Anxiety (or fear) is an unavoidable part of our lives and accompanies us from birth to death. It is part of our existence and is a reflection of our dependence and knowledge about our own mortality. Anxiety always appears in our lives when we are in a life-threatening situation that we feel is challenging [35]. Every developmental step, every maturational step, is associated with anxiety because it leads us to something new and unknown, in internal or external situations that we have not experienced yet. This becomes especially apparent in our development stages, in which we have to part from the old and trusted in order to accomplish new tasks, i.e., change is necessary [25].

There are, therefore, completely normal age- and development-related fears that healthy people go through and outgrow, which is important for further development [25]. At the end of our lives, we are confronted in this context with coming to peace with aging and death and the fears that are associated with it [31, 36, 51].

Patients with life-threatening illnesses experience a variety of fears. Anxiety in this context is to be understood as a natural reaction to the unknown and one’s pending death [31, 58]. The prevalence of anxiety disorders in patients with far-advanced cancer lies between 2 and 28% [29, 30, 34, 41]; the prevalence of physical and psychological symptoms that are associated with anxiety lie between 25 and 48% [29]. Stiefel and Razavi [58] divided anxiety in cancer patients into four categories: situational anxiety, psychiatric anxiety, organic anxiety, and existential anxiety. In the development of physical anxiety in cancer patients, not only numerous physical changes but symptom burden play fundamental roles [62]. In a Cochrane review, fear or worry, autonomous hyperactivity, diarrhea, sweating, dyspnea, insomnia, nervousness, trembling, palpitations, paresthesia, and also varying degrees of vigilance ranging up to delirium ([22], summary of: [8, 7, 37, 42, 53]) are listed as psychological and somatic symptoms of anxiety. Situational anxiety and existential anxiety have numerous aspects in common and are accompanied by sorrow, increased dependence, and at the same time the impending loss of relatives and with a loss of autonomy [55]. Psychiatric anxiety is what an individual experiences as a reaction to death [51] and includes adjustment disorder, obsessive-compulsive disorder, phobia, panic disorder, posttraumatic stress disorder, and generalized anxiety disorder [66].

Numerous medications used in palliative care can precipitate anxiety or enhance existing anxiety. Thus, careful examination of medications is necessary, when anxiety is suspected [21]. The abrupt discontinuation of various substances can also result in anxiety, including alcohol, anticonvulsants, benzodiazepines, clonidine, corticosteroids, nicotine, opioids, sedatives, and hypnotics [37].

As in every intervention, the advantages and disadvantages should be weighed prior to starting anxiolytic treatment in a terminal situation. In the palliative care situation, the majority of patients experience moderate anxiety and they can benefit from supportive, nonpharmacological therapy [37].

Although there are reports with smaller numbers of patients concerning the topic of anxiety in palliative care patients, there is only one systematic literature review on the pharmacological treatment of anxiety in palliative care patients (Cochrane Database, [22]). This work forms the basis of the present work to a large extent. We have orientated our work (the literature search, methods, and evaluation) on the Cochrane review. The goal of the present systematic literature review is similar to the Cochrane review article in evaluating the evidence for the pharmacological treatment possibilities for anxiety in patients during their final phase of life. However, in contrast to the Cochrane review we have not set a defined time limit—3 months in the Cochrane review article.

The work concentrates on anxiety as an independent symptom. Articles with anxiety as a concomitant symptom with various physical symptoms or in association with a pre-existing anxiety disorder were excluded.

Although often done in the literature, we have avoided differentiating between anxiety and fear in this review article. It does not appear convincing enough to us how these two terms are expressed in
### Materials and methods

#### General search strategy

Systematic searches of the literature databases PubMed (Tab. 1), Embase (Tab. 2), Cochrane Central Register of Controlled Trials, Cochrane Library, Cochrane Pain Palliative and Supportive Care Register, CINAHL, PsycLIT and PsycINFO were performed in January 2012. The searches in these databases were based on the search strategy in Embase; therefore, they are not presented in a separate table. The databanks selected were derived from the Cochrane review article [22]. The CINAHL database was selected because a series of interesting research articles in palliative medicine were published in patient care journals. The search strategies for the exemplary search strategy for the systematic literature review which had been commissioned by the AkdÄ in order to develop therapy recommendations and was modified for the specific questions at hand. All databases were searched from their inception through January 2012.

#### Definition of the query terms

Because the topic of anxiety treatment is so broad, the search was initially limited to the common language—in German anxiety and fear are often not differentiate clearly (e.g., “Todesangst” and “Todesfürcht” have similar translations), and in the Anglo-American language, no differentiation is made, despite different words (anxiety and fear).

The present systematic literature review is one of several works that were commissioned within the framework of developing therapy recommendations for palliative medicine by the “Arzneimittelkommission der Deutschen Ärztekammer” (AkdÄ, Drug Commission of the German Medical Association).

### Tab. 1 Search strategy for PubMed

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<tr>
<td>Search palliative OR hospice OR terminal care OR terminally ill OR End of life care</td>
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</table>
Drug therapy of anxiety and fear in palliative care patients with cancer or other illnesses.
A systematic review

Abstract

Background. Pharmacological treatment of anxiety is an important part of drug treatment in palliative care. In this review we searched for the current evidence of pharmacological treatment of anxiety in palliative care. Materials and methods. A systematic search of PubMed, Embase, PsycLIT, PsycINFO, CINAHL for studies of anxiety in palliative care was carried out in January 2012. Furthermore we searched the Cochrane Library, references of literature and leading textbooks. Studies were identified and information was filled in a standardized extraction sheet. Studies have been categorized and anxiety as an endpoint determined. Results. A total of four controlled studies, three uncontrolled studies, two retrospective studies, one case report, two surveys, one systematic Cochrane review and one unsystematic review were analyzed and included in this review. This indicates an overall low number of studies for the pharmacological treatment of anxiety in palliative care. According to our results, benzodiazepines are the most commonly used drugs in palliative care. However, based on our review, there is no evidence-based recommendation for the therapeutic use in palliative care. Conclusions. With the existing evidence no general recommendation for pharmacological treatment of anxiety in palliative care can be given. Even for the commonly used benzodiazepines, neuroleptics, antidepressants, antihistamines and beta-blockers for the treatment of anxiety no evidence-based recommendations can be made. However, these medications are commonly used to treat anxiety in other patient populations and can also be used in palliative care patients. According to our review we cannot recommend a single drug or give recommendations regarding the dosage of drugs. There is a strong need for randomized controlled trials to evaluate the effect of drug treatment of anxiety in palliative care patients.

Keywords

Anxiety · Fear · Drug therapy · Palliative care · Systematic review

Medikamentöse Therapie der Angst bei Patienten mit fortgeschrittenen Tumorerkrankungen bzw.
Patienten in der palliativen Situation. Systematische Literaturübersicht

Zusammenfassung


Schlüsselwörter

Angst · Furcht · Medikamentöse Therapie · Palliativversorgung · Systematische Übersicht

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G. Nübling · S. Allmendinger · S. Lorenzl

Symptom-related anxiety such as anxiety with dyspnea or pain was not evaluated. The term anxiety was used based on the currently valid Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) with the text revision from 2000 (DSM-IV-TR).

In line with the Cochrane review article [22], the following pharmaceuticals and medicine classes were included in the search: benzodiazepines, antidepressants, anxiolytics, antipsychotics, buspiron, chlorpromazine, haloperidol, hydroxyzine, methotrimeprazine, olanzapine, risperidone, and thiordazine.

In addition to the search in the databases, the references of relevant publications from German and international textbooks [1, 3, 4, 16, 28, 64] were searched. Experts in the treatment of anxiety in palliative care and in psychiatric care were contacted concerning newer or ongoing studies.
The following sources were also searched: the references of articles and studies that were included in the present review and unpublished abstracts of national and international palliative medicine congresses/meetings.

Measurement instruments used to assess anxiety

Of the numerous measurement instruments used for the evaluation of anxiety, none have yet been specifically validated for nonsymptom-related anxiety in terminally ill patients. Therefore, all studies that used not only measurement instruments specific for anxiety [5], but also measurement instruments with a subscale for anxiety [63] were included. Examples of well-validated instruments are the Hamilton Anxiety Scale (HAM-A), Symptom Checklist 90 (SCL-90), Support Team Assessment Schedule (STAS), the Anxiety Subscale of Affects Balance Scale (ABS), the Hospital Anxiety and Depression Scale (HADS), the Edmonton Symptom Assessment System (ESAS), the Profile of Mood States, the Rotterdam Symptom Assessment System (RASS), the Neurology Quality of Life Questionnaire, and the Profile of Mood States. The following studies were excluded after viewing the abstracts: experimental animal studies; studies with patient groups that were not considered palliative care patients; studies examining the efficacy of nonpharmacological drugs or interventions for the treatment of anxiety; studies on depression; studies on fatigue, in which the treatment of anxiety was a side effect from the treatment (anxiety was not a primary endpoint). Nonclinical articles were excluded. The full-text manuscripts of the remaining studies were analyzed.

In agreement with the other review articles for the development of treatment recommendations, the following data were obtained in table form: publication details, patient characteristics, study location (e.g., hospital, hospice, palliative care station), medicines/pharmacotherapy, measurement instruments, and results. In the selection of the studies, the quality criteria of the Oxford scale [24] were used. Meta-analyses were not possible, because a variety of measurement instruments, medicines, doses, and time intervals were used in the studies. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33] were observed.

Tab. 2 Search strategy for Embase

<table>
<thead>
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<tbody>
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</tr>
<tr>
<td>#14 #7 AND #12 AND #13</td>
</tr>
<tr>
<td>#13 #10 OR #11</td>
</tr>
<tr>
<td>#12 #8 OR #9</td>
</tr>
<tr>
<td>#11 Alprazolam*/OR lorezepam*/OR oxazepam*/OR temazepam*/OR clonazepam*/OR diazepam*/OR midazolam*/OR haloperidol*/OR olanzapine*/OR quetiapine*/OR levomepromazine*/OR promethazine*/OR hlorpromazine*/OR sertaline Agonists*/OR paroxetine*/OR citalopram*/OR escitalopram*/OR clonazepam*/OR venlafaxine*/OR duloxetine*/OR malprotiline*/OR doxazepine*/OR trazadone*/OR zolpidem*/OR zaleplon*/OR eszopiclone*/OR diphenhydramine*/OR hydrazine*/OR propanolol*/OR bisoprolol*/OR buspirone*</td>
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</tr>
<tr>
<td>#9 Obsessive compulsive disorder:ab, ti OR generalized anxiety disorder:ab, ti OR terminal restlesslessness:ab, ti OR Panic disorders:ab, ti OR posttraumatic stress disorder:ab, ti OR phobias:ab, ti OR adjustment disorder:ab, ti OR posttraumatic stress disorder:ab, ti OR adjustment disorder:ab, ti OR agitation:ab, ti</td>
</tr>
<tr>
<td>#8 ‘Anxiety’/exp/mj OR ‘Fear’/exp/mj OR ‘Worry’/exp/mj OR ‘Anxiety disorders’/exp/mj</td>
</tr>
<tr>
<td>#7 #1 OR #2 OR #3 OR #4 OR #5 AND #6</td>
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<td>#6 ‘Clinical trial’:ti OR ‘clinical trial’:exp OR ‘clinical trial’:ab, ti OR ‘single’:ti OR ‘double’:ti OR ‘triple’:ti AND (‘masked’:ti OR ‘blinded’:ti) OR ‘placebos’/exp OR ‘placebo’/ab, ti OR ‘random’:ti OR ‘research design’:de OR ‘Follow-up studies’:exp OR ‘Prospective studies’:exp OR ‘Control’:ti OR ‘placebo’:ti OR ‘double’:ti OR ‘single’:ti OR ‘random’:ti OR ‘research design’:de</td>
</tr>
<tr>
<td>#5 ‘Lung diseases’:exp OR ‘Heart diseases’:exp OR ‘Pulmonary heart disease’:exp AND ‘Progressive’:ti OR ‘End-stage’:ti OR ‘End-stage’:ti</td>
</tr>
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<td>#4 ‘Acquired immunodeficiency syndrome’:exp OR ‘Aids-related complex disease’:exp OR ‘hiv’:exp OR ‘Hiv wasting syndrome’:exp OR ‘Aids’/exp</td>
</tr>
<tr>
<td>#3 ‘Multiple sclerosis’:exp OR ‘Amyotrophic lateral sclerosis’:exp</td>
</tr>
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<td>#2 ‘Cancer’/exp OR ‘Neoplasm’/exp OR ‘Tumour’/exp OR ‘Onco*’ OR ‘Carcinoma*’ OR ‘Malignant’*</td>
</tr>
<tr>
<td>#1 ‘Palliative’/exp OR ‘Hospice’/exp OR ‘Terminal care’/exp OR ‘Terminal illness’:exp OR ‘End of life care’:exp</td>
</tr>
</tbody>
</table>

The following studies were also searched: the references of articles and studies that were included in the present review and unpublished abstracts of national and international palliative medicine congresses/meetings.

Selection of relevant studies

The studies were selected in the following manner: title and abstract were reviewed by one author (SL) in order to determine appropriateness as to whether the manuscript should be further evaluated. The full text of the studies that were appropriate were examined by 3 review authors (SL, GN, SA). Prospective, randomized clinical trials with or without a pooled evaluation on the use of anxiolytics in palliative care patients were selected. In addition, a search for retrospective and review studies was performed. To be included, participants in the studies had to fulfill the following: terminally ill adult patients (≥18 years) who had received the diagnosis of “anxiety”. The studies were categorized; six endpoints were defined: anxiety, anxiety and depression, anxiety disorder, posttraumatic stress disorder, panic disorder, and phobia.

The following studies were excluded after viewing the abstracts: experimental animal studies; studies with patient groups that were not considered palliative care patients; studies examining the efficacy of nonpharmacological drugs or interventions for the treatment of anxiety; studies on depression; studies on fatigue, in which the treatment of anxiety was a side effect from the treatment (anxiety was not a primary endpoint). Nonclinical articles were excluded. The full-text manuscripts of the remaining studies were analyzed.

In agreement with the other review articles for the development of treatment recommendations, the following data were obtained in table form: publication details, patient characteristics, study location (e.g., hospital, hospice, palliative care station), medicines/pharmacotherapy, measurement instruments, and results. In the selection of the studies, the quality criteria of the Oxford scale [24] were used. Meta-analyses were not possible, because a variety of measurement instruments, medicines, doses, and time intervals were used in the studies. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33] were observed.
Results

The PubMed search, performed in January 2012, resulted in 947 hits, the Embase search through January 2012 had 1012 hits, the CINAHL search until January 2012 had 435 hits, the PsycLIT search until January 2012 resulted in 613 hits and the PsychINFO search until January 2012 resulted in 387 hits. The search in the Cochrane Library (until January 2012) resulted in 256 hits (Fig. 1). A total of 4 controlled studies and 3 uncontrolled studies on the pharmacotherapy of anxiety, 2 retrospective analyses, 1 case report, and 1 Cochrane review as well as 1 nonsystematic review article were included (Fig. 1).

A total of 4 controlled studies and 3 uncontrolled studies on the pharmacotherapy of anxiety, 2 retrospective analyses, 1 case report, and 1 Cochrane review article were included (Fig. 1). The studies included are characterized below.

Controlled studies for anxiety treatment in terminally ill patients

In a randomized, controlled trial, alprazolam administered at a dose of 0.5 mg orally over 10 days was compared to progressive muscle relaxation in 40 cancer patients with a low Karnofsky Index score (<60) [18]. The symptom anxiety was evaluated with various measurement parameters: HAM-A, SCL-90, Affects Balance Scale. No significant difference between the two treatments was observed, whereby both forms of treatment significantly reduced anxiety. Slightly superior efficacy was observed for alprazolam.

In another randomized, double-blind, placebo-controlled study, treatment with increasing doses of alprazolam over 4 weeks was studied in 36 cancer patients with actively metastasizing cancer and patients who were in remission [65]. The dose was increased stepwise during the first week to a maximum of 4 mg/day. The average dose of alprazolam was 1.2 mg/day. The average Karnofsky Index score for the two groups was 78.9. The symptom anxiety was measured using the HAM-A. The study showed no significant difference between alprazolam and placebo. However, anxiety was significantly reduced in both study arms, although 3% of the patients in the placebo group reported an increase of their anxiety symptoms.

In a randomized, double-blind, placebo-controlled cross-over study, Bruera et al. [10] examined the effect of mazindol (dose 2 mg) in 26 terminally ill cancer patients. Treatment duration was not provided. The primary endpoint was pain intensity. Anxiety was measured using the HAM-A. It showed that pain intensity and pain reliever use in the treatment group had decreased significantly, but that anxiety was reported to worsen over the course of the study.

Methylprednisolone at a daily dose of 32 mg over 34 days was examined in a randomized, double-blind, placebo-controlled cross-over study with 31 terminally ill cancer patients [11]. The primary endpoint in this study was pain intensity. No effect on anxiety was observed.

Noncontrolled studies on anxiety treatment in terminally ill patients

Barreto et al. [2] prospectively studied various medicines for the treatment of anxiety in 100 terminally ill cancer patients. The study did not report the dose or the type of escalation or administration of the medicines. For the evaluation and assessment of change of anxiety of over time, nonstandardized questionnaires, which the patients completed on notebooks, were used. Nevertheless, 66% of the patients questioned indicated that anxiety was a burdensome symptom. An evaluation of the efficacy of drug treatment was not performed in this study.

In a prospective study with 140 men with HIV/AIDS, anxiety was evaluated in...
### Tab. 3  Controlled studies on anxiety treatment in patients with a terminal illness

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Design</th>
<th>Patients</th>
<th>Measurement parameters</th>
<th>Therapy</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holland, 1991 [18]</td>
<td>Randomized, controlled trial (simple blind)</td>
<td>40 cancer patients with a low Karnofsky Index (&lt;60) over 10 days</td>
<td>Hamilton Anxiety Scale, Symptom Checklist 90, Affects Balance Scale</td>
<td>Alprazolam 0.5 mg/day for 10 days and progressive muscle relaxation for 10 days</td>
<td>Alprazolam was slightly more effective than progressive muscle relaxation, which was not clinically significant. Both therapies resulted in significant reduction of the endpoint compared to the baseline value</td>
<td>No untreated control group, Low dose of alprazolam, Small number of patients</td>
</tr>
<tr>
<td>Wald, 1993 [65]</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>36 cancer patients with an average Karnofsky index &gt;78.9 over 4 weeks</td>
<td>Hamilton Anxiety Scale</td>
<td>Increasing doses of alprazolam to a maximum of 4 mg/day during week 1. The average daily dose of alprazolam was 1.2 mg. Duration: 4 weeks</td>
<td>In the two treatment arms, placebo and alprazolam both resulted in significant reductions of the anxiety. In the placebo group, 3% of the patients reported and increase of their anxiety symptoms</td>
<td>Low dose of alprazolam, Uptitration of dose was not controlled, Low number of patients</td>
</tr>
<tr>
<td>Bruera, 1986 [10]</td>
<td>Randomized, double-blind placebo-controlled cross-over study</td>
<td>26 cancer patients</td>
<td>Hamilton Anxiety Scale</td>
<td>Mazindol at a dose of 1 mg, twice daily (n=12), Placebo (n=14) Duration: 3 weeks</td>
<td>Pain intensity and pain reliever use in the treatment group decreased significantly; however, anxiety became worse</td>
<td>Anxiety was not a primary endpoint in this study, Low number of patients</td>
</tr>
<tr>
<td>Bruera, 1985 [11]</td>
<td>Randomized, double-blind placebo-controlled cross-over study</td>
<td>31 terminally ill cancer patients over 14 days</td>
<td>Hamilton Anxiety Scale</td>
<td>32 mg methylprednisolone (16 mg twice daily) Duration: until end of life or for a maximum of 8 weeks</td>
<td>Depression was significantly reduced in 22 patients, while no effect was observed in anxiety.</td>
<td>Anxiety was not a primary endpoint in this study, Low number of patients</td>
</tr>
</tbody>
</table>

### Tab. 4  Noncontrolled studies on treatment of anxiety in terminally ill patients

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Design</th>
<th>Patients</th>
<th>Measurement parameters</th>
<th>Therapy</th>
<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Barreto, 1996 [2]</td>
<td>Noncontrolled, prospective, nonblinded study</td>
<td>100 cancer patients</td>
<td>No standardized scale, questionnaire on a notebook</td>
<td>Nonstandardized medicines</td>
<td>66% of the patients reported anxiety, no correlation with drug treatment</td>
<td>Prospective design, No standardized scale to measure anxiety, Medicines were not stated</td>
</tr>
<tr>
<td>Butters, 1992 [12]</td>
<td>Uncontrolled, prospective nonblinded study</td>
<td>140 patients with HIV/AIDS over 4 weeks</td>
<td>Support Team Assessment Schedule</td>
<td>Medicines for control of anxiety not stated</td>
<td>Symptom control was overall very difficult, only anxiety as an item of the Support Team Assessment Schedule was significantly improved</td>
<td>Only male patients, Medicines not stated</td>
</tr>
<tr>
<td>Laug- sand, 2009 [30]</td>
<td>Europe-wide prospective study</td>
<td>3030 cancer patients</td>
<td>No standardized scale, questionnaire</td>
<td>Medicines not standardized</td>
<td>In this study, 28% of the patients stated that anxiety was a severely burdensome symptom. However, almost 40% of the patients did not receive adequate treatment. The majority of patients receiving treatment were administered benzodiazepines</td>
<td>No statement on pharmacological or nonpharmacological treatments</td>
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addition to other symptoms [12]. There was no influence on medicine selection. The majority of patients were inpatients (62%), while 35% were outpatients. The average care or observation time was 31 weeks and 5 days. The STAS scale was used. The items of this scale include anxiety of the patients, anxiety of the relatives, but also the anxiety reactions of the care team. However, only the anxiety of the patients showed significant improvement in this study.

In a Europe-wide, prospective study, Laugsand et al. [30] examined the intensity and treatment of symptoms in palliative care patients. In this study, 28% of patients reported that anxiety was a severely burdensome symptom. Nearly 40% of patients, however, did not receive adequate treatment. The majority of patients who did receive treatment were treated with benzodiazepines. There were large differences between countries concerning dosage and administration.

### Retrospective studies

In a retrospective case analysis of 39 patients with far-advanced cancer, the efficacy of alprazolam at a dose of 1.5–4.0 mg orally (treatment started with 1.25 mg and was thereafter escalated individually by 0.5 or 0.75 mg) was studied [15]. A nonstandardized questionnaire was used. Moderate to significant improvement was documented in 87% of patients.

In a retrospective case analysis of 160 patients from the palliative care station showed that 70% of the patients were administered benzodiazepines [59]. Due to the commonly observed association of anxiety and agitation, lorazepam was prescribed most often, followed by oxazepam as a sleep-inducing medicine. In 5 patients, midazolam was used with the intention of terminal sedation.

### Case reports

Irwin and Iglewicz [20] described the oral administration of ketamine (27.5 mg and 32.5 mg ketamine, respectively) for the treatment of depression and a possible effect on anxiety. In both patients, there was not only good efficacy on the depressive symptoms, but there was also a significant reduction of anxiety, which was evaluated using the HADS.

### Systematic reviews

The Cochrane review by Jackson and Lipman [22] identified and included 6 studies on anxiety which are included in the present review. Due to deficiencies in the studies or the analyses, no recommendation for the pharmacological treatment of anxiety could be made based on these studies. An update in 2009 did not result in the inclusion of any new studies; thus, there were no changes in the recommendations.

### Nonsystematic treatment recommendations

Kolva et al. [29] listed the following classes of medicines in their review article on the pharmacological treatment of anxiety in patients in the last phase of their lives: benzodiazepines (led by alprazolam), histamines (hydroxyzine and diphenhydramine), neuroleptics (haloperidol, olanzapine, and quetiapine) and antidepressants (Tab. 7).

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### Tab. 5 Retrospective articles

<table>
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<th>First author, year</th>
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<th>Patients</th>
<th>Measurement parameters</th>
<th>Therapy</th>
<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fernandez, 1987 [15]</td>
<td>Despite prospective design, retrospective data evaluation</td>
<td>39 cancer patients with an average Karnofsky index of 80 and weekly patient contact over an undetermined period of time</td>
<td>No standardized scale, questionnaire</td>
<td>Alprazolam at a dose of 1.0–4.0 mg/day</td>
<td>87% of patients reported a moderate to significant improvement of anxiety</td>
<td>33 of the 39 patients were women from the gynecological outpatient department</td>
</tr>
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</table>

| Stiel, 2008 [59] | Retrospective data evaluation | 160 patients from the palliative care station | None | Benzodiazepines | 70% of the patients received benzodiazepines. Lorazepam was most often administered due to the commonly observed association of anxiety and agitation, followed by oxazepam as a sleep-inducing medicine | Anxiety was not a specific endpoint |

### Tab. 6 Case reports

<table>
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<tr>
<th>First author, year</th>
<th>Design</th>
<th>Patients</th>
<th>Measurement parameter</th>
<th>Therapy</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irwin, 2010 [20]</td>
<td>Prospective study</td>
<td>2 cancer patients</td>
<td>Hamilton Anxiety Scale</td>
<td>Ketamine at a dose of 27.5 mg and 32.5 mg, respectively</td>
<td>In both patients, not only was a good effect on the depressive symptoms observed, but also a significant reduction of the anxiety</td>
<td>None</td>
</tr>
</tbody>
</table>
Discussion

This systematic literature review on the pharmacotherapy of anxiety in patients with advanced stages of cancer or patients receiving palliative care included 4 controlled clinical trials, 3 noncontrolled clinical studies, 2 retrospective studies, 1 case report, 1 systematic Cochrane review and 1 nonsystematic treatment recommendation. The Cochrane review from 2009 [22] was updated from the original work in 2004; however, there were no important studies during this time period. In addition, no controlled studies regarding anxiety in palliative care had been performed in the last 3 years. This is surprising, because anxiety plays an important role as a single symptom in palliative care that should not be underestimated in maintaining the quality of life of patients [14].

The causes, consequences and especially the treatment of anxiety in terminally ill patients were only reported in a few systematic reviews [23, 29, 34, 45, 54, 63, 66]. Most of these reviews do not go into detail concerning the pharmacological treatment of anxiety. Thus, they were not able to support their recommendations with a sufficient number of qualified studies, but are in line with recommendations from psychiatry. Therefore, no guidelines for the treatment of anxiety in palliative care patients have been published until now. In addition, there is a lack of a generally accepted definition of anxiety and a generally validated measurement instrument for anxiety in patients in the terminal phase of life, which makes comparison of the studies difficult.

This is surprising, if one considers that anxiety is one of the most common symptoms in palliative care and approximately 30–70% of palliative care patients are administered anxiolytics during their inpatient stay [59].

The 4 controlled studies that were already included in the Cochrane review [22] do not have sufficient statistical power, because the numbers of patients were too small and the study durations were very short. In particular, in the studies by Holland et al. [18] and Wald et al. [65], smaller doses of alprazolam, which may have possibly been insufficient dosages, were studied. On the other hand, in palliative care, it is often not necessary or not possible to administer higher doses due to limited organ function. The reasons for the low dosages, however, were not mentioned in these two studies.

In a further study by Bruera et al. [11], in which the primary effect of methylprednisolone on pain was studied, no in-
fluence of the medicine on comorbid anxiety was found, although depression could be improved. In addition, this study only included a small number of patients over a duration of one month. Changes in the clinical situation of the patients or non-pharmacological factors influencing on the parameter examined were not provided.

In further studies on anxiety in patients with far-advanced terminal illnesses, information concerning the medicines prescribed was lacking completely [2, 12]; thus, evaluation with respect to a therapeutic recommendation could not be made.

In the few clinical studies presented here on the treatment of anxiety in terminally ill patients, alprazolam was mainly administered. It was used, because it is also broadly used in psychiatry due to the short half-life and its favorable side-effect profile. Lorazepam, which is also short acting in its highly soluble form, has not been observed in any studies, because no controlled studies for the pharmacological treatment of anxiety in terminally ill patients have been performed since it has become available. Midazolam and propofol, which are commonly used in palliative care for the treatment of anxiety, have not been compared in any controlled study. The Cochrane review refers to an article containing recommendations from the American College of Critical Care Medicine and the Society of Critical Care Medicine on the treatment of anxiety in intensive care patients [56]. These guidelines can be a useful approach for the meaningful administration of pharmacotherapy in palliative care. In this work, the use of midazolam or propofol was advocated for use in intensive care patients. In longer-term treatment of anxiety, lorazepam is mentioned as the medicine of choice.

As already mentioned in the introduction, anxiety can also occur as a natural reaction. It accompanies the development of the individual in the process of dying. With respect to anxiety based on the realization of pending death in cancer patients and severely ill, there are varying study results. Several studies show that anxiety during the dying process increases [39, 57], whereby another study contradicts this [29]. The essential difference between the studies is the different definitions for anxiety and the measurement parameters used; thus, it is not possible to compare them.

In most studies, psychosocial support correlates negatively with the development of anxiety [26, 29, 43]. It can be assumed that the patients in the studies we identified also received psychosocial support. In none of the studies, however, was this form of nonpharmacological anxiety treatment mentioned, so that a possible bias cannot be excluded here. With respect to belief in life after death, there are contradictory data. Most studies show, however, that believing in life after death positively influences the perceived anxiety [38, 52]. The effect of spirituality on the patients included in the studies or how much additional support in the form of spiritual support had taken place was not mentioned in any of the studies we identified.

As already mentioned, anxiety as the only symptom in palliative care is not unusual. In the terminal phase of life, anxiety and depression are often comorbid symptoms. Thus, a mixed anxiety–depression phenotype of depression in cancer patients was a result [9]. This newly classified phenotype, which is not generally accepted yet, was taken into consideration in the present literature search, but which did not result in any further study evidence. Concerning depression as a unique symptom in terminally ill patients, numerous studies [19, 32, 48, 50] already exist from which good classification possibilities and recommendations for treatment can be identified; this is not the situation for anxiety.

Furthermore, for anxiety as a unique symptom, it is not easy to identify limitations based on confounder effects of somatic symptoms, which can appear as a physical manifestation of anxiety, especially in patients with far-advanced, severe illnesses [23, 44, 45]. Many people in the terminal phase develop anxiety based on symptom progression and the appearance of new symptoms. These are not isolated forms of anxiety, but are situational, organic, and existential anxiety in association with symptom progression or with progressing physical deterioration and weaknesses. Thus, the treatment of these different forms of anxiety is initially based on the treatment of the underlying somatic disease or symptom control.

In the pharmacological treatment, it must be taken into consideration that the anxiety of patients with advanced cancer can be increased [47] or even decreased [49] by the use of palliative care services. In a survey of 291 rehabilitation patients with progressing disease, it could be shown that palliative and curatively treated patients both had similarly high levels of anxiety; however, palliative care patients had greater fear of relapse compared to the group treated with curative intent [6]. From this article, knowledge alone that one is in the palliative phase can cause anxiety. Good patient information and open discussions in the palliative situation decrease anxiety [60]. Thus, a general, ethical problem certainly arises when performing a blinded, randomized trial on the treatment of anxiety in palliative care patients, because alone the perception of anxiety and open patient information discussions are a reasonable intervention to reduce anxiety.

Thus, pharmacological treatment should only be started after careful clinical and, if necessary, psychiatric evaluation. In the diagnosis and differential diagnostic classification of anxiety, the scales mentioned above are helpful. Particularly worth mentioning is the STAS [17], because several items inquire about anxiety and also the anxiety of family members is taken into consideration, which can have among other things an influence on the anxiety of a patient.

No studies on the treatment of patients with psychiatric diseases (particularly anxiety) and terminal cancer were found. In our experience, patients who are already psychologically ill and are in the terminal phase often require professional psychological care [46, 61], because these illnesses, even if they possibly were previously well controlled, may need intensive therapeutic care due to the presence of stressors in the terminal phase of life.

Furthermore, no study on terminal sedation for the treatment of anxiety was identified, despite terminal sedation commonly being used in this context. In addition, in the recommendations on the ter-
minal sedation of palliative patients, benzodiazepines are listed as the first line treatment for reducing anxiety [13] but without being able to refer to controlled studies.

When making the decision concerning pharmacotherapy of anxiety in palliative care patients, the severity of the symptoms and their influence on quality of life are important. In addition, it must be taken into consideration that treatment should generally begin with lower doses of medicine because of reduced organ functions and increased sensitivity to pharmaceuticals.

Due to a lack of specific studies, the treatment of anxiety should be orientated toward psychiatric recommendations. Based on the present articles, a patient who continuously suffers from anxiety and for whom anxiety represents a burdensome stress factor in the terminal phase should be treated with benzodiazepines. For the majority of palliative care specialists, benzodiazepines are the medicine of choice for the treatment of anxiety in terminally ill patients [22, 23, 29, 42, 53, 58, 59]. In the palliative situation, however, it must be taken into consideration that benzodiazepines may cause slight confusion. This is especially true in older patients and those with renal impairment. Therefore, in the case of benzodiazepine therapy, short-acting benzodiazepines, e.g., alprazolam, lorazepam or oxazepam, should preferably be administered. Alprazolam is particularly used in panic disorders and can be also used as an antiemetic. Longer-acting benzodiazepines, e.g., clonazepam, also have a stabilizing effect on the psyche (mood stabilizer) and should therefore be used in patients with severe, long-term anxiety.

Sedating antidepressants also have therapeutic use in the treatment of long-term anxiety. Mirtazapine and trazadone are especially important, because sleeping disorders often accompany anxiety. Duloxetine is used in anxiety and sleep disorders and can also be used when neuropathological pain is present.

In terminally ill patients, in whom anxiety occurs along with sleep disorders and confusion, non-sedating neuroleptics (e.g., haloperidol) or sedating neuroleptics (e.g., olazapine and quetiapine) can be used. Neuroleptics can also be effective in drug-induced anxiety. They are used until changes in the patient’s medication results in improvement of anxiety.

The effect of antipsychotics in the treatment of anxiety in palliative care patients has not, however, been sufficiently documented [27, 40]. In patients with reduced pulmonary function or central breathing disorders, benzodiazepines can not be used without risks. In these patients, antihistamines, e.g., diphenhydramine and hydroxyzine, can be used [29]; however, the anticholinergic effect of these medicines must be taken into consideration especially in the elderly and patients with delirium.

Buspirone should be used in patients with generalized anxiety disorder and in patients who appear to have the potential of abusing the medicine. The fact that an effect only occurs after approximately 10 days can be problematic in palliative care [22].

In anxiety that is accompanied by panic, alprazolam or lorazepam should be used. Both have a rapid effect on panic disorder. It is also reasonable in these patients to combine their use with serotinin reuptake inhibitor or with a tricyclic antidepressant. Serotonin reuptake inhibitors such as sertraline, paroxetine, citalopram, and escitalopram should be preferred to tricyclic antidepressants, because they have fewer side effects and are effective for depression and anxiety, which often occur simultaneously. However, antidepressants require 1–4 weeks before an effect can be observed and, therefore, are not appropriate for acute situations. Also the use of β-blockers are reasonable for the treatment of patients in the terminal phase, especially if the patients are already being administered β-blockers. It is then possible that low-dose β-blocker therapy should be continued presuming that the blood pressure situation allows this.

Conclusion

On the basis of this literature review, no general recommendations for the pharmacological treatment of anxiety in palliative care can be made.

In addition, no sufficient proof for the use of benzodiazepines in palliative care patients was found in controlled trials. In review articles, benzodiazepines, antidepressants, neuroleptics, hypnotics, antihistamines, and β-blockers have been listed for the treatment of anxiety in terminally ill patients. From the current studies, it was not possible to determine the correct dose and duration of relief for the various substances.

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