

Evidenztabelle der S3- Leitlinie Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung

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Evidenztabelle

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1 Informationen zum Leitlinienreport

In diesem Dokument wird das methodische Vorgehen bei Erstellung der aktualisierten Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Version 3.0, beschrieben.

Informationen zu vorherigen Versionen der Leitlinie sind in den Leitlinienreporten der jeweiligen Version abgebildet und auf der Website des Leitlinienprogramms Onkologie abrufbar.

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1.3 Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche
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onkologie.de/leitlinien/palliativmedizin/](https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/)] (Zugriff am TT.MM.JJJJ)

2 Evidenztabellen

Es werden im Folgenden nur Evidenztabellen aufgeführt, die im Rahmen der Aktualisierung der Leitlinie (2026) entstanden sind. Für weitere Tabellen verweisen wir auf frühere Versionen des Leitlinienreports.

Kapitel 5: Versorgungsstrukturen

Kapitel 5.4: Die drei Stufen der Palliativversorgung

Kapitel 5.4.3: Spezialisierte Palliativversorgung (SPV)

Literaturreferenzen: [\[1\]](#), [\[2\]](#), [\[3\]](#), [\[4\]](#), [\[5\]](#), [\[6\]](#), [\[7\]](#), [\[8\]](#), [\[9\]](#), [\[10\]](#), [\[11\]](#), [\[12\]](#), [\[13\]](#), [\[14\]](#), [\[15\]](#), [\[16\]](#), [\[17\]](#), [\[18\]](#), [\[19\]](#)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxford Level of Evidence
Byrne et al., 2022,	Cochrane Systematic Review Aim: To assess the evidence for early palliative care interventions, including referral to specialist palliative care services, for improving outcomes in adults diagnosed with a primary malignant brain tumour and their carers.	Databases: CENTRAL, MEDLINE, CINAHL, Web of Science, PsycINFO, plus clinical trial registries and grey literature. Inclusion: RCTs, non-randomised studies, qualitative and mixed-methods studies evaluating early palliative care interventions for adults with primary malignant brain tumours and/or their informal carers.	Intervention: Early palliative care interventions (specialist or generalist) within a defined timeframe post-diagnosis or surgery. Outcomes: Quality of life, symptom control, psychological outcomes, survival, and carer outcomes.	Only one small RCT was included, focusing on early cognitive rehabilitation within 2 weeks of surgery (Zucchella 2013). This showed limited benefits in visual attention and verbal memory but no impact on broader cognitive functions or quality of life. No studies were found addressing early referral to specialist palliative care services.	There is a significant lack of evidence on early palliative care for people with primary brain tumours. High-quality research is needed to define effective early palliative care interventions in this population.	2
Cui et al., 2023,	Systematic Review and Meta-analysis. Aim: To evaluate the	Databases: PubMed, Embase, Cochrane Library Inclusion:	Intervention: Early palliative care versus	19 RCTs included. EPC has a positive effect on quality of life	Findings support early palliative care as	1

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxford Level of Evidence
	effects of early palliative care on quality of life (QoL), depression, anxiety, and survival in patients with advanced cancer.	Randomized controlled trials involving patients with advanced cancer receiving early palliative care.	standard care Outcomes: QoL, depression, anxiety, survival	(SMD = 0.14, 95% CI [0.06, 0.22], p = .001), symptom burden (SMD = 0.14, 95% CI [0.01, 0.26], p = .028), and levels of satisfaction (MD = 4.31, 95% CI [2.87, 5.75], p < .001). However, EPC did not have a significant positive effect on anxiety (MD = -0.10, 95% CI [-0.26, 0.05], p = .199) or survival rates (HR = 0.88, 95% CI [0.74, 1.03], p = .119).	beneficial for QoL; psychological outcomes showed mixed results. Heterogeneity across studies was generally low for QoL outcomes.	
Gautama et al., 2023,	Systematic Review and Meta-analysis Aim: To determine the effectiveness of early palliative care (EPC) on quality of life (QoL) in patients with advanced cancer.	Databases: „PubMed, ProQuest, MEDLINE (EBSCOhost), Cochrane Library, ClinicalTrials.gov Inclusion: RCTs on adults with advanced/metastatic cancer, assessing effects of EPC vs. standard oncology care on QoL, mood, and symptoms.	Intervention: Early palliative care Outcomes: QoL (primary), mood and symptom control (secondary)",	12 RCTs (N=2364). Significant improvement in QoL (SMD = 0.16, 95% CI: 0.04,- 0.28). No significant effect on mood (MD = -0.90, 95% CI: -2.32,- 0.51) or symptom control (MD = -1.49, 95% CI: -3.81, - 0.81).",	Supports effectiveness of EPC for QoL in advanced cancer. No consistent effects on mood or symptom burden. Moderate heterogeneity varied intervention timing and cancer types.	1
Hoomani et al., 2022,	Systematic Review and Meta-analysis Aim: To examine the impact of palliative care on quality of life in adults with advanced cancer.	Databases: Web of Science, Scopus, MEDLINE (via PubMed, and ProQuest), Science Direct and Google Scholar Inclusion: RCTs involving adults with advanced cancer receiving palliative care.	Intervention: Palliative care vs. usual care Outcomes: Quality of life at multiple follow-up intervals,	25 RCTs (N=5160) Significant improvement in QoL: g=0.25 at 1 - 3 months (95% CI: 0.1,- 0.41), g=0.1 at 4,- 7 months (95% CI: 0.019,- 0.18). Outpatient (g=0.27), early (g=0.27), and end-of-life palliative care (g=0.24) showed benefit. ,> 10 months follow-up	Results support benefit of early and outpatient palliative care for QoL. Less clear effect at longer-term follow-up. No pooled results for other outcomes.	1

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxofrd Level of Evidence
				showed non-significant effect (g=0.19 95% CI: -0.03 to 0.42).		
Huo et al., 2022	Systematic Review and Meta-analysis Aim: To compare the effects of early palliative care versus standard oncologic or on-demand palliative care in patients with incurable cancer.,	Databases: "PubMed, Embase, Web of Science, Cochrane Library, ClinicalTrials.gov, WHO ICTRP. Inclusion: Randomized controlled trials in patients with incurable cancer receiving early palliative care versus standard care."	Intervention: Early palliative care Outcomes: quality of life, symptom burden, mood, survival, place of death, resource use"	16 RCTs included. Early palliative care improved <i>quality of life</i> (SMD=0.737), <i>symptom control</i> (SMD=0.304), <i>mood</i> (SMD=-.443), <i>survival</i> (HR=1.521), and <i>increased probability of dying at home</i> (HR=1.153). No significant differences in resource use.	Quality of evidence considered low due to heterogeneity and limited number of studies for some outcomes. Effects are promising but need further validation	1
Kochovska et al., 2020, (+Curov)	Systematic Review and Meta-analysis Aim: To evaluate the effectiveness of early integrated palliative care in people with lung cancer and their caregivers.	Databases: MEDLINE and PubMed Inclusion: Studies on lung cancer patients and/or their caregivers receiving early palliative care.	Intervention: Early integrated palliative care Outcomes: Patient and caregiver QoL, mood, symptom burden, satisfaction, survival	11 included studies: Mixed results. Some studies showed improved QoL and symptom control in patients, and reduced caregiver burden. Meta-analyses conducted where possible, but variation in measures limited pooling.	Narrative synthesis with some pooled data. Highlights potential benefit of early palliative care, but heterogeneity in outcomes and delivery models limits conclusions	2
Kumari et al., 2024	Systematic Review and Meta-analysis. Aim: To examine the effectiveness of palliative care versus conventional care in advanced gynecological cancer patients and their caregivers.	Databases: PubMed, PubMed Central, Clinical Key, Embase, Grey Literature. Inclusion: RCTs on advanced gynecological cancer patients receiving specialist palliative care.	Intervention: Specialist palliative care Outcomes: Quality of life, symptom burden, depression (patients and caregivers).	4 RCTs included. QoL: SMD = 0.26 (95% CI: -0.29-0.80), symptom burden: SMD = -0.75 (95% CI: -1.75-0.25), patient depression: SMD = 0.08 (95% CI: -0.19-0.34), caregiver depression: SMD = -0.16 (95% CI: -0.56-0.24).	Low to very low certainty. Small effect sizes and high heterogeneity. Results suggest some benefit of palliative care on QoL and symptom burden; cautious interpretation recommended.	1
Shih et al., 2022,	Meta-analysis Aim: To evaluate the effects of early	Databases: "PubMed, Embase, CINAHL, MEDLINE, Cochrane	Intervention: Early palliative care Outcomes:	12 RCTs (N=2980). Early palliative care improved QoL ,< 3 months	,Consistent small-to-moderate benefits across	1

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxofrd Level of Evidence
	palliative care on quality of life (QoL), symptom intensity, and functional well-being (TOI) in advanced cancer patients.",	Library Inclusion: RCTs including patients with advanced cancer receiving early palliative care.	Quality of life (QoL), functional wellbeing., symptom intensity, Trial Outcome Index (TOI)",	(SMD = 0.16 95% CI: 0.05,- 0.27) and >3 months (SMD = 0.26 95% CI: 0.11,- 0.40). Reduced symptom intensity >3 months (SMD = 0.18 95% CI: 0.06, - 0.31) and improved TOI , < 3 months (SMD = 0.28 95% CI: 0.11,- 0.45).	outcomes. Supports early palliative care as clinically meaningful addition to cancer treatment. Heterogeneity moderate.,	

Kapitel 5.4.3.2: Palliativdienst im Krankenhaus

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxofrd Level of Evidence
Bajwah et al., 2020,	Cochrane Systematic Review and Meta-analysis Aim: To assess the effectiveness and cost-effectiveness of hospital-based specialist palliative care (HSPC) for adults with advanced illness and their caregivers.	Databases: CENTRAL, CDSR, DARE, MEDLINE, Embase, CINAHL, PsycINFO, NHS EED Inclusion: RCTs evaluating hospital-based specialist palliative care for adults with advanced illness and caregivers	Intervention: Hospital-based specialist palliative care. Outcomes: HRQoL, symptom burden, patient satisfaction, preferred place of death, caregiver burden, anxiety, depression, cost-effectiveness", "	42 RCTs (N=7779). HSPC improved HRQoL (SMD=0.26), reduced symptom burden (SMD=-0.26), improved satisfaction (SMD=0.36), and increased chance of dying at home (OR=1.63). No consistent effects on caregiver burden or costs. Quality of evidence: low to very low.",	Comprehensive review with high heterogeneity. Limited caregiver outcome data. Most effects small but clinically meaningful in end-of-life context.	1

Kapitel 5.4.3.3: Spezialisierte ambulante Palliativversorgung (SAPV)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis) Aim	Databases, Inclusion Criteria, Population	Interventions & Outcome	Results	Comments	Oxofrd Level of Evidence
Hwang et al., 2023,	Systematic Review Aim: To evaluate the impact of home-based supportive care (HbSC) programs on quality of life in patients with advanced cancer.,	Databases: PubMed, Embase, Cochrane, CINAHL, Web of Science Inclusion: Clinical trials evaluating HbSC in patients with advanced cancer."	Intervention: "Home-based supportive care (HbSC) programs including home visits, caregiver education, home nursing, psychotherapy, exercise, phone consults Outcomes: Quality of life (QoL)",	17 studies included. 9 reported improved QoL in various domains (emotional, social functioning, subjective well-being). Effects varied based on HbSC components.,	Narrative synthesis due to heterogeneity No pooled effect estimates reported. HbSC appears promising but further standardization and evaluation needed.	1
Shepperd et al., 2021,	Cochrane Systematic Review Aim: To assess whether providing home-based end-of-life care reduces hospital deaths and affects patient and caregiver outcomes compared with inpatient care.,	databases: "CENTRAL, MEDLINE, Embase, CINAHL Inclusion: RCTs comparing home-based end-of-life care with inpatient or hospice care for terminally ill patients."	Intervention: Home-based end-of-life care Outcomes: Place of death, symptom control, patient and caregiver satisfaction, healthcare use, costs	9 RCTs included (N=1571). Home-based care increased probability of dying at home (RR=1.33, 95% CI: 1.14, 1.55), improved satisfaction, and showed no adverse effects on symptom control or caregiver burden. Some reductions in healthcare use and costs.,	Moderate-quality evidence. Consistent direction of effect. Most benefit seen in achieving preferred place of death and satisfaction with care.	2

Kapitel 6: Kommunikation

Kapitel 6.5: Vorausschauende Versorgungsplanung

Verknüpfte Empfehlungen:

Empfehlung 6.10:

Gegenstand der Gespräche zur vorausschauenden Versorgungsplanung *soll* sein:

- Umfang und Grenzen der Behandlung im Fall (erkrankungs-)typischer sowie häufiger und möglicher Szenarien und Komplikationen;
- individuelle Präferenzen hinsichtlich der Versorgung in der letzten Lebensphase, des Betreuungs- und Sterbeortes sowie ggf. der Bestattung;
- Benennung eines Vorsorgebevollmächtigten oder Vorschlag einem/einer Betreuer: in.

Empfehlung 6.12:

In die Gespräche zur vorausschauenden Versorgungsplanung *sollen* im Einvernehmen mit den Patient: innen dessen Angehörige sowie gegebenenfalls Vorsorgebevollmächtigte/Betreuer: innen einbezogen werden.

Empfehlung 6.9:

Patient: innen mit einer nicht heilbaren Krebserkrankung *sollen* das Angebot einer vorausschauenden Versorgungsplanung erhalten.

Literaturreferenzen: [\[20\]](#), [\[21\]](#)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	Oxford Level of Evidence
Levoy et al. (2024) [20]	Meta-Analysis; To investigate the association between, and moderators of, ACP and aggressive versus comfort-focused EOL care outcomes among patients with cancer.	Five databases (CINAHL, Cochrane Library, PubMed, Scopus, Web of Science) were searched for peer-reviewed observational/experimental ACP-specific studies that were published between 1990-2022 that focused on samples of patients with cancer.	Interventions: three types of ACP: 1. Documentations, 2. Communication components 3. Full ACP (combination of communication and documentation) Outcomes: 1) aggressive; and 2) comfort-focused care	<p>20 studies included (4RCTs, 16 non-experimental) with 33,541 patients.</p> <p>1. Aggressive EOL (End-of-Life) Care: Significant associations between ACP (Advance Care Planning) and: Chemotherapy: OR = 0.72, p = .007, k = 7; ICU Admissions: OR = 0.71, p < .001, k = 7; Hospital Admissions: OR = 0.55, p < .001, k = 6; Hospice use for fewer than 7 days: OR = 0.60, p = .032, k = 5; Hospital Death: OR = 0.48, p = .021, k = 4 Composite Aggressive Intervention; Outcomes: OR = 0.59, p < .001, k = 4. Non-significant associations with: Cardiopulmonary Resuscitation, Mechanical Ventilation, Emergency Department Admissions</p> <p>2. Comfort-focused EOL Care Outcomes: Hospice Use: Non-significant association (p = .185). Do Not Resuscitate Orders: Significant association: OR = 1.51, p = .048, k = 5. Patients engaged in ACP had 1.51 times higher odds of completing a DNR order compared to those who did not engage in ACP. Hospice Use in Observational vs. Experimental Studies: Observational designs: Significant association, OR = 1.52, 95% CI: 1.14; 2.03, p = .004 vs. Experimental designs: Non-significant association (p = .559)</p> <p>3. Moderation: ACP Type as Moderator of ACP and hospital admissions at EOL: All ACP types significantly reduced hospital admissions, but variations in effectiveness were observed: Communication-only ACP: OR = 0.40, p < .001</p>	<p>End-of-life discussions are associated with less aggressive, less costly EOL care. Clinicians should initiate these discussions with cancer patients earlier to better align care with preferences.).</p> <p>Mixed methods</p> <p>Heterogeneity in Populations</p>	3

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	Oxford Level of Evidence
				(60% reduced odds); Documentation-only ACP: OR = 0.67, p < .001 (33% reduced odds); Full ACP: OR = 0.67, p = .019 (33% reduced odds)		
Malhotra et al. 2022 [21]	Systematic Review of RCTS To conduct an up-to-Date systematic review of all randomised controlled trials assessing efficacy of advance care planning (ACP) in improving patient outcomes, healthcare use/costs and documentation.	Three databases: (MEDLINE/PubMed, Embase and Cochrane databases) Inclusion criteria: English-language, randomised or cluster randomised controlled trials on 11 May 2020 and updated it on 12 May 2022 29% cancer patients	Intervention: ACP as a process that supports adults at any age or sage of health in understanding and sharing their personal values, life goals and preferences regarding future medical care'. (ADs, Communication, or test of decision aids) Outcome: distal, proximal & Helathcare use /costs	<ul style="list-style-type: none"> - Quality of life: 14 RCTs assessed quality of life; none showed improvement in quality of life. - Of the 19 RCTs evaluating mental health outcomes, only 4 (21%) showed improvement in mental health. - Treatment preference: 23 RCTs evaluated the effect of ACP on treatment preference/goals/values. Majority (16, 70%) found that the intervention increases a preference for comfort care - 14 RCTs assessed decisional conflict. Of these 9 (64%) showed that ACP reduced decisional conflict - Health/Care Cost: This outcome was assessed by 22 RCTs. Of these four (18%) RCTs showed significantly reduced healthcare use/costs. - Two RCTs conducted in specific settings/patient groups found evidence of reduced hospitalisations as a result of ACP. 	<ul style="list-style-type: none"> - Hetrogenity in ACP - Hetrogenity in Designs - 36% included studies of low quality 	2

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	Oxford Level of Evidence
Malhotra et al. 2024	SR und MA of RCT We conducted a systematic review and meta-analysis to identify and quantify the impacts of ACP interventions on caregiver outcomes.	MEDLINE, Embase and Cochrane databases for English-language randomised or cluster randomised controlled trials (RCTs) published until May 2021.	Intervention ACP Outcome: Congruence in EOL Carepräferenzen Bereavement Outcomes; satisfaction with care quality, decisional conflict, burden on caregivers.	<ul style="list-style-type: none"> - 35 RCTs met eligibility; 68.6% were rated high quality - Meta-analysis of 17 RCTs showed that ACP had large and significant improvement in congruence in EOL care preferences between caregivers and patients (standardised mean difference 0.73, 95% CI 0.42 to 1.05). - The effect of ACP on this outcome, however, declined over time. - some evidence that ACP improved bereavement outcomes (three of four RCTs), satisfaction with care quality/communication (four of the six RCTs), reduced decisional conflict (two of the two RCTs) and burden (one RCT). - No study showed that mental health of caregivers were adversely affected. 	<ul style="list-style-type: none"> - Heterogeneity in interventions - Only 11.4 % Cancer Patients (possible downgrading for indirect evidence) 	1

Kapitel 7: Angehörige

Verknüpfte Empfehlungen:

Empfehlung 7.1:

Angehörige von Patient: innen mit einer nicht-heilbaren Krebserkrankung *sollen* unterstützt und begleitet werden. Dabei *sollen* sie in ihren physischen, psychischen, sozialen und spirituellen Bedürfnissen im Versorgungsalltag wahrgenommen werden.

Empfehlung 7.10:

Angehörige von Patient: innen mit einer nicht heilbaren Krebserkrankung *sollen* bedarfsadaptiert (psycho-)edukative Unterstützung erhalten.

Literaturreferenzen: [\[90\]](#), [\[91\]](#), [\[92\]](#), [\[93\]](#), [\[94\]](#), [\[95\]](#), [\[96\]](#), [\[97\]](#), [\[98\]](#), [\[99\]](#), [\[100\]](#), [\[101\]](#), [\[102\]](#), [\[103\]](#), [\[104\]](#)

Übergreifende Suche nach Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE Oxford 2011
Ahn, Patient Educ Couns, 2020 [105]	Systematic Review (SR); to examine the characteristics and effects of interventions for family caregivers of patients with advanced cancer receiving home care.	<u>Databases:</u> CINAHL, MEDLINE, PsycINFO, Web of Science, Cochrane Library; <u>Design:</u> RCTs and quasi-experimental studies (2007–2018), <u>Population:</u> caregivers of adult patients with advanced cancer (Stage III/IV) receiving home care	<u>Intervention:</u> psychosocial, educational, and psychoeducational interventions; <u>Outcomes:</u> psychological distress, quality of life, caregiving burden, self-efficacy, and caregiving competence	Most interventions showed significant improvements in psychological distress, burden, self-efficacy, and QoL. Effects varied by intervention type. Inconsistencies in outcome measures noted. Psychische Belastung (Psychological Distress): Untersucht in 8 von 11 Studien 5 Studien berichteten signifikante Reduktionen von Angst, Depression oder Stress 2 Studien zeigten keinen signifikanten Unterschied (bei 4- und 8-Monats-Follow-up) 1 Studie zeigte postmortale Erhebung: Belastung stieg zwar an, war aber signifikant niedriger in der Interventionsgruppe	11 studies included (9 RCTs, 2 quasi-experimental); Mixed quality (Cochrane RoB, ROBINS-I); Interventions and outcomes were heterogeneous; Long-term efficacy rarely studied.	3

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE Oxford 2011
				<p>Lebensqualität (Quality of Life) Untersucht in 6 Studien 3 Studien berichteten signifikante Verbesserungen z. B. Verbesserung der emotionalen Lebensqualität über 3- und 6-Monats-Follow-up eine Studie zeigte Verbesserung in physischen und sozialen QoL-Dimensionen 3 Studien fanden keine signifikanten Veränderungen Pflegerbelastung (Caregiving Burden) Untersucht in 3 Studien Alle 3 Studien zeigten signifikante Reduktion der Belastung Effektgrößen: groß (z. B. Cohen's d = 2.3) in einer dyadischen Intervention bei Lungenkrebs klein (d = 0.39) in einer E-Health-Intervention andere Studie: weniger Probleme mit Alltagsbewältigung (subjektive Belastung) Selbstwirksamkeit & Kompetenz (Self-Efficacy & Competence for Caregiving) Mehrere Studien berichteten positive Effekte Keine gepoolten Effektgrößen Verbesserung des subjektiven Bewusstseins, mit den Anforderungen im Alltag umgehen zu können</p>		
Chow, J Natl Cancer Inst, 2023 [106]	Systematic Review and meta-analysis; to evaluate the effects of interventions to support <i>family caregivers of</i>	<u>Databases:</u> MEDLINE, EMBASE, Cochrane CENTRAL, CINAHL; <u>Inclusion:</u> RCTs with adult family caregivers of	Interventions: Psychoeducation, skills training, counseling, team-based interventions.	49 trials with 8,554 caregivers: QoL (1-3 Mo.): SMD = 0.24 [95% CI: 0.10 to 0,39], p 0,01 4-6 monaten non significant improvement Mental well-being 1-3 month: SMD = 0.14 [95% CI: 0.02-0.25], p=0,30	Fokus ausschließlich auf <i>Caregiver Outcomes</i> . Insgesamt signifikante Effekte	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE Oxford 2011
	patients with advanced cancer.	adult patients with advanced cancer;	Primary outcomes: QoL, physical well-being, mental well-being, anxiety, depression (1-3 months). Secondary: Outcomes at 4-6 months, caregiver burden, self-efficacy, family functioning, bereavement.	Depression 1-3 month: SMD = 0.34 [95% CI: 0.16-0.52], I ² = 64% Anxiety: SMD = 0.27 [95% CI: 0.06-0.49], I ² = 74% Physical well-being: SMD = -0.02 [95% CI: -0.12-0.08], n. s. Self-efficacy: Verbesserungen in mehreren Studien berichtet, keine zusammenfassende Effektgröße.	auf mentale Gesundheit und Depressionen, jedoch hohe Heterogenität. Physische Outcomes zeigten keine Verbesserung. Studienqualität überwiegend niedrig bis moderat; viele RCTs mit hohem Risiko für Bias.	
Yan, Int J Nurs Stud, 2024 [100]	Systematic Review + meta-analysis; to evaluate the effects of targeted palliative care interventions on depression, quality of life, and caregiver burden among informal caregivers of patients with advanced cancer.	PubMed, Embase, CINAHL, PsycINFO, Cochrane, CNKI, VIP, WANFANG (search until May 2024). Inclusion: RCTs in adult informal caregivers (≥ 18 years) of patients with advanced cancer or in palliative care.	Interventions: targeted palliative care interventions (e.g. psychoeducation, counseling, skills training, dignity therapy, death education, supportive programs). Outcomes: Depression, quality of life, caregiver burden.	16 RCTs (n = 2,046 caregivers). Depression: SMD = -0.74 (95% CI [-1.25, -0.23], p < 0.01) Quality of life: SMD = 0.63 (95% CI [0.08, 1.17], p = 0.03) Caregiver burden: not significant (SMD = -0.33 [-0.95, 0.29], p = 0.30) Subgroup results: Interventions < 3 months: improved depression (p = 0.03) Caregiver-only interventions: improved depression (p = 0.03) Offline delivery: improved depression (p = 0.02) and QoL (p = 0.02).	Participants = informal caregivers, not patients. Most studies small, some risk of bias. Overall low certainty of evidence (GRADE). Results suggest that palliative care interventions can reduce depression and improve QoL but not burden.	1-2
Yıldız,	Systematic review; to evaluate the effectiveness	<u>Databases:</u> PubMed (MEDLINE), Cochrane, APA	Interventions: Mindfulness, stress	8 RCTs included.	Interventions and delivery methods	1-2

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE Oxford 2011
Int J Nurs Knowl, 2024 [107]	of psychosocial interventions in reducing psychological distress and enhancing mental health in family caregivers of patients with cancer in the palliative period.	PsycNet, ProQuest, Science Direct, TR Dizin, Wiley Online Library. <u>Inclusion:</u> RCTs published 2016–2021 in English or Turkish; family caregivers of palliative cancer patients.	management, Acceptance and Commitment Therapy (ACT), Cognitive Behavioral Therapy (CBT), meaning-centered psychotherapy, psychoeducation. Outcomes: Depression, anxiety, stress, caregiver burden, QoL, coping, self-efficacy, awareness.	Most reported improvements in depressive symptoms, anxiety, stress, caregiver burden, QoL, coping, and self-efficacy. Some studies found no significant between-group differences. No meta-analysis conducted due to heterogeneity.	varied (face-to-face, online, telephone). Small sample sizes; some non-significant results; overall evidence limited but promising for psychological distress and well-being.	

Kapitel 9: Atemnot

Kapitel 9.3: Nicht-medikamentöse Therapie

Verknüpfte Empfehlungen:

Empfehlung 9.4:

Patient: innen mit einer nicht-heilbaren Krebserkrankung und Atemnot sollen zu Atemübungen (u.a. Lippenbremse, Zwerchfellatmung, Atemkontrolle zur Frequenzsenkung) zur symptomatischen Linderung von Atemnot angeleitet werden.

Literaturreferenzen: [\[50\]](#), [\[51\]](#)

Systematic Reviews und Primärstudien

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OLOE
Liu et al., 2019	SR; to evaluate the effects of breathing exercises on dyspnea, six-minute walk distance (6MWD), anxiety, and depression in patients with lung cancer	Cochrane Library, Web of Science, Embase, PubMed, Weipu, Wanfang, and Chinese National Knowledge Infrastructure databases (until April 6 th , 2018); 15 RCTs; A total of 870 participants; inclusion criteria: English or Chinese, RCT, Patients were diagnosed with lung cancer, or a mixed cancer cohort that included lung cancer, main	I: breathing exercises of various forms (e.g., abdominal breathing, pursed-lip breathing) O: - 1 st : dyspnea, 6MWD - 2 nd : anxiety, depression	- Dyspnea: breathing exercises could significantly improve dyspnea (SMD = -1.11; 95% CI [-1.79, -0.44]; p = 0.001) - 6MWD: considerable beneficial effects of breathing training, which increased the 6MWD by 37.72 meters on average (MD = 37.72; 95% CI [15.06, 60.37]; p = 0.001) - Anxiety: breathing exercises did not improve anxiety in patients with lung cancer (SMD = -1.18; 95% CI [-2.65, 0.28]; p = 0.11) - Depression: depression level was not statistically different between the experimental group and the control group	Subgroup analysis available for more detailed results of the primary outcomes; Breathing exercises can bring many benefits to patients with lung cancer, because they improve dyspnea symptoms and increase 6MWD, even though they did not improve anxiety and depression scores	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OLOE
		intervention methods: breathing exercises, primary outcome measures: dyspnea and 6MWD, secondary outcome measures: anxiety and depression		(SMD = -0.16; 95% CI [-1.15, 0.83]; p = 0.75).		
Tan et al., 2019	RCT; to examine the effect of 20-minute mindful breathing on the rapid reduction of dyspnea at rest in patients with lung cancer, chronic obstructive pulmonary disease, and asthma	Inclusion criteria: patients with moderate to severe dyspnea due to lung disease; population: n = 63 (n = 32 intervention and n = 31 for control)	I: 20-minute mindful breathing + standard care vs. standard care alone O: - Outcomes assessed at minute 0 (T0), minute 5 (T5), and minute 20 (T20) by the same research assistants - Outcomes: 1) dyspnea at rest measured with MBDS (Modified Borg Dyspnea Scale), 2) oxygen saturation measured with a Nellcor Oximax N-65 pulse oximeter, and 3) respiratory rate (RR)	significant reduction in dyspnea in the mindful breathing group compared with the control group at minute 5 (U = 233.5, n1 = 32, n2 = 31, mean rank1 = 23.28, mean rank2 = 37.72, z = -3.574, P < 0.001) and minute 20 (U = 232.0, n1 = 32, n2 = 31, mean rank1 = 23.00, mean rank2 = 36.77, z = -3.285, P = 0.001); For the mindful breathing group, improvement in oxygen saturation was significant at T5, and improvement in RR was significant at T20	a single session of 20-minute mindful breathing is effective in reducing dyspnea rapidly for patients with lung cancer, chronic obstructive pulmonary disease, and asthma; there are subgroup analysis available for more detail	2

Kapitel 9.4: Medikamentöse Therapie

Kapitel 9.4.1: Opioide

Systematic reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results
Takagi, International Journal of Clinical Oncology, 2023 [164]	SR To evaluate the efficacy and safety of opioids for dyspnea in cancer patients	12 RCTs, (7 placebo CENTRAL, MEDLINE, EMBASE, and ICHUSHI of the Japan Medical Abstract Society databases for literature reported up to September 23, 2019 up-date search using PubMed was conducted on November 15, 2020.	Patients with cancer	Opioids for refractory dyspnea, placebo or any other pharmacological as control	1.O: effect of opioid treatment (morphine, oxycodone, hydromorphone, and fentanyl, or morphine inhalation) on dyspnea 2.O. effects on: ▪ Somnolence ▪ Serious adverse events ▪ Quality of Life	Studies included: 12 RCTs (n=326) Dyspnea: 7 RCT morphine; 1 RCT oxycodone, 5 RCT fentanyl, 1 RCT morphine inhalation: The effect on dyspnea was significant with a standardized mean difference of - 0.43 (95% CI - 0.75 to - 0.12) Severe adverse events: 4 RCTs (3 morphine, 1 RCT fentanyl): no significant increase in serious adverse events with opioids compared to placebo or other drugs
Luo J Pain Symptom Manage 2021 [165]	SR, MA To test the effect of opioids in relieving cancer-related dyspnea	11 RCTs, placebo, 6 crossover PUBMED, EMBASE, and the Cochrane Central Register of Controlled Trials for articles published up to January 13, 2020 with publication	Patients with any type of cancers	Subcutaneous, oral or nebulized opioids compared to placebo, any other pharmacological interventions or any opioid as control	1.O: Effect of opioids on intensity of cancer-related dyspnea 2.O: effect of opoids on ▪ exercise capacity ▪ adverse events	11 RCTs (n=290) Dyspnea: 9 RCTs; Pooled result from the meta-analysis showed a small positive effect of opioid administration on dyspnea, SMD-0.82 (95%CI = -1.54to-0.10.

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results
		language restricted to English				<p>Subgroup analysis yielded a small positive effect for morphine on dyspnea, SMD-0.78 (95%CI = -1.45 to -0.10), whereas fentanyl showed no improvement in dyspnea, SMD-0.44 (95%CI = -0.89 to 0.02)</p> <p>3 RCTs reported outcomes of the Borg score (1 RCT morphine, 2 RCT fentanyl): pooled data showed that opioid therapy was beneficial to Borg score improvement compared to control, WMD-0.95 (95%CI = -1.83to-0.06, I2 = 37%)</p> <p>Exercise capacity (6MWT test) 4 RCTs fentanyl: A meta-analysis of these trials showed no significant difference between fentanyl therapy and control, WMD6.49 (95%CI = -34.23to47.21, I2 = 0%, Figure 7).</p> <p>Adverse events 5 RCTs: Somnolence was the most common reported adverse event. The pooled results showed no statistical difference in it as compared to control, OR0.93 (95%CI = 0.34to2.58, I2 = 0%</p>
Chow, Palliative & Supportive Care 2021	SR, network MA	12 RCTs; double blind, 5 crossover, 1 open-label, placebo	Patients with cancer	Opioids	Effect of pharmacologic agents prophylaxis for exertional dyspnea	Prophylaxis for exertional dyspnea:

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results
[166]	To compare pharmacologic agents for the prophylaxis and treatment of cancer-related dyspnea.	Search in atabases of PubMed, Embase, and Cochrane CENTRAL through May 2021			and for studies reporting on treatment of everyday dyspnea	<p>6 RTCs (3 RCTs compared rapid onset fentanyl relative to placebo, 1 CTs parenteral fentanyl relative to placebo, 1RCT dexamethasone relative to placebo, 1 RCT high-dose rapid onset fentanyl relative to rapid onset fentanyl): Rapid onset fentanyl had similar prophylactic effects on dyspnea compared with placebo (SMD 0.179; 95% CI: -0.495 to 0.853). No difference between parenteral fentanyl to placebo, dexamethasone to placebo, and high-dose rapid onset fentanyl compared with rapid onset fentanyl, respectively</p> <p>Treatment of everyday dyspnea: 5 RCTs (2 RCTs morphine sulfate to placebo, 1 RCT morphine sulfate to morphine hydrochlorate 1 RCT morphine sulfate to morphine hydrochlorate to placebo, 1 RCT morphine sulfate to oral oxycodone): Morphine sulfate is better at controlling everyday dyspnea than placebo (SMD 1.210; 95% CI: 0.415-2.005)</p> <p>Treatment of episodic dyspnea: 1 RCT: No difference was reported between rapid onset fentanyl and placebo for the treatment of exertional dyspnea.</p>

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results
Feliciano, JAMA Network Open 2021 [167]	SR, MA to examine the associations of pharmacologic options with improved breathlessness, anxiety, and physiologic outcomes in patients with advanced cancer	17 RCTs (9 placebo), 2 retrospective studies Searches in PubMed, Embase, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials through May 31, 2020	adult patients with advanced cancer	benefits and/or harms of pharmacologic interventions with the intent to alleviate breathlessness	breathlessness, anxiety, exercise capacity, health-related QOL (HRQOL), and physiologic outcomes	<p>Opioids vs Placebo 6 RCTs (4 RCTs fentanyl, 1 RCT hydromorphone, 1 RCT subcutaneous morphine): All studies reported an active placebo effect on within-group differences. On the basis of the overall pooled results from the meta-analysis, opioids were not more effective than placebo for improving breathlessness in patients with advanced cancer</p> <p>Opioids vs Opioids 7 RCTs: no difference between opioid doses or routes in treating breathlessness in patients with advanced cancer (calculated SMD, 0.15; 95% CI, -0.22 to 0.52; I2 = 4.8%)</p> <p>Opioids vs Anxiolytics 2 RCTs (midazolam compared with morphine or combination of both drugs): opioids were not more effective than anxiolytics (midazolam) for improving breathlessness (SOE, low).</p> <p>Exercise Capacity 3 RCTs (fentanyl compared with placebo in terms of distance in a 6-minute walk test): Meta- found no differences in 6-minute walk distance (calculated SMD, 0.06; 95% CI, -0.43 to 0.55; I2 = 0.0%) (eFigure 3 in the Supplement).</p> <p>HRQOL</p>

Study	Type of study (SR=Systematic Review; MA=Meta- analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results
						1 RCT (oral dexamethasone compared with placebo): no difference

Kapitel 11: Fatigue

Kapitel 11.3: Symptomatische nicht-medikamentöse Verfahren

Körperliche Übung: Systematic Reviews

Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Oxford 2011
Chen et al., JAMA Oncology, 2019 (SR)	15 RCTs; PubMed, Cochrane Database of Systematic Reviews, EMBASE, and Web of Science from their inception to February 3, 2019	Patients with cancer who were diagnosed with metastatic or advanced disease, typically incurable disease, or who were receiving palliative care	Exercise training (aerobic, resistance, or combined), supervised or home-based	physical and psychological symptoms (including fatigue, pain, insomnia, dyspnea, nausea and vomiting, constipation, diarrhea, appetite lose, anxiety, and depression), QoL, and physical functioning (physical, social, emotional, role, and cognitive functioning).	Exercise significantly improved fatigue vs. usual care (SMD -0.25, 95% CI -0.45 to -0.04; p=0,02)	Mixed populations; unclear stage allocation; moderate heterogeneity	1
Gauche et al., Support Care Cancer, 2024 (SR)	9 RCTs; PubMed, CENTRAL, CINAHL	Patients with advanced cancer receiving palliative care	Physiotherapy including aerobic exercise, strength, breathing training	six patient-reported outcomes (PROMs): fatigue, quality of life (QoL), nutrition, pain, psychosocial functioning (PSF), and PHF	4 RCTs, N=281: Questionnaires FU: range 4 weeks to 13 months Relative Effect improved, Half of the studies reported statistical significance (p < 0.05).	Review includes small and diverse RCTs; limited long-term outcomes	1
Heywood et al., J Pain Symptom Manage, 2018	16 RCTs; 9 pretest-posttest-experimental studies PubMED, Medline, CINAHL, Embase,	Patients with advanced cancer	Exercise (resistance, aerobic, yoga)	physical function, QOL, fatigue, body composition, psychosocial function, sleep quality, pain, survival, any other	8 RCT (50%) reported significant improvement in 1 or more measure of fatigue in response to the exercise intervention	High heterogeneity; many small trials; some unclear allocation It is also plausible that participants' interpretation of fatigue was confounded by the usual physiological	2

Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Oxford 2011
	PEDRO, Web of Science, and Scopus from earliest time point to march 2017			outcomes assessed, other events, length of follow-up		response to increases in physical exercise, which may include shortness of breath/dyspnea, muscle soreness, and transient reductions in physical working capacity	
Mochamat et al., BMJ Support Palliat Care, 2021	15 RCTs; PubMed, CENTRAL, MEDLINE, PsycINFO up to February 28th 2019	participants suffering from any chronic progressive disease in advanced stage associated with palliative care cancer (10 studies), amyotrophic lateral sclerosis (two studies), end stage renal disease (ESRD) (one study) and cirrhosis (one study)	Non-pharmacological interventions: physical training, energy conservation, energy restoration, or psychoeducational intervention	1°: Fatigue 2°: Depression, physical activity, muscle strengths, QoL, treatment-related burden	Fatigue (10 RCTs) significant effect of intervention (standardised mean difference (SMD) 0.31, 95% confidence interval (CI) 0.07-0.55;	Sources of potential bias included lack of description of blinding and allocation concealment methods, and small study sizes. Physical exercise as treatment for fatigue in patients with advanced cancer was supported by moderate-quality evidence.	1
Nadler et al., Support Care Cancer, 2019	16 RCTs; MEDLINE	patients with metastatic solid cancers, n=1318 patients	aerobic and/or resistance exercise	1°: Fatigue (FACIT-F, BFI); 2°: QoL, safety, function	There was a numerical difference in the FACT-F score (3.8 vs. 5.7, P ¼ 0.47) in those with baseline scores 2SD below the mean. There were no clinically meaningful or statistically significant differences in fatigue in any group of patients	Not all studies palliative; exercise type and dose varied strongly	1
Peddle-McIntyre et al., Cochrane, 2019	6 RCTs;	adults diagnosed with advanced lung cancer, specifically	exercise training (aerobic exercise, resistance exercise,	1°: Exercise capacity 2°: Fatigue (e.g. FACIT-F)	Fatigue (3 RCTs, n=90): no significant difference in fatigue between the	Narrow population (lung only); few trials per outcome; limited power	2

Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Oxford 2011
	CENTRAL, MEDLINE (via PubMed), Embase (via Ovid), CINAHL, SPORTDiscus, PEDro, and SciELO on 7 July 2018.	stage IIIb to IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer.	respiratory muscle training, or a combination thereof)		intervention and control group (SMD 0.03; 95% CI - 0.51 to 0.58;)		
Rogers-Shepp et al., BMC Palliat Care, 2023	8 RCTs; Pubmed/Medline, Embase, CINAHL, PsychInfo, and Web of Science from inception to 2022	advanced cancer palliative care patients	Exercise intervention, which in principle participants could learn to do on their own at home	Palliative outcomes 1°: Fatigue (BFI, FACIT); 2°: Physical/mental wellbeing Most reduced fatigue; high feasibility	2 RCTs: Fatigue (FACT-F) improved in one aerobic and one combination resistance-aerobic study	Mixed interventions; several studies with unclear blinding or follow-up	2
Tanriverdi et al., IJERPH, 2023	14 RCTs; EMBASE, PubMed, and Web of Science from inception until 2021	adults with cancer receiving palliative care	exercise intervention	1°: Exercise capacity 2°: Fatigue (e.g. FACIT-F)	6 RCTs: fatigue was significantly different between the exercise group and control group and this favored of exercise group (SMD - 0.48; 95% CI - 0.83 to - 0.12; I2 = 63%, 386 participants, low-certainty evidence)	Some studies lacked fatigue as primary outcome; inclusion criteria broad	1
Toohey et al., Palliat Med, 2022	22 RCTs; Cochrane Library, EMBASE, SPORTDiscus (via EBSCOhost), ProQuest Health and Medical Complete, ProQuest Nursing and Allied Health Source, Science Direct,	adult participants, diagnosed with any type of incurable cancer currently in the stable palliative care phase	any form of planned, structured, and repetitive bodily movements performed to improve or maintain fitness, performance or health	Health-related outcomes included QOL, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression, pain and sleep	there were small to moderate effects (all p < 0.05) in favour of exercise for QOL (SMD = 0.27 (95% CI = 0.14, 0.39)), fatigue (SMD = 0.30 (95% CI = 0.13, 0.47)), aerobic fitness (SMD = 0.30 (95% CI = 0.12, 0.49)) and lower-body strength (SMD = 0.48 (95% CI = 0.12, 0.84)); No overall effects were observed for upper-	outcomes heterogeneously reported	2

Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies and data bases	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Oxford 2011
	Web of Science, CINAHL, Scopus and PubMed				bodystrength (SMD = 0.45 (95% CI = - 0.09, 0.98), p = 0.10), pain (SMD = 0.24 (95% CI = - 0.01, 0.48), p = 0.06), depression (SMD = 0.33 (95% CI = - 0.07, 0.72), p = 0.10) and anxiety (SMD = 0.11 (95% CI = - 0.13, 0.35), p = 0.36).		
Vira et al., Indian J Palliat Care, 2021	9 studies (4 single arm pre-post intervention design; 3 RCTs; 1 non-RCT, 1 a case series); PubMed, Scopus, Web of Science, CINAHL and PEDro from inception until April 2020	Hospice patients with advanced cancer	Physiotherapy-based interventions	physical symptoms like loss of function, pain, fatigue, edema, sleep disturbances and quality of life.	Although studies (pre-post intervention and non RCT) showed significant improvement in the level of fatigue an RCT showed some improvement which could not be reflected statistically.	Weak overall evidence; high heterogeneity and unclear reporting	3

Kapitel 12: Schlafbezogene Erkrankungen / Nächtliche Unruhe

Kapitel 12.6: Medikamentöse Therapien

Kapitel 12.6.1.2.1: Z-Substanzen (Zopiclon und Zolpidem)

Verknüpfte Empfehlungen:

Empfehlung 12.8:

Zur Behandlung der Insomnien bei Patient:innen mit einer nicht-heilbaren Krebserkrankung sollten nur kurzfristig bevorzugt Eszopiclon, Zopiclon und Zolpidem, mittelfristig aber bevorzugt sedierende Antidepressiva eingesetzt werden.

Empfehlung 12.9:

Benzodiazepine *sollten* zur Behandlung der Insomnie bevorzugt nur bei ebenfalls bestehenden anderen Indikationen für ihren Einsatz verwendet werden.

Empfehlung 12.10:

Bei Patienten mit einer nicht-heilbaren Krebserkrankung *können* sedierende Antipsychotika zur Behandlung der Insomnie eingesetzt werden, wenn andere Therapien nicht möglich sind, oder wenn sie für andere Symptome synergistisch genutzt werden können.

Empfehlung 12.11:

Melatonin *kann* als Therapie einer Insomnie nach den anderen Substanzklassen eingesetzt werden.

Literaturreferenzen: [\[55\]](#), [\[56\]](#), [\[57\]](#), [\[58\]](#), [\[59\]](#), [\[60\]](#), [\[61\]](#), [\[62\]](#), [\[63\]](#)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
Pan, 2023	SR and Network MA; to determine the relative effectiveness, safety, and tolerability of drugs for insomnia	PubMed, Embase, Cochrane Central Register of Controlled Trials, PsycINFO, and ClinicalTrials.gov (searched until January 10, 2022); 148 RCT's (including 46,412 participants) that compared one or more drugs with one another or placebo in adults aged 18 years or older with insomnia disorders	I: non-benzodiazepines (including eszopiclone, zopiclone, zolpidem, indiplon, gaboxadol, zaleplon, and propofol); primary outcomes of interest: insomnia symptoms (sleep onset latency (SOL), total sleep time (TST), wake time after sleep onset (WASO)),	Sleep time significantly improved with non-benzodiazepine (both subjectively and objectively measured) compared with placebo (subjective: mean difference [MD] 25.07, 95% confidence interval [CI] 15.49–34.64, low certainty; objective: MD 22.34, 95% CI 7.64–37.05, high certainty); sleep onset latency significantly shortened with non-benzodiazepines (subjective: MD – 10.12, 95% CI – 13.84 to – 6.40, moderate certainty; objective: MD – 12.11, 95% CI – 19.31 to – 4.90, moderate certainty), in particular, zopiclone was among the most effective drugs with a lower risk	potential limitations of the available evidence, thus potentially resulting in uncertainties, including the characteristics of the patient, dose, treatment setting, severity of the insomnia, etcetera	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
			secondary outcomes: sleep quality, safety (including any adverse events [AEs], drug-related AEs, serious AEs, and serious drug-related AEs), tolerability (dropouts due to AEs)	of any AEs but worse tolerability; Non-benzodiazepines could significantly decrease (subjective: MD - 16.67, 95% CI - 21.79 to - 11.56, moderate certainty; objective: MD - 13.92, 95% CI - 22.71 to - 5.14, moderate certainty) wake time after sleep onset		
Brasure, 2015	SR - Comparative Effectiveness Review	Ovid Medline, Ovid PsycINFO, Ovid Embase and the Cochrane Library; In total: 169 RCT's; included are RCTs of pharmacologic therapies available in the US and other interventions if they enrolled adults with insomnia disorder, provided at least 4 weeks of followup and reported global or sleep outcomes,	I: Psychological, Pharmaceutical (available in the United States), CAM; O: Global Outcomes (measuring improvements in sleep symptoms and daytime functioning or distress associated with sleep symptoms), Patient recorded sleep outcomes: sleep diaries (including sleep-onset latency, wake time after sleep onset, total sleep time, sleep efficiency, and sleep quality), Functioning, mood/well-being, and quality of life (measuring daytime fatigue, mood, and quality of life), Adverse effects of intervention(s) and timing of adverse effects (e.g., headache,	CBT-I bei Erwachsenen: Moderate Evidenz zeigt Verbesserungen: SOL um 12 Minuten verkürzt (95% CI: 7-18 Minuten), TST um 14 Minuten erhöht (95% CI: 4-26 Minuten), WASO um 22 Minuten reduziert (95% CI: 8-37 Minuten), Schlaf-Effizienz um 7 Prozentpunkte verbessert (95% CI: 5-9), ISI sank um 7 Punkte vs. 2 Punkte bei Kontrolle (WMD - 5,15; 95% CI: -7,13 bis -3,16), CBT-I erhöhte die Remissionsrate fast dreifach (basierend auf 4 kleinen RCTs), Effekte über 6 Monate und länger erhalten CBT-I bei älteren Erwachsenen: Niedrige bis moderate Evidenz, Verbesserungen gegenüber Kontrolle: WASO um 27 Minuten reduziert (95% CI: 18-36 Minuten), SOL um 10 Minuten verkürzt (95% CI: 4-16 Minuten), Schlaf-Effizienz um 9 Prozentpunkte verbessert (95% CI: 6-13), PSQI-Wert um 2,98 Punkte verbessert (95% CI: -4,01 bis -1,95), TST ähnlich wie Kontrolle, Verbesserungen langfristig stabil CBT-I bei Erwachsenen mit Schmerzen: Niedrige Evidenz zeigt:	data were limited for specific comparisons; limited research establishing MIDTs for specific instruments commonly used to measure global outcomes	

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
			somnolence, myalgia, poor taste, dependence, falls, abnormal sleep behaviors	<p>ISI um 7 Punkte besser als Kontrolle (95% CI: -12,87 bis -1,32), SOL um 26 Minuten verkürzt (95% CI: -43,25 bis -9,75), WASO um 38 Minuten reduziert (95% CI: -65,57 bis -10,78), Schlaf-Effizienz um 13 Prozentpunkte verbessert (95% CI: 5,07 bis 21,38), TST ähnlich wie Kontrolle</p> <p>Multikomponentige Verhaltenstherapie bei älteren Erwachsenen: Niedrige Evidenz zeigt Verbesserungen gegenüber Kontrolle: SOL um 10 Minuten verkürzt (95% CI: 5-16 Minuten), WASO um 15 Minuten reduziert (95% CI: 7-23 Minuten), Schlaf-Effizienz um 6 Prozentpunkte verbessert (95% CI: 3-9)</p> <p>Nebenwirkungen: Daten unzureichend, selten berichtet.</p> <p>Langzeitdaten (>12 Wochen): Selten, deuten auf Abflachen des Nutzens von CBT-I über Monate hin.</p>		
Zheng 2020	modellbasierte Meta-Analyse	Datenbanken: PubMed/EMBASE/Cochrane; 43 Studien (14535 Patienten); Inklusion: RCTs bei primärer Insomnie	Intervention: Eszopiclon, Zolpidem (IR/ER), Zaleplon; Outcomes: SL, WASO, TST, Schlafqualität, Drop-out	<p>Detaillierte Daten auch für 1, 12 und 24 Wochen vorhanden</p> <p>Nach 4 Wochen : Eszopiclon</p> <ul style="list-style-type: none"> ○ Schlaflatenz: -31,2 min (95 %-KI -35,4 bis -26,9) ○ Wake after Sleep Onset: -31,3 min (-36,9 bis -25,7) ○ Totale Schlafzeit: +63,4 min (+54,2 bis +72,5) ○ Schlafqualität (7-P-Likert, ↓ = besser): -1,6 Punkte (95%CI: -2,0 bis -1,2) 	<ul style="list-style-type: none"> - Eszopiclon mit stärkster Wirkung und geringster Abbruchrate - Insgesamt liefert Eszopiclon das stärkste und zugleich konsistenteste Wirksamkeitsprofil, dicht gefolgt von beiden Zolpidem-Formulierungen. Zaleplon wirkt primär auf das 	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
				<ul style="list-style-type: none"> ○ Therapieabbruch: 2,2 % vs 8,8 % Placebo (KI 0 bis 4,7 %) Zolpidem (IR) ○ Schlaflatenz: -28,4 min (-32,0 bis -24,8) ○ Wake after Sleep Onset: -33,0 min (-39,9 bis -26,1) ○ Totale Schlafzeit: +54,5 min (+47,6 bis +61,4) Zolpidem (ER) ○ Schlaflatenz: -24,7 min (-32,3 bis -17,2) ○ Wake after Sleep Onset: -33,2 min (-40,9 bis -25,5) ○ Totale Schlafzeit: +61,1 min (+47,2 bis +75,1) Zaleplon ○ Schlaflatenz: -27,6 min (-31,1 bis -24,1) ○ Totale Schlafzeit: +41,3 min (+35,0 bis +47,6) ○ Schlafqualität: kein signifikanter Unterschied zu Placebo 	<p>Einschlafen und bleibt bei anderen Parametern zurück.</p> <ul style="list-style-type: none"> - Eszopiclon zeigt die beste Therapietreue, während bei den anderen Z-Substanzen keine besonderen Probleme mit Nebenwirkungen oder Abbrüchen genannt wurden. - Eine Behandlungsdauer von mind. 6 Wochen wird für stabilen Unterschied zum Placebo empfohlen <p>Limitationen: Patientendaten (z.B. Patientengeschichte) teilweise nicht einsichtig; keine Generalisierung der Ergebnisse möglich, wenn Komorbidität vorliegt; teilweise heterogene Gruppen; teilweise kleine Patientengruppen; nur englische Studien inkludiert</p>	

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
Liang 2019	Systematische Review + Meta-Analyse zur Wirksamkeit/Sicherheit von Eszopiclon	Datenbanken: MEDLINE, EMBASE, PsycINFO, Cochrane Central Register, PubMed, ClinicalTrials.gov (bis Juni 2018); Inklusion: nur doppelblind-RCTs bei primärer Insomnie.	Intervention: Eszopiclon 2 mg (>65), 3 mg (<65) vs Placebo Outcome: subjektive SL, WASO, TST, Schlafqualität, Funktions-Scores, UAW.	<ul style="list-style-type: none"> - 6 RCTs mit 2 809 Teilnehmenden. - SL -38,53 min (1 Woche) bis -20,26 min (6 Monate); - TST +51,81 min (1 Woche) bis +43,23 min (6 Monate); - WASO -29,85 min (1 Woche) bis -11,77 min (6 Monate); - signifikante Verbesserungen der Schlafqualität und Tagesfunktion; - häufigste UAW unangenehmer Geschmack und Schwindel bei Älteren 	<ul style="list-style-type: none"> - Konsistente Effekte bei geringer Heterogenität; 	1
Chiu et al., 2021	SR + Netzwerk-Metaanalyse randomisierter kontrollierter Studien, um Wirksamkeit und Sicherheit verschiedener Hypnotika bei älteren Insomnie-Patient*innen zu vergleichen, mit besonderem Blick auf die best-rankenden Substanzen pro Schlafparameter.	Datenbases: EMBASE, PubMed, ClinicalTrials.gov und ProQuest Dissertations bis 12. September 2020; Inclusion: nur RCTs mit Teilnehmer*innen ≥ 59 J; 24 Artikel (5917 Patienten)	Interventionen: Eszopiclon, Zolpidem (IR und ER) sowie Zaleplon vs Placebo Outcomes: <ul style="list-style-type: none"> - objektive & subjektive Gesamtschlafzeit (TST) - objektive & subjektive Schlaflatenz (SOL) - objektive & subjektive Wachzeit nach Schlafbeginn (WASO) - objektive Schlaf-effizienz (SE) - Gesamtinzidenz behandlungsbedingter Nebenwirkungen. 	<p>Eszopiclon</p> <ul style="list-style-type: none"> - objektive TST: + 28,6 min; als bestes Mittel von der SUCRA eingestuft (81%). - subjektive TST: + 25,08 min; ebenfalls signifikant verlängert. - objektive SE: + 5,90 % (signifikant). - subjektive WASO: - 12,32 min (signifikant). <p>Zaleplon</p> <ul style="list-style-type: none"> - objektive SOL: - 21,63 min; als bestes Mittel von der SUCRA eingestuft (96 %). - subjektive SOL: - 15,86 min; ebenfalls Spitzenplatz (89,7%). - Keine signifikanten Effekte auf TST oder WASO. <p>Zolpidem</p> <ul style="list-style-type: none"> - IR-Form: <ul style="list-style-type: none"> o subjektive TST: + 23,07 min; o subjektive SOL - 9,75 min. - ER-Form: 	<ul style="list-style-type: none"> - Bei älteren Patient*innen bietet Eszopiclon die verlässlichste Verlängerung der Schlafdauer und Verbesserung der Effizienz, - Zaleplon ist am wirksamsten für das rasche Einschlafen, wird aber wegen Nebenwirkungen bei älteren Menschen nicht empfohlen. - Zolpidem ER reduziert v. a. nächtliche Wachphasen. - Insgesamt wurden für die Z-Substanzen keine erhöhten 	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
				<ul style="list-style-type: none"> objektive WASO: – 15,60 min; verbesserte Schlafkontinuität. Objektive SE: + 3,32% (signifikant) 	Gesamtraten unerwünschter Ereignisse festgestellt; das größte AE-Signal betraf einen Benzodiazepin-Vergleich (Triazolam).	
Yue et al, 2023	<p>Systematic Review & Netzwerk-Metaanalyse von doppelblinden RCTs.</p> <p>Die die Wirksamkeit und Verträglichkeit von 20 Arzneimitteln bei primärer Insomnie quantifiziert; Schwerpunkt auf objektiven Schlafparametern (PSG/Aktigraphie);</p> <p>69 Studien (17319 Patienten)</p>	<p>Databases: CINAHL, Embase (Ovid), LILACS, ProQuest, PsycINFO, PubMed/MEDLINE; Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, Scopus, China National Knowledge Infrastructure (CNKI) und Protokollregister von Anbeginn bis 1. März 2022; nur RCTs an Erwachsenen ≥ 18 J. mit diagnostisch gesicherter primärer Insomnie; Doppelblinddesign obligatorisch.</p>	<p>Intervention: Z-Substanzen (Eszopiclon, Zolpidem IR, Zaleplon, Zopiclon) vs, Placebo / vs. Andere Wirkklassen</p> <p>Outcomes: Primär: Schlaflatenz (SL), Wake After Sleep Onset (WASO) und Therapieabbrüche wegen UAW (AED). Sekundär: Total Sleep Time (TST), Schlaffeffizienz (SE), subjektive Schlafqualität (SQ), Gesamt-UAW (ADE).</p>	<p><i>Klassenebene</i></p> <ul style="list-style-type: none"> Z-Drugs verkürzten SL und WASO und verlängerten TST & SE versus Placebo; gleichzeitig höhere Abbruchrate durch Nebenwirkungen (OR 1,67; 95 % CI 1,29–2,15). <p><i>Einzelwirkstoffe</i></p> <ul style="list-style-type: none"> Zolpidem (IR): SL –0,55 SMD (-1,07 bis -0,02); WASO –1,09 SMD (-1,68 bis -0,49); TST +1,53 SMD (0,92 bis 2,15); SE +1,40 SMD (0,44 bis 2,36). Zaleplon: Verlängerte WASO gegenüber Placebo (+2,51 SMD; 0,60 bis 4,42); rangierte aber hoch für TST-Verlängerung (SUCRA 0,93); niedrigste AEDs (0,33) und ADEs (0,16); Eszopiclon: Signifikante Verbesserung der subjektiven Schlafqualität gegenüber Placebo (0,52 SMD (0,19 bis 0,85)); Zopiclon: In den Netzvergleichen enthalten, zeigte kein signifikantes Alleinstellungsmerkmal gegenüber den oben genannten Z-Drugs (keine separaten Zahlen berichtet). 	<ul style="list-style-type: none"> Zolpidem bietet unter den Z-Substanzen den konsistentesten objektiven Nutzen über alle Kernparameter (SL, WASO, TST and SE), während Zaleplon primär die Gesamtschlafzeit (TST) verbessert, aber die Schlafterhaltung eher verschlechtert. Eszopiclon punktet vor allem bei der subjektiven Schlafqualität. Allen Z-Drugs gemeinsam ist ein erhöhtes Abbruch- und UAW-Risiko, sodass klinisch ein sorgfältiges Nutzen-Risiko-Abwägen erforderlich bleibt, insbesondere im Vergleich zu 	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
De Crescenzo et al., 2022	Systematische Review und frequentistische Netzwerk-Metaanalyse zur relativen Wirksamkeit, Akzeptanz, Verträglichkeit und Sicherheit sämtlicher zugelassener Schlafmittel bei Erwachsenen mit Insomnie;	Datenbanken: Cochrane CENTRAL, MEDLINE, PubMed, Embase, PsycINFO, Register & Behörden-Websites: WHO ICTRP, ClinicalTrials.gov sowie FDA/EMA-u. a. Sites (Zeitraum: Inception – 25 Nov 2021; keine Sprachbeschränkung); 154 double-blind RCTs; Auswahl: orale Monotherapie-RCTs bei erwachsenen Patient*innen mit diagnostischer Insomnie, Doppelblind-Design für Netzwerkanalyse	Interventionen: <i>Eszopiclon, Zolpidem, Zopiclon, Zaleplon vs Placebo</i> Outcome: Primär: - subjektive Schlafqualität (Primär-Effektmaß; SMD), - Abbrüche wegen UAW (Toleranz), - Abbrüche gesamt (Akzeptanz), - Sicherheit (Patienten mit ≥ 1 unerwünschtes Ereignis), Sekundär: objektive/ subjektive Schlaflatenz, WASO, TST, Anzahl Wachwerden, UAW	- Akute Behandlung (≈ 4 Wochen) <ul style="list-style-type: none"> Wirksamkeit ggü. Placebo: Eszopiclon, Zolpidem und Zopiclon waren signifikant wirksamer als Placebo (SMD-Bandbreite 0,36 – 0,83) und Zaleplon (Head-to-head: Eszopiclon 0,33; Zolpidem 0,27) Akzeptanz: Eszopiclon senkte Abbrüche vs Ramelteon (OR 0,71) Toleranz: Zolpidem (OR 1,79) und Zopiclon (OR 2,00) verursachten mehr AE-bedingte Drop-outs als Placebo; Zopiclon auch mehr als Eszopiclon (OR 1,82). Sicherheit: Eszopiclon, Zolpidem und Zopiclon zeigten höhere Gesamt-AE-Raten als Placebo und Zaleplon (Bandbreite 1,27 – 2,78); Zaleplon wies das niedrigste OR im Z-Cluster auf - Langzeitbehandlung (> 3 Monate) <ul style="list-style-type: none"> Wirksamkeit: Nur Eszopiclon blieb Placebo überlegen (SMD 0,63); es war zugleich wirksamer als Ramelteon und Zolpidem (Differenz SMD $\approx 0,60$) Akzeptanz: Langfristig geringere Gesamtabbrüche für Eszopiclon und Zolpidem vs Ramelteon (beide OR 0,43) Toleranz: Zolpidem verursachte weiter mehr AE-bedingte Drop-outs als Placebo (OR 2,00) 	neueren Orexin-Antagonisten, die sowohl stärker als auch verträglicher abschneiden - <i>Eszopiclon</i> bietet das breiteste Nutzenprofil: beste Kombination aus Wirksamkeit und niedrigen Abbruchraten kurz- und langfristig, aber erhöhtes AE-Risiko bleibt. - <i>Zolpidem</i> zeigt gute akute Effekte, verliert langfristig an Evidenz und weist ein deutlich höheres Risiko für AE-bedingte Therapieabbrüche auf. - <i>Zopiclon</i> ist wirksam, jedoch besonders schlecht verträglich (höchste Drop-out-ORs). - <i>Zaleplon</i> gilt als gut verträglich, liefert aber in dieser Analyse keinen signifikanten Effektnachweis auf primäre Outcomes.	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
				<ul style="list-style-type: none"> Zu Zaleplon lagen keine Langzeitdaten; Zopiclon fehlte bei Effizienz-Analysen. 		
Rösner et al., 2018	<p>Aktualisierte Cochrane-Übersicht mit Meta-Analyse. Ziel war es, Wirksamkeit, Verträglichkeit und Sicherheit von Eszopiclon bei erwachsenen Patient*innen mit Insomnie zu bewerten.</p>	<p>Datenbanken: Cochrane CENTRAL, MEDLINE, Embase, PsycINFO, PSYINDEX sowie WHO ICTRP und ClinicalTrials.gov. (Suchende bis 10. Feb 2016, Update-Suche 21. Feb 2018)</p> <p>Inclusion: - Eingeschlossen wurden ausschließlich parallel-gruppige, randomisierte, doppelblinde RCTs, die Eszopiclon (Mono-Therapie) mit Placebo oder aktivem Komparator verglichen und eine diagnostisch gesicherte Insomnie (primär oder komorbid) behandelten.</p> <p>- Insgesamt 14 RCTs (n = 4 732) erfüllten die Kriterien.</p>	<p>Intervention: Eszopiclon in üblicher Dosierung (1 – 3 mg) versus Placebo.</p> <p>Outcomes: Primär: Schlaflatenz (SOL), Wake after sleep onset (WASO), Entzugssymptome, Wiederkehrende Schlaflosigkeit (SOL und WASO)</p> <p>Sekundär: Totale Schlafzeit (TST), subjektive Tageswachheit, unerwünschte Ereignisse</p>	<p>Wirksamkeit (patientenberichtete Daten)</p> <ul style="list-style-type: none"> Schlaflatenz (SOL): -11,94 min (95 % KI - 16,03 bis -7,86) – 9 RCTs / 2 890 Teilnehmende Wachzeit nach Schlafbeginn (WASO): - 17,02 min (-24,89 bis -9,15) – 8 RCTs / 2 295 Totale Schlafzeit (TST): +27,70 min (+20,30 bis +35,09) – 10 RCTs / 2 965 Tageswachheit: +0,46 Punkte auf einer 0-10-Likert-Skala (+0,28 bis +0,63) – 8 RCTs / 2 061 (klinisch kleiner, aber statistisch signifikanter Zuwachs) <p>Sicherheit & Verträglichkeit</p> <ul style="list-style-type: none"> Kein Anstieg schwerwiegender unerwünschter Ereignisse (Risikodifferenz 0,00) und kein signifikanter Unterschied bei AE-bedingten Therapieabbrüchen (RD 0,01; 95 % KI -0,01 bis 0,02) Häufigste, signifikant vermehrte Nebenwirkungen: <ul style="list-style-type: none"> Unangenehmer Geschmack (RD 0,18; Number Needed to Harm ≈ 6) Mundtrockenheit (RD 0,04; NNTH ≈ 25) Tagesmüdigkeit / Somnolenz (RD 0,04; NNTH ≈ 25) Schwindel (RD 0,03; NNTH ≈ 33) 	<p>- Eszopiclon zeigt eine moderate, aber stabile Verbesserung der Schlafqualität (kürzere Einschlafzeit: -12 min, längere Schlafdauer: +28 min, weniger nächtliches Wachsein: -17 min) im Vergleich zu Placebo. Eszopiclon steigert subjektiv die Tageswachheit geringfügig.</p> <p>- Das Nebenwirkungsprofil ist insgesamt moderat; auffällig ist jedoch ein klar erhöhtes Risiko für metallischen/bitteren Geschmack sowie milde anticholinerge Effekte (Mundtrockenheit) und zentrale Dämpfung (Somnolenz, Schwindel).</p>	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
				<ul style="list-style-type: none"> Kein Hinweis auf klinisch relevanten Rebound oder Entzug nach Therapieende (z. B. SOL-Rebound +17 min. WASO Rebound -6,71 min.; statistisch nicht signifikant) 	<ul style="list-style-type: none"> Weder die Abbruch- noch die SAE-Rate stiegen an. Die Evidenzqualität wurde für Wirksamkeit und allgemeine AEs als moderat eingestuft. 	
Samara et al., 2020	<p>Systematische Review + frequentistische Netzwerk-MA</p> <p>53 RCTs, n = 6 832 zur vergleichenden Wirksamkeit, Akzeptanz und Sicherheit aller pharmakologischen und nicht-pharmakologischen Insomnie-Interventionen im Alter.</p>	<ul style="list-style-type: none"> Datenbanken: MEDLINE, Embase, PsycINFO, CENTRAL, CDSR sowie ClinicalTrials.gov & WHO-ICTRP; Suche bis 25 Mai 2019. Eingeschlossen: Doppelblind-RCTs > 5 Tage bei Patient*innen > 65 J.; 	<p>Intervention: Z-Drugs als Klasse (Eszopiclon, Zolpidem, Zaleplon, Zopiclon)</p> <p>Outcomes: Primär: TST, SQ Sekundär: Schlaflatenz (SOL), Wachzeit nach Schlafbeginn (WASO) und Anzahl nächtlicher Aufwachereignisse.</p>	<p>Ergebnisse für Z-Substanzen (vs. Placebo)</p> <ul style="list-style-type: none"> Totale Schlafzeit: +24 min mittlerer Zuwachs mit Eszopiclon; rangierte hinter Nahrungsergänzung und Benzodiazepinen Schlafqualität: Standardisierte MD -0,38 (negativ = besser) mit Eszopiclon; besser als Placebo, aber schwächer als mehrere Alternativen (z. B. Melatonin) Schlaflatenz (SOL): Eszopiclon verkürzte SOL um ca. 7 - 25 min; klinische Präzision begrenzt Wake After Sleep Onset: Zolpidem und Eszopiclon reduzierten WASO um 12 - 24 min; Effektschätzungen mit breiten Konfidenzintervallen Nächtliche Aufwachereignisse: Zolpidem zeigte die stärkste Reduktion (MD -0,96 bis -0,30 Aufwache / Nacht), jedoch große Unsicherheit <p>Sicherheit & Verträglichkeit</p> <ul style="list-style-type: none"> Für Abbrüche insgesamt und AE-bedingte Abbrüche fanden sich keine signifikanten Unterschiede zwischen Z-Drugs und Placebo; Konfidenz aufgrund weniger Daten sehr niedrig 	<ul style="list-style-type: none"> Bei Senior*innen liefern Z-Substanzen nur moderate Vorteile: eine knappe halbe Stunde mehr Schlaf und kleine Verbesserungen der subjektiven Qualität. Die Evidenz ist sehr gering (spärliche Daten, schwach vernetzte Vergleiche, breite KI), sodass sich keine sichere Rangfolge innerhalb der Z-Gruppe ableiten lässt. Klinisch sollte angesichts der unklaren Sicherheitssignale und des marginalen Zusatznutzens eine sorgfältige Nutzen-Risiko-Abwägung erfolgen, 	1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	OL OE
				<ul style="list-style-type: none"> Auch bei Gesamt-AE-Raten ließen sich wegen breiter KI keine klaren Effekte nachweisen. 	alternativen Klassen (v. a. Orexin-Antagonisten) bieten mitunter günstigere Profile.	
Xiang et al., 2021	<p>Meta-Analyse randomisierter placebo-kontrollierter Studien; Zweck: Wirksamkeit und Sicherheit einer vierwöchigen Zolpidem-Monotherapie bei Erwachsenen mit Insomnie bewerten.</p> <p>6 Studien (n = 1068)</p>	<p>- Datenbanken: PubMed, MEDLINE, Embase, PsycINFO, Web of Science, Cochrane CENTRAL plus ClinicalTrials.gov. (Zeitraum: Anbeginn – 13 Mai 2021);</p> <p>- nur RCTs ≥ 18 J., Zolpidem als Monotherapie ≥ 4 Wochen, placebokontrolliert, englische Volltexte.</p>	<p>Intervention: Zolpidem IR (10 mg Erwachsenen; 5–6,25 mg Ältere) vs Placebo.</p> <p>Outcomes: Primär: Total Sleep Time (TST), Schlaflatenz (SL). Sekundär: Wake After Sleep Onset (WASO), subjektive Schlafqualität (SQ), Gesamt- und Ereignis-bezogene Nebenwirkungen.</p>	<p>Gesamt (6 RCTs, n = 1 068)</p> <ul style="list-style-type: none"> TST: deutliche Verlängerung (SMD 0,3 (95% KI: 0,17 bis 0,43)). SL: signifikante Verkürzung (SMD -0,25 (95% KI: -0,37 bis -0,12)). WASO: kein signifikanter Unterschied (p = 0,106). Schlafqualität: signifikante Verbesserung (SMD 0,25 (95% KI: 0,05 bis 0,46)). <p>Subgruppen</p> <ul style="list-style-type: none"> Ältere (≥ 55/65 J.): TST-Zuwachs (SMD: 0,4 (95% KI: 0,23 bis 0,56)) und SL-Verkürzung (SMD -0,32 (95% KI: -0,49 bis -0,16)) ausgeprägter als Placebo. Nicht-Ältere: Unterschiede zu Placebo bei TST und SL nicht signifikant. <p>Sicherheit</p> <ul style="list-style-type: none"> Kein signifikanter Unterschied in der Gesamt-NW-Rate zwischen Zolpidem und Placebo (jeweils Erwachsene und Ältere). Häufigste NW (ohne Signifikanz gegenüber Placebo): Kopfschmerz, Schläfrigkeit/Somnolenz, Schwindel, Dyspepsie, Nasopharyngitis, Oberbauchschmerzen 	<p>- Eine einmonatige Zolpidem-Therapie verbessert Schlafdauer, Einschlafzeit und Selbstbeurteilung der Schlafqualität signifikant, jedoch ohne gesicherten Effekt auf nächtliches Wachliegen.</p> <p>- Der Nutzen konzentriert sich vor allem auf die ältere Subgruppe; bei jüngeren Patient*innen bleibt der Vorteil gegenüber Placebo fraglich.</p> <p>- Nebenwirkungsprofil vergleichbar mit Placebo, dennoch sollten Schwindel- und Somnolenz-Risiken bei älteren Personen beachtet werden.</p>	1

Kapitel 13: Übelkeit und Erbrechen (nicht Tumorthherapie-induziert)

Kapitel 13.5: Medikamentöse Therapien

Verknüpfte Empfehlungen:

Empfehlung 13.7:

Antipsychotika mit einem breiten Wirkspektrum, wie z. B. Olanzapin* oder Levomepromazin*, *können* bei unzureichendem Ansprechen auf andere Antiemetika als Therapie zur Linderung von Übelkeit und Erbrechen bei Patient: innen mit einer nicht-heilbaren Krebserkrankung eingesetzt werden.

Literaturreferenzen: [\[67\]](#), [\[68\]](#), [\[69\]](#)

Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
Navari et al., 2020	RCT, double-blind, placebo-controlled, parallel-group design	30 patients total (15 per group); 1 drop-out (placebo group)	Patients with advanced cancer, chronic nausea >1 week, no chemo/radiation in past 14 days; mean age 63 (range 39–79); 16 women, 14 men	Intervention: Olanzapine 5 mg orally daily for 7 days Control: Placebo orally daily for 7 days	1.O: Change in nausea score (NRS 0–10) from baseline to day 7; 2.O: Emesis frequency, use of antiemetics, appetite, sedation, fatigue, well-being	Olanzapine reduced the median nausea score from 9/10 to 1/10 after 7 days, compared to no change (9/10) in the placebo group. The between-group difference was 8 points (95% CI: 7–8; $p < .001$). Patients receiving	strong treatment effect despite small sample size. Rapid onset of action (after 1 day). Well tolerated. Limitations include short study duration and limited generalizability due to	3

Study	Type of study/ Design (RCT/CCT, blinded, cross- over/parallel)	Number of included patients/ Drop- outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
						olanzapine also reported less vomiting, reduced use of other antiemetics, better appetite, less fatigue and sedation, and improved overall well-being. No adverse events were reported in the olanzapine group; one patient in the placebo group discontinued due to lack of benefit.	small population. Potentially practice-changing in palliative care settings.	

Kapitel 17: Angst

Kapitel 17.6: Medikamentöse Therapie

Verknüpfte Empfehlungen:

Akute Panikattacken bei Patient: innen mit einer nicht-heilbaren Krebserkrankung *sollen* mit kurzwirksamen Benzodiazepinen behandelt werden.

Es *soll* stufenweise vorgegangen werden: Zunächst erfolgt die akute Symptomlinderung mit kurzwirksamen Benzodiazepinen. Bei wiederholtem Auftreten *sollte* die Indikation für eine längerfristige Behandlung mit Antidepressiva, Antipsychotika oder sonstigen Medikamenten mit anxiolytischer Wirksamkeit geprüft werden.

Literaturreferenzen: [\[71\]](#)

Ketamin

Es wurde keine Studien eingeschlossen

Psychedelika: Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Level of Evidence Oxford 2011
Schipper, Cochrane 2024	SR; MA To assess the benefits and harms of psychedelic-assisted therapy compared to placebo or active comparators (e.g.	6 RCTs	studies randomised 149 participants with life-threatening diseases and analysed data for 140 of them. The age range of	substance-induced psychedelic experience preceded by preparatory therapeutic sessions and followed by integrative therapeutic sessions.	Anxiety Depression Existential distress	(only results on anxiety are reported here) Psychedelic-assisted therapy using classical psychedelics (psilocybin, LSD) may result in a reduction in anxiety when compared to active placebo (or low-dose psychedelic): State Trait Anxiety Inventory (STAI-Trait, scale 20 to	Oxford 2011: 3 (downgrading due to high risk of bias and small sample size)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Level of Evidence Oxford 2011
	antidepressants) for treatment of anxiety, depression, and existential distress in people with life-threatening diseases.		participants was 36 to 64 years.	The interventions were compared to therapy assisted by placebo or active placebo (e.g. low-dose psychedelic), or active comparators (e.g. antidepressants).		80) mean difference (MD) -8.41, 95% CI -12.92 to -3.89; STAI-State (scale 20 to 80) MD -9.04, 95% CI -13.87 to -4.21; 5 studies, 122 participants; low-certainty evidence. The effect of psychedelic-assisted therapy using MDMA (methylenedioxy-methamphetamine) on anxiety, compared to placebo, is very uncertain: STAI-T MD -14.70, 95% CI -29.45 to 0.05; STAI-S MD -16.10, 95% CI -33.03 to 0.83; 1 study, 18 participants; very low certainty evidence.	

Kapitel 18: Depression

Kapitel 18.6: Medikamentöse Therapien

Kapitel 18.6.2: Andere Wirkstoffe: Ketamin, Psychostimulanzien, Psychedelika

Ketamin: Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1. O=primary outcome; 2. O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
Fan, Oncotarget, 2016	RCT, double-blind, placebo-controlled To investigate the rapid antidepressant effects of a single dose of ketamine on suicidal ideation and overall depression levels in patients newly diagnosed with cancer	n=42, no drop-outs	hospice patients · 17 male; 25 female · newly diagnosed with cancer (within 3 months): lung, gastric, bone, and pancreatic cancers · moderate to severe baseline depression and suicidal	1 st arm: sub-anesthetic dose of racemic ketamine hydrochloride (0.5 mg/kg) 2 nd arm: placebo, sub-anesthetic dose of midazolam (0.05 mg/kg) a Doses were administered intravenously over 40 minutes	rapid antidepressant effects of a single dose of ketamine on: 1.O.: suicidal ideation in cancer patients using Beck Scale for Suicidal Ideation (BSI) suicidal ideation section of the Montgomery-Asberg Depression Rating Scale (MADRS-SI) 2.O.: overall depression level (MADRS)	Suicidal Ideation: significantly lower scores in the ketamine group compared to the midazolam group on both day 1 (BSI: 9.53 ± 9.53 v.s. 16.79 ± 7.07 , $P = 0.0474$; MADRS-SI: 1.69 ± 1.93 v.s. 3.42 ± 1.75 , $P = 0.011$) and day 3 post-treatment (BSI: 9.07 ± 8.21 v.s. 16.93 ± 8.27 , $P = 0.0265$; MADRS-SI: 1.77 ± 1.84 v.s. 3.52 ± 1.89 , $P = 0.0107$) Depression level: significant reduction in overall depression levels in the ketamine group on day 1 (24.46 ± 8.04 v.s.	The study had several limitations, including the lack of long-term observations of ketamine's effect on depressive symptoms. The study also noted that chronic treatment with ketamine has been reported to prolong the antidepressant response, but the potential risk of addiction was a concern.	2

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1. O=primary outcome; 2. O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
						31.89 ± 7.39, P = 0.0339), with a trend toward significance on day 3 (25.09 ± 7.07 v.s. 32.03 ± 7.21, P = 0.0546). The effect was no longer significant by day 7 following treatment.		

Psychostimulanzien: Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1. O=primary outcome; 2. O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
Spathis et al., J Clin Oncol, 2014	RCT, double-blind, placebo-controlled, parallel	208 randomized (Modafinil: 104, Placebo: 104); 160 included in analysis	Patients with advanced NSCLC, fatigue ≥5/10 on NRS, WHO PS 0-2, no chemo-/radiotherapy in last 4 weeks	Modafinil 100 mg (day 1-14), 200 mg (day 15-28) vs. placebo	1.O: Change in FACIT-Fatigue (baseline to day 28); 2.O: Sleepiness (ESS), Depression (HADS), QoL (QOL-LAS), Adverse Events Outcome Measures: FACIT-Fatigue (0-52), ESS, HADS, QOL-LAS Follow-up: 28 days	Improvement in both groups in FACIT-F (Modafinil: +5.29, Placebo: +5.09); no significant difference ($\Delta=0.20$; $p=0.92$). No significant group differences in secondary outcomes. HADS-Depression scores remained stable in both groups without statistically significant changes.	Clinically relevant within-group improvement likely due to placebo effect; Modafinil well tolerated	1

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1. O=primary outcome; 2. O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
Stone et al., J Clin Oncol, 2024	RCT, double-blind, placebo-controlled, multicenter	162 randomized (Methylphenidate: 84, Placebo: 78); 159 included in analysis	Advanced cancer, fatigue >3/10, receiving palliative care; multiple tumor types; ECOG 0-3	Individually titrated methylphenidate (start 5 mg BID, max 20 mg TID) vs. placebo for 6 weeks	1.O: Difference in FACIT-F at 6±2 weeks; 2.O: QoL (EORTC QLQ-C15-PAL), HADS, AE, patient satisfaction, survival Outcome Measures: FACIT-F (0-52), EORTC QLQ-C15-PAL, HADS, EQ-5D-5L, AE reporting Follow-up: 10 weeks (6-week titration, 2-week maintenance, 1-week taper, 1-week washout)	FACIT-F: +1.97 in methylphenidate vs. placebo (95% CI: -0.95 to 4.90, p=0.186); no MCID reached. Nominally significant reduction in HADS-Depression in methylphenidate group ($\Delta = -1.35$; 95% CI: -2.41 to -0.30). No differences in other secondary outcomes or adverse events.	No superiority of methylphenidate over placebo; well tolerated; effect did not reach clinical relevance	1
Boele et al., Neuro-Oncol Pract, 2013	RCT, double-blind, placebo-controlled, parallel	37 randomized (Modafinil: 18, Placebo: 19); 1 withdrawal	Patients with primary brain tumors, experiencing significant fatigue; mean age ~47; ECOG 0-2	Modafinil 100-200 mg/day for 4 weeks vs. placebo	1.O: Fatigue reduction (MFI); 2.O: Cognitive function (neuropsychological battery), mood (HADS), QoL. Outcome Measures: MFI-20, HADS, standardized cognitive tests, self-reports. Follow-up: 4 weeks.	No significant difference in fatigue or cognitive outcomes between groups. HADS-Depression scores showed a trend toward improvement in the modafinil group, but did not reach statistical significance. Both groups showed small, non-significant reductions in depressive symptoms over time.	Pilot study with small sample; underpowered for subgroup effects. Well tolerated; suggests possible mood-related benefit deserving further research.	1
Laigle-Donadey et al., Neuro-Oncol Adv, 2019	RCT, double-blind, placebo-controlled, phase III	53 randomized (Dexamphetamine: 25, Placebo: 28)	Patients with primary brain tumors and fatigue; no recent antitumor therapy; ECOG ≤2	Dexamphetamine 10-20 mg/day for 30 days vs. placebo	1.O: FACIT-F change; 2.O: HADS (depression/anxiety), cognition, adverse events Outcome Measures: FACIT-F, HADS, neurocognitive battery	No significant improvement in fatigue or depression scores. HADS-Depression did not differ significantly between groups. Higher AE rate in dexamphetamine group	Well-designed trial; no evidence for benefit on fatigue or mood; adverse events more common under dexamphetamine.	1

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1. O=primary outcome; 2. O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence Oxford 2011
					Follow-up: 30 days	(mostly mild to moderate).		
Mitchell et al., J Clin Psychiatry, 2015	RCT, double-blind, placebo-controlled	42 randomized; 36 completed	Patients with advanced cancer and fatigue; life expectancy ≥ 3 months	Methylphenidate up to 20 mg/day for 2 weeks vs. placebo	: 1.O: Fatigue (FACT-F); 2.O: Depression (CES-D), anxiety, QoL, cognition Outcome Measures: FACT-F, CES-D, MMSE Follow-up: 2 weeks	Modest improvement in fatigue in methylphenidate group; no significant differences in CES-D depression scores. Mood remained stable across both groups.	Small sample; short duration; no impact on depression detected; intervention well tolerated.	1
Ng et al., Gen Hosp Psychiatry, 2014	RCT, double-blind, placebo-controlled, parallel-group	88 randomized (Methylphenidate + Mirtazapine: 44; Placebo + Mirtazapine: 44); no major dropouts reported	Terminally ill cancer patients diagnosed with major depressive disorder (DSM-IV), baseline HAMD ≥ 18 , life expectancy < 6 months	Mirtazapine 30 mg/d + Methylphenidate (10–30 mg/d titrated) vs. Mirtazapine + Placebo	1.O: Depression severity (MADRS); 2.O: Response rates ($\geq 50\%$ MADRS reduction), CGI-S, adverse events Outcome Measures: MADRS, CGI-S, HAMD Follow-up: 4 weeks	Significant reduction in depressive symptoms in the methylphenidate group as early as day 3 (MADRS Day 3: 24.3 ± 3.9 vs. 29.3 ± 4.4 ; $p < 0.001$). Higher response rates and greater improvement in CGI-S scores. Adverse events were mild and comparable between groups.	Well-conducted RCT with strong methodology and rapid onset of antidepressant effect; short follow-up is a limitation; high relevance for palliative settings.	1

Psychedelika: Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Level of Evidence Oxford 2011
Schipper, Cochrane 2024	SR; MA To assess the benefits and harms of psychedelic-assisted therapy compared to placebo or active comparators (e.g. antidepressants) for treatment of anxiety, depression, and existential distress in people with life-threatening diseases.	6 RCTs	Studies randomised 149 participants with life-threatening diseases and analysed data for 140 of them. The age range of participants was 36 to 64 years.	Substance-induced psychedelic experience preceded by preparatory therapeutic sessions and followed by integrative therapeutic sessions. The interventions were compared to therapy assisted by placebo or active placebo (e.g. low-dose psychedelic), or active comparators (e.g. antidepressants).	Anxiety Depression Existential distress	(only results on depression are reported here) <u>Depression reduction:</u> Psychedelic-assisted therapy using classical psychedelics (psilocybin, LSD) may result in a reduction in depression when compared to active placebo (or low-dose psychedelic): Beck Depression Inventory (BDI, scale 0 to 63) MD -4.92, 95% CI -8.97 to -0.87; 4 studies, 112 participants; standardised mean difference (SMD) -0.43, 95% CI -0.79 to -0.06; 5 studies, 122 participants; low-certainty evidence. The effect of psychedelic-assisted therapy using MDMA on depression, compared to placebo, is very uncertain: BDI-II (scale: 0 to 63) MD -6.30, 95% CI -16.93 to 4.33; 1 study, 18 participants; very low certainty evidence. <u>Adverse events (AE):</u> No treatment-related serious AE or AE grade 3/4 were reported. Common minor to moderate AE for classical psychedelics were elevated blood pressure, nausea, anxiety, emotional distress, and psychotic-like symptoms (e.g. pseudohallucination where the	Oxford 2011: 3 (downgrading due to high risk of bias and small sample size, and indirect population, as not all studies included advanced cancer)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Level of Evidence Oxford 2011
						participant is aware they are hallucinating); for MDMA, common minor to moderate AE were anxiety, dry mouth, jaw clenching, and headaches. Symptoms subsided when drug effect wore off or up to one week later.	

Kapitel 19: Spiritualität

Kapitel 19.2: Inhalte spiritueller Bedürfnisse

Verknüpfte Empfehlungen:

Empfehlung 19.1:

Patient: innen mit einer nicht-heilbaren Krebserkrankung und ihre Angehörigen haben häufig spirituelle Bedürfnisse (spiritual needs), die sich auf verschiedene Bereiche beziehen, wie z. B. existenzielle Fragestellungen, Werte und Werthaltungen, religiöse Aspekte und Grundlagen sowie die Bedürfnisse nach innerem Frieden und nach Geben und Generativität.

Empfehlung 19.2:

Es gibt Hinweise darauf, dass spirituelle Belastung bei Patient: innen mit einer nicht-heilbaren Krebserkrankung mit einer schlechteren Lebensqualität und verstärkten Symptomen wie Angst und Depression assoziiert ist.

Empfehlung 19.3:

Die an der Behandlung und Begleitung von Patient: innen mit einer nicht-heilbaren Krebserkrankung Beteiligten *sollten* deren spirituellen Bedürfnisse initial und im Verlauf wahrnehmen, und entsprechend den Wünschen der Betroffenen darauf eingehen.

Empfehlung 19.4:

Personenzentrierte Verfahren analog der Würdezentrierten Therapie, der Existentiellen Kommunikation und der Biographiearbeit sollten Patient: innen mit einer nicht-heilbaren Krebserkrankung bei spiritueller Belastung (spiritual distress) angeboten oder vermittelt werden.

Empfehlung 19.9: Spiritual Care *sollte* Gegenstand von Aus-, Fort- und Weiterbildung für alle an der Behandlung und Begleitung von Menschen mit einer nicht-heilbaren Krebserkrankung Beteiligten sein.

Literaturreferenzen: [\[108\]](#) [\[109\]](#) [\[110\]](#)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
Balboni, JAMA, 2022 [108]	SR	371 studies on role of spirituality in serious illness: cohort, cross-sectional, RCTs, MA) (+ 215 studies on role of spirituality in health, not considered for the S3 guideline)	Populations of ≥ 100 patients with serious illness , defined as a major life-threatening illness, e.g., cancer, congestive heart failure, HIV/AIDS, end-stage renal disease	Association / impact of spirituality on serious illness	Valid measures of spirituality	<p>Frequency spiritual needs (SpN): 37/47 studies with low to moderate risk of bias: <u>Patients</u> (34 studies; 10/34 in advanced cancer): SpN common (23% to 98%) <u>Relatives</u> (4 studies): SpN may also be common, but too little data available</p> <p>Association of SpN with QoL: <u>Patients</u> (6/34 studies): 5/6 studies showed sign. association of increased SpN and decreased QoL <u>Relatives</u>: no study</p> <p>Association of SpN with symptoms of anxiety/depression: <u>Patients</u> (9/34 studies): 9/9 studies showed sign. association of increased SpN and increased symptoms of anx./depr. <u>Relatives</u>: 1/4 study with sign. ass. with depression</p> <p>Association of SpN with other outcomes:</p>	Search strategy limited to spirituality. Term "existential" was not considered.	2

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
						<p><u>Patients</u> (single studies): meaning in life, satisfaction with care, suicidal ideation, anorexia, fatigue</p> <p>Preferences for Religious/Spiritual Care (SpC):</p> <p><u>Patients</u> (13 studies): SpC desired by 46-97%</p> <p><u>Relatives</u> (4 studies): same trend</p> <p>SpC education for HCPs:</p> <p>7 studies (1 RCT, 1 CCT, 5 pre-post observational) with 5/7 studies for HCPs in oncology or palliative setting.</p> <p>Interventions varied (short guide for spiritual history up to educational training)</p> <p>Improved outcomes like HCPs' competencies and patients' outcomes</p>		
<p>Austin, Palliat Med, 2025 [109]</p>	<p>Umbrella review (SR of SR)</p>	<p>27 SR (12 with MA) with 431 studies</p>	<p>N = 55,759 patients receiving specialist palliative care</p>	<p>Spiritual Care (SpC) interventions defining:</p> <ul style="list-style-type: none"> · Spiritual construct relating to (e.g. 	<ul style="list-style-type: none"> · valid measures of at least one spiritual/existential construct relating to QoL, emotional symptoms, distress, 	<p>Dignity therapy (16 SR, out of them 5 SR with exclusively patients with advanced cancer):</p> <ul style="list-style-type: none"> · Most reviewed SpC intervention · Outcomes: most effective for reducing levels of existential 		<p>1</p>

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
				religious beliefs, dignity therapy, life review). · Objective of interventions (e.g. improve spiritual wellbeing, hope, life meaning)	wellbeing, hope and life-meaning · Qualitative results describing verbal interactions on SpN	distress (6 SR) and improving QoL (2 SR); findings are mixed for emotional symptoms (anxiety, depression); results for physical symptoms (1 SR) are inconsistent; positive influence on spiritual wellbeing and meaning and purpose in life (4 in 5 SR) · Quality (AMSTAR-2): 9/10 SR were assessed as critically low for methodological quality due to failure to report publication bias, excluded studies and pre-registered study protocols. Life-review (8 SR, out of them 5 SR with exclusively patients with advanced cancer): · Outcomes: positive therapeutic effects on spiritual wellbeing (6 SR), QoL (5 SR), and distress (3 SR); only two reviews showed pooled decreases in anxiety and depression, another showed reduced depression and not anxiety; physical symptoms (1 SR) where no significant decreases were found		

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
						<p>- Quality (AMSTAR-2): all SR assessed as critically low for methodological quality, especially concerning risk of bias assessments, details of excluded studies and failure to register study protocols and report details of excluded studies.</p> <p>Meaning-centered interventions (4 SR, out of them 3 SR with exclusively patients with advanced cancer):</p> <ul style="list-style-type: none"> · Outcomes: improvements in quality of life, spiritual wellbeing, anxiety and depression (4 SR), reduction of physical symptoms (1 SR) · Quality (AMSTAR-2): critically low in 3/4 SR <p>Other spiritual interventions:</p> <ul style="list-style-type: none"> · Fostering hope (2 SR): hope improvement (2 SR), spirituality increasement (1 SR), depression reduction (1 SR), no effect on hopelessness or QoL (1 SR). · Meditation (2 SR): conflicting evidence for QoL and wellbeing 		

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
Yang, Support Care Cancer, 2024 [110]	SR/MA	RCTs	Palliative care patients and their family caregivers	Family dignity intervention (FDI)	Effects of FDI on patients' psycho-spiritual well-being, which encompasses their sense of meaning, dignity, hope, and spiritual well-being. Effects on caregivers' psychological distress, assessed through measures of anxiety, depression, and anticipatory grief.	<ul style="list-style-type: none"> · Mindfulness-based stress reduction (3 SR) · Yoga (1 SR): inconclusive results for QoL <p>7 RCTs included, with 556 pairs of subjects</p> <p><i>1. Patients' outcomes:</i></p> <p>Sense of dignity (3 RCTs): small sign. effect size (SMD, - 0.27; 95% CI, - 0.43 to - 0.10; $p = 0.002$)</p> <p>Hope (3 RCTs): moderate sign. effect size (SMD, 0.50; 95% CI, 0.24 to 0.75; $p < 0.001$)</p> <p>Meaning (2 RCTs): small sign. effect size (SMD, 0.39; 95% CI, 0.18 to 0.59; $p = 0.003$)</p> <p>Spiritual well-being (3 RCTs): small sign. effect size (SMD, 0.43; 95% CI, 0.24 to 0.61; $p < 0.001$)</p> <p><i>2. Family caregivers' outcomes:</i></p> <p>Anxiety (3 RCTs): moderate sign. effect size (SMD, - 0.61; 95% CI, - 0.92 to - 0.30; $p < 0.001$)</p>	Low evidence quality rating of the results, attributed to the high heterogeneity among studies, small sample sizes, poor overlap of confidence intervals, and high risk of bias.	2

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence (Oxford 2011)
						<p>Depression (3 RCTs): moderate sign. effect size (SMD, - 0.52; 95% CI, - 0.69 to - 0.34; $p < 0.001$)</p> <p>Anticipatory grief (2 RCTs): sign. effect size (SMD, - 0.71; 95% CI, - 1.12 to - 0.31; $p < 0.001$)</p> <p>1-month measures (subgroup analysis): benefit on spiritual well-being, anticipatory grief, anxiety and depression remained at 1 month, but not for sense of dignity, hope, meaning.</p>		

Kapitel 20: Todeswünsche

Übergreifende Suche nach Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	OLoE
Rodríguez-Prat (2024)	Systematic Overview: To provide an updated synthesis of the literature on the wish to hasten death among patients with life-limiting conditions.	<u>Databases:</u> PubMed, CINAHL, Scopus, Web of Science (through 2023). <u>Inclusion criteria:</u> Systematic reviews and primary studies focusing on the wish to hasten death	<u>Evaluation:</u> Tools for assessing the wish to hasten death, prevalence estimates. <u>Outcomes:</u> Related factors (e.g., depression, pain, reduced quality of life).	<u>Study number:</u> Included 11 systematic reviews and 35 primary studies. Depression, pain, functional disability, and sense of being a burden identified as key factors influencing the wish to hasten death.	Terminological inconsistencies and varying assessment tools impact comparability of findings.	Oxford 11: 4
Wang et al. (2023)	Systematic Review; To synthesize prevalence, associated factors, and adverse outcomes of demoralization in cancer patients	Seven databases (PubMed, PsycINFO, Embase, Web of Science, Medline, CINAHL, and Cochrane Library) searched (2012–2022). Inclusion: Observational studies on cancer patients reporting prevalence or factors related to demoralization.	No interventions were assessed; Outcomes included prevalence, factors associated with demoralization, and its correlation with outcomes such as suicidal ideation, depression, and quality of life.	36 studies with 12,427 participants. Prevalence ranged from 13.5% to 49.4%. Strongest evidence for association with suicidal ideation. Factors influencing demoralization included psychological distress, symptom burden, and social isolation.	- Demoralization overlaps significantly with depression and anxiety. - Variability in definitions and measurements limits comparability. - Studies indicate the need for clearer diagnostic frameworks and targeted interventions	Oxford 11: 2
Zhang et al. (2024)	Systematic Review and Meta-Analysis; To evaluate the effects of death education interventions on anxiety, depression, attitudes toward	Nine databases (PubMed, PsycINFO, Embase, Web of Science, Medline, CINAHL, Cochrane Library, and two Chinese databases) searched from inception to April 2022.	<u>Interventions:</u> Death education programs focusing on life and death cognition and meaning. Formats included individual and group education, lectures, videos, and	22 studies included (11 RCTs, 11 CCTs) with 2,374 patients. Death education significantly improved: Anxiety and depression ($p < 0.05$) Attitudes toward death ($p < 0.05$) Quality of life ($p < 0.01$).	Heterogeneity noted in intervention formats and outcome measures. Most studies conducted in China ($n = 21$). Quality assessment identified strong or	Oxford 11: 1

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	OLoE
	death, and quality of life in cancer patients in palliative care.		activities such as writing a will or creating an epitaph. <u>Outcomes:</u> Anxiety, depression, attitudes toward death, and quality of life.	Negative attitudes toward death included fear, despair, a high level of pressure, lack of happiness, and suicidal tendencies. The overall random effects pooled estimate was 0.52 for negative attitudes toward death [95% CI (0.45, 0.61, $p < 0.01$)], suggesting that the percentage of negative attitudes toward death in the experimental group was lower than that of the control group	moderate methodological rigor. high variability in duration (2 weeks to 10 weeks) and delivery formats (group vs. individual). further standardization of interventions is needed.	

Kapitel 20.3: Screening und Erfassung (proaktives Thematisieren)

Suche nach indirekter Evidenz (Suizidalität bei psychiatrischen Patienten/gesunder Bevölkerung): Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O=secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
Bender, 2019	RCT: analyse iatrogenic risks of suicide risk assessment focusing on	N= 147 (I: N=73; C: n= 74)	Undergraduate students, mean age 19.3;67.3% female; low Base rate of suicide attempts	I: suicide risk assessment (SITBI) C: Non-suicide specific questions	1: Immediate and persistent distress. (POMS - Profile of Mood States) 2: Implicit suicidality (S-IAT scores).	1: No significant difference between groups ($F(1, 142) = .15, p = .87$) 2: Reduction in S-IAT scores for participants with a history of suicide attempts ($d = -0.28$); no change in	<u>Content:</u> Consistent with literature it suggests suicide risk assessment is not harmful and may have	Oxford 11: 1

Referenc e	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
	distress and implicit suicidality.				Outcome Measurement: POMS (Profile of Mood States) at 3 time points; S-IAT measured once.“	other participants ($p = .89$)	therapeutic value <u>Method:</u> Small sample size predominantly Caucasian -findings may not generalize to clinical populations	
Zhan, 2022	RCT: To evaluate the impact of suicide-related interviews on negative emotions among high- risk college students	N=126 (I: n=64; C: n=62); no drop-outs	College students (18–23 years), 60% male, screened for suicidal ideation using UPI.	I: Structured interviews conducted by psychological counselors or peer monitors. C: No interview.	1: Negative affect (PANAS). 2: Depression (CES-D) and hopelessness (BHS). Outcome Measurement: PANAS measured before and after the interview. BHS and CES-D measured before and one week after the interview.	Negative affect decreased significantly ($P < 0,01$) after interviews, more with counselors ($d=1.34$) than peer monitors ($d=0.36$). Depression reduced in the experimental group after one week; no change in control. Hopelessness did not differ between groups.	<u>Content:</u> In line with the literature: asking questions related to suicide does not lead to a significant increase in short- term and long-term emotional distress. Second, after the interview, the short- term negative affect of the subjects interviewed by psychological counselors was significantly lower than that interviewed by psychological monitors <u>Method:</u> Small sample size Screening within	Oxford 11: 1

Referenc e	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
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Suche nach direkter Evidenz (Todeswunsch in der Palliativsituation): Primärstudien

Referenc e	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
Bornet et al. (2020)	Cross-sectional study: To assess the prevalence and determinants of the wish to die (WTD) in elderly patients hospitalized in acute internal medicine wards.	N=232; no drop-outs reported	Elderly patients aged ≥65 years; 44.8% female; mean age 79.3 years; all without cognitive impairment	I: Assessment of WTD using validated tools (SAHD-senior and CADO). C: No specific control group, observational only.	1: Prevalence of WTD. (SAHD-Senior, CADO) 2: Determinants of WTD (e.g., quality of life, age, depressive symptoms). Outcome Measure: SAHD-senior and CADO scores; no follow-up due to cross-sectional design.	1: Prevalence of WTD: 8.6% 2: Determinants: Higher age (OR = 1.43 for 5-year increase, p = 0.048) and lower quality of life (OR = 0.54, p < 0.001) 2. The reported stress score during interviews had a median of 0 [interquartile range 0–1] for patients with WTD and 0 [0–0] for those without (p = .102), indicating minimal to no distress from discussing the WTD	One out of twelve patients expressed a WTD, and QoL was the main determinant of the WTD. Our hypotheses were therefore only partially supported. Generalizability limited by single-center design and lack of diversity.	Oxofrd 11: Level 4
Crespo et al. (2021)	Proof-of-Concept Study: To evaluate the practical potential and acceptability of	N=30; no drop-outs reported	Advanced cancer patients in the palliative setting; Mean age: inpatients 58 years, outpatients	I: Semi-structured interview assessing WTHD (AFEDD) embedded in a multidimensional needs assessment during the	1: Practical potential (Patient-reported importance, helpfulness)	1: 94% understood the questions; 80% found the assessment helpful. 2: 87% reported little to no bother from the assessment. No	A small proof-of-concept study with a limited sample size, conducted in a single institution. Generalizability may be limited to advanced	Oxofrd 11: Level 4

Referenc e	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
	screening for the wish to hasten death (WTHD) in the first palliative care encounter.		71 years; Two-thirds male	first palliative care encounter. C: No control group.	2: Acceptability (Patient-reported bother, understanding)	significant correlation between WTHD and symptom burden.	cancer patients in similar settings. Long-term effects or broader clinical outcomes were not assessed. Further studies are needed.	
Porta-Sales et al. (2019)	Cross-sectional study: To assess the opinions of advanced cancer patients about the proactive evaluation of the wish to hasten death (WTHD) and its impact on distress.	N=193 advanced cancer patients admitted to an oncology ward; no drop-outs reported.	Mean age: 62.6 years; 58.5% male; majority with high Karnofsky Performance Status (KPS \geq 80); varied cancer diagnoses; 23.8% reported WTHD.	I: Proactive assessment of WTHD through a semi-structured interview. C: No control group; observational design	1: Patient-reported distress from assessment (HADS - Hospital Anxiety and Depression Scale) 2: Importance of WTHD discussions, associations with mood, quality of life, and performance status Semi-structured interviews; HADS (Hospital Anxiety and Depression Scale); Karnofsky Performance Status (KPS); no follow-up	1: 94.8% reported no distress; 2: 79.3% considered the discussion important. Patients with WTHD had higher HADS scores and lower KPS.	Study suggests proactive WTHD assessments are feasible and not harmful. Provides important insights for integrating WTHD discussions into routine palliative care. Generalizability limited by exclusion of emotionally or physically unstable patients.	Oxford 11: Level 4
Voltz et al. (2021)	Prospective cohort study: To evaluate whether trained communication about the desire to die is harmful to palliative care patients and to	N=85; Drop-outs: 64 completed 1-week follow-up (t1), 46 completed 6-week follow-up (t2)	Palliative care patients with prognosis of death within 3-12 months; mean age 69.1 years; 22% had a desire to die (DD) at baseline.	I: Desire-to-die conversations conducted by trained health professionals. C: No specific control group; observational data collected pre- and post-conversations.	1: Depressiveness (PHQ), hopelessness (BHS), wish to hasten death(SAHD). 2: Patient-health professional relationship, will to live, and death anxiety.	Significant reduction in depression scores at t1 ($p=0.001$, $d=0.42$); medium-severe depression group showed largest improvement. No deterioration in other outcomes; descriptive trends suggested positive effects.	Content: Study suggests trained conversations are not harmful and may reduce depression in palliative care patients. Method: include small sample size high drop-out rate.	Oxford 11: Level 2

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O=secondary) Outcome measure Follow up	Results	Comments	LoE Oxford 11
	explore its impact on patient-relevant outcomes.				Validated questionnaires (PHQ-9, BHS, SAHD) assessed at baseline (t0), 1 week (t1), and 6 weeks (t2).			

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