to generally distinguish between quantitative and qualitative taste/smell disorders,[18,19] that is, a change of sensitivity or a distorted perception. Assessment can be done by determining detection thresholds, recognition thresholds, and intensity differences within the suprathreshold range.[20] Regarding taste, recognition thresholds and intensity differences require the recognition of the basic tastes, whereas detection thresholds do not include the classification of a basic taste perception. In general, the basic tastes are bitter, sweet, sour, and salty, but during the past decade, umami (amino acid or savoriness of protein-rich foods) has come to be recognized as one of the basic tastes as well, especially in the Asian culture. Landis et al.[21] reported that umami was excluded in the development of "taste strips" because it was too difficult to explain this taste to Europeans.

Literature suggests that such psychophysical measurements of chemosensory dysfunction do not necessarily reflect self-reported taste and smell changes.[22] Therefore, the present review incorporates literature on psychophysically measurable taste and smell changes as well as on self-reported taste and smell sensations, with taste alterations (TAs) and smell alterations (SAs) serving as umbrella terms.

This review aims to: 1) provide a detailed overview and quality evaluation of the existing

literature on TAs and SAs in chemotherapy patients; 2) summarize current knowledge on assessment methods, on the course of TAs and SAs in chemotherapy patients, and the interventions for their management; and 3) disclose understudied research questions.

Methods

To identify and appraise studies on TAs and SAs in cancer patients, a systematic approach based on the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[23] and the Cochrane Consumers and Communication Review Group's Extraction Template[24] was used.

Search Strategy

The database search was performed using MEDLINE and Embase in September 2010 and included studies from 1980. The development of the search strategy required several iterations until sufficient sensitivity was expected. We performed two separate searches, combining the following Medical Subject Heading (MeSH) terms and free-text terms: cancer [MeSH], chemotherapy [MeSH], taste disorders [MeSH], taste perception [MeSH], taste thresholds [MeSH], taste, gustatory, smell disorders [MeSH], smell, olfactory, olfactory perception [MeSH], chemosensor*, perception, disorder, threshold. The search was restricted to titles and abstracts. Articles without English translation and animal studies were excluded. Studies on patients with head and neck tumors were excluded because of the high prevalence of chemosensory disorders caused by the disease itself.[25,26] Although not within the scope of the present review, radiotherapy as a search term was not excluded in order not to miss possibly relevant studies.

An exemplar search history for MEDLINE can be seen in Table 1. Database searches were augmented by a manual search of reference lists of included articles to identify further eligible studies not detected by our search terms. An update database search was conducted in May 2011.

In addition, the Cochrane Library was browsed for existing systematic reviews on TAs and SAs in cancer patients.

Inclusion Criteria and Data Extraction

A pilot search in MEDLINE revealed that the literature on this topic is scarce. Therefore, it was decided not to impose restriction criteria regarding study design or type of outcome measure to comprehensively capture the available information. Furthermore, several articles concerning taste only peripherally, for example, in terms of conditioned aversions, were detected. As TAs and taste aversions/preferences were deemed nonsynonymous, it was decided not to include such articles. Eligible for the review was any study with a quantitative approach published in English and investigating TAs and SAs in cancer patients receiving chemotherapy during the study period. Thus, studies on patients receiving radiochemotherapy have been excluded. Studies with mixed samples of patients receiving chemotherapy or radiotherapy or both were considered eligible if calculations and presentation of results were done separately for chemotherapy patients. We only were interested in studies that had TAs or SAs as primary outcomes. Publications that were letters, editorials, narrative reviews, and reviews based on expert opinion were excluded. Inclusion criteria were applied by three independent researchers.

We developed a data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template, pilot-tested it on five randomly selected studies, and refined it accordingly. One reviewer extracted the data from included studies, and the second author (A. Z.) checked the extracted data. In case of uncertainty about the inclusion or appraisal of studies, a third reviewer was included in the discussion to provide advice and guidance.

Study Evaluation

The articles were evaluated by a predefined set of criteria, conveyed from the Minimum Standard Checklist for Evaluating Health-Related Quality of Life Outcomes in Cancer Clinical Trials.[27]

According to study design, different sets of criteria for quality assessment have been applied. For all studies, it was documented if:

- There was a rationale for the instrument
- Reliability of the used instruments were reported (or referenced)

Table 1
Exemplar Search History in MEDLINE

Search Number and Terms		Results
#29	Search **#26 NOT "review"[filter]** Limits: **Humans, English, Publication Date from 1980 to 2010**	428
#27	Search **#26**	497
#26	Search **(#24) NOT #15** Limits: **Humans, English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	497
#25	Search **(#24) NOT #15** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	1038
#24	Search **((#1) OR #2) AND #23** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	1209
#23	Search **(((((#3) OR #4) OR #10) OR #17) OR #18) OR #19** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	15,768
#19	Search **taste thresholds [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	865
#18	Search **olfactory perception [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	273
#17	Search **taste perception [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	10,825
#16	Search **(#12) NOT #15** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	290
#15	Search **(#13) OR #14** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	207,166
#14	Search **nervous system neoplasms [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	91,605
#13	Search **head and neck neoplasms [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	118,782
#12	Search **(#5) AND #11** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	422
#11	Search **(#7) OR #10** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	5215
#10	Search **chemosensor*** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	3149
#9	Search **(#5) AND #7** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	355
#8	Search **(#6) AND #7** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	18
#7	Search **(#4) OR #3** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	2201
#6	Search **(#1) AND #2** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	135,179
#5	Search **(#1) OR #2** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	1,887,131
#4	Search **smell disorder [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	1443
#3	Search **taste disorder [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	903
#2	Search **cancer [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	1,387,462
#1	Search **chemotherapy [MeSH Terms]** Limits: **English, Publication Date from 1980 to 2010** Field: **Title/Abstract**	634,848

- The timing of assessment was reported
- Instrument administration was reported

For cross-sectional studies, it was additionally documented if:

- Compliance was reported (documenting patients who were asked to participate but refused)

For all kinds of prospective studies, it was documented if:

- Baseline compliance and missing data were documented

For studies with an *a priori* hypothesis, it was additionally documented if:

- Sample size considerations were reported

For randomized controlled trials (RCTs), it was additionally documented if:

- The method of randomization was adequate
- The allocation concealment was adequate

Results

Study Selection and Study Characteristics

The two separate searches yielded a total of 602 articles. After removing duplicates, we reviewed the remaining 460 abstracts and excluded comments, letters to the editor, and studies that did not meet the predefined inclusion criteria; a total of 47 potentially relevant articles remained and were reviewed. Twenty-eight articles did not fulfill the inclusion criteria. The reference lists of the remaining 19 articles were screened, which resulted in three additional relevant studies (Fig. 1).

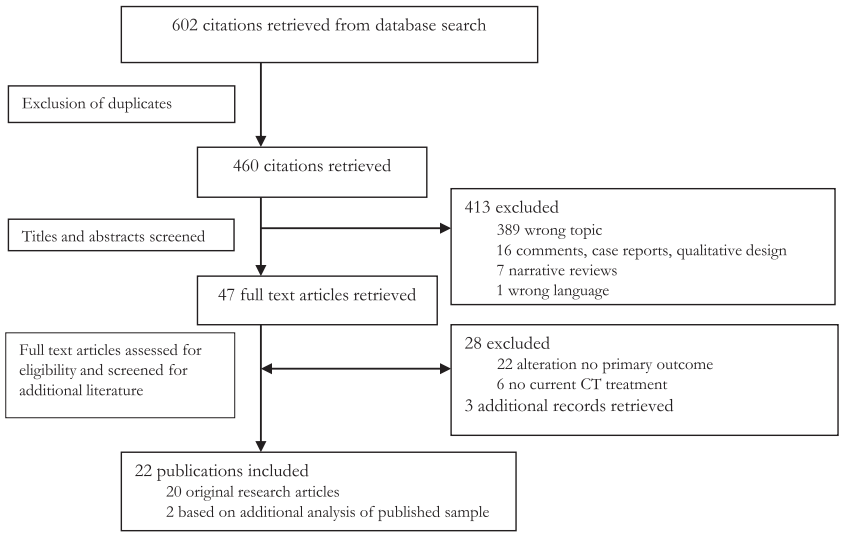

Fig. 1. Flow diagram of study selection process.

In total, results from 22 publications were included, of which two were based on additional analysis of previously published samples (as indicated in the articles). Thus, study characteristics are given for 20 publications only. Sample sizes ranged between seven and 518 patients, with a mean of 89.9 and median of 45.0. The most common diagnoses were breast and lung cancer. Accordingly, the most frequent chemotherapy agents were 5-fluorouracil (5-FU), anthracyclines, platines, methotrexate, and taxanes. Details of the study characteristics are presented in Table 2.

Study Evaluation

Of the 20 original studies, three were RCTs (including one pilot trial), nine were prospective studies and eight were cross-sectional studies. Altogether, 11 studies included a control group, consisting of either people without cancer or cancer patients not receiving chemotherapy.

Most studies were observational and were rated as evidence Level 2c according to the Oxford Level of Evidence.[28] Three studies fulfilled the criteria for Level 1b, which includes individual RCTs.

The application of the predefined quality criteria resulted in the following:

All Studies. Ten studies[3,11,29–36] (50%) reported a rationale for the instrument. Reliability of the instrument only was reported for eight instruments[11,12,32,33,35–38] (36%) (studies presenting the development of a new instrument were excluded from analysis). Fourteen studies[10,12,29–33,35,37–43] (75%) reported on the timing of assessment, and 17 studies[10–12,29–37,39–43] (85%) reported on instrument administration.

Cross-Sectional Studies. Four studies[3,30,41,44] (50%) reported on compliance.

Prospective Studies and RCTs. Six studies[10,11,29,32,37,38,42] (50%) reported on baseline compliance. Only five studies[11,29,37,38,42] (42%) reported on missing data.

Studies With an A Priori *Hypothesis.* Of the five studies with an *a priori* hypothesis, none reported on sample size considerations. One explorative study, however, performed an *a priori* power analysis for subgroup comparisons.[3]

RCTs. In two of the three RCTs, the method of randomization was deemed adequate.[38,42] Allocation concealment was considered adequate in only one study.[38] The one pilot trial[32] did not report on randomization or allocation concealment. Table 3 presents more details.

Assessment Methods

Six studies (30%) used only self-reported methods for TA and SA assessment, eight (40%) used only psychophysical methods, and six studies (30%) assessed TAs and SAs

Table 2
Characteristics of Studies That Have Assessed Taste or Smell Alterations in Chemotherapy Patients

Author, Year	Design (Intervention)	*N*	Cancer Patients	Chemotherapeutic Substances	Study Endpoints	Measure	Assessment Method
Zabernigg et al. 2010[36]	PS	197	Colorectal, lung, pancreatic	5-FU, capecitabine, etoposide, folinic acid, gemcitabine, irinotecan, platinum, vinorelbine	Taste alterations	Self-reported	Taste scale
Sánchez-Lara et al. 2010[43]	CS controlled	30	Breast, lung, prostate, multiple myeloma, lymphoma	n.s.	Taste thresholds, calorie intake, nutrient consumption	Psychophysical and self-reported	Dilutions for sweet, bitter, and umami
Rehwaldt et al. 2009[11]	PS	42	Breast, lung, lymphoma, ovarian	Doxorubicin, carboplatin, cisplatin, cyclophosphamide, other	Taste alterations and management strategies	Self-reported	Questionnaire
Steinbach et al. 2009[35]	PS	87	Breast, gynecological	5-FU, cyclophosphamide, doxorubicin, epirubicin, methotrexate, taxane,	Taste and smell alterations	Psychophysical and self-reported	Taste Strips, Sniffin' Sticks, questionnaire
Bernhardson et al. 2008[3]	CS	518	Breast, gastrointestinal, gynecological	5-FU, folinic acid, gemcitabine, irinotecan, platinum, taxanes, vinorelbine,	Taste and smell alterations	Self-reported	Questionnaire
Jensen et al. 2008[10]	PS controlled	45	Breast	5-FU, cyclophosphamide, epirubicin, methotrexate	Oral mucosal and microbial changes and taste disturbances	Self-reported	Structured interview
Strasser et al. 2008[38]	RCT (glutamate)	21	Breast, lung, prostate, other	Taxanes	Taste recognition; taste alterations (dysgeusia)	Psychophysical and self-reported	Soaked cottonwood tips; question
Schiffman et al. 2007[42]	RCT (flavor enhancement, nutritional information)	54	Breast, lung	n.s.	Taste and smell thresholds; taste and smell alterations and quality of life impairments, nutritional status	Psychophysical and self-reported	Dilutions of salty and sweet; dilutions of phenethyl and menthol; questionnaire
Skolin et al. 2006[41]	CS controlled	22	Children with brain tumors, leukemia, lymphoma, and various solid tumors	Cyclophosphamide, cytarabine, dacarbazine, doxorubicin, ifosfamide, methotrexate, platinum, procarbazine	Impact of physical/psychological aspects, in particular taste alterations, on food intake/eating problems; nutritional status	Psychophysical and self-reported	Dilutions for sweet, salty, sour, and bitter; questionnaire
Yakirevitch et al. 2005[12]	PS	21	CUP, gastrointestinal, gynecological, lung,	Cisplatin containing	Olfactory function, serum zinc levels	Psychophysical	Sniffin' Sticks

(*Continued*)

Table 2
Continued

Author, Year	Design (Intervention)	*N*	Cancer Patients	Chemotherapeutic Substances	Study Endpoints	Measure	Assessment Method
			skin				
Bertertetche et al. 2004[33]	CS controlled	110	n.s.	Alkylating agents, antimetabolites, antispindle agents, intercalating agents, others	Taste thresholds	Psychophysical	Electrogustometer
Yamagata et al. 2003[32]	Pilot RCT (zinc supplementation)	7	Lung	Etoposide, mitomycin C, platinum, vindesine sulfate	Taste thresholds, serum zinc levels	Psychophysical	Electrogustometer
Wickham et al. 1999[34]	CS	284	Breast, colon, lung, lymphoma, ovarian, other	5-FU, cyclophosphamide, doxorubicin, etoposide, folinic acid, methotrexate, platinum, taxanes	Taste and smell alterations, quality of life	Self-reported	Questionnaire
Ovesen et al. 1991[29]	PS controlled[a]	27	SCLC	CCNU, cyclophosphamide, doxorubicin, etoposide, hexamethylamine, platinum, teniposide, vincristine, vindesine	Taste thresholds	Psychophysical	Dilutions for sweet, salty, sour, and bitter
Ovesen et. al. 1991[37]	PS controlled	51	Breast, lung, ovarian	5-FU, CCNU, cyclophosphamide, doxorubicin, epirubicin, etoposide, hexamethylamine, platinum, teniposide, vincristine, vindesine	Taste and smell thresholds	Psychophysical	Electrogustometer; dilutions in mineral oil of phenyl methyl-ethyl-carbinol (Research Kit No. 11, Olfacto Labs)
Ovesen et al. 1991[31]	PS	31	Breast, lung, ovarian	n.s.	Taste and smell thresholds and their impact on dietary intake	Psychophysical and self-reported	Electrogustometer; dilutions in mineral oil of phenyl methyl-ethyl-carbinol (Research Kit No. 11, Olfacto Labs); symptom questionnaire at baseline
Fetting et al. 1985[44]	CS retrospective	45	Breast	5-FU, cyclophosphamide, methotrexate,	Taste alterations, vomiting	Self-reported	Structured interview
Bruera et al. 1984[40]	CS controlled[a]	36	Breast, gastrointestinal, gynecological, kidney,	5-FU, dacarbazine, bleomycin,	Relationship of nutritional status,	Psychophysical	Glucose test

			lung, skin, soft tissue sarcoma urological	cyclophosphamide, doxorubicin, methotrexate, mitomycin, platinum, semustine, vinblastine	caloric intake, depression, glucose taste alteration and tumor mass		
Mulder et al. 1983[39]	PS	n.s.	Skin	Bleomycin, dacarbazine, vindesine, actinomycin	Taste thresholds	Psychophysical	Dilutions for sweet, salty, sour, and bitter
Wall et al. 1983[30]	CS controlled	49	Children with leukemia	6-Mercaptopurine, methotrexate, vincristine, other	Taste thresholds, food preferences, changes in eating habits	Psychophysical	Dilutions for sweet, salty, sour, and bitter
Studies Based on New Analysis of Already Published Sample							
Bernhardson et al. 2009[54]	See Bernhardson et al. 2008				Taste and smell alteration induced distress and impact on quality of life	See Bernhardson et al. 2008	
Bernhardson et al. 2009[55]	See Bernhardson et al. 2007 and 2008				Smell alterations	See Bernhardson et al. 2007 and 2008	

PS = prospective study; 5-FU = 5-fluorouracil; CS = cross-sectional study; n.s. = not specified; RCT = randomized controlled trial; CUP = cancer with unknown primary; SCLC = small-cell lung cancer; CCNU = *N*-(2-chloroethyl)-*N*-prinecyclohexyl-*N*-nitrosourea.
[a]Controls for taste-tested group only.

psychophysically as well as in a self-reported manner (Table 2).

Psychophysical Methods—Taste. Electrical thresholds were assessed by means of electrogustometry,[31–33,37] which works via the application of electric current to the tongue by means of an electrode. Usually, patients are not told when exactly a stimulus is applied and are asked to report any perceived taste sensation. Thus, electrogustometry assesses taste detection thresholds rather than recognition thresholds and is not applicable for measuring basic taste qualities.

Chemical thresholds for the basic tastes were assessed with different application methods of dilutions of basic taste substances[29,30,38–43] and with impregnated filter papers called Taste Strips.[35] In chemical threshold testing, patients identify the presented taste; therefore, with this method, taste detection and recognition thresholds can be assessed.

Psychophysical Methods—Smell. Psychophysical smell assessment was done using dilutions of phenyl methyl-ethyl-carbinol in mineral oil presented in squeeze bottles,[31,37] dilutions of phenethyl and menthol,[42] and Sniffin' Sticks, a test battery for assessing odor identification as well as olfactory recognition and discrimination thresholds.[12,35]

Self-Reported Methods. Self-reports of taste and smell were collected through structured interviews,[10,44] questionnaires,[3,11,34,35,41,42] and taste scales.[36] As no internationally validated questionnaire for self-reported TA and SA assessment is available, question-sets were derived from previous studies,[11] previous findings, or literature and clinical experience.[3]

Review of Current Knowledge

Owing to an array of different manifestations, concepts, and measurement approaches of TAs and SAs, as well as different types of cancer and chemotherapy, prevalence estimates vary considerably. Details on cancer types and chemotherapies under investigation in the individual studies are provided in Table 2.

Across all studies the prevalence of TAs was high, ranging between 45% and 84%.[3,10,11,33,36] The prevalence of SAs ranged between 5% and 60%.[3,12,34,41] For both, TA and SA prevalence

Table 3

Adaptation of the Minimum Standard Checklist for Evaluating HRQOL Outcomes in Cancer Clinical Trials as Applied to Studies That Have Assessed Taste or Smell Alterations in Chemotherapy Patients

	Conceptual		Measurement				Methodology				
Author, Year	*A priori* Hypothesis	Rationale for Instrument	Psychometric Properties	(Instrument) Administration	(Baseline) Compliance	Timing of Assessments	Missing Data Documented	Method of Randomization	Allocation Concealment	Power Analysis	Level of Evidence
Zabernigg et al., 2010[36]	N/A	X	X	X				N/A	N/A	N/A	2c
Sánchez-Lara et al., 2010[43]	N/A			X		X	N/A	N/A	N/A	N/A	2c
Rehwaldt et al., 2009[11]	N/A	X	X	X	X		X	N/A	N/A	N/A	2c
Steinbach et al., 2009[35]	N/A	X	Psychophysical: X Self-reported:	X		X		N/A	N/A	N/A	2c
Bernhardson et al., 2008[3]	N/A	X			X		N/A	N/A	N/A	X	2c
Jensen et al., 2008[10]	N/A			X	X	X		N/A	N/A	N/A	2c
Strasser et al., 2008[38]	X		Psychophysical: Self-reported: X		X	X	X	X	X	[a]	1b
Schiffman et al., 2007[42]	X			X		X	X	X			1b
Skolin et al., 2006[41]	N/A			X	X	X	N/A	N/A	N/A	N/A	2c
Yakirevitch et al., 2005[12]	X		X	X		X		N/A	N/A		2c
Bertertetche et al., 2004[33]	N/A	X	X	X		X	N/A	N/A	N/A	N/A	2c
Yamagata et al., 2003[32]	X	X	X	X	X	X		Not reported	Not reported	N/A	1b
Wickham et al., 1999[34]	X	X		X			N/A	N/A	N/A	N/A	2c
Ovesen et al., 1991[29]	N/A			X	X	X	X	N/A	N/A	N/A	2c
Ovesen et. al., 1991[37]	N/A	X	X	X	X	X	X	N/A	N/A	N/A	2c
Ovesen et al., 1991[31]	N/A	X		X		X		N/A	N/A	N/A	2c
Fetting et al., 1985[44]	N/A				X		N/A	N/A	N/A	N/A	2c
Bruera et al., 1984[40]	N/A			X		X	N/A	N/A	N/A	N/A	2c
Mulder et al., 1983[39]	X			X		X		N/A	N/A		2c
Wall et al., 1983[30]	N/A	X		X	X	X	N/A	N/A	N/A	N/A	2c

N/A = not applicable because of study design.
X indicates "yes" and empty space indicates "no."
[a]Power analysis not applied but provided in discussion.

estimates were higher than in control groups, except in one study[37] that did not find a difference between chemotherapy and control groups regarding smell function.

Psychophysical Assessment of TAs

Electrical Thresholds. Berteretche et al.[33] observed an increase in electrical thresholds in chemotherapy patients compared with healthy controls, as well as during the five days of 5-FU application. Yamagata et al.[32] also found an increase in electrical thresholds during the first two weeks of chemotherapeutic treatment in a zinc supplementation intervention study.

Decreased electrical thresholds were observed by Ovesen et al.[37] for patients with small-cell lung cancer, ovarian cancer, or breast cancer undergoing chemotherapy compared with 29 matched control patients with non-neoplastic disease. Furthermore, a significant decrease in electrical thresholds at two or three months of chemotherapy compared with a prechemotherapy baseline was observed for lung cancer patients[31] and for lung cancer treatment responders compared with nonresponders.[37] However, the authors did not provide information on chemotherapy regimens and dosages applied in responders and nonresponders.

Chemical Thresholds. Most studies investigating chemical taste thresholds found them increased in chemotherapy patients. Increased thresholds were found for bitter,[30,41,43] sweet,[30,40,43] sour,[30,35] and salty tastes.[30] For the perception of umami taste, no difference between chemotherapy patients and healthy controls[43] was found. Steinbach et al.[35] observed increased taste thresholds during chemotherapy compared with a prechemotherapy baseline; the salty taste was affected the most. Ovesen et al.[29] observed an increase in bitter thresholds in treatment responders only, without providing information as to whether this group was somehow treated differently compared with nonresponders in terms of chemotherapeutic substances and dosages. Strasser et al.[38] did not find any changes during the study period of 12 weeks. Mulder et al.[39] found that patients showed an increased intensity for low concentrations of sweet, salt, and sour tastes and a decreased intensity for high concentrations of sweet taste approximately one week after the end of chemotherapy compared with those before chemotherapy. These paradoxical findings also might be attributable to a rather small sample size.

Self-Reported Assessment of TAs. Results of self-reports consistently describe an increase of TAs during chemotherapy. In no study in which a change of taste was self-reported was there a change for the better. The major drawback of self-reported measures is that they very often do not account for the different taste disorders but simply ask for a change in taste. Furthermore, it is difficult to determine to what extent changes of smell influence what patients experience as changes of taste. Thus, in the following, the term "flavor" is used for a self-reported overall change in taste perception. There is evidence for such changes of flavor perception.[36,38,43] However, one study showed that this self-reported overall change was not reflected in a self-reported change of the basic taste qualities,[38] highlighting the complex character of flavor perception. Several studies found quantitative taste disorders presenting as a decrease in[3,10,34,35] or loss of taste sensation[11,43] during chemotherapy. Qualitative taste disorders very often seem to manifest as a metallic taste,[3,10,11,34] which is one of the most common complaints. Changes in sour,[3] bitter,[3,11,44] sweet, and salty sensations[3] also were found frequently. A large percentage of those patients who experienced TAs reported that more than one taste quality was affected.[3,34] Furthermore, Rehwaldt et al.[11] report relationships between ageusia and dry mouth, bitter taste and decreased appetite, as well as between sour taste and nausea, decreased appetite, and dry mouth.

Psychophysical Assessment of SAs. Only a few studies prospectively investigated SAs in chemotherapy patients. Some studies found smell thresholds to be unchanged during chemotherapy.[12,37] A decrease in olfactory function (assessed with Sniffin' Sticks) during chemotherapy was observed by Steinbach et al.[35] Moreover, Steinbach et al.[35] found that smell thresholds were more affected than smell discrimination and identification, the latter being affected only minimally. Yakirevitch et al.[12] found the identification value, although unchanged during chemotherapy, to be higher after the end of treatment than at baseline.

As suggested by the authors of these two studies, learning effects of verbal tasks may play an essential role for these outcomes. However, another interpretation could be that the final assessment was done three weeks after the last cycle of chemotherapy when the epithelium has been only just restored and olfactory function has recovered.

Self-Reported Assessment of SAs. Bernhardson et al.[3] found that of the eight odors, "perfume" and "cooking" were the most frequently affected. Typically, more than one odor was affected in those reporting SAs. Wickham et al.[34] found small but significant correlations between degree of smell loss and degree of taste change, as well as frequency of taste changes and distress from taste changes.

Chemotherapeutic Substances and TAs and SAs. Results from the included studies suggest that a broad range of chemotherapy agents, such as 6-mercaptopurine, methotrexate, vincristine, cisplatin, and doxorubicin as well as carboplatin, cyclophosphamide, and 5-FU, can be associated with TA. However, studies providing comparisons between agents and their impact on TAs and SAs are scarce. There is, however, some evidence that the degree of TAs may differ across patient and treatment groups.[3,34,36] Zabernigg et al.[36] provide expected values of TAs in patients with lung and colorectal cancer treated with different chemotherapy regimens. Patients receiving irinotecan reported a high prevalence of TAs, whereas patients treated with a gemcitabine/platines protocol reported low levels of TAs. Similarly, patients reported a low level of TAs when treated with gemcitabine monotherapy.[3,34] Based on the reviewed literature, metallic or sour taste sensations, which are often associated with cisplatin and carboplatin (based on clinical experience and isolated studies), cannot be attributed to certain regimens. Regarding SAs, Steinbach et al.,[35] using psychophysical measures, found no difference in olfactory function during chemotherapy with respect to the chemotherapeutic agent; neither did Ovesen et al.[29,37]

Onset of TAs and SAs, and Recovery. Some studies surmise that TAs may start within a few minutes after drug administration.[41,44] Whereas some patients seem to experience TAs immediately after the first treatment, others experienced the onset up to 10 weeks later.[3] Zabernigg et al.[36] suggest a stepped increase of TAs under epirubicin-containing regimens within the first 30 days after drug baseline. One study reports TAs to persist for a few hours up to weeks.[34] After completion of chemotherapy, TAs may even last up to one year until recovery.[10] Steinbach et al.[43] found taste and smell thresholds to be recovered at three months after chemotherapy. Bernhardson et al.[3] report that patients very often experience TAs and SAs intermittently, which makes it difficult to determine onset and recovery.

Interventions for the Treatment of TAs and SAs. The sole pilot RCT investigated the supposed positive effect of zinc on taste perception.[30] Based on the promising results of zinc supplementation in head and neck cancer patients undergoing radiotherapy[45,46] and the assumption that lower zinc serum levels are associated with taste and smell dysfunctions,[47] Yamagata et al.[32] investigated the effect of zinc supplementation in lung cancer patients undergoing chemotherapy. This study provides evidence for the supportive effect of zinc on patients' taste perception during chemotherapeutic treatment. All patients showed low serum zinc levels before the onset of chemotherapy. Patients receiving infusions containing zinc sulfate showed improved or maintained taste thresholds whereas patients in the placebo group worsened two weeks after the start of therapy. These results seem encouraging, but limiting issues are a small sample size and an age bias toward younger patients being assigned to the intervention group. Yakirevitch et al.[12] did not investigate zinc as an intervention method but controlled serum zinc levels in chemotherapy patients. They detected an association neither between low serum zinc levels and SAs nor between normal serum zinc levels and unaffected smell function. The supposed positive effect of glutamine administration on TA and SA in patients who receive taxane-based chemotherapy could not be confirmed, on either a psychophysical or a self-reported measurement basis.[38]

Schiffman et al.[42] found that patients receiving a combination of flavor enhancement, detailed nutritional information, and specific recipes had better physical functioning and a better self-rating of taste perception eight

months after the beginning of treatment than patients who received nutritional information only. However, a difference in the abilities of taste perception could not be supported by means of psychophysical measures.

In a study by Rehwaldt et al.,[11] patients received an educational intervention comprising a list of management strategies for TAs and SAs, such as marinating meat, eating cold foods, and adding something sweet with meats, derived from a previous investigation.[34] Most patients tried out more than one strategy, and among those who did, found them helpful. In addition, Rehwaldt et al.[11] suggested that there is a relation between the type of alteration and the helpfulness of a strategy. For example, metallic taste is alleviated by eating more cold foods, whereas patients who had a salty TA did not benefit from this strategy.

Considering the lack of interventions, it seemed important to us to report results from an additional study although it has not met the inclusion criteria for the present review. In a recently published study, Brisbois et al.[48] report evidence for delta-9-tetrahydrocannabinol improving not only chemosensory perception but also appetite in patients with advanced cancer, results that could have important implications, especially for palliative care.

Discussion

The main aim of the present review was to systematically evaluate studies on TAs and SAs in cancer patients undergoing chemotherapy. Having carried out a pilot literature search, it was evident that because of a lack of RCTs on this topic, a systematic review of the evidence as suggested by the Cochrane Collaboration would not be possible. We decided to apply broad inclusion criteria and to incorporate all original research papers that had TAs or SAs in chemotherapy patients as a primary outcome. Therefore, although applying a systematic methodology, we cannot make firm recommendations for clinical practice and ongoing research because of the heterogeneity of the reviewed studies. However, it seemed important to us to provide a comprehensive evaluation of the existing literature as well as to disclose under-studied research questions.

Between 1980 and May 2011, 22 publications on TAs and SAs in cancer patients undergoing chemotherapy were published. A diversity of approaches used to measure TAs and SAs was identified and evaluation criteria, therefore, have been adapted to the scope and design of the study. In addition, the Oxford Level of Evidence system has been applied for a crude rating of evidence, with most studies qualifying for Level 2c.

Reports on the reliability of instruments and those on the rationale for the instrument use were surprisingly rare. Instrument administration and timing of assessment were reported by most studies. Reporting on (baseline) compliance and reporting on missing data are still uncommon, and so is conducting sample size considerations, which has not been done by any study with an *a priori* hypothesis. One explorative study, however, performed an *a priori* power analysis for subgroup comparisons.[3] Two of the three available RCTs (including one pilot study) were clearly underpowered and, therefore, provide only weak evidence on the effectiveness of interventions.

Measurement Issues

Psychophysical measurement of taste has been simplified with the development of the taste strips, which compared with the electrogustometer, facilitate the measurement of basic tastes and provide a time- and cost-effective assessment of gustatory impairments. However, according to critics, this simplification might be at the expense of reliability, as thresholds may differ depending where on the tongue the stimulus is applied.[37] Whereas there are a few reliable methods available for measuring taste, psychophysical and self-reported smell assessment pose a bigger challenge. With the development of instruments such as the University of Pennsylvania Smell Identification Test (UPSIT) or the Sniffin' Sticks (testing of identification, discrimination, and thresholds), the assessment of olfactory function has been simplified. However, the suggestion[12,35] that repeated identification tasks in the Sniffin' Sticks battery could be prone to learning effects may lead to the advice to measure smell thresholds and discrimination instead.

Regarding the assessment of TAs and SAs, a clear trend toward the increased use of self-report measures can be observed. This might

reflect the general trend to devote more attention to patient self-report, as this is increasingly demanded of researchers and clinicians[49,50] and reflected by the U.S. Food and Drug Administration's 2006 approval of patient-reported outcomes as a criterion in admission to trials.[50]

Patients may even be burdened by changes in the perception of taste or smell that are not noticeable in psychophysical testing.[22,32] Furthermore, there are dimensions that cannot be measured psychophysically, such as patients' TA- and SA-related distress and loss of quality of life. Qualitative taste and smell disorders such as phantogeusia/phantosmia (taste/smell hallucinations) and parosmia (odor-triggered false unpleasant smell) are especially difficult to assess, as they seem to develop under neuronal involvement[51] rather than on a receptor level. Such distortions have not been explicitly reported in the reviewed studies, and it is not clear if they even occur as a result of cancer chemotherapy. Respective investigations will need to be based on valid self-report measures.

In addition to the complex character of TAs and SAs, difficulties in assessment and in the development of adequate interventions also arise from a very heterogeneous terminology, not clearly differentiating between taste, flavor, and food hedonics.[52]

Directions for Future Research

The available literature only draws a fragmented picture of chemotherapy-related TAs and SAs, their etiology, the impact of specific treatment modalities or substances on chemosensory function, and possible interventions. Assessment methods are either psychophysical or self-report measures; no study applying an objective approach, such as evoked potentials, has been revealed in the literature search. The apparent lack of RCTs might indicate, on the one hand, that there are also very few interventions available and that corresponding hypotheses concerning etiologies are missing; on the other hand, this might also reflect the often-held view that TAs and SAs are unavoidable side effects. Thus, in addition to research on etiologies, the focus might be set on the following questions:

Which TAs and SAs Are Clinically Meaningful? Psychophysically measurable TAs and SAs do not necessarily reflect self-reported changes of flavor or predict associated burden.[53] We do not know which patient groups are at risk for developing problems with food intake or in which treatment situations TAs and SAs are perceived as most burdensome. Thus, further investigation on self-reported TAs and SAs, including their impact on quality of life, is needed.

How Do Different Chemotherapy Regimens Impact Taste and Smell Perception? Issues hardly discussed in the literature are the role of chemotherapy regimens and the role of chemotherapy line with regard to their impact on the severity and duration of taste and smell. Furthermore, over the past 30 years, several new cytostatic agents have been approved for clinical use and dosages have been changed. Expected values for TAs and SAs under specific treatment modalities are needed to improve patient information and adopt measures for the prevention of appetite loss and malnutrition. This is especially important in the palliative care setting where patients often are suffering from cachexia, and TAs and SAs can have a devastating effect on the patient's physical condition and quality of life.

Which Possible Interventions Need Further Investigation? Although closely associated with taste and smell sensation, zinc has not yet been proven to be an effective intervention for chemosensory distortions. Furthermore, the promising results of THC in patients with advanced cancer warrant further investigation. As for how we can help patients best to help themselves, it might be worthwhile to invest in patient education programs because there is some evidence that patients can benefit from information on self-management strategies, such as those described above.[11,34,42]

Conclusion

Because of the complex character of TAs and SAs, the identification of patient populations at risk for being burdened by these side effects or their possible consequences and the development of adequate interventions require the collaboration of different health care professionals. The move toward shared clinical

decision making involves the patient having the best information, which enables the patient to make a personal trade-off between a therapy's benefit and additional strains. Furthermore, in times of intensive research on tumor-related cachexia and possible drug interventions, TAs and SAs are worth being examined in a much broader context than has been done so far.

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