Leitlinienprogramm Onkologie

Evidenztabellen

S3-Leitlinie Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung

Version 1.0 – Mai 2015

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Evidenztabellen

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
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Inhaltsverzeichnis

1. Informationen zu dieser Leitlinie

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1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH).

1.3. Federführende Fachgesellschaft

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1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.5. Kontakt

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1.6. Weitere Dokumente zu dieser Leitlinie

Bei diesem Dokument handelt es sich um die Evidenztabellen zur S3-Leitlinie Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung. Die Leitlinie steht als Langversion und Kurzversion zur Verfügung. Es wird außerdem eine Version für Patienten bzw. Laien geben. Das methodische Vorgehen bei der Erstellung der Leitlinie ist in einem Leitlinienreport dargelegt. Alle Dokumente sind auf den Seiten des Leitlinienprogramms Onkologie (http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html) sowie auf den Seiten von AWMF (www.awmf.org) und der Deutschen Krebshilfe (www.krebshilfe.de) frei verfügbar

1.7. Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung, Evidenztabellen 1.0, 2015, AWMF-Registernummer: 128 / 001OL, http://leitlinienprogramm-onkologie.de/Palliativmedizin.80.0.html (Zugriff am: TT.MM.JJJJ)

2. Hinweise zur methodischen Bewertung der Studien

Zur Klassifikation des Verzerrungsrisikos der identifizierten Studien wurde in dieser Leitlinie das in Tabelle 1 aufgeführte System des Scottish Intercollegiate Guidelines Network (SIGN) verwendet (siehe www.sign.ac.uk/pdf/sign50.pdf).

Unter dem in den Empfehlungen angegebenen Level of Evidence nach SIGN (siehe Langversion dieser Leitlinie) wird ein Body of Evidence verstanden, der die gesamte identifizierte Evidenz zusammenfasst. Deshalb ist auch der Level of Evidence einer Empfehlung, deren Evidenzgrundlage auf einem Systematic Review basiert, der Body of Evidence der in diesem Review eingeschlossenen Primärstudien. Dieser Body of Evidence kann vom Level of Evidence des Systematic Reviews selbst (in den Evidenztabellen angegeben) abweichen. Die Qualität des Systematic Reviews kann nämlich hoch sein, während die Qualität der eingeschlossenen Studien, die sich im Body of Evidence widerspiegelt, niedrig ist.

Tabelle 1: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

3. Atemnot

3.1. Opioide

3.1.1.1. 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	Comments	Level of Evidence SIGN
Jennings, Cochrane Review 2001 [1]	SR (18 RCT's) MA (12 trials)	18 RCT´s, doubleblind, cross-over, placebo-controlled	Patients with dyspnea n=293 COPD(178) cancer (92) CHF (13) IPD (10)	Any opioid to alleviate breathlessness: ▪ oral or parenteral opioids (dihydrocodeine in the range of 15- 60mg 3x/d, diamorphine in the range of 2.5- 5 mg 4x/d, oral morphine 30mg and morphine sc. average 34 mg) ▪ nine nebulised opioids (1mg- 50mg)	1.O: subjective measures of breathlessness: ▪ Borg und modifizierte Borg-Tests ▪ Verbal categorical scales of breathlessness ▪ VAS of breathlessness 2.O: ▪ Exercise tolerance ▪ Arterial blood gases ▪ Pulse oximetry ▪ Adverse effects of opioid drugs ▪ Quality of life	This review shows a strong effect of treatment for breathlessness (12 studies: SMD = -0.31; 95 % confidence interval -0.50 to - 0.13, P = 0.0008). For the breathlessness results, meta-regression comparing the non-nebulised and nebulised studies showed a significantly stronger effect for the non-nebulised studies (P = 0.02). A small but statistically significant positive effect of opioids was seen on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids. For the exercise tolerance outcome, an effect of treatment is	Small sample sizes	1++

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 SIGN
						indicated, although statistical significance is not achieved (12 studies: SMD=0.20; 95 % confidence interval -0.03 to 0.42, p = 0.09.)		
King Palliative Med 2011 b [2] *[Although this paper refers to the symptom pain, it was included regarding evidence for the use of opioids in renal impairment which is unrelated to the indication, e.g. pain, breathlessness]*	SR / no MA to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment and to produce guidelines.	15 trials (no RCTs) • 8 prospective • 7 retrospective	N=1179	Assessment of ▪ pharmacokinetics and neuropsychological effects of morphine ▪ morphine and metabolite levels ▪ relationship between morphine concentrations and opioid side-effects ▪ relationship between plasma concentrations of morphine and its metabolites and pain scores ▪ whether routine monitoring for morphine and morpine metabolite concentrations ▪ biochemical and haematological factors ▪ the use of alfentanil, fentanyl, sufentanil, hydrmorphone ▪ factors associated with pethidine toxicity ▪ the effect of rotation from oral morphine to oxycodone ▪ the occurrence of toxicity	Different clinical outcomes that are relevant to the use of selected opioids in cancer-related pain and renal impairment.	• Risk of opioid use in renal impairment is stratified according to the activity of opioid metabolites, potential for accumulation and reports of successful or harmful use. • Fentanyl (1st line), alfentanil (2nd line) and tramadol/hydromorphone (use with care) are identified, with caveats, as the least likely to cause harm when used appropriately. • Morphine may be associated with toxicity in patients with renal impairment. ▪ Unwanted side effects with morphine may be satisfactorily dealt with by either increasing the dosing interval or reducing the 24 hour dose or by switching to an alternative opioid. ▪ No results for diamorphine, codeine, dihydrocoedeine, buprenorphine, tramadol, dextropropoxyphene, methadone, remifentanil	▪ Recommendations regarding opioid use in renal impairment and cancer pain are made on the basis of pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience. • All included studies have a significant risk of bias inherent in the study methodology and there is additional significant risk of publication bias • Overall evidence is of very low quality • Direct clinical evidence in cancer-related pain and renal impairment is insufficient to allow formulation of guidelines but is suggestive of significant differences in risk between opioids.	2++

3.1.1.2. 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 SIGN
Abernethy, BMJ 2003 [3]	RCT, double-blind, crossover	n=48 10 drop outs	▪ Opioid naive outpatient adults with dyspnea at rest in spite of receiving optimal treatment of reversible factors. ▪ 88% **COPD** ▪ 6% **cancer** ▪ 2% **motor neuron disease** ▪ 4% **restrictive lung disease** ▪ 73% male ▪ 71% received supplemental oxygen ▪ Overall poor functional status	▪ 4 days of 20mg oral morphine with sustained release followed by ▪ 4 days placebo, or vice versa. Laxatives provided as needed	1.O: **Dyspnea intensity** in the evening (VAS, 0-100 mm), 2.O: ▪ Dyspnea in the morning (VAS, 0-100 mm), ▪ exercise tolerance (self-report) ▪ respiratory rate, blood pressure, heart rate, oxygen saturation ▪ self-report of sleep disturbance by breathlessness, nausea, vomiting, constipation, confusion, somnolence, appetite, and overall wellbeing as measured at the mend of the four days treatment period. Outcomes analysed at 4th day of respective treatment and compared to 4th day of other treatment (but not to baseline values)	▪ morphine superior to placebo in evening **dyspnea** (improvement of 9.5 mm (95% confidence interval 3.0 mm to 16.1 mm)) ▪ morphine superior to placebo in morning dyspnea (improvement of 6.6 mm (95% confidence interval 1.6 mm to 11.6 mm)) ▪ less sleep disturbances by breathlessness with morphine compared to placebo(P = 0.039) ▪ no effects on exercise tolerance, overall well-being, sedation and respiratory rate ▪ morphine caused more distressing constipation than placebo ▪ dropouts due to (potential) side effects of morphine	▪ Only very weak strategy to control compliance with medication intake ▪ no washout period ▪ baseline values were not taken into account ▪ no details on measurement procedures of respiratory rate, blood pressure, heart rate, oxygen saturation provided ▪ for some secondary measures, no data is provided, but only statements such as "no difference" between treatments occurred"	1+
Allard, J Pain Symptom Manage 1999 [4]	randomized continuous sequential clinical trial, double-blind	n=33 (for some measures only 30 patients available)	Terminally ill **cancer** patients (median days of survival: 14,5-19) who were already receiving opioids regularly for pain relief and had persis-	Patients received in addition to regular opioid regimen once either: ▪ Arm 1: 25% or ▪ Arm 2: 50% of their regular 4-hourly opioid dose	1.O: **Intensity of dyspnea** as measured 5x during 4 hours after drug administration on 10cm VAS 2.O:	▪ significant reduction of **dyspnea** relative to baseline after both treatments, but no difference between 25% or 50% supplementary dose; The overall mean difference between pre- and post-	▪ no details on measurement procedures of respiratory frequency ▪ Impact of regularly scheduled or "as-needed" medications for breakthrough pain	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 SIGN
			tent dyspnea after rest and treatment with oxygen of ≥ 2 on 10cm VAS	Route of administration was same as the regular opioid regimen (oral and subcutaneous)	Respiratory frequency	randomization respiratory frequencies was 1.56 (SD =2.28 paired t-test: P = 0.0004). ▪ dyspnea reduction lastet up to 4 hours ▪ sign. reduction of respiratory frequency relative to baseline after both treatments, but no difference between 25% or 50% supplementary dose ▪ reduction of respiratory frequency lastet up to 4 hours ▪ dyspnea reduction was relatively greater in patients with low /moderate dyspnea at baseline (33.1; (95% CI:1.0-65.4)) compared to those with high dyspnea intensity at baseline (11.1 (95% CI: 3.0-19.2))	or dyspnea on outcomes cannot be estimated ▪ small sample size ▪ treatment duration too short with only 1 treatment	
Bruera, J Pain Symptom Manage 2005 [5]	RCT, double blind, crossover	n=12 (1 drop out)	▪ Patients with advanced **cancer** and resting dyspnea intensity ≥3 on 0-10 scale who received regular oral or parenteral opioids ▪ Patients had pre-	▪ 1 day with subcutaneous morphine plus nebulized placebo followed by ▪ 1 day with nebulized morphine plus subcutaneous placebo, or vice versa (in addition to patients' regularly scheduled opioid	1.O: **Intensity of dyspnea** as measured 1 hour after drug administration on 0-10 scale 2.O: ▪ global assessment of benefit, nausea, sweat, wheezing, and sedation on 0-10 scale	▪ significant reduction of **dyspnea** after both treatments, but no difference between subcutaneous and nebulized morphine ▪ no significant differences in nausea, sweat, wheezing, sedation between treatments	▪ no washout period ▪ very small sample → power problem ▪ treatment duration too short with only 1 day	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 SIGN
			dominant restrictive ventilation	dose)	▪ dyspnea ratings ▪ over time	▪ dyspnea reduction lastet up to 4.5 hours for both treatments ▪ preference of patients and investigators greater for nebulized morphine, but not statistically tested		
Charles, J Pain Symptom Manage 2008 [6]	Pilot-RCT, double blind, crossover	n=25 (5 drop outs)	**Cancer** patients experiencing incident dyspnea who were using a stable regular dose of an opioid.	On 3 occasions of breathlessness patients received either ▪ nebulized hydromorphone or ▪ a systemic breakthrough dose of hydromorphone ▪ or nebulized saline together with a blinding agent	1.O: **Intensity of dyspnea** as measured 10 min post-treatment (nebulizer) and 18-19min post-treatment (oral or subcutaneous) on 10cm vertical VAS 2.O: ▪ Intensity of dyspnea as measured 20, 30, and 60 minutes post-treatment on 10cm VAS ▪ patients subjective reports which treatment was most effective ▪ pulse rate, peripheral oxygen saturation, respiratory rate	▪ sigificant reduction of **dyspnea** relative to baseline after all 3 treatments, but no sign. difference between treatments ▪ dyspnea reduction continued up to 60min post-treatment with no sign. difference between treatments ▪ no difference in patients subjective reports on which treatment was most effective ▪ significant reduction in respiratory rate 10min post-treatment lasting until 60min post-treatment $F(1,19)=10.04$, $P=0.005$, but no differences between treatments ▪ no consistent effects for pulse rate and peripheral oxygen saturation	▪ small sample size ▪ treatment duration too short with only 1 use of each treatment ▪ nebulized saline (as control treatment) as effective as medical treatments → placebo effects or psychological effects (i.e., anxiety)? ▪ occasions of acute breathlessness were based on patients wish to receive treatment→ could be influenced by psychological factors	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 SIGN
Grimbert, Rev Mal Respir 2004 [7]	RCT, placebo-controlled, double-blind, cross-over	n=12 (2 Drop-outs (not intervention-related)	Adults receiving palliative care with dyspnea due to primary or secondary **lung neoplasia**, despite conventional treatment	▪ Arm 1: Morphine aerosols 20 mg, every 4 hrs during the day and on demand in the night (max 6 times in 24hrs) ▪ Arm 2: Placebo = normal saline (Wash-out period of 24 hrs)	1.O: dyspnea score by means of VAS before and within 15 min after nebulisation; evaluation by 7 categories of persons independently of each other (patient, physiotherapist, nurse, enrolled nurse, physician, resident, medical student) 2.O: respiratory rate and oxygen saturation before and after nebulisation	▪ Significant improvement in the **dyspnea score** after inhalation of morphine and placebo (p =0,00001; effect size not mentioned) ▪ No significant difference in the **dyspnea score** between morphine and placebo (p > 0,05). It.suggests that humidification or placebo effect leads to an subjective improvement ▪ No change in respiratory rate or oxygen saturation ▪ Significant differences between the **dyspnea score** according to the evaluator: the scores of the physicians, residents and medical students were similar to those of the patients; scores of the nurses, enrolled nurses and physiotherapists underestimated the subjective sensation of the patients. ▪ Upward trend of **dyspnea score** by higher dosis of morphine ▪ No side effects in the morphine group	▪ Small sample size ▪ Inclusion of 5 patients receiving oral or transdermal morphine for pain ▪ 11 men and 1 woman recruited > general applicability? ▪ No details to baseline data	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 SIGN
Jensen, J Pain Symptom Manage 2011 [8]	RCT, placebo-controlled, double-blinded	n=12	patients with stable **COPD**, ≥ 40 years, ≥ 20 py nicotine abuse	• 50 µg fentanyl inhalation vs. • placebo 10 min. later measurement of pulmonary function and exercise tests within 1 h, cross over for each patient on two separate days	▪ pulmonary function testing ▪ exercise endurance time ▪ dyspnoea intensity during exercise (Borg scale)	Fentanyl inhalation significantly increases exercise endurance time (p=0.01) and inspiratoy capacity at peak exercise (p≤0.03); increase in **dyspnoea intensity** less with fentanyl (p=0.03)	Fentanyl inhalation significantly increases exercise endurance time and improves inspiratory lung capacity at peak exercise. Small study but sample size calculation. No wash-out	1+
Johnson, Eur J Heart Fail 2002 [9]	RCT, placebo-controlled, double-blinded (pilot study)	n=10	Patients. with **chronic heart failure**, NYHA III/IV (EF ≤ 35%), clinically stable without changed NYHA status for 1 month and unchanged medication for 2 weeks, male gender, age 45-85, median 67 years	▪ 5 mg morphine p.o. 4x per day for 4 days vs. ▪ placebo cross over for each patient on day 2	**dyspnoea intensity** by VRS (0-100)	morphine relieves breathlessness (p=0.022), when given orally by day 2; side effects with sedation from day 3 (p=0.013) and constipation (p=0.026) under morphine treatment	• Orally taken morphine can reduce breathlessness due to chronic heart failure, • small underpowered study • All men > general applicability?	1-
Mazzocato, Ann Oncol 1999 [10]	RCT, placebo-controlled, double-blinded	n=9; (opioid-naiv: n=7; opioid pretreated: n=2)	Elderly patients. (66-83, median 73 y.) with **advanced cancer** disease	▪ 5 mg morphine s.c. in opiate naïve patients (or +3.75 mg morphine additionally to preexisting oral morphine dosage), versus ▪ placebo, cross over for each patient on day 2	1.O: dyspnoea intensity by VAS (0-100) and Borg scale 2.O: • pain, somnolence, anxiety • respiratory effort • respiratory rate • O2 saturation before and 45 min after injection of Mo or placebo. VAS every 15 min for 2 hrs, then every hour up to 4 hours after injection	morphine significantly better than placebo for **dyspnoea** relief (VAS p<0.01; Borg: p=0.03)	morphine s.c. appears effective for cancer dyspnoea, but very small study with n=9 patients without achieving recruitment aim of 20 patients. No description of randomisation, concealment and blinding.	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 SIGN
Navigante, J Pain Symptom Manage 2006 [11]	RCT , single-blinded	n=101; morphine treated group (Mo; n=35), midazolam treated group (Mi; n=33), morphine + midazolam treated group (MM; n=33) Drop-outs: n=31 (death)	Terminal **advanced cancer** disease, life expectancy < 1 week, ≥ 18 years, ECOG 4, severe dyspnoea	▪ Mo group: 2.5 mg morphine s.c. every 4 h for opioid naive patients., in case of opioid baseline therapy 25% increase above baseline dosage, in case of breakthrough dyspnoea midazolam 5 mg ▪ Mi group: 5 mg midazolam s.c. every 4 h, in case of breakthrough dyspnoea morphine 2.5 mg s.c. ▪ MM group: combination of both baseline drugs, in case of break-through dyspnoe ▪ a morphine 2.5 mg s.c.	1.O: ▪ dyspnoea intensity (Borg scale), ▪ dyspnoea relief after 24 / 48 h (yes/no)	Dyspnoea relief after 24 h significantly better in MM group with p=0 0004 vs. Mi and with p=0.03 vs. MO group, at 48 h percentage of pt. without dyspnoe relief with 4% in MM group (p=0.04 vs. Mi) **Dyspnea intensity:** The median values of dyspnea intensity (considering all the patients) were 3 (IR 2--5.5), 4 (IR 2--6.2), and 3 (IR 2--5) for Mo, Mi, and MM, respectively (P=NS for intergroup comparison).	Addition of midazolam to morphine therapy is beneficial in controlling dys- pnoea for dying cancer patients. Single blinding questionable: Patients who received mo. were systematically premedicated with laxatives. No mention of ITT-analysis. Drop-out ca. 33% (due to death by terminal advanced disease). No sample size calculation	1-
Navigante, J Pain Symptom Manage 2010 [12]	RCT, single-blinded	n=63; morphine treated group (Mo; n=31), midazolam treated group (Mi; n=32). Drop out: n=2	ambulatory patients. with **advanced cancer** disease, ≥ 18 years, ECOG ≤ 3, moderate and severe dyspnoea	▪ Mo group: 3 mg morphine p.o. with incremental steps of 25% every 30 min. until dyspnoea intensity is reduced at least 50%, then every 4h (except for sleeping time) ▪ Mi group: 2 mg midazolam p.o. with incremental steps every 30 min. until dyspnoea intensity is reduced at least 50%, then every 4 h (ex-	▪ dyspnoea intensity by NRS (0-10 scale) for follow-up phase (FUP) ▪ dyspnea relief for fast titration phase ▪ side effects	Dyspnea relief in both groups, after 2d significantly better in midazolam vs. morphine group, p<0.001. **Dyspnea intensity:** significantly lower dyspnea intensity level in midazolam group in comparison with the morphine group, during the four days of follow-up.(midazolam 6 (MAD = 1) and morphine 4.5 (MAD = 1.5) (P < 0.001, to baseline) No serious **AEs** that required	midazolam p.o. appears to be a better option than morphine p.o. for controlling dys-pnoea in ambulatory cancer patients Single blinding questionable: Patients who received morphine were systematically premedicated with laxatives. Sample size calculation > powered study.	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 SIGN
				cept for sleeping time)		drug discontinuation. Most common AE: somnolence.		
Oxberry, Eur J Heart Fail 2011 [13]	RCT, placebo-controlled, double-blinded	n=39 (drop out: n=4)	patients with **chronic heart failure**, NYHA III/IV (EF < 45%), clinically stable without changed NYHA status for 1 month and unchanged medication for 2 weeks, age 41-89, mean 70.2 years	▪ 5 mg morphine p.o. 4x per day for 4 days vs. ▪ 2.5 mg oxycodone p.o. 4x per day for 4 days vs. ▪ placebo Cross over for each patient after 3 days	1.O: mean change in dyspnoea intensity by NRS (0-100) over the past 24h. 2.O: • change in worst dyspnoea intensity by NRS (0-100) over the past 24h. • breathlessness now • breathlessness severity (Borg) • coping with breathlesseness and satisfaction with treatment (NRS) • change in physical function (Karnofsky) • QoL (SF-12) • Adverse events	**Mean change in dyspnoea intensity**: no statistically significant effect for low-dose opioids (both morphine or oxycodone) in chronic heart failure detected [21.37 in NRS score for placebo group vs. 20.41 in morphine group (P ¼ 0.13) and 21.29 for oxycodone group (P ¼ 0.90)] **Adverse event**: opioids well tolerated. **QoL** unchanged.	no benefit shown for the relief of breathlessness with low-dose oral opioids in chronic heart failure, follow-up study to Johnson, 2002, short treatment period for opioids to discover significant differences. Sample size calculation > powered study. ITT analysis.	1++

3.2. Andere Medikamente (Benzodiazepine, Phenothiazine, Antidepressiva, Buspiron, Steroide)

3.2.1. Benzodiazepine

3.2.1.1. 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	Comments	Level of Evidence
Simon, Cochrane Review 2010 [14]	SR mit MA	5 RCT, cross-over, double-blind and 2 RCT parallel, single-blind	N=200: COPD (52), Cancer (148)	Clorazepate 7,5-22mg/day, Lorazepam 1mg/day, Midazolam 8-20mg/day, Alprazolam 0,75-1mg/day, Diazepam 25mg/day; control: Placebo, Morphin, Promethazin or combination; treatment durations ranged between 48h and two weeks	1.O: subjective measurement of breathlessness on validated and reliable scale: categorical scales (e.g. VAS, NRS, modified Borg) 2.O: measurement of anxiety, depression, quality of life and attrition, adverse effects of benzodiazepine, functional exercise capacity (e.g. walking test)	There is no evidence for a beneficial effect of benzodiazepines in the relief of breathlessness in patients with advanced cancer and COPD. There is a slight, non-significant trend towards a beneficial effect but the overall effect size is small (SMD of -0.13 (95%CI -0.52 to 0.25)).		1++

3.2.1.2. 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 SIGN
Allcroft, J Pall Med 2013 [15]	Single-site open-label phase II study (pilot)	N=11 drop-out=1	COPD patients (median age 78 years) 8 male 3 female	clonazepam 0.5 mg nocte orally plus 10 mg sustained release morphine sulphate orally mane together with docusate/sennosides	1.O: Breathlessness intensity on day 4 (VAS 0-100)	The median score for morning average dyspnea right now was 49.5 (6 to 87) with a median reduction of 9mm (23mm worsening to 80mm	• One person withdrew on day 4 because she was feeling unsteady on her feet. • Quality of sleep showed	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 SIGN
						improvement) over baseline and in the evening a median of 45.4 (2 to 84) with a median improvement of 6.5mm (18mm worsening to 64mm improvement) over baseline.	no change over baseline.	
Stege, Resp Med 2010 [16]	RCT, double-blind, cross-over, placebo-controlled	n=14, dropout=3	Stable patients with COPD 10 male, 4 female	Temazepam 10mg/day Control: placebo Duration: one week	1.0: pCO2 and pO2, oygen saturation 2.0: subjective measurement of dyspnoea (VAS) and other secondary Outcomes	One week usage of temazepam 10mg did not cause statistically significant changes in VAS dyspnea compared to placebo (temazepam 4.2±2.9 vs placebo 4.1±2.5, p=0.90).		1+

3.2.2. Phenothiazine

3.2.2.1. 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= 18ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
O´Neill, Br J Clin Pharmac 1985 [17]	RCT, double-blind, cross-over	n=12 n=6 out of n=12	**Healthy subjects**: mean age 30 years (range=23-39 years, 10 non-smokers, 2 smokers) n=6 Six of these subjects were selected on the basis of availability proceeded to the second part of the study	n=12 ▪ Promethazine 25mg vs.placebo n=6 ▪ chlorpromazine 25mg vs.mebhydroline 50mg vs.placebo	1.O: dyspnea-intensity 2.O: lung function Measurement: ▪ VAS ▪ peak expiratory flow rate ▪ breath-holding time ▪ peak level of CO2 ▪ sedation Measurements started 75min after administration of the treatment.	Promethazin: ▪ there were no significant difference between treatments in the relationship of **breathlessness** to ventilation during exercise. At the standardised level of ventilation the mean breathlessness score after placebo was 51.4% and after promethazine 50.2%. ▪ Mebhydrolin: ▪ had no effect Chlorpromazine: ▪ reduced breathlessness without influencing ventilation and sedation	▪ small sample size ▪ only healthy participants ▪ old study	1-
Rice, Br J Dis Chest 1987 [18]	RCT, double-blind, cross-over trial	n=11 (4 drop out)	Clinically stable male patients, primary diagnosis **COPD** (FEV1<60%), aged between 50 and 70 years, long history of cigarette smoking. Exclusion criteria: PCO2>55mmHg, history of chemical	▪ Codeine 30mg 4xd vs. ▪ promethazine 25mg 4xd each for one month	1.O: intensity of dyspnea 2.O: lung function Measurements: ▪ VAS ▪ spirometer ▪ arterial blood gas analysis ▪ 12min walking test (all datas were collected daily,	▪ No improvement in **breathlessness** or **exercise tolerance** with long-term administration of codeine (M=5,7; SEM= 0,6) or promethazine (M=6.0; SEM=0,4) ▪ Statistic significant increase of pCO2 while taking codeine (P<0,01 at 24 hours;	▪ 1 patient dropped out after developing acute urinary retention while taking codeine ▪ 2 patients exacerbate while taking codeine, 1 patient exacerbated while taking promethazine - all of them required hospitalisa-	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= 18ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			dependence, significant liver or kidney disease		beginning one week before taking drugs the first time except the 12min walking test: once a week, duration of study=2month)	P>0,05 at 1 month)	tion. ▪ Drowsiness was reported often as a side effect. ▪ small sample size ▪ old study	
Stark, Clin Sci 1981 [19]	CCT, (double-blind), cross-over	n=6	**Healthy men**: 20-39 years old	Induction of dyspnea by exercise/ exposure to carbon dioxide to ▪ 10mg diazepam or ▪ 25mg promethazine or ▪ placebo	1.O: sensation of dyspnea, lung function; Measurement by ▪ VAS ▪ lung function parameter (before exercise or exposure to CO2, measure conducted 75 min after drug intake; during exercise or exposure to CO2, measure every 2-3 min)	No reduction of acute **dyspnea** during exercise or CO2 exposure by diazepam or promethazine (slight trend for promethazine for the improvement of dyspnea intensity during exercise without statistical significance)	▪ Placebos and drugs looked different and were applied by assistans ▪ Each patient received each drug and placebo during the study ▪ small sample size ▪ old study	1-
Woodcock, BMJ 1981 [20]	RCT, cross-over, double-blind, placebo-controlled	n=18 (3 dropout)	Men with **severe COPD**: without hyperkapnia with moderate or severe dyspnea (pink puffer), ex-smokers: packages per year (m=41,6; R=10-160) abstinent since (m=4,3 Jahre; R=0,5-20 Jahre)	▪ 25mg diazepam (5-5-5-2x5mg), ▪ 125mg promethazine (25-25-2x25 mg), ▪ placebo (1-1-1-2) in three consecutive two-week periods	1.O: exercise tolerance, dyspnea intensity ▪ dyspnea-measurement: VAS lungfunction measurement: expiratory flow rate, FEV1, FVC ▪ Walking distance/ bodily symptom scores /treadmill test/ progressive exercise test on bicycle ergometer 2.O: intensity of fear- and depression ▪ Psychological measurement with Morbid Anxiety Inventory/ Beck Depression Inventory	▪ Promethazine: Small but significant reduction of **breathlessness** and improvement of **exercise tolerance**, no effect on lung function (effect size not mentioned) ▪ Diazepam: Had no effect on breathlessness and noticeably reduced exercise tolerance, contraindicated in patients with obstructive airways disease, unless there is a serious unrest and a lower PaCO2	▪ 1 patient died during an exacerbation of breathlessness while taking diazepam ▪ 1 patient withdrawed because he suffered intolerable drowsiness (diazepam) ▪ Patients needed a reduction in dosage because of drowsiness (5 diazepam - 1 promethazine) ▪ It is unclear if they were provided between the two-week periods without taking sedating	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= 18ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
					(measurement after five minutes exercise)		medications ▪ small sample size ▪ old study	

3.2.3. Antidepressiva

3.2.3.1. 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 SIGN
Borson, Psychosomatics 1992 [21]	RCT, double-blind, placebo-controlled	n =36	Patients with ▪ **COPD** (FEV1/FVC<60%) ▪ **coexisting depressive disorder**	▪ 1x0,25mg/kg per day Nortryptilin (n=13), increased weekly till 1mg/kg, then for 8 weeks administered (12 week duration) ▪ placebo (n=17)	**1.O**: ▪ „Mood" (Clinical Global Improvement Scale, CGI) **2.O:** ▪ Dyspnea (Pulmonary Function Status Instrument, PFSI) and VAS. In addition, measurements with VAS before and after a 12min walking test. The most severe dyspnea and the median change were recorded before and after exercise. ▪ „Distressing physical symptoms" (35-item „Patient Rated Anxiety Scale")	**1.O**: ▪ Mood: 10 of 13 sustained improvement compared with placebo group and 2 of 17 in the placebo group showed improvement (Shi-Square=13.0, p=0,0003) **2.O:** ▪ **dyspnea**: no difference between the groups neither during rest nor during load. Only in ADL with mild exercise shows a positive effect of nortryptilins (p=0,04) ▪ „Distressing Physical Symptoms": improvement with nortryptilin of somatic 21ymptoms (p=0,08) There is no significant effect about the relief of dyspnea. The authors ascertaining, there could be significancy with a bigger sample size at least for light exercise.	Although the study reached its primary endpoint, there is no significant effect on dyspnoea The authors speculate, that this could be due to the low patient number COPD Patients are not readily comparable with cancer patients. Fromm y point of view, nortryptiline cannot be recommended as a therapy for dyspnoea in cancer patients.	1-
Eiser, COPD 2005 [22]	randomized, placebo-controllled trial	N=28 (14 women, 14 men)	▪ **depressed COPD** (FEV1 ≤60%) **patients**	▪ Paroxetine 20mg daily or ▪ Matched placebo for six weeks. ▪ Subsequently, all patients took un-blinded Paroxet-	**1.0:** ▪ QoL [St. Georges Respiratory Questionnaire (SGRQ)] ▪ Depression [Montgomery Asberg Score (MADR)]	▪ After 6 weeks there were no clinically significant changes in 6MWD or SGRQ values, but all depression scores improved, particu-	The study was named as a „pilot study" by the authors due to a protocol Amendement. They speculate, that the inter-	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 SIGN
				ine for 3 months.	▪ 6 minute walking distance (6MWD) **2.0:** ▪ Lung function ▪ peak-flow ▪ dyspnea and effect of breathlessness on a quality of life on a 5-point scale (not mentioned in detail)	larly the MADR score. (baseline HAD(depression), BDI and MADRS scores of 12, 21 and 23 respectively fell significantly to 8, 12 and 9 ($p < 0.0001$) at the 12th week) ▪ After 3 month in the open label study, there is a significant improvement in 6MWD($r = -0.424$, $p < 0.01$), SGRQ and MADR (significantly correlated with improved symptom scores of the SGRQ ($r = 0.3372$, $p < 0.02$, and $r = 0.279$, $p < 0.05$, respectively)) compared to the baseline scores ▪ But no improvement in lung-function or **dyspnea-scores** ▪ The authors conclude, because of a number of problems in the conduct of the study, it should be regarded as a pilot study only. ▪ Besides 6 weeks of antidepressant treatment was insufficient to significantly ameliorate the depression. ▪ The study does not allow any valid information re-	val of six weeks might have been too short to see an effect. Due to the endpoint "dyspnoea", no valid conclusion is possible.	

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 SIGN
						garding dyspnoea.		
Lacasse, Monaldi Arch Chest Dis 2004 [23]	Randomized, placebo-controlled	n=23	Patients with ▪ **COPD** ▪ **significant depressive symptoms**	▪ Paroxetine 5mg daily,(n=12) with weekly 5-mg increments up to a maximum of 20 mg ▪ placebo (n=11) ▪ 12 week-duration	1.O: ▪ „Emotional Function": change in score of this domain after 12 weeks, Chronic respiratory questionnaire (CRQ)	▪ The trial was stopped prematurely because of difficulties in patients' accrual. ▪ Significant improvement in the primary outcome, [emotional function (adjusted mean difference: 1.1; 95% confidence interval [CI]: 0.0- 2.2)] but its losing significancy in the ITT-analysis ▪ Improvement of **dyspnea** and fatigue without reaching statistical significance	The study is not feasible to answer the key question. Dyspnoea was not defined as an endpoint, the drop-out rate was too high and no cancer patients were included.	1+
Perna, Depress Anxiety 2004 [24]	Case series	n=6	Patients with **severe COPD**	Citalopram 1x20mg/d for 4 weeks	1.O: ▪ FEV 1 ▪ paO2 ▪ paCO2 ▪ subjective measurement of dyspnea with the Borg-scale ▪ 6min. walking test	▪ Improvement in all parameters. **Dyspnea** measurement on the Borg-scale from 7,7 to 3,5. ▪ Extension of walking distance in average from 165m to 220m.	Placebo effect is not negligible, as long as there is no control group.	3
Smoller, Psychosomatics 1998 [25]	Case series	n=7	Patients with ▪ **COPD (n=1)** ▪ **asthma (n=5)** ▪ **idiopathic emphysema (n=1)** ▪ **with and without mood or anxiety disorders**	Sertraline 25-100mg/day for four weeks up to 16 months	▪ FEV1 ▪ FVC	▪ Report of **dyspnea** improvement in general without measurement ▪ SSRI may be particularly useful and well tolerated in anxious or depressed patients with COPD and might diminish **dyspnea** in some pulmonary patients, even in the absence of a diagnos-	No data on dyspnea given only very unspecific description that dyspnoea improved. Only case series.	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 SIGN
						able psychiatric disorder ▪ No clinically significant changes in FEV1		
Ström, Eur Respir J 1995 [26]	Randomized, placebocontrolled, parallel-group, double-blind multicentric	n=26	Patients with ▪ **COPD** ▪ mild or moderate hypoxaemia (pAO2 :6,7- 8,7 kPa; FEV1 / FVC < 0,7) following a run-in period of 4 weeks, in order to assess the stability of hypoxaemia	▪ Protryptiline 10mg daily (n=14) ▪ placebo (n=12) ▪ 12 week-duration	▪ **a**rterial blood gas tensions ▪ spirometry volumes ▪ QoL (Sickness Impact Profile; SIP; Mood Adjective Check List; MACL; und Hospital Anxiety and Depression Scale; HAD) ▪ dyspnoea score (graded on a six stepp scale, ranging from 0=no dyspnoea to 6=dyspnoea at the last effort))	▪ the mean PaO2 increased 0.2 kPa in both groups during the same time after exclusion of patients having an exacerbation of COPD ▪ **QoL** and **dyspnoea**: no differences ▪ High incidence of protriptyline-induced anticholinergic side-effects observed during the 12 week treatment period of our trial suggests that the tolerability of higher doses might be quite limited.	Placebo-group is significantly younger.	1-

3.2.4. Buspiron

3.2.4.1. 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 SIGN
Argyropolou, Respiration 1993 [27]	RCT, Double-blind, cross-over trial	n=16 (no dropouts)	**COPD** patients: FEV1 <1,5l PaCO2/ FVC ratio <65%	▪ 20mg Buspiron (5-5-10mg) daily ▪ placebo ▪ 2 consecutive15 days periods in a cross-over design	**1.O**: ▪ dyspnea on exertion and exercise tolerance (measurement: 6min walking test, incremental cycle ergometer test, incremental treadmill walking test ▪ self-assessment of dyspnea (Borg´s scale during exercise) **2.O**: ▪ respiratory drive (P 0,1) ▪ arterial blood gas ▪ Inspiration: expiration relation ▪ „Symptom Check List 90R“ (SCL-90)	**1.O:** ▪ significant improvement of **walking distance** while taking buspirone (placebo:377m, buspirone:387m) ▪ Perception of **dyspnea during exercise** improved as assessed by an increment in distance walked at dyspnea score 5 during buspirone treatment (placebo: 77m, buspirone: 86m). **2.O:** ▪ Arterial blood gases and respiratory drive do not differ significantly after the two different treatments. ▪ Significant improvement of SCL-90 Index in the dimensions general symptom index, depression, anxiety, hostility and phobic anxiety while taking buspirone.	In addition to the small sample size the cross-over design is not described in detail, neither about the wash-out period nor about the intra-individual differences.	1-
Singh, Chest 1993 [28]	RCT, Double-blind, placebo-controlled	Included in study n=15, included in analysis n=11 (due to 4 drop outs)	patients with stable **COPD**: FEV1< 1,4 and FEV1 / FVC < 0,5,	▪ 3xd 10-20mg buspirone ▪ Placebo ▪ for 6 weeks with the option to double the	**1.O:** ▪ reducing anxiety (State Trait Anxiety Inventory, STAI) ▪ improving exercise tolerance:	No significant differences in anxiety scores, workload, maximum oxygen consumption per minute, maximum	Imbalances between the arms. The patients cannot be described as anxious (STAI at screening >50, at	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 SIGN
			Score >50 on Spielberger State-Trait Anxiety Inventory Scale (STAI), aged 40-75 years	dosis after 3 weeks	spirometry, 12min walk, Incremental exercise (ergometer) ▪ dyspnea: modified BORG	expired volume per minute, PETCO2, PETO2, 12 min **walking distance** or **dyspnea scores** after 6 weeks of buspirone or placeboe therapy. The mean Borg score at the end of the 12-min walk tended to be lower after the treatment with buspirone (4.6±3.8 vs 5.8±3.6 with placebo), but the difference did not achieve statistical significance and was due to one patient having a much higher Borg score while receiving placebo.	baseline <50). Sample size too small for valid results.	

3.2.5. Steroide (Glucocorticoide)

3.2.5.1. 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	Comments	Level of Evidence SIGN
Walters, Cochrane Review 2009 [29]	SR/MA	24 RCTs: ▪ 19 crossover ▪ 5 parallel	Stable **COPD** (moderate or severe in 15 studies)	Arm 1: Oral corticosteroids: ▪ Prednisolone (23) – Betamethasone (1) ▪ High dose (equivalent prednisolone 30-40mg/d) (21) ▪ Short term therapy (≤3 weeks) (19) ▪ Inhaled steroids excluded (16) Arm 2: Placebo	1.O: ▪ FEV1 (23) ▪ HRQL (3) 2.O: ▪ Proportion of responders ▪ Acute exacerbations (4) ▪ Symptom severity (13), of which breathlessness (3) ▪ Functional capacity (6) ▪ Adverse effects (6)	▪ Differences in **symptom scores** were not significant. ▪ The clinical importance of the differences found in **12min walk distance and shuttle walk distance** is uncertain and it probably depends on the severity of COPD ▪ All differences in health-related **quality of life** were less than the minimum clinically important difference. ▪ Increased risks of **adverse effects** on blood pressure, blood glucose, plasma cortisol and serum osteocalcin.	The absence of a washout period in many of the trials with a crossover design is of concern, particularly as the duration of improvement in outcomes detailed above is not clear. Fortunately, from the perspective of meta-analysis, this is likely to minimise rather than exaggerate the difference between active intervention and control.	1++
Yang, Cochrane Review 2007 [30]	SR/MA	47 RCTs (n=13.139), double-blind ▪ 12 crossover ▪ 35 parallel	**COPD** (according to international criteria or lung function and smoking history)	Arm 1: Inhaled (not nebulised) corticosteroids (ICS): ▪ Budesonide, beclomethasone, fluticasone, triamcinolone, mometasone ▪ Study duration: short term ≤2 months (16), medium term 2-6 months (15), long term ≥ 6 months (16)	1.O: ▪ Lung function 2.O: ▪ Mortality ▪ Exacerbations (4) ▪ QoL (SGRQ) and symptoms (CRQ) ▪ Use of rescue bronchodilators ▪ Exercise capacity ▪ Biomarkers ▪ Predictors of response	▪ Some medium term studies showed an improvement in **respiratory symptoms**, but not all studies were able to demonstrate this. ▪ **Exercise capacity** was only infrequently measured, and overall no significant difference was found with ICS. ▪ ICS slowed the rate of decline in **quality of life**, as	There was wide variability in study characteristics, including dose and duration of ICS, severity of COPD, inclusion criteria and outcomes studied. Furthermore, results for outcomes were sometimes either missing or not able to be pooled.	1++

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 SIGN
				▪ Long-acting ß2-agonists as co-intervention excluded Arm 2: Placebo	▪ Adverse effects	measured by the St George's Respiratory Questionnaire (WMD -1.22 units/year, 95% CI -1.83 to -0.60, 2507 participants) ▪ There was an increased **risk** of oropharyngeal candidiasis (OR 2.49, 95% CI 1.78 to 3.49, 4380 participants) and hoarseness. The few long term studies that measured bone effects generally showed no major effect on fractures and bone mineral density over 3 years.		

3.2.5.2. 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 SIGN
Aaron, NEJM 2003 [31]	RCT, double-blind	n=147 (7 drop-outs)	Patients after emergency treatment for **COPD** exacerbations, asthma excluded, broad spectrum antibiotics 10d and inhalative broncholytics for all	• 1st arm: 40 mg Prednisone • 2nd arm: Placebo	• Unscheduled visit to a physician's office or a return to the emergency department because of worsening dyspnea within 30 days after randomization • FEV1, Dyspnoea, QoL within 10 days	Significant improvement for **dyspnoea** and **QoL**. Transitional dyspnea index score on day 10: placebo 2.07±5.53, prednisone 3.95±4.62 (p 0.04); Chronic Respiratory Disease Index Questionnaire: mean change		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 SIGN
			patients		• Measures: FEV1 nach inhal. Bronchodilatation, Dyspnoe Index (-9/0/+9)	per question in dyspnea score from day 1 to day 10: placebo 0.97±1.83, prednisone 1.04±1.47 (p 0.02); Mean change per question in total score from day 1 to day 10: placebo 1.04±1.47, prednisone 1.42±1.43 (p 0.14)		
Choudhury, Resp Res 2007 [32]	RCT, double-blind, placebo - controlled 1 year follow - up	Fluticasone group: 128 Placebo group:132	**COPD** age 67 y; current smokers: ca. 40%; mean FEV: ca. 1.3 L Recruitment : primary care	Discontinue/ continue with inhalative corticosteroids (ICS) Fluticasone 500µg/d	1.O: Number of exacerbations 2.O: Time to first exacerbation Outcome measures: diary cards, medical records, symptoms: cough, wheeze, dyspnoea. HQL (SGRQ)	**Dyspnoea** OR 2.11 (1.25 to 3.57) sig. greater in placebo group after 3 months (similar for other symptoms). No sig. difference in **HRQL** and **adverse effects**.	Careful practical study in primary care. Indication of therapy with ICS not in conformity with guidelines. No data on symptoms about effect after 12 months.	1+
DuBois, Eur Respir J 1999 [33]	RCT, single-blind	n=43 (6 drop-outs)	Stable **chronic sarcoidosis** with limited lung function (<75% of predicted normal value), with stable corticoid medication or without corticoids.	• 1st arm: Fluticasonpropionate (FP) 2000µg/d for 1-3 and 4-6 months • 2nd arm: Placebo	• Differences in standard lung function parameters (FEV1, PEF, FRC, DLCO), SF36 and ACE) • 4 points symptoms scala for cough, dyspnea, wheeze.	No statistical sign. difference for **breathlessness** between FP and placebo. Breathlessness: baseline FP 0.89 ±0.76, 3 months FP 0.72 ±0.57, 6 months FP 0.73 ±0.59; baseline placebo 1.33 ±0.91, 3m placebo 1.14 ±0.85, 6m placebo 0.95 ±0.78 > all scores (incl. baseline) are lower in the FP group (statistically not sign.) No difference between groups and over time re SF36	Groups different at baseline. Statistical data sometimes not provided. 1/5 authors Fa. Glaxo	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 SIGN
Guenette, Resp Med 2011 [34]	RCT double-blind, cross-over	n=17 (0 drop-outs)	Stable **COPD** (FEV1 <70% of predicted normal value)	• 1st arm: Fluticasonpropionate 1000 µg/d in addition to maintenance LABA and SABA therapy • 2nd arm: Placebo	1.O: • Dyspnea score measured during exercise (Borg) 2.O: • Cycle endurance performance • Spirometric parameters • Static and dynamic lung volumes	No **exercise dyspnoea** relief	Steroid only in combination with other drugs. 1/6 authors in relation with various industries.	1+
Melani, Monaldi Arch Chest Dis 1999 [35]	Randomized double-blind cross-over study	n = 20 (6 withdrawals)	Stable **COPD**: Exertional dyspnoea for ≥ 1 y without any significant symptom free survival; baseline FEV1 < 50%; history of previous tobacco smoking, difficulty in correct use of metered-dose (MDI) and dry powder inhalers (DPIs).PaO2 at rest > 7.3 kPa (55 mmHg); excluded if not stable state. Age 69.7 (SD 5.7)	▪ Intervention: Inhaled beclomethasone dipropionate 2 mg via nebulizer twice a day for 4-week period ▪ Control: placebo First treatment period followed by 1-3 month wash-out phase	1.O: ▪ dyspnoea level triggered by daily activities using the oxygen cost diagram 2.O: ▪ Spirometry ▪ exercise tests (12 MWD) on last 2 days of treatment period (greater distance recorded) ▪ VAS perceived intensity of dyspnoea after each 12 MWD (not at all breathless, the most breathlessness that you have ever experienced)	**OCD**: BDP 2.8 (0.8), placebo 2.6 (0.9), **VAS** 6.0 (1.9) placebo 6.2 (2.0); not significant differences	Only male patients	1-
Milman, J Intern Med 1994 [36]	RCT, double blind	n= 21 (3 drop outs after 6 months) 5 subjects had to take additional oral prednisolone during treatment due to disease	pulmonary **sarcoidosis** (radiological stage I-III) with normal or slightly reduced lung function	▪ Intervention: inhaled budesonide 1.2 - 2.0 mg/day (n = 9) or ▪ Control: placebo (n = 12) for 12 months given in two doses (1x morning, 1x evening)	▪ cough, chest pain, dyspnoea at rest and during exercise ▪ chest X-ray, gallium scintigraphy, pulmonary function tests, Erythrocyte sedimentation rate (ESR), haemoglobin, leucoytes, neutrophilocytes, eosinophilocites, lympho-	No difference in any outcome between groups (P>0,1 minimum)	▪ small sample size and not enough power to detect differences ▪ strange way to create subgroups ▪ confounding effects due to additional use of oral prednisolone possible	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 SIGN
		progression (2 in budesonide group)			cytes, plasma (P-) creatinine, P-calcium, P-phosphate, P-aspartate aminotransferase, P-alkaline phophatase, P-immunoglobulins (Ig) G, A, M, E Outcomes measured before treatment, after 1, 3, 6, 9, 12 months during treatment, and 6 months after treatment had been discontinued		▪ majority of subjects were male ▪ not enough details on how outcomes were measures (e.g., dyspnea, cough, chest pain) ▪ no data shown for dyspnea, cough, chest pain only p-values	
Rice, Am J Respir Crit Care Med 2000 [37]	RCT double-blind	n=38 (11drop-outs)	**COPD** (criteria of AmThSoc) with steroid maintenance therapy of at least 5 mg prednisone equivalent ("steroid dependent")	• 1st arm: Prednisone reduction of 5 mg/week and withdrawal • 2nd arm: continuation of prednisone maintenance therapy	1.O: ▪ exacerbations (resulting in rescue cortisone administration, antibiotic administration, first-aid provision, unscheduled clinic visit.for dyspnea) 2.O: ▪ Dyspnea index (Mahler 1984), HRQoL	Spirometric results, **dyspnea**, and **health-related quality** of life did not differ significantly in the two groups.	Conflict of Interest not mentionned. Only male patients.	1+
Sayiner, Chest 2001 [38]	Randomised single-blind study	n = 36 (2 drop-outs)	severe **airway obstruction** (FEV1 < 35% predicted), presented with an exacerbation necessitating hospitalization	▪ Intervention: Methylprednisolone (MP) 0.5 mg/kg 6 hourly for 3 days ▪ Control: Methylprednisolone (MP)0.5 mg/kg 6 hourly for 3 days, then tapered and terminated on day 10	1.O: ▪ FEV1 and PaO2 levels on day 3 and day 10 2.O: ▪ symptom scores (dyspnoea, cough with physical and emotional function on a 7-point scale, higher scores represent better function), recurrence of exacerbation in the following 6 months, and adverse events	Both groups showed significant improvements in PaO2 and FEV1 levels, but these were more marked in group 2 (p 5 0.012 and p 5 0.019, respectively). Significant improvements in **shortness of breath** at daytime, at night, and on exertion. Improvement in dyspnoea on **exertion** observed in group 2 was significantly	Predominantly male patients	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 SIGN
						better than that obtained in group 1 [GROUP 1: Day 0: 3.0± 0.3; Day 3 5.4 ± 0.3; Day 10: 5.5 ± 0.2; GROUP 2: Day 0: 2.8 ± 0.3; Day 3: 5.1 ± 0.3 Day 10: 6.3 ± 0.2 (p=0.024)]. This was associated with the fact that, although both groups had similar increases in this symptom score at day 3, further significant improvement occurred between day 3 and day 10 in group 2 only (p < 0.01)		
Shmelev & Kunicina, Clin Drug Invest 2006 [39] I (Part II see below)	RCT plus… (see below)	122 patients assigned to either RCT (part I) or observational study (part II, see below) In RCT: **58 patients** with stable COPD stage 1 oder 2, of which 35 divided into 3 groups with Ns </= 13 and 23 patients in 2 control groups	Patients with **COPD** stage 1 and 2 without active therapy (stable or with exacerbation) Note: No indication on which criteria COPD stages were based! FEV1% values suggest staging was not conform to GOLD stages! Some patients were stable, others had non-infectious exacerbations	In addition to bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide (based on individual level of bronchoconstriction, doses not further specified) patients received either: • F1: fenspiride (2xdaily 80mg for 6 months) in COPD patients stage 1 • F2: fenspiride (2xdaily 80mg for 6 months) in COPD patients stage 2 • B2: beclomethasone inhalation (2xdaily 200mg for 6 months) in COPD patients stage 2	• Symptoms (dyspnea, cough, rales, sputum, nightly symptoms) • lung function (FEV1, FVC) • 6min walking test (6MWT) outcomes measured before treatment, after 1 month and then every 2nd month up to 6 months total	• The most significant reduction in respiratory symptoms with fenspiride related to sputum parameters, which showed a decrease in mean ± SD values from 2.58 ± 0.27 to 0.33 ± 0.18 (p < 0.001). • somewhat greater improvements in symptoms in both fenspiride groups compared to control or beclomethasone • effects seem more pronounced in COPD stage 1 patients compared to stage 2 patients • only very small reductions	• very small sample sizes and not enough power to detect differences • too many statistical tests for the small Ns (=inflation of alpha errors) • Strange way to create these subgroups. Looks like as if groups were build post-hoc • high drop outs and no explanation for it • No indication on which criteria COPD stages were based! FEV1% values suggest staging was not conform to	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 SIGN
		(Out of the 122 patients, 38 drop outs in intervention groups; 26 drop outs in control groups) Drop outs were examined in additional observational study (see below)		• C1: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 6 months in COPD patients with stage 1 • C2: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 6 months in COPD patients with stage 2		in **dyspnea** after beclomethasone • Dyspnoea decreased significantly by the second month of treatment in stage 1 COPD patients receiving fenspiride (from 1.67 ± 0.18 to 0.83 ± 0.18; $p < 0.001$) • after fenspiride improved lung function) in COPD stage 1 patients • after fenspiride improved 6MWT in COPD stage 1 patients (walking distance increased by 14.22%: from 403.83 ± 18.60m to 461.25 ± 14.7m; $p < 0.05$ • reduced number of exacerbations in fenspiride groups and beclomethasone groups compared to control groups	GOLD stages and rather stage 2 or 3 than 1 and 2 • no details on lung function measurements • baseline differences in group characteristics (e.g FEV1%) could be confounders • remains unclear who rated symptoms (patient or clinician) • not enough patient characteristics presented	
Shmelev & Kunicina, Clin Drug Invest 2006 [39] II	additional observational controlled study without mentioning whether randomized or not (but presumably not)	64 patients with COPD with exacerbations divided into 3 groups	Idem (see above)	• F: fenspiride (2xdaily 80mg for 2 weeks) • C: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 2 weeks • SC: prednisolone (20 mg daily for 1 week than	Symptoms (dyspnea, cough, rales, sputum, nightly symptoms) after 2 weeks	• Symptoms improved similar after 2 weeks of beclomethasone and fenspiride compared to control during exacerbation phases	(continuation:) • no description on what exact statistics were performed→ impossible to judge effects	

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 SIGN
				gradually reduced in week 2)				
Tashkin, Drugs 2008 [40]	Randomised double-blind, double-dummy placebo controlled parallel group multicentre study	n = 1704	age ≥ 40 years, **COPD**, symptoms > 2 years, history of at least one COPD exacerbation treated with course of oral steroids and/or antibacterials within 1-12 months before screening; FEV1 predicted ≤ 50%MRC dyspnoea scale ≥ 2, BCSS ≥ 2/day for at least half of the 2 weeks run-in period	Intervention: 5 different treatments twice daily 1) BUD/FMpMDI 160/4.5 µg x 2 inhalations (320/9 µg bd; 2) BUD/FMpMDI 80/4.5 µg x 2 inhalations (160/9 µg bd; 3) BUDpMDI 160 µg x 2 inhalations (320 µg) bd + FMDPI 4.5 µg x 2 inhalations (9 µg) bd; 4) BUDpMDI 160 µg x 2 inhalations (320 µg) bd 5)FMDPI 4.5 µg x 2 inhalations (9 µg) bd Control: Placebo BUD= budesonide FM = formoterol pMDI = pressurized metered-dose inhaler DPI=dry powder inhaler	1.O: ▪ pre-does FEV1 and 1-hour-post-dose FEV1 2.O: ▪ dyspnoea (Breathlessness diary based on BCSS, 0-4), HR-QoL, COPD exacerbations	Both budesonide/ formoterol dosage strengths experienced significantly greater improvements in **dyspnoea** scores compared with budesonide, formoterol and placebo (p ≤ 0.044). No sign. improvement in dyspnea scores between budesonide and placebo. Improvements in dyspnoea were clinically meaningful (i.e. reduction of ≥ 0.2 units [MID]) for all active treatment groups compared with their baseline values, although neither budesonide/formoterol dosage strength reached the pre-specified MID compared with placebo (based on comparison of least squares mean changes from baseline).		1+
Vestbo, Thorax 2005 [41]	Randomised, double blind, placebo-controlled study	n = 1465/ 75 drop outs/ 456 withdrawals after randomisation	**COPD** (ERS definition), age 40-79 years, .10 pack-years, pre-bronchodilator FEV1 25-70% predicted, FEV1 /forced vital capacity (FVC) <70%, poor short term reversibility	▪ 1st arm: salmeterol / fluticasone propionate combination (50/500 µg twice daily) ▪ 2nd arm: salmeterol alone (50µg twice daily) ▪ 3rd arm: fluticasone propionate (500 µg twice daily)	1.O: ▪ peak expiratory flow: time at which treatment effect was first observed in three treatment arms 2.O: ▪ dyspnoea time at which treatment effect was first observed in three treatment arms	After 14 days: OR for **dyspnoea** improvement: combination treatment significantly better than other treatments; OR salmeterol group 1.4 (95% CI 1.0 to 1.9, p=0.035) and compared with fluticasone propionate OR 1.7 (95% 1.3 to 2.3, p<0.001) No sign. Difference between	Text about change of dyspnoea scores is not reflected in data provided in table	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 SIGN
			(<10% predicted FEV1 30 minutes after inhaling 400 mg salbutamol), and chronic bronchitis with exacerbations in the last 3 years	▪ 4th arm: Control: Placebo		fluticasone and placebo (p=0.111)		
Worth, Resp Med 2010 [42]	RCT doppelblind crossover	n=111 (20 drop-outs)	**COPD** (FEV1 <50% of predicted normal value)	• 1st arm: Budenoside/Formoterol • 2nd arm: Formoterol • 3rd arm: Placebo for 1 week	• Exercise Endurance Time 1h and 6h after medication • Spirometry • inspiratory capacity during exercice (ICex)) • Borg CR10-scale	**Breathlessness score** only sig. better after 1h for Budenoside/Formoterol vs placebo (but not vs. Formoterol and not after 6h). Budesonide/formoterol resulted in a significant improvement in **endurance time** 1 h after the last morning dose in a 1-week treatment period versus formoterol [by 69 s (P < 0.005)] and placebo [by 105 s (P < 0.0001)].	Steroid only in combination with other drugs. 3/6 of the authors by Astra/Zeneca	1+
Wouters, Thorax 2005 [43]	RCT, double-blind, parallel group design	n=497 patients enrolled: 373 randomized 293 completions	**COPD** age 64 y Current smokers ca 50% Pack-years ca 37 Mean FEV 1.44	1 year withdrawal after a 3 months run-in randomized to • Fluticasone/Salmeterol 500/50µg twice daily • Salmeterol 50µg twice daily	• Dyspnoea at rest (0-4) and other symptoms • Spirometry, • exacerbation	An immediate and sustained increase in **dyspnoea score** (scale 0-4; mean difference between groups 0.17 (0.04), p 0.001) and in the percentage of disturbed nights (6 (2) percentage points, p 0.001) occurred after withdrawal of fluticasone.	Steroid only in combination with other drug. The effects are small and not clearly clinical relevant. Authors emphasize, however, the importance of ICS in COPD.	1++
Yennurajalingam, J Clin Oncol 2013 [44]	RCT, double-blind, placebo-controlled	N=84	Patients with **advanced cancer** with ≥ three **cancer- related fatigue** symptoms (ie,	4 mg dexamethason or placebo orally twice per day for 14 days	1.O: ▪ Change in the functional Assessment of Chronic Illness-Fatigue subscale	No differences were observed for ESAS overall symptom distress (P=0.22) or **dyspnea** (P=0.06).	Dexamethasone is more effective than placebo in improving cancer-related fatigue and quality of life	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 SIGN
			fatigue, pain, nausea, loss of appetite, depression, anxiety or sleep disturbance) ≥ 4 of 10 Edmonton Symptom Assessment Scale (ESAS) were eligible.		2.O: ▪ **ESAS** (including dyspnea)		in patients with advanced cancer.	

3.3. Nicht-medikamentöse Therapien

3.3.1. Therapien ohne „körperliche Übungen (*exercise*)“

3.3.1.1. Systematic Reviews

Study, journal, year	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 SIGN
Bausewein, Cochrane Review 2008 [45]	SR (MA not possible)	47 RCTs and CCTs (n=2532)	Patients with breathlessness due to: • Advanced cancer • COPD • ILD • Chronic heart failure • Motor neurone disease Most studies have been conducted in COPD patients.	• Interventions: Non-pharmacological and non-invasive (walking aids (n = 7), distractive auditory stimuli (music) (n = 6), chest wall vibration (CWV, n = 5), acupuncture/acupressure (n = 5), relaxation (n = 4), neuro-electricalmuscle stimulation (NMES, n = 3) and fan (n = 2)) • Control: placebo or usual therapy (Intervention excluded as already topic of other Cochrane Reviews: Pulmonary rehabilitation, non-invasive ventilation, nutritional supplementation, oxygen, self-management, exercise)	1.O: • Subjective measures of breathlessness on VAS, NRS, categorical scales, modified Borg scales. • If subj. measures were not present, breathlessness specific scales or disease specific scales were defined as a 1.O. 2.O: • Domain specific measures for depression and anxiety. • Quality of life. • Participants satisfaction. • Adverse-effects. • Participants withdrawal from the studies.	**Breathlessness (no MA)**: • High strength of evidence that NMES and CWV could relieve breathlessness • Moderate strength for the use of walking aids and breathing training. • Low strength of evidence that acupuncture/ acupressure is helpful • No evidence for the use of music. • Not enough data to judge the evidence for relaxation, fan, counselling and support, counselling and support with breathing-relaxation training, case management and psychotherapy.	• Breathlessness was mostly a secondary outcome • Metaanalysis not possible due to heterogeneity	1++
Effing, Cochrane Review 2007 [46]	SR (MA where possible)	14 RCTs and CCTs	**COPD**	COPD **education** defined as a programme which transfers information about COPD and treatment of	• health-related quality of life scores, • symptom scores, • number and severity of exac-	• A small but significant reduction was detected in **dyspnoea** measured with the BORG-scale (WMD -	Because of heterogeneity in interventions, study populations, follow-up time, and outcome meas-	1++

Study, journal, year	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 SIGN
				COPD Form: written, verbal, visual or audio. Content: smoking cessation, improving exercise, nutrition, self-treatment of exacerbations, inhalation technique or coping with activities of daily living or a combination of these	erbations, • courses of oral steroids or antibiotics, • use of rescue medication, • hospital admissions, • emergency room visits, • use of other health care facilities, • days lost from work, • lung function, • exercise capacity.	0.53; 95% CI (−0.96 to −0.10)) • On the disease specific **SGRQ**, differences reached statistical significance at the 5% level on the total score (WMD −2.58; 95% CI (−5.14 to −0.02)) and impact domain (WMD −2.83; 95% CI (−5.65 to −0.02)), but these difference did not reach the clinically relevant improvement of 4 points. • No significant effects found in **exercise capacity**	ures, data are still insufficient to formulate clear recommendations regarding the form and contents of self-management education programmes	
Ferreira, Cochrane Review 2005 [47] Update 2012	SR, MA	14 RCTs (n=487) Update: 3 RCTs (n=145)	Stable COPD	• Interventions: oral, enteral or parenteral **nutritional support** • Control: placebo or usual patient's diet or other treatment regimens such as anabolic substances	1.O: • Anthropometric (body weight, lean body mass, body mass index) and functional exercise (timed walk test, submaximal or graded exercise) 2.O: • Included pulmonary mechanics (lung volumes, respiratory muscle function), • peripheral muscle function • health related quality of life incl. CRQ "Dyspnea" subdomain score	Too few studies reported **dyspnea** or quality of life to generate combined effect estimates. Three studies (n=123) reported data to the CRQ subdomain "dyspnea" and showed no sign. benefit of supplemental nutrition.	Data of dyspnea only in three RCT	1+

3.3.1.2. Primärstudien

Study, journal, year	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 SIGN
FAN								
Bausewein, BMC Pall Care 2010 [48]	RCT embedded in longitudinal cohort study	n=70 (dropouts=34)	• **primary and secondary lung cancer** • **COPD III/IV**	▪ Hand held fan (HHF) ▪ wristband	1.O: ▪ use of the HHF and the wristband after 2 months measured on the modified Borg scale 2.O: ▪ recruitment into the trial and change of breathlessness severity after 2 months on modified Borg scale	Post intervention, about half of the patients used the HHF but only 20% the wristband without a statistical difference (Fisher's exact test p = 0.2). 9/16 patients judged the HHF as helpful and 4/5 patients the wristband. No difference in mean breathlessness change scores between the HHF (Borg change score: mean 0.6 (SD 2.10)) and the wristband (mean 0.8 (SD 2.67)) after two months (p = 0.90). No significant difference but high drop out		1-
Galbraith, J Pain Symptom Manag 2010 [49]	RCT crossover	n= 50 (drop-outs=1)	refractory breathlessness from any **non-malignant or malignant** cause and **Dyspnea Exertion Scale (DES)** Level 2 or above	Hand held fan directed on face region innervated by the second and third branches of the trigeminal nerve or leg mid-calf 5 min with washout period of 10min.	1.O: ▪ Decrease in breathlessness of 1cm or more assessed by a 10cm vertical visual analog scale (VAS) ▪ Monitoring of SaO2, VAS and pulse rate ▪ Measurement timing: baseline, after each use of fan and end of washout period	1.O:significant (P= 0.003) improvement of breathlessness with an effect size of 7.0 mm (95% confidence interval [CI]: 2.5-11.7 mm) but potentially carry over effect in washout period ▪ no detectable effect on participants' SaO2 or PR after use of the fan		1+
SELF-MANAGEMENT PROGRAM								
Garcia, Resp Med 2007 [50]	RCT, parallel	n=113 (51 drop-outs = 43%: death, lost,	**COPD** patients after hospital discharge following episode of	• 1st arm: Integrated care - IC (n=44) with: (1) comprehensive as-	• Dyspnea (MRC) • HRQL (SGRQ, EQ-5D) • Self-management, lifestyle,	There were no differences in the evolution of **dyspnea** (UC: 0.15 (1.44) - IC: -0.52 (1.12))	• Adequate randomisation and concealment • 43% drop-outs > ITT	1+

Study, journal, year	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 SIGN
		…)	exacerbation. 86% male, >70y, FEV1 1.2 (0.5)l	sessment of the patient at discharge by a spec. nurse (2) educational session at discharge by spec. nurse (3) individually tailored care plan. Joint visit of the spec. nurse and the primary care team within 72h. Weekly phone calls during the first month; one phone call at months 3 and 9. (4) access to the specialized nurse at the hospital was guaranteed through a web-based call centre • 2nd arm: Usual care (n=69)	BMI • Treatment adherence • Identification of exacerbation • Skills for administration fo drugs • Drug treatments • Pulmonary function tests Measures at baseline, 6 and 12 months	or **quality of life** scores.	analysis not possible • No details to baseline data	
Nguyen, J Med Internet Res 2008 [51]	Pilot RCT	n=50 (11 drop-outs)	Moderate to severe **COPD**, FEV1 < 80% predicted. Current Internet users.	A 6-month Dyspnea self-management programm (DSMP), delivered in 2 modalities: • 1st arm (n=24): internet-based (eDSMP) • 2nd arm (n=26): face-to-face (fDSMP)	1.O: Dyspnea with activities of daily living (ADL) (by means of CRQ) 2.O: • Exercise behaviour in 1 week • Exercise performance (6 min walking test) • HRQL (CRQ and SF-36) • COPD exacerbations • Mediators such as self-efficacy and social support Measured at baseline, 3 and 6	The fDSMP and eDSMP showed similar clinically meaningful changes in **dyspnea** with ADL from baseline to 3 months (fDSMP: + 3.3 points; eDSMP: + 3.5 points) and sustained these improvements at 6 months (fDSMP: + 4.0 points; eDSMP: + 2.5 points; time effects $P < .001$; group by time $P = .51$). Distance covered during the **6-min. walk test** declined in the fDSMP and increased in	• Compares 2 modalities of self-management. No “placebo”. • Stopped early due to technical challenges (eDSMP), but follow-up for 6 months • ITT analysis for the 39 pts who completed the study • Adequate randomisation and concealement • Small sample size > underpowered	1-

Study, journal, year	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 SIGN
					months	the eDSMP over time with a marginal group by time difference (P = .05). Total scores on the CRQ, reflecting disease-specific **HRQL**, improved over time for participants in both the eDSMP and fDSMP ($P < .001$). There were also positive changes in the SF-36 physical composite scores over time for both groups ($P = .04$).		
Wakabayashi, Geriatr Gerontol Int 2011 [52]	RCT, parallel-group	n=102 (Drop-outs: 17)	**COPD**, older patients > 65 years. No specific grade of disease.	• 1st arm I (n=52): Integrated care: individually tailored education program according to the patients' needs (measured with LINQ) + booklet. Intensive education monthly for 6 months, then usual care for 6 months. • 2nd arm U (n=50): usual care: general education based on the domains of LINQ but without knowing the individual LINQ scores obtained by the patients; no booklet	• Information needs of patients with COPD (LINQ = Lung Information Needs Questionnaire) • Pulmonary function tests • Dyspnea severity (MMRC) • Exercise capacity (6-min walk test) • BMI • Activities of daily living • BODE index (=BMI+airflow obstruction+dyspnea + exercise capacity) • Health status (SGRQ) • Comorbidities (Charlson index) At baseline, 6 and 12 months	No significant differences between the baseline and the 6-month follow up in either group for **6MWT distance**, **MMRC**. A significant improvement was noted in **MMRC** at 12 months compared to the baseline in group I (P < 0.01), whereas group U showed a significant worsening in MMRC at 12 months (P < 0.03). No sign. Between group difference for **MMRC** and **6MWT distance** (p=0.88, p=0.363 resp.). There were no significant changes in the total **SGRQ**.	• Adequate randomization and concealment • Proposed sample size not achieved • No mention of ITT	1+
OTHERS								
Neuromuscular stimuli								
Lau,	Randomised,	N=46	Patients>60years; had	Intervention:	▪ Pulmonary Function (FEV1,	• Increase of FEV1 by 0.12	▪ COPD GOLD I and II	1-

Study, journal, year	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 SIGN
Australian J Physiotherapy 2008 [53]	placebo-controlled trial	(no drop-outs reported)	to have stable **COPD** GOLD I or II	▪ 45 Minutes of Acu-Trans-cutaneous-nerve-stimulation (ACU-TENS) at a single time. Control: • Sham Procedure without electrical output	FVC) • Dyspnoea (100mm VAS-Scale)	litres more in the intervention group compared to control (p<0.001). • Increase of FVC by 0.05 litres more in the intervention group compared to control (p=0.09). • Dyspnoea decreased by 11mm more in the intervention group, p not provided but confidence interval suggests significance).	patients do not suffer from dyspnoea at rest or light exertion normally. ▪ A difference of 120ml in FEV1 is of questionable relevance. • The sham procedure is not really a placebo procedure because in opposite to the TENS-Procedure, patients do not experience the flow of current.	
Chestwall vibration								
Mahajan, Resp Res 2011 [54]	multi-center, double-masked phase II RCT	n=52 active (n = 25) or sham (n = 27) treatment	**COPD, Asthma**	▪ High frequency chest wall oscillation active or sham treatment for 15 minutes three times a day for four treatments. • Medical management was standardized across groups.	1.O: ▪ Patient adherence to therapy after four treatments (minutes used/60 minutes prescribed) and satisfaction. 2.O: ▪ change in Borg dyspnea score (≥ 1 unit indicates a significant change) ▪ spontaneously expectorated sputum volume • forced expired volume in 1 second.	1.O: ▪ Adherence similarly high in both groups (91% vs. 93%; p = 0.70). Patient satisfaction was also similarly high in both groups. 2.O: After four treatments, patients in the active treatment group had a clinically significant improvement in **dyspnea** ((70.8% vs. 42.3%, p = 0.04).	•	1+
Breathing training								
Barton, Lung Cancer 2010 [55]	Feasibility RCT	n=22 (drop-outs =14)	**Malignant lung/ intrathoracic disease** with refractory breathlessness.	• Intervention: 3 three breathlessness management training sessions of 1h once a week, provided	As this was a feasibility study there were no designated primary or secondary outcome measures	Study appears to indicate that three sessions of training may be more effective for **breathlessness** management than a	Study design was shown to be inadequate. Strategy for patients' recruitment, inclusion and	1-

Study, journal, year	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 SIGN
			Inclusion criteria: • Expected prognosis of > 3 months • Karnofsky > 40% • Therapy refractory breathlessness Exclusion criteria: • Intercurrent illness • Severe co-morbidity • Rapidly worsening breathlessness • Radical radiotherapy in the las 6 months • Palliative radiotherapy within 4 weeks • Chemo/anti-cancer hormone treatment in the last 2 weeks Prior experience of breathlessness training	by a specialist physiotherapist (AE) or a lung cancer nurse specialists trained by AE. Sessions include: diaphragmatic breathing, pacing, anxiety management and relaxation). Patients received written and DVD/video reinforcement material and a telephone call from their therapist aweek after the last training session. • Control: 1 session of 1h, otherwise same as intervention	Outcome measures: • *Questionnaire*: - Severity of breathlessness - Distress caused by breathlessness - Ability to cope with breathlessness (10=Fähigkeit, Luftnot zu bewältigen (10=have coped very well) - satisfaction with management of breathlessness (respectively NRS 0-10) • *QoL:* EQ-VAS, EQ-5D • *Depression/anxiety:* HADS • *Coping response:* BriefCOPEQuestionnaire Follow up: Measures at baseline, 1, 2, 3, 4 and 8 weeks	single session	exclusion criteria, Method of randomization will be changed for follow-on study.	
Battaglia, Arch Phys Med Rehabil 2009 [56]	RCT Double blind	n=32	Patients with **COPD** GOLD I-IV without significant improvement after bronchodilation test. Mean age 68y	• Intervention: breathing training with inspiratory device Respivol ® in combination with expiratory Respilift®, 15 min twice daily over 12 months.	1.O • Maximal inspiratory pressure (MIP), max. expiratory pressure (MEP) • Dyspnea perception	Patients benefit from training with the combined insp. and exp. devices: Sign. improvement of MIP (81±4 at 12 months vs 57±7 as basal values expressed in cm H20;	4 patients of the intervention group and 2 patients of the control group had an exacerbation during the study. No sample size calculation	1-

Study, journal, year	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 SIGN
			All ex-smokers All with inhaled steroids	• Control: sham training		p<0.5) and MEP and of **dyspnea** grade on Borg Scala (97±2 at 12 months vs 62±4 as basal values; p<0.5) Patients with COPD GOLD III + IV sign. less than GOLD I + II.	> underpowered, no mention of ITT	
Bosnac-Guclu, Resp Med 2011 [57]	Prospective RCT Double blind	n=36, drop-out = 6 Intervention: n=16 control: n=14	Pat. with **heart failure** Inclusion criteria: • Clinically stable • LVEF<40% • NYHA II-III • No change in medication over 3 monthskeine Änderung in der Medikation in den letzten 3 Monaten • Patients with pacemaker if 6 weeks after implementation Exclusion criteria: • Acute myocardial infarction • Cognitive disorders • Complex arrythmias • Uncontrolled hypertension • Angina pectoris • viral infection in the last 6 months	A one-week familiarization period and instruction about IMT= Inspiratory Muscle Training (20-30% of MIP) or sham IMT Intervention: • Pat. received IMT at 40% of MIP *(pressure threshold device - POWERbreathe®),* 30 min per day for 6 weeks. Control: ▪ Pat. received sham IMT 30 min per day for 6 weeks. • In total, 8 sessions were supervised, 2 calls a week, diary.	Pulmonary function tests, dyspnea, quality of life Outcome measure: • Pulmonary function tests (spirometry with FEV1, FVC, PEF) • Respiratory muscle strength (Max. inspiratory pressure (MIP) and max. expiratory pressure (MEP) with MicroRPM). Quadriceps femoris isometric strength (JTECH Power Track Commander II) • Functional capacity (6MWT in combination with dyspnea (Borg)) • Balance (Berg Balance Scale) • Fatigue (Turkish version of Fatigue Severity Scale with 9 Items) • Depression (Turkish version of Montgomery Asberg Depression Rating Scale) • Dyspnea severity (Medical Research Council dyspnoe scale, 0-4)	Sign. improvement with IMT for: • **Functional capacity** (418.59±123.32 to 478.56±131.58 m, p < 0.001) and functional balance • Respiratory (MIP=62.00±33.57 to 97.13±32.63 cmH2O, p < 0.001) and periphery muscle strength (240.91±106.08 to 301.82±111.86 N, p < 0.001) • **Dyspnea** (2.27±0.88 to 1.07±0.79, p < 0.001 • Depression (11.47±7.50 to 3.20±4.09, p < 0.001), No sign. Improvement with IMT for: • **QoL** Fatigue	Patients without resp. muscle weakness improved too. Sample size calculation: n=15/group No mention of ITT Adequate randomization, no mention of concealment	1+

Study, journal, year	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 SIGN
			• orthopedic problems rheumatologic disease		• Quality of life (SF-36) Follow up • Before and after interventions			
Ekman, Eur J Heart Fail 2011 [58]	RCT	n= 72 (m=52, w=20), drop-out=7 Intervention: n=35, drop-out=5 Control: n=37, drop-out=2	Patients with stable chronic heart failure (NYHA II-IV) with persistent symptoms of breathlessness despite optimal pharmacological treatment. Inclusion of patients with Dyspnea ≥2/5 on Likert-scale Exclusion criteria: • if performing Device-guided breathing (DGB) not possible (psychiatric illness, chemical dependency, unstable angina pectoris, or COPD) • expected survival shorter than study • poor communication skills or compliance	• Intervention: a 20 min, twice-daily session of DGB=Device Guided Breathing (with RESPeRATE®) for 4 weeks. Goal of the respiratory modulation (RM) was to progressively slow the respiration rate to 10 breaths per min and to increase the exhalation time (Tex) • Control : a 20 min, twice-daily session with music using a CD player über einen CD-Player for 4 weeks	Dyspnea, changes in NYHA class, Fatigue Outcome measure: • NT-proBNP • Blood pressure • Self-rated sleep quality • Dysnea (5 point Likert-scale) • Fatigue (5 point Likert-scale) *In addition fort he DGB-group:* Respiratory rate, inspiration time (Tin), exhalation time (Tex), Tex/Tin ratio Follow-up: Before start of the study and at the end *In the intervention group:* • Before and after every session	No sign. Improvement of dyspnea and of NYHA-class by DGB. Some patients (responder, n=14) seem to respond to DGB. They show a symptom improvement and a significant change of NYHA-class (20.64+0.20, P , 0.01). The criteria of a responder are not further defined. With DGP, the responders raise their Tex/Tin ratio.	No ITT, no sample size calculation No description of randomization	1-
Faager, Clin Rehabil 2008 [59]	RCT Open-label cross-over	n=32	Moderate to severe **COPD** Inclusion criteria:	• Pre-test: ISWT • Intervention: endurance shuttle walking test-ESWT: Walking speed 85%	Endurance by walking, O2 saturation and dyspnea Outcome measure:	Pursed lips breathing sign. increases **endurance** (patients walked for 37 seconds (16%) longer (p<0.01) and reduces	During the test, 25 were responders and 7 non-responders (walking distance, O2 saturation)	1-

Study, journal, year	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 SIGN
			- clinically stability - physical performance limited by dyspnoea - oxygen desaturation to less than 95% at the end of the incremental shuttle walking test (ISWT) Exclusion criteria - cardiac comorbidity - neurological or orthopaedic mobility impairments	of max. ISWT performance. Patients used spontaneously pursed lips breathing and became a nose clip. • Control: patients received a mouthpiece during ESWT, to prevent them using pursed lips breathing, and a nose clip	• Heart rate • O2 saturation • Perceived dyspnea (Borg scale CR-10) • Leg fatigue (Borg scale CR-10) • Peak expiratory flow (Mini-peak Flow Meter) Follow up Before, directly after, 5 and 10 min later	O2 desaturation. No sign. change of **dyspnea** with pursed lips breathing (nor of leg fatigue, heart rate or Peak expiratory flow).	Bei dem Test galten 25 als „Responder“ und 7 als „Non-Responder“ (Gehstrecke, Sauerstoffsättigung). Discussion: Breathing through mouthpiece is uncomfortable and wearing. Non-responder had usually a lower FEV1, worse O2-saturation and a lower endurance. One patient had a FEV1 > 80%. Normal mouth or nose breathing through nose clip/mouthpiece not possible. No sample size calculation > underpowered; no ITT No details to randomisation or concealment	
Kunik, Psychol Med 2008 [60]	RCT	n=238	**COPD**	Intervention: Treatment consisted of eight 1-h sessions of CBT: ▪ education and awareness training ▪ relaxation training	1.O: ▪ COPD-specific QoL (Chronic Respiratory Questionnaire) ▪ generic QoL (SF-36) 2.O: ▪ depressive and anxiety symp-	▪ Both treatments significantly improved QoL, anxiety and depression ($p<0.005$) over 8 weeks; the rate of change did not differ between groups.		1-

Study, journal, year	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 SIGN
				▪ increasing pleasurable activity and decreasing anxiety-related avoidance ▪ cognitive therapy ▪ problem-solving techniques ▪ sleep management skills ▪ skills review and planning for maintenance of gains ▪ additional home practice were assigned Control: ▪ Eight 1-hour sessions of COPD education	toms ▪ 6-minute walking distance (6MWD) ▪ use of health services	▪ Improvements were maintained with no significant change during follow-up.		
Lidell, Physiotherapy 2010 [61]		n=30	**COPD**	Intervention I (n=15): • once-weekly group received one supervised rehabilitation session per week Intervention II (n=15): • Twice-weekly group received two sessions per week • Both for 8 weeks • Together with a home exercise plan	1.O: ▪ Incremental Shuttle Walking Test (ISWT) ▪ Endurance Shuttle Walking Test (ESWT) ▪ St George's Respiratory Questionnaire (SGRQ) ▪ Assessed at baseline and at completion of the supervised programme. 2.O: ▪ home-exercise activity ▪ attendance levels ▪ patient satisfaction with the programme	groups showed similar improvements in ▪ exercise tolerance (median values: ISWT once-weekly 60 metres, twice-weekly 50 metres; ESWT once-weekly 226 seconds, twice-weekly 109 seconds) ▪ Patient satisfaction with both formats was high and almost identical between the groups. Intervention I: ▪ No improvement in QoL (SGRQ 0) Intervention II: ▪ Improvement in QoL (SGRQ 3.7).		1-

Study, journal, year	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 SIGN
Magadle, Resp Med 2007 [62]	Cross-sectional RCT Double blind, placebo controlled	n=34 (m=26,w=8) Drop-out Phase1=3 Drop-out Phase2=4	Significant **COPD** FEV1 <50%, FEV1/FVC <70% All were on regular long-acting bronchodilators and inhaled corticosteroid therapy. All new to a pulmonary rehabilitation program Exclusion: • Cardiac disease • Bad compliance • Patients with long-term supplemental O2	*Phase1:* All patients participated in a general exercise reconditioning (GER) for 12 weeks, then randomization. *Phase2:* • Intervention: inspiratory muscle training (pressure threshold device - POWERbreathe®) (IMT) three times a week for 12 weeks. • Control: sham IMR three times a week for 12 weeks.	Spirometry, insp. muscle strength, dyspnea, quality of life Outcome measure: • Spirometry (FVC and FEV1) • 6 min walking test (6 MWT) • Insp. Muscle strength (PImax) • Perception of dyspnea by breathing against resistance (BORG CR-10 Skala (POD) • Quality of life by means of St George Respiratory Questionaire Score (SGRQ) Follow up Before, 3, 6 and 9 months after intervention	Pat. benefit from IMT. *Phase1:* a small but non-significant decrease in the POD (from 22.870.6 to 20.670.5 total Borg score), SGRQ score (from 60.1±2.1 to 56.3±2.5 total SGRQ score) significant increase in the 6MWT (from mean±SEM 254can to 322±42 m, 26%, p<0.01), *Phase2:* Significant decrease in the POD in the training group (from 20.2±0.4 to 14.9±0.3 total Borg score, p<0.001), but not in the control group. The difference between the two groups was statistically significant. No change of **6 MWT**	No details to randomization or concealment No sample size calculation > underpowered; no ITT	1-
Masanga, Respirology 2011 [63]	RCT	n=21 (11 IMT, 9 control)	moderate to severe **COPD**	Intervention (n=11): ▪ Education ▪ dietary instruction ▪ occupational therapy ▪ ± daily High-intensity Inspiratory Muscle Train-	▪ FEV1 ▪ PiMax ▪ 6MWT ▪ Dyspnea and QoL (CRDQ) ▪ Measured at baseline and end of the study	▪ sub-analyses: improvement after pulmonary rehabilitation - 6MWT (p<0.0001), CRDQ (p= 0,022), EV1(p=0,9573) ▪ among the IMT group	▪ Small number of patients ▪ short duration of intervention ▪ No details about division between moderate	1-

Study, journal, year	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 SIGN
				ing (IMT) Control (n=9): ▪ Education ▪ Dietary instructions ▪ Occupational therapy Duration 4 weeks	IMT – reached intensity level 40 -90cmHg (baseline 10 cmHg)	significant improvement PiMax p=0,0001- but no additional improvement in exercise capacity, CRDQ and FEV1 ▪ Adverse effects were at all minimal and self-limited.	and severe COPD	
Mota, Respir Med 2005 [64]	RCT, placebo-controlled	n=18 (drop outs=2)	severe **COPD**	Intervention: ▪ expiratory muscle training Control: ▪ sham training group both completing: ▪ 4-weeks run-in ▪ 5-week program ▪ 3xweekly 30min breathing through an expiratory threshold valve -50% max. exspirat.pressure vs. placebo	▪ lung function ▪ exercise tolerance (bic.ergomet. and walking test) ▪ clinical outcomes (dyspnea and QoL>SGRQ) ▪ Measurement timing at baseline and following training period	▪ Lung function unchanged ▪ Sign. improvement in exercise capacity, symptoms and **quality of life** (r=0.634, P<0.05).	▪ Small number of patients	1+
Mularski, J Altern Complem Med 2009 [65]	RCT	n=86 (drop outs=36)	advanced and symptomatic **COPD** GOLD stage ≥ II (64% severe, pre6MWTdistance 278m) Nonreversible airflow limitation Average age 67 years	Mindfulness-based breathing therapy (MBBT)- once-weekly-group meetings and daily self-administered MBBT practice (defin.strategy mindfulness-based stress reduction program with supplemental relaxation response training) improving dyspnoea and HRQoL • compared to support	▪ 6MWT ▪ modified BORG dyspnoea scale other outcome measures: ▪ HRQoL(SGRQ) ▪ 6MWTdistance ▪ symptom scores ▪ exacerbation rates ▪ measures of stress and mindfulness 8-week program and evaluation	▪ No measurable improvement in **dyspnoea** or/and any other outcome measures	▪ No details about division between moderate and severe COPD ▪ High risk of bias ▪ High dropout rate	1-

Study, journal, year	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 SIGN
				groups				
Nield, J Cardiopulm Reha 2007 [66]	RCT	n=40 (drop outs=2(w4) and 12(w12))	Stable **COPD** 65±9y	Intervention I: ▪ Pursed-Lips Breathing Intervention II: ▪ Expiratory Muscle Training Control ▪ Daily practice sessions ▪ Logs to record practice times and potential adverse events ▪ 4 weekly visits research laboratory Intervention: Patients education handouts and audiovisual aids Control: education pamphlet and the same monitoring	Focus: voluntary prolongation of experatory time SF-36 physical function score - greatest improvement in the PSBgroup ▪ Dyspnea: modified Borg after 6MWD and Shortness of Breath Questionnaire ▪ Functional performance: Human Activity Profile and physical fuction scale of Short Form 36-item Health Survey	▪ No significant Group x Time difference was present for PEmax (P = 0.93). ▪ Significant reductions for the modified Borg scale after 6MWD (P = 0.05) and physical function (P = 0.02) from baseline to 12 weeks were only present for pursed-lips breathing. ▪ Positive effects on **self-care management** and self-efficacy.	▪ Small groups of intervention ▪ short time	1-
Padula, Appl Nurs Res 2009 [67]	RCT	n=32	Chronic stable **HF** 74,7(32-94)y 47% male NYHA II 51,8 % NYHA III 48,3 %	Intervention: ▪ 3month nurse-coached IMT program and education control: • education alone with standard educational protocol	▪ PImax ▪ Borg scores ▪ Blood pressure ▪ Heart rate ▪ Respiratory rate a. o. ▪ Health-related QOL	▪ No statistically differences ▪ Borg scores from baseline to Week 12 were significantly different as evaluated by repeated-measures analysis of variance (ANOVA), Wilk's k = 0.626, F(2,30)=17.36, p b .0001. ▪ Home-based IMT can be effective in improving **dyspnoea** and IM Strength ▪ Questionable improvement in **QoL** and self-efficacy for breathing	▪ Sample size relatively small	1+

Study, journal, year	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 SIGN
Pinto, Respir Man 2012 [68]	RCT, delayed start study design	n=19 (drop outs=4)	**ALS**,13 men 57,7±8,8y mean disease duration 13,2± 7,7mo ALS-FRS 25-38	randomized in two groups: G1- efficient load group G2-non-efficient load group (after 4 month (first 4 month work-out with lowest possible load, after 4 month exercise with efficient load	Evaluation 3 times- at entry and every 4 month: ▪ Functional amyothrophic lateral sclerosis rating score-ALSFRS ▪ FCV ▪ MIP ▪ MVV ▪ SNIP ▪ VAS for fatigue and dyspnoea ▪ Subj. respire.control feeling ▪ FSS ▪ Epworth`s scale ▪ FIM ▪ Euro-QoL 5D ▪ Hamilton`s scale	▪ ALSFRS (Mean difference 0.846 (SD 1.455)) and MVV higher decrease in G2 (first four month) ▪ VAS for dyspnea: Mean difference -0.231 (SD 0.715) ▪ No other differences ▪ All patients described a better voluntary control over respiratory dynamics	▪ Small number of patients	1-
Acupressure/acupuncture								
Suzuki, J Altern Complem Med 2008 [69]	prospective trial with matched-pair parallel groups of patients	n=30	**COPD**	▪ Intervention: Acupuncture 1per week for 10 weeks and medication ▪ Control: medication only	1.O: Breathlessness before and immediately after the 6-minute walk test (6MWT), using a modified 10-point Borg category scale. 2..O: ▪ SpO2, lung function, vent. Musclestrength /endurance, Fletcher Hugh-Jones categories	1.O: Improvement in ▪ Borg scale (p=0.000) ▪ 6MWT (p =0.0002) 2.O: Improvement in ▪ SpO2 (p= 0.0001)minimum and mean ▪ Fletcher Hugh-Jones categories significantly higher in intervention group	Japanese study: ▪ Cultural influences? ▪ Transferability and generalization might be questionable?	2++
Whale, Acupuncture in Medicine 2009 [70]	Prospective double blinded RCT	N=11 (drop outs=2)	**COPD** with acute exacerbation	▪ Intervention: real acupuncture device (n=4) ▪ Control: sham needle device (n=5) ▪ over three consecutive	▪ Credibility of acupuncture (Borkovec and Nau Credibility Questionnaire) ▪ Dyspnea and anxiety (Modified borg scale)	▪ Credibility of acupuncture was acknowledged ▪ Mean dyspnea and anxiety scores improved, no difference between intervention		1-

Study, journal, year	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 SIGN
				days		and control group		
Wu, J Altern Complem Med 2007 [71]	randomized, block experimental design	n=44	**COPD**	▪ Intervention: true acupressure group received an acupressure program that used the acupoints of Great Hammer, Celestial Chimney, Lung Transport, Kidney Transport, Fish Border ▪ Control: sham acupoints used were Shang Hill, Supreme White and Large Pile ▪ Both treatments extended over 4 weeks and consisted of 16-minute sessions given five times a week.	1.O: ▪ Geriatric Depression Scale (GDS) ▪ Dyspnea Visual Analogue Scale (DVAS) ▪ on baseline and post intervention 2.O: ▪ SpO2, blood pressure, respiratory rate and pulse pre/post session	▪ GDS scores (decreased in sham acupuncture group by 0.14 points)**, DVAS scores (p<0.01)**, oxygen saturation, and physiological indicators significantly improved p=0.00	Taiwanese study: ▪ Cultural influences? ▪ Transferability and generalization might be questionable?	2++
Music								
Singh, Chron resp Disease 2009 [72]	RCT	N=72 (drop-outs=8)	Patients who just recovered after an acute COPD exacerbation and are stable for at least seven days since then. COPD defined as FEV1/FVC <70% und FEV1<80% of predicted. "Self reported Shortness of breath (SOB)"	Arm A: ▪ music (self selected, indian instrumental music with 60-80 beats per minute) for 2x30 Minutes in the morning and afternoon. Arm B: ▪ Progressive muscle relaxation (PMR): Patient listened to instructions and performed the re-	▪ Dyspnoea: 100mm VADS ▪ Anxiety now: Speilbergers state anxiety inventory (SSAI) ▪ General Anxiety: Speilberger´s trait anxiety inventory (STAI) ▪ Physiologic paramters: Blood pressure (BP), pulse (HR), and respiratory rate (RR)	▪ SSAI 8.4 Points better after second session of music compared to baseline, ▪ SSAI 4.8 points better after PMR compared to baseline. ▪ STAI change was significant for interaction but not clinically significant. ▪ **Dyspnoea** reduction was 23,1 mm on 100mm VAS in the music group and 12.9 mm in the PMR group.	▪ Statistic is hard to understand. ▪ No information about cancer patients.	1-

Study, journal, year	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 SIGN
				laxation of 16 muscle groups.		▪ BP, RR and HR decreased after both interventions significantly. ▪ Music: Systolic BP pre: 136.88 to 127.8 post; diastolic BP 87 to 85; HR 89 to 81; RR 27 to 19. ▪ PMR: SPB 134 to 130; DBP 84 to 83; HR: 87 to 81 and RR 22 to 17.		
Relaxation								
Chan, Complement Ther Med 2011 [73]	RCT single blind	n=206	**COPD**	Intervention: ▪ 3 months Tai Chi Qigong with two 60-min sessions each week, 1 hour daily self-practice 1st control: ▪ exercise group with pursed-lip breathing, diaphragmatic breathing and self-paced walking, 1 hour daily self-practice 2nd control: ▪ usual care	▪ Lung functions ▪ Borg scale before and after 6-min walk test ▪ COPD exacerbation rate ▪ Timing of measurement: baseline, 6 weeks, 3 months	Significant interaction effects between time and group in : ▪ forced vital capacity ($p = .002$) ▪ forced expiratory volume in 1 s ($p < .001$) ▪ walking distance ($p < .001$) ▪ Exacerbation rate ($p = .006$) at 3 months. ▪ Improvements were noted in the TCQ group. ▪ No changes were observed in the exercise group, while a decline in lung functions was noticed in the control group. ▪ No significant differences in Borg scale		1+
Donesky-Cuenco, J Altern Com-	Open label, randomised study	N=41 (no drop-outs)	Pts > 40 Years/ old ADL limited by dyspnoea	Intervention: ▪ 12-week Yoga training program (twice weekly)	▪ Dyspnoea intensitiy (DI) and Dyspnoea related distress (DD) measured with a modi-	▪ DI did not improve after intervention ▪ DD improved significantly	▪ The population was not representative (recruitment via advertising)	1-

Study, journal, year	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 SIGN
plem Med 2009 [74]			Stable COPD Pts were recruited by advertising!	with posture and breathing elements. Control: ▪ "Usual care", interventions and no. of visits not specified	fied Borg scale after a 6MWD and every minute within an ergometer test:Two Questions: "How short of breath are you right now?" for DI and "How bothersome or worrisome is your shortness of breath to you right now?" for DD. ▪ A 5-item dyspnoea subscale of the CRQ was used to measure dyspnoea during five patient-chosen ADL´s, ▪ Secondary: Pulmonary Function, HRQL, physical performance on Ccke and 6MWD	in the intervention arm measured by 6MWD but not on ergometer. ▪ The 6MWD improved significantly after the intervention but not in the control arm. (+71.7 ± 21.8 feet versus -27.6 ± 36.2 feet; ES = 0.78, p = 0.04) ▪ No difference in the other secondary endpoints.	with more females than males. ▪ Primary endpoint was not precisely defined (DI or DD?) so levels of significance are questionable.	
Oh, Am J Chin Med 2008 [75]	RCT	N=30 (dropouts=12)	**Cancer** diagnosis any state, ECOG 0-3, expected survival length > 12 months	Intervention: ▪ in addition to usual medical care a MQ group intervention once or twice a week for eight weeks, daily self-practice one hour ▪ end of the program: all patients completed the follow-up QOL measure and blood test. Control: ▪ continued usual care	1.O: ▪ QoL and symptoms (EORTC QLQ-C30) 2.O: ▪ Inflammation (CRP)	▪ Individually reported better **QoL** and lower symptoms, lower inflammation ▪ Results were not statistically significant between treatment and the control groups.		1-
Yeh, Resp Care 2010 [76]	RCT	N=10	Pts with **COPD** FEV1<65% predicted FEV1/FVC<0,7 Age 45 or older	Intervention: ▪ 12 Weeks of tai chi classes biweekly plus usual COPD care	▪ "Exercise Capacity and functional status" (Ergometry and 6 MWD at baseline and 12 Weeks as well as "timed-up-	▪ Although there was a nonsiginifcant relief of Dyspnoea in both arms, the baseline value was signifi-	▪ Nearly more endpoints than patients.	1-

Study, journal, year	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 SIGN
				Control: ▪ Usual COPD Care alone ▪ (Defined as pharmacologic therapy + exercise advice per ACCP-Guidelines)	and-go" assessment) ▪ HRQL (CRQ), ▪ Dyspnoea (UCLA San Diego Shortness of Breath Questionaire and Modified Medical Research Council Dyspnoea Scale and many more…) ▪ Pulmonary function (spirometry) ▪ Physical Activity ("Community Healthy Activities Model Program for Seniors (CHAMPS)")	cantly worse in the control group. (1.4 ± 1.1) vs. (-0.1 ± 0.4) (P = 0.03). ▪ Significant improvements were seen in the CRQ total score and CRQ emotion domain.		
Counseling, support and breathing								
Moullec, Clin Rehabil 2010 [77]	Prospective controlled trial	N=40	moderate to severe **COPD**	Intervention: (n =11) maintenance integrated health care programme for 12 months Control: (n =16) usual care for 12 months	1.O: ▪ change in functional and emotional dimensions of quality of life (SGRQ), (Brief-WHOQOL) and six specific questions (VAS) 2.O: ▪ change in exercise tolerance measured by six-minute walking test and cycle exercise.	1.O: ▪ improvements in functional and emotional dimensions scores of **quality of life** and exercise tolerance in intervention group. ANCOVA revealed a significant interaction effect (time x group) for symptom (F(3,75)=5.11, P< 0.01; β=0.80; n"P=0.18) and activity (F(3,75)=8.24, P<0.001; b=0.95; n"P=0.26) ▪ In control group maintenance of functional dimension scores of **quality of life**, clinically relevant decline in emotional scores of quality of life and in six-minute walking distance.	▪	2+

Study, journal, year	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 SIGN
Singing class								
Bonhila, Int J COPD 2009 [78]	RCT	N=43 (drop-outs=30)	**COPD**	Intervention: ▪ Singing group (weekly classes for 1 hour, 24 weeks) Control: ▪ Handcraft work (weekly classes for 1 hour, 24 weeks)	▪ Baseline Dyspnoea Index (BDI) ▪ Borg scale	▪ singing group: directly after singing small but significant increase in **dyspnoea** ▪ after 24 session no significant difference between groups		1+
Nutrition								
Laviolette, J Med Food 2010 [79]	Double-blind, randomized controlled pilot study	N=22 (no drop-outs)	**COPD**	Intervention: ▪ Active pressurized whey Control: ▪ Placebo (casein) dietary supplementation ▪ Duration: 16 weeks ▪ Patients continued their usual activities for the first 8 weeks ▪ In the remaining 8 weeks they were subjected to an exercise training program	▪ cycle endurance test (CET) ▪ CRQ Measurement timing: ▪ 8 weeks ▪ 16 weeks	week 8: ▪ no increase in both groups week 16: ▪ statistically significant increase in CET time in the whey only group (277.2±108.8 vs. 226.6±77.1 seconds for whey and casein, respectively; P=0.23) ▪ clinically significant improvement in the **Dyspnea scale** of the CRQ in both groups		1+
Laughing								
Lebowitz, Heart Lung 2011 [80]	RCT	N=46 (drop-outs=22)	**COPD**	Intervention: ▪ 30 min humoreous video presentation Control: ▪ 30 min instructional videos on practical topics	▪ Dyspnoea NRS	▪ No effect on dyspnea		1+

Study, journal, year	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 SIGN
				▪ Timing of measurement: before and during video presentation (after 15 min)				

3.3.2. Intervention „körperliche Übungen (*exercise*)“

Die systematische Literatursuche ergab keine Systematic Reviews oder Primärstudien zu Interventionen mit körperlichen Übungen bei Patienten mit einer Krebserkrankung für die Linderung von Atemnot.

3.4. Sauerstoff

3.4.1.1. Systematic Reviews

Studie	Studientyp (SR=Systematic Review MA=Meta-analyse) Titel	Untersuchte Studien/ Materialien	Population	Welche Interventionen wurden geprüft	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Ergebnisse	Bemerkungen	LoE
Cranston, Cochrane Review 2008 [81]	SR, MA	8 RCT´s, cross-over (incl. un-blinded)	Participants with **chronic terminal illness (excluding COPD)** and breathlessness at rest or on mild exertion: Cancer (97), CHF (35), Kyphoscoliosis (12), n=144	Oxygen (30%, 50% or 100%), control: medical air or compressed air or room air or placebo air	1.O: subjective measures of breathlessness: verbal categorical scales, VAS, NRS, modified BORG test or BORG test. Various physiological parameters were tested as well: SpO2, respiratory rate, heart rate, cardiac output, VO2max	No consistent beneficial effect of oxygen inhalation. Some cancer study participants appeared to feel better during oxygen inhalation.(oxygen inhalation at rest, Peto Odds Ratio (95% CI); 4.94 (1.48 to 16.43) and during exercise, Peto Odds Ratio (95% CI); 2.62 (1.00 to 6.85)	Low volume of research studies, small sample sizes of the studies, variations in study methodologies.	1++
Uronis, Brit J Cancer 2008 [82]	SR, MA	5 studies (n=134)	Participants with **cancer** and dyspnoea	Oxygen versus medical air	1.O: dyspnea (oxygen at rest or 6MWD - standard mean difference (SMD) were used to combine scores)	Oxygen failed to improve dyspnea in mildly- or non-hypoxaemic cancer patients (SMD=-0.09, 95%CI; -0.22-0.04; P=0.16) In this small meta-analysis, oxygen did not provide symptomatic benefit for cancer patients with refractory dyspnoea, who would normally qualify for home oxygen therapy.	Further study of the use of oxygen in this population is warranted given its widespread use.	1+
Uronis, Cochrane Review 2011 [83]	SR, MA	SR: 28 RCT´s, n=702 (of which MA: 18 RCT´s, n=431)	Mildly or non-hypoxaemic people with **COPD**, who would not qualify for home oxygen therapy	Oxygen versus medical air	1.O: VAS, modified BORG, NRS or any other validated scale for measuring dyspnoea. For those studies measuring dyspnea during exercise, isotime scores were used when available.	Oxygen was effective reducing dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy, with a standardised	Small sample sizes and heterogeneity amongst studies included in this review make it difficult to provide general recommendations.	1++

Studie	Studientyp (SR=Systematic Review MA=Meta-analyse) Titel	Untersuchte Studien/ Materialien	Population	Welche Interventionen wurden geprüft	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Ergebnisse	Bemerkungen	LoE
					2.O: 1. Quality of life, 2. Patient preference, 3. Functional status as recorded on a recognised scale	mean difference (SMD) of -0.37 (95% CI -0.50 to -0.24, P < 0.00001) translating into a reduction of 0.78 cm on a 10 cm visual analogue scale (VAS) and a reduction of 0.9 points on a 0 to 10 numerical rating scale (NRS). . Impact on QoL cannot be determined from currently available data.		

3.4.1.2. Primärstudien

Studie	Studientyp/ Design	Anzahl der Patienten/ Drop-out	Patienten-merkmale	Intervention/Kontrolle	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure • Follow up	Ergebnisse	Bemerkungen	LoE
Abernethy, Lancet 2010 [84]	RCT, double-blind	Oxygen (n=120, drop out=8), room air (n=119, drop out=20)	239 adults form outpatient clinics with life-limiting illness, refractory dyspnoea, and partial pressure of oxygen in arterial blood (paO2) more than 7-3 kPa from Australia, USA and the UK. **COPD** 64 %, Primary and secondary **cancer** 16%.	1st arm: oxygen 2nd arm: room air for 7 days.	1.0: „breathlessness right now" with NRS (0=not breathless at all, 10=breathlessness as bad as you can imagine), twice daily. 2.0: average dyspnoea in the previous 24h, worst breathlessness in previous 24h, relief of dyspnoea during the previous 24h (0-10 NRS), and ordered categorical scales for functional impact, sleep, disturbance, drowsiness, anxiety, nasal	No additional symptomatic benefit of O2 for relief of refractory dyspnoea in patients with life-limiting illness compared with room air: Over the 7-day period, **dyspnea** decreased by -0.8 (95% confidence interval [CI]: -1.1, -0.5) and -0.4 (CI: -0.7, 0.1), respectively (p<0.001), regardless of intervention. Baseline dyspnea predicted improvement with medical	• ITT analysis • Full-powered study • Adequate randomisation, concealment and blinding • It is possible that palliative oxygen is more beneficial than medical air for some subgroups (e.g., COPD patients vs. cancer patients), and that our study was not ade-	1++

Studie	Studientyp/ Design	Anzahl der Patienten/ Drop-out	Patienten-merkmale	Intervention/Kontrolle	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure • Follow up	Ergebnisse	Bemerkungen	LoE
			Restrictive lung disease 5,9% Bronchiectasis 2,9% Primary pulmonary hypertension 1,3% End-stage cardiomyopathy 2,9% Other 7,5%		irritation and nose bleeds, QoL (MQoLQ), functional changes (MRC)	gas; participants with moderate (4-6 NRS) and severe (7-10 NRS) baseline dyspnea had average decreases in morning dyspnea of -0.7 (CI: -1.1, -0.4) and -2.4 (CI: -3.0, -1.8), respectively. There was no clinically meaningful difference between interventions in **side effects**, and few adverse effects.	quately powered to identify these patients	

4. Tumorschmerz

4.1. Systematic Reviews der EAPC/Caraceni 2012-Guideline

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 SIGN
Bennett, Pall Med 2011 [85]	SR (MA not possible) Aim: to determine the effectiveness of antiepileptics when added to opioids, compared to opioids alone, for the management of pain caused directly by cancer	8 studies ▪ 5 RCTs ▪ 3 BAs (Observational Before-After Studies)	In total 465 adult **cancer patients** with chronic **moderate to severe (neuropathic) pain**, 370 (79.5%) completed the study period (almost non naïve) RCTs included 354 patient (of whom over 80% completed the study period)	Opioid + antiepileptic or antidepressant adjuvants (Gabapentin, Imipramine, Phenytoin) 5 RCT Opioid + adjuvant vs. Opioid alone (2 RCTs) ▪ 1st Arm: Opioid + Gabapentin (1),Imipramine (1) ▪ 2nd Arm: Opioid alone Opioid + adjuvant vs. Opioid + placebo (2 RCTs) ▪ 1st Arm: Opioid + Gabapentin (1), Amitriptyline (1) ▪ 2nd Arm: Opioid + Placebo Opioid + adjuvant vs. Adjuvant alone vs. Opioid alone (1 RCT) ▪ 1st Arm: Opioid + Phenytoin ▪ 2nd Arm: Phenytoin alone ▪ 3rd Arm: Opioid alone 3 BAs	Mainly 1.O: ▪ **Pain modification**/relief (effectiveness) (5 studies) 2.O: ▪ **Adverse events /Side effects** (4 Studies) 3 Studies 1.O: ▪ **Adverse events /Side effects** (In 3 RCTs pain relief and in 1 RCT adverse events not reported)	**Pain modification/relief** ▪ adjuvants improve pain control within 4-8 days when added to opioids for cancer pain (strongest evidence for gabapentin) ▪ overall, the effect size was much less than reported for patients with non-cancer neuropathic pain (unlikely reduction in pain intensity of greater than 1 point on a 0-10/NRS) **Adverse events:** increase likely	MA not possible, due to clinical and methodological heterogeneity Methodological limitation of included studies: ▪ bias/confounding factors, i.e. loss to follow up, opioid dose variation between and within studies, study duration ▪ in 3 RCTs pain intensity/relief and in 1 RCT adverse events not reported ▪ studies on various adjuvants commonly used in non-cancer neuropathic pain are missing (i.e. pregabalin, nortriptyline, duloxetine) No info. on search strategy or on funding of the included studies; no quality assessment re-	1+ Body of evidence SIGN: 1+

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 SIGN
				▪ Opioid + Gabapentin (2) ▪ Opioid + Sodium valproate (1)			ported	
Candy, Cochrane Library 2011 [86]	SR (MA not possible) Cochrane Review up date 2010 (first version 2006) Aim: to determine (1) the effectiveness of laxatives and methylnaltrexone for the management of constipation in PC patienss and (2) the differential efficacy of laxatives used to manage constipation	7 studies (n=616) 7 RTCs, among them 2 crossover design	**palliative care / hospice patients** (most with advanced cancer and (anticipated) **opioid induced constipation)**	Methylnaltrexone (MN) and/or conventional laxatives -4 RCTs: senna (+ lactulose) vs various other laxatives -1 RCT (n=91/75) ▪ 1st Arm: starting dose daily of 15 ml (10 g) lactulose, up to max. 60ml (40 g) ▪ 2nd Arm: starting dose daily of 0.4 ml (12 mg) senna, dose increase up to max. 1.6ml -1 RCT (n=36) ▪ 1st Arm: misrakasneham (starting dose 2.5 ml) ▪ 2nd Arm: senna (starting dose 24 mg) -1 RCT (crossover) (n=118): ▪ 1st Arm: magnesium hydroxide + liquid paraffin 2nd Arm: senna + lactulose -1 RCT (crossover) (n=51): ▪ 1st Arm: senna + lactulose ▪ 2nd Arm: co-danthramer MN dose ranging: 1 RCT: sc	1.O: ▪ **Constipation management** (relief) 2.O: ▪ **Adverse effects** ▪ opioid withdrawal ▪ quality of life (1 study)	**Constipation management:** subcutaneous methylnaltrexone seems to be effective in opioid-induced constipation and where conventional laxatives have failed (odds ratio 6.95; 95% confidence interval 3.83 to 12.61) **Adverse effects:** in total no difference in the occurrence of side effects (although higher proportion of flatulence and dizziness under methylnaltrexone) but drug safety of methylnaltrexone not yet fully evaluated (serious adverse events possible, i.e. severe diarrhoea, subsequent dehydration and cardiovascular collapse) **Opioid withdrawal:** evidence of opioid withdrawal was found **Quality of life** results not reported	MA not possible, due to clinical and methodological heterogeneity and study limitations ▪ evidence remains limited due to insufficient RCTs ▪ All RCTs underreported key design features (randomisation, allocation, incomplete outcome data) > unclear risk of bias ▪ further rigorous, independent trials needed (6 of 7 studies were funded by pharmaceutical companies) broad search strategy, summary and discussion of study limitations information on funding of included studies	1++ Body of evidence SIGN: 1+

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 SIGN
				MN (n=33, out of them 29 on conventional laxatives) ▪ 1st Arm: sc MN 1 mg ▪ 2nd Arm: sc MN 5 mg ▪ 3rd Arm: sc MN 12.5 mg 2 RCTs: sc MN vs.placebo 1 RCT: dose variation (n=154) ▪ 1st Arm: single sc injection MN (0.15 mg/kg) ▪ 2nd Arm: single sc injection MN (0.3 mg/kg) ▪ 3rd Arm: placeo 1 RCT: (n=133) ▪ 1st Arm: sc MN (0.15 mg/kg) ▪ 2nd Arm: placebo				
Caraceni, Pall Med 2011 [87]	SR + MA (Cochrane review up-date 2010, first version 2007) Aim: To address the question: In adult patients with moderate to severe pain directly due to cancer and never treated	21 studies (n=2478) ▪ 17 RCTs (n=2053) ▪ 1 Meta-analysis (4 RTCs, n=425)	**Patients with chronic cancer pain** (most not opioid naïve) ▪ 17 RCTs with 2053 patients in total ▪ The Meta-analysis included 4 RCTs with 425 patients in total	**oral morphine vs other orally or transdermal administered opioids** oral Morphine vs. other orally administered opioids (8 RCTs) ▪ 1st Arm: Morphine ▪ 2nd Arm: Oxycodone (4 RCTs) . Hydromorphone (3 RCTs), Methadone (1 RCT) oral IR Morphine vs. other orally administered opioids (4 RCTs)	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Adverse events /Side effects Meta-analysis 1.O ▪ Adverse events /Side effects *	Studies published in between 2007/2009 did do not add significant information to the previous Cochrane review **Pain modifiation** ▪ oral morphine, oxycodone and hydromorphone seem to have similar **efficacy**. **Adverse events/side effects** ▪ oral morphine, oxycodone and hydromorphone seem to have have similar **toxicity**	Except the given MA of 4 RCTs, MA not possible due to clinical and methodological heterogeneity and limitations of the identified 17 RCTs The available evidence suggests that oral mo, hydromorphone, oxycodone and methadone offer similar pain relief in this patient population with a similar pattern of side effects.	1++ Body of evidence (SIGN): 1-

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 SIGN
	with strong opioids, which is the evidence that oral morphine is better than placebo, or other oral/ transdermal opioids in the management of pain?			▪ 1st Arm: IR Morphine ▪ 2nd Arm: Brompton Cocktail (1 RCT), Methadone (1 RCT), Oxycodone (1 RCT) oral Morphine vs. transdermal administered opioids (5 RCTs) ▪ 1st Arm: Morphine ▪ 2nd Arm: Buprenorphine TTS (1 RCT), Fentanyl TTS (3 RCTs), Fentanyl TTS + Methadone (1 RCT) Meta-analysis (4 RCTs) ▪ Oral Morphine vs. transdermal administered opioids (Fentanyl/ Buprenorphine TTS)			On the other hand, limitation of efficacy and tolerability data on opioid-naive and non-selected populations of cancer patients treated with morphine: • Population mostlynon-naive • Risk of bias in most of the studies (above all lost of follow-up) 8 studies were (partly) sponsored by pharmaceutical companies (for 8 other studies no funding details given)	
Cherny, Pall Med 2011 [88]	SR (MA not possible) Aim: To address the question: is oral methadone better than placebo, or other oral/transdermal opioids in the	5 studies (RCTs) (n=301 patients, group size 18-108)	most adult **cancer patients** with **moderate to severe cancer** related pain; 1 study: patients with **neuropathic pain** (variety of disease)	oral methadone vs. other oral/transdermal opioids 4 RTCs :methadone vs. oral/ transdermal Opioids, among them 2 RCT oral morphine vs. oral methadone treatment. ▪ 1st Arm: oral morphine ▪ 2nd Arm: oral methadone and 1 RCT: intravenous (IV)	1.O: ▪ **Pain modification** (efficacy) 2.O: ▪ **Adverse events** /Side effects (1 RCT)	**Pain modification** ▪ no evidence that methadone provides more effective analgesia than oral morphine, or transdermal fentanyl ▪ comparable, but not superior, analgesia achieved Over all the RCTs indicate **comparable adverse effects**	No MA due to clinical and methodological heterogeneity/limitations possible Authors state that no studies comparing methadone to placebo for cancer pain were identified. But: The application of placebo seems to be more than ethically question-	1- Body of evidence SIGN: 1-

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 SIGN
	management of cancer pain?			followed by oral application of methadone/morphine ▪ 1st Arm: IV methadone, followed by oral methadone ▪ 2nd Arm: IV morphine followed by oral morphine 1 RCT oral methadone vs. oral/transdermal morphine (with access to immediate release oral morphine for each patient) ▪ 1st Arm: oral morphine ▪ 2nd Arm: transdermal fentanyl ▪ 3rd Arm: oral methadone			able in moderate to severe cancer pain. search strategy limeted to MEDLINE + CANCERLIT, 1966-2009; low sensibility; no information on funding of included studies	
Dale, Pall Med 2011 [89]	SR / no MA (Cochrane review up-date 2004-2010, first Version 2004) Aim: to address the question: what is the evidence of opioid switching resulting in improved	11 studies (MA not possible) uncontrolled prospective observational studies (n=280 patients, (group size 10-32).	mostly **adult cancer patients** with inadequate relief of **moderate to serve pain** and/or intolerable opiode associated adverse/side effects	Opioid switch (variety of opioids, routes and switching strategies) ▪ transdermal Buphrenophine → transdermal Fentanyl (vice versa) ▪ transdermal Fentanyl → Methadone ▪ Morphine→ transdermal Fentanyl ▪ Morphine → Methadone ▪ Methadone → transdermal Fentanyl	1.O: ▪ **Pain modification** (efficacy) 2.O: ▪ **Adverse events** /Side effects (reduction)	▪ **Pain modification:** significant **reduction of pain intensity** in the majority of studies ▪ **Adverse events**: significant **reduction of** serious **adverse events/side effects** in the majority of studies .	All in all still low level of evidence due to methological study limitations: open uncontrolled studies with bias risk and data imprecision (GRADE D) Quantitative review (and MA) not possible due to lack of RCTs Search and assessment strategy described	2++ Body of evidence SIGN: 3

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 SIGN
	analgesia or reduced adverse effects in adult patients suffering from cancer pain?			▪ transdermal Fentanyl → Methadone ▪ transdermal Fentanyl → Methadone or Morphine and and Morphine → Methadone ▪ Morphine → transdermal and parentetral Fentanyl ▪ transdermal Fentany/ Morphine or Hydromorphone → Methadone ▪ Morphine → Oxycodone ▪ Morphine →transdermal Fentany			no information on funding of included studies	
King, Pall Med 2011a [90]	SR (incl. 1 MA was possible) Aim: to identify and assess the quality of evidence for the use of oxycodone for cancer pain in adults	29 Studies ▪ 1 MA (including 4 RCTS, n=160 patients) ▪ 14 RCTs. ▪ 14 CTs (observational studies:10 prospective, 4 retrospective)	Adult **cancer patients** with **moderate to serve cancer related pain**	**Oxycodone** (Ox) in cancer pain treatment (different release and routes) MA (4 RTCS): (n=160) ▪ 1st Arm: oxycodone ▪ 2nd Arm: morphine (3 RCTS), hydromorphone (1 RCT) 14 RCTs: (n=34/28) ▪ 1st Arm: oxycodone ▪ 2nd Arm: morphine ▪ 3rd Arm: codeine Controlled release (CR) (n=32/23) Mo vs. Ox CR (n=44/31) Ox vs HydroMo CR (n=45/27) Ox vs. HydroMo	1.O: ▪ **Pain modification** (efficacy) 2.O: **Adverse events** /Side effects	**Pain modification** no significant difference in analgesia or adverse effects of oxycodone compared to other opioids (data from one MA: pooled standardized mean difference, 0.04; 95% CI _0.29 to 0.36, p=0.8, I2=62%) **Adverse events:** no significant difference in adverse effects of oxycodone compared to other opioids - Oxycodone ▪ seems to be effective for first-line opioid therapy ▪ possibly less expensive ▪ close monitoring and conservative dose selection in-	MA for 4 RCTs, well conducted and unlikely to have been significantly biased in its conclusions RCTs found in addition to the MA: significant limitations; therefore, lower quality evidence and MA not possible. However, consistency of the results. considerable number of studies were (partly) funded by pharmaceutical companies broad systematic search	1++ Body of evidence: 1++

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 SIGN
				Titration with patient controlled IV analgesia (n=20/19): ▪ 1st Arm: IV morphine ▪ 2nd Arm: IV oxycodone CR (n=101/79) Ox vs. Mo IM vs. oral Ox (n=17/13) CR Ox vs MR Ox (n=45) Immediate release (IR) vs CR Ox (n=180) CR Ox vs. CR Mo (n=26) IV vs. rectal oxycodone (n=12) CR vs. immediate release (IR) oxycodone (n=111) CR vs. IR oxycodone (n=40) CR vs. IR Ox (n=50) 14 CTs (10 prospective, 4 retrospective)		evitable due to propensity to sedation and dose accumulation inevitable oxycodone might be an alternative treatment option to morphine or hydromorphone for cancer-related pain	strategy, incl. reference screening and hand search GRADE approach to assess study quality information on funding of included studies	
King, Pall Med, 2011b [2]	SR (MA not possible) Aim: to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with	15 CTs, among them ▪ 8 prospective CTs ▪ 7 retrospective CTs	adult/older **cancer pain patients** (with moderate to severe pain) with **renal impairment and/or advanced cancer**	Opioid treatment in renal impairment (various opioids + routes) 8 prospective CTs ▪ oral or sc mo treatment (n=18 hospice inpatients) ▪ oral or continuous sc infusion (CSCI) mo (n=36 hospice pts) ▪ oral or parenteral mo (n=109 cancer pain service patients) ▪ oral mo (n=11 cancer	**1.O** **adverse events**/side effects (incl. renal and cognitive functining/impairment	**Adverse events** ▪ fentanyl, alfentanil and methadone seem to be the least likely to cause harm in patients with renal impairment ▪ morphine may be associated with toxicity cancer pain treatment with opioids in renal impairment primarily relies on pharmacokinetic data, extrapolation from non-cancer pain studies	Very low empirical evidence (GRADE) relating to the use of morphine, alfentanil, pethindine, fentanyl, sulfentanil, oxycodone, hydromorphone (no RCTs available/MA not possible) study quality is limited due to high risk of methodological and publication bias	2++ Body of evidence SIGN: 3

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 SIGN
	renal impairment and to produce guidelines.			pain patients) ▪ mo (n=300 chronic pain patients with cancer) ▪ mo (n=186 patients) ▪ pethidine (n=64 patients with neurological symptoms, 19 cancer pain patients) ▪ mo → oxycodone (n=27 patients, 9 with renal impairment) 7 retrospective CTs ▪ mo (n= 177 pts non-responsive to mo or with intolerable side effects) ▪ afentanil (n=4 patients diamorphone intolerance) ▪ afentanil (n=48 hospital patients) ▪ fentanyl (n=53 hospital palliative care patients) ▪ sufentanil (n= 48 hospital palliative care patient) ▪ hydromo (n=45 pain patients, 26 with renal impairment) ▪ codeine, mo, diamorphone, oxy or combination of opiods (n=40 patients with chronic kidney disease CKD, among them 34 cancer patients)		and clinical experience no CTs on treatment with diamorphine, codeine, dihydrocodeine, buprenorphine, tramadol, dextropropoxyphene, methadone in the respective data bases .	Broad systematic review according to the Cochrane protocol GRADE approach to assess study quality No information on funding of included studies.	

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 SIGN
Klepstad, Pall Med 2011 [91]	Narrative SR / no MA (papers published until the end of 2009) Aim: to analyse the evidence regarding the start of treatment with opioids and dose titration in adults pts with moderate to severe cancer pain	14 studies ▪ 2 RCTs (n=102) ▪ 12 clinical/ observational studies (1 additional paper reported results of an extended analysis of a CT included in the review)	**adult cancer patients** with **moderate to severe pain**	Starting Step III opioids (dose titration) 2 RCTs comparing tritation strategies with different routes/releases of morphine oral vs. intraveanous morphine (1RCT) ▪ 1st Arm: tritation with intravenous (IV) morphine ▪ 2nd Arm: tritation with immediate release (IR) oral morphine Oral IR morphine vs. sustained release oral morphine (1 RCT) ▪ 1st Arm: oral IR morphine ▪ 2nd Arm: sustained release (SR) oral morphine 12 CTs opioid on tritation with ▪ oral morphine (6 studies) ▪ intravenous morphine (2 studies) ▪ transdermal fentanyl (4 studies).	1.O: ▪ **Pain modification**/ control (efficacy) 2.O: ▪ **Adverse events** /Side effects	**Pain modification** RCTs indicate ▪ faster onset of pain relief with IV morphine compared to oral morphine - but similar pain relief after 24 hours, ▪ no difference in onset pain relief or adverse effects in tritation with oral IR morphine compared to oral sustained release (SR) morphine According to the CTs all treatment strategies resulted in acceptable pain control **Adverse events /Side effects** RCTs indicate ▪ apart from drowsiness after IV titration no serious adverse effects reported ▪ no difference in adverse effects in titration with oral IR morphine compared to oral sustained release (SR) morphine apparent CTs indicate that all treatment strategies were well tolerated.	empirical evidence low 2 RCTs published until the End of 2009 only, MA not possible due to the diversity of methods and serious study limitations of 1 RCT (not blinded, no sample estimation) With the exception of the 2 RCTs research mostly focuses on descriptive studies (CTs of different quality) broad search strategy but limited to Medline) GRADE approach to assess study quality Study limitations discussed No information on funding of included studies.	2++ Body of evidence SIGN: 1-

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 SIGN
Kurita, Pall Med, 2011 [92]	SR / no MA Aim: to analyse analgesic efficacy and side effects of spinal opioids in adult cancer patients previously treated with systemic opioids.	44 studies: (n= 2126): ▪ 9 RCTs (n = 639) ▪ 28 uncontrolled prospective studies (n = 1378) ▪ 2 non-randomised cohort studies (n= 24) ▪ 5 CS (n = 85)	Adults patients with **severe cancer pain** (mostly patient havew been pretreated with opioids)	Morphine by the spinal route: - implantable pump system in 5 of 9 in RCTs. - implantable pump system in 16 of 28 uncontrolled prospective studies - implantable pump system in 4 of the non-randomized cohort studies and CS In the remaining studies morphine has been delivered by epidural route via spinal tap.	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Side effects	▪ **Pain modification**: weak recommendation for the use of spinal opioids, in the RCT 6 did not show a significant difference between oral or epidural application. ▪ The comparison of **side effects** showed minor differences with an advantage of the spinal route.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ No MA due to heterogeneity ▪ Most non-naive patients	1+ Body of evidence SIGN: 1-
Laugsand, Pall Med, 2011 [93]	SR / no MA Aim: to review the existing literature on management of opioid-induced nausea and vomiting in cancer patients and summarize the findings into evidence-based	55 studies (n = 5741) ▪ 19 RCT (n = not given) ▪ 13 case reports or case series (n = not given) ▪ 18 studies with nausea as primary outcome (with 8/18 studies opioid-induced nausea) ▪ 37 studies with nausea not primary outcome	Adult patients with cancer pain receiving opiods for cancer pain addressing nausea and vomiting either as a primary or secondary outcome	• use of analgetics for opiod sparing • change of opiod • change of route • other	1.O: ▪ Nausea and vomiting (opiod induced emesis) 2.O: ▪ Nausea and vomiting 3.O: ▪ Nausea and vomiting	▪ **Nausea and vomiting**: weak recommendation for changing the opiod or the opiod administration route. ▪ Too less evidence for a prioritization between symptomatic treatment and adjustment of opiod treatment	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low to very low quality (C-D) ▪ No MA due to heterogeneity ▪ Most non-naive patients ▪ Lack of consistency	1++ Body of evidence SIGN: 1-

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 SIGN
Mercadante, Pall Med, 2011 [94]	SR / no MA Aim: to describe the results of a systematic search of the literature on conversion ratios during opioid switching	31 studies (n =) ▪ 26 uncontrolled, non-randomized, prospective (n = 1505) ▪ 2 non-randomized crossover (n = 33) ▪ 6 RCT (n = 267)	Adult patients with chronic **cancer pain** with opiod treatment	Efficacy and reliability of conversion rates of **opiod switching** during opioid treatment	1.O: Efficacy and reliability of opioid switching rates in treatment of pain	▪ **Switiching an opioid**: no specific generalized recommendation can be made. Use of established available evidence of conversion ratios. ▪ Opioid switching to methadone should needs more experience	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ Low statistical power ▪ Various opioid administration route	1+ Body of evidence SIGN: ORmo/ TDfe to TDbu: 3; ORmo to ORhy: 3; ORox to ORhy: 1++ (only 1 RCT, but high quality); ORmo to TDfe: 2-; ORmo to ORox: 1+
Nabal, Pall Med, 2011 [95]	SR / no MA due to differences in NSAIDs molecules employed, paracetamol dosages (3-5 g/day), and the different fol-	7 studies for NSAID (n = 200) ▪ 9 double-blind cross over (n = 150) ▪ Open parallel study (n = 50) 5 studies for	Adult patients with moderate to severe pain **cancer pain** d s	Efficacy and safety of NSAID and paracetamol added to step III WHO opioid treatment for cancer pain	1.O: ▪ Efficacy of pain modification 2.O: ▪ Safety	▪ **Pain modification**: weak recommendation for the use of NSAID in addition to opioids in WHO ladder step III regimen. ▪ No evidence for the use of paracetamol. ▪ The risk / benefit ratio was considered low.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ Low statistical power ▪ Opioid-naive and non-naive patients were evaluated	1+ Body of evidence SIGN: 1-

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 SIGN
	low-up periods Aim: To perform a systematic literature review of the evidence of the efficacy and toxicity of NSAIDs or paracetamol added to WHO Step III opioid treatment for cancer pain.	paracetamol (n = 200) ▪ 3 double-blind cross over (n = 107) ▪ 2 double-blind (n = 93)						
Pigni, Pall Med 2011 [96]	SR (MA not possible) Aim: to evaluate the scientific evidence for the efficacy and side effects of hydromorphone in the management of moderate to severe cancer pain.	13 studies (n=1208): ▪ 9 RCTs ▪ 2 CCTs ▪ 2 observational studies (OS)	Adults patients with chronic **moderate to severe cancer pain** (most non-naïve)	**Hydromorphone** (HM) by any route: -7 RCTs/CCTs: HM vs. other drug ▪ 1st Arm: HM ▪ 2nd Arm: Mo (5), Oxycodone (1), Fentanyl/Buprenorphine (2), -4 RCTs comparing various routes (sc, iv, po, im) or release forms (slow/intermediate) -2 OS: administration of HM	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Side effects	▪ **Pain modification**: similar analgesic results showed by RCTs comparing HM with morphine and oxycodone > evidence that HM can be used as an alternative to mo. ▪ The comparison of **side effects** showed minor differences, not consistent across studies.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ No MA due to heterogeneity ▪ Most non-naive patients	1+ (no details to study quality assessment) Body of evidence SIGN: 1-
Radbruch, Pall Med, 2011 [97]	SR / no MA planned because of differences in the	72 studies; 18 included a total of n = 674 patients ▪ 3 SR (n = 916)	Adult patients with moderate to severe pain **cancer pain** who are unable to take	Efficacy and safety of alternative routes of opioid application	1.O: ▪ Efficacy of pain modification 2.O: ▪ Safety	▪ **Pain modification**: good evidence for subcutaneous administration of morphine. ▪ The risk/benefit ratio was	▪ Methodological limitations of most of the studies (missing data), resulting in a low qual-	1++ Body of

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 SIGN
	outcome indicators Aim: to update the EAPC recommendations on opioids in cancer pain management.	▪ 11 CCS (n = 537) ▪ 2 crossover non-randomized study (n = 58) ▪ 2 crossover RCTs (n= 38) ▪ 7 CS (n = 230) ▪ 1 CR (n =1) ▪ 1 crossover randomized trial (n = 23) ▪ 2 sequential cohort series (n =70)	oral opioids			considered low.	ity ▪ Low statistical power ▪ Various medications compared	evidence SIGN: sc route, iv titration: 1+; switch from iv or oral to ohter route: 3
Stone, Pall Med, 2010 [98]	SR / no MA because of low-quality studies with multiple outcomes) Aim: to examine the management of opioid-induced central side effects.	26 studies (n = 432) ▪ 9 RCT ▪ 20 case series ▪ 3 case reports ▪ 2 uncontrolled prospective trials ▪ 3 retrospective case reviews ▪ 1 uncontrolled pilot study	Adult patients with chronic **cancer pain** and reported side effects	Efficacy of pharmacological treatment of opiod induced side effects.	1.O: ▪ Management of side effects o opiod use: sedation, cognitive impairment, myoclonus, hyperalgesia, insomnia 2.O: ▪ Safety	▪ **Management of side effects**: no recommendation for the use of any of the pharmacological interventions. ▪ The risk / benefit ratio was not reported	▪ Methodological limitations of most of the studies (missing data), resulting in a low quality ▪ Low statistical power ▪ Endpoints have not been well defined, sometimes two endpoints ▪ One study Included also non-adolescents	1+ Body of evidence SIGN: 1-
Tassinari, Pall Med, 2011a [99]	SR / no MA Aim: To analyse the evidence supporting the	18 studies (n = 2974) ▪ 11 RCT (n = not given) ▪ 7 CT (n = not	Adult patients with **mild to moderate cancer pain** resistant to NSAID ± adjuvants and intervention with	1. Efficacy of 3rd-step opioids vs. 2nd followed by 3rd-step opioids 2. Efficacy of oral tramadol in patients pretreated with	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Safety	▪ **Pain modification**: weak negative recommendation for the use of modiefied analgesic ladder or the use of oral tramadol in the sec-	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality of evidence	1 + Body of evidence

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 SIGN
	widespread use of modified analgesic ladders or oral tramadol as alternatives to codeine/ paracetamol for mild to moderate cancer pain.	given)	oral tramadol	oral NSAIDs and not previously treated with opioids vs. placebo or codeine/paracetamol		ond step. ▪ The risk / benefit ratio was considered uncertain.	▪ Low statistical power ▪ Endpoints have not been well defined	SIGN: 1- (most results based on low quality RCTs)
Tassinari, Pall Med, 2011b [100]	SR / no MA Aim: To assess the role of transdermal opioids as a front-line approach to moderate to severe cancer pain.	13 studies (total n not provided) ▪ 11Randomized clinical trials ▪ 2 Metaanalyses	Adult patients with moderate to severe cancer pain requiring stable doses of strong opioids	Efficacy of **transdermal** opiods (fentanyl and buprenorphine) in comparison with oral morphine.	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Safety	▪ **Pain modification:** weak negative recommendation for the use of transdermal fentanyl and strong negative for transdermal buprenorphine. ▪ **The risk / benefit ration** was considered uncertain. Weak data report on less side effects with the use of transdermal opioids (constipation, diarrhoe, nausea, urinary retention).	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ Low statistical power ▪ Most non-naive patients	1- Body of evidence SIGN: 1-
Zeppetella, Pall Med 2011 [101]	SR (MA for transmucosal fentanyl) Aim: to determine the evidence for the utility of opioids in the management of	8 RCTs	adult patients with **cancer** and **breakthrough pain** in any setting	Oral transmucosal fentanyl citrate (OTFC): ▪ 2 RCTs: Dose titration ▪ 3 RCTs: OTFC vs placebo (1), normal release Mo (1) or Mo iv (1) Fentanyl buccal tablet (FBT): ▪ 2 RCTs: FBT vs placebo and dose titration	▪ Reduction in pain intensity ▪ Adverse effects (AEs) ▪ Patient's satisfaction	▪ **Reduction in pain intensity**: Most studies reported the utility of transmucosal fentanyl products and confirmed their efficacy, safety, and tolerability provided that they are first titrated to a successful dose in the individual patients already using opioids as ATC medi-	Good quality of the included studies. Most industry sponsored	1+ (no details to study quality assessment) Body of

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 SIGN
	breakthrough pain in patients with cancer.			Intranasal fentanyl spray (INFS): ▪ 1 RCT: INFS vs placebo and dose titration		cation. One study demonstrated the utility of parenteral morphine and its faster onset of action compared with transmucosal fentanyl. ▪ **Meta-analysis** (Weighted mean difference=WMD (95%CI) in pain intensity): 1) at 10 min. following transmucosal fentanyl or comparator: WMD =0,51 (0,91 to 1,65); 2) at 15 min following transmucosal fentanyl or comparator: WMD =0,52 (0,33 to 0,70); 3) at 15 min following OTFC or Mo iv: WMD=0,80 (0,64 to 0,96) ▪ **AEs:** generally mild and tolerable. Serious adverse events were commonly considered to be related to underlying conditions. All patients were also taking concomitant ATC opioids, thus it was not possible to definitively separate the effects of transmucosal opioids alone.		evidence SIGN: 1+; for timing: 1-

4.2. Update der EAPC/Caraceni 2012-Guideline

4.2.1.1. 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	Comments	Level of Evidence SIGN
Zeppetella, Cochrane 2013 [102]	SR and MA Aim: update of a Cochrane Review (Issue 1, 2006) To determine the efficacy of opioid analgesics given by any route, used for the management of breakthrough pain in patients with cancer, and to identify and quantify, if data permitted, any adverse effects of this treatment	15 trials (1699 paticipants)	1699 cancer patients and BTP in any setting. Patients (both male and female) of all ages who were treated with opioids for cancer pain.	Opioid analgesics versus placebo or other opioid analgesics, or both, or other active controls regardless of the dose (single or multiple doses) or mode of administration for the relief of BTP. All studies reported on the utility of seven different transmucosal fentanyl formulations, 5 of which were administered orally and 2 nasally. 8 studies compared the transmucosal fentanyl formulations versus placebo, 4 studies compared them with another opioid, 1 study was a comparison of different doses of the same formulation and two were randomised titration studies.	1. O: • Patient-reported pain • AE 2. O: • rescue analgesia • patient preference in the analysis	Oral and nasal transmucosal fentanyl formulations were an effective treatment for breakthrough pain. When compared with placebo (6 studies: Pain Intensity Difference (PID): 0.39 [0.27, 0.52]or oral morphine (2 studies: PID: 0.37 [0.00, 0.73]), participants gave lower pain intensity and higher pain relief scores for transmucosal fentanyl formulations at all time points. Global assessment scores also favoured transmucosal fentanyl preparations. One study compared intravenous with the transmucosal route and both were effective.	No change to conclusions in this update; 11 new studies were identified through the updated search with 1306 participants. The RCT literature for the management of breakthrough pain is relatively small. Most identified studies were industry sponsored and undertaken for registration of either oral or nasal transmucosal opioids specifically developed for the management of BTP. Two studies were judged at a high risk of bias because of a small size.	1++

4.2.1.2. 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 SIGN
Ahmedzai, Palliative Medicine 2012 [103]	RCT, double blind Aim: to examine whether oxycodone/naloxone prolonged-release tablets (OXN PR) can improve constipation and maintain analgesia, compared with oxycodone prolonged-release tablets (OxyPR) in patients with moderate/ severe cancer pain.	n=184 Dropouts: n=51 Patients who needed to titrate up to oxycodone PR 120 mg/day and who regularly required two or more rescue doses of OxyIR were withdrawn from the study.	aged 18 years or older, with a diagnosis of **cancer** and a documented history of moderate/ severe, chronic cancer pain, requiring round-the-clock opioid therapy (equivalent to OxyPR 20-80 mg/day at the start of the trial).	120 mg/day of OXN PR or OxyPR over 4 weeks Open-label oxycodone immediate-release capsules (OxyIR) were available to patients as rescue medication, up to a maximum of six doses per 24 h.	**1.O:** Efficacy assessments: • Bowel Function Index (BFI) • Brief Pain Inventory Short-Form (BPI-SF) **2.O:** • laxative use • rescue medication use. • Quality of life (QoL) • safety	**Efficacy**: Mean BFI score was significantly lower with OXN PR [ΔBFI= -11.14; 95% confidence interval [CI]: -19.03 to -3.24; p<0.01)] ; Mean BPI-SF scores were similar for both treatments. Mean total **laxative intake** was 20% lower with OXN PR [(26.10 [27.60] vs. 32.69 [31.26] mg, respectively), (p=0.17)]. The average rate of analgesic **rescue medication** use was low and comparable. **QoL** assessments were stable and comparable with greater improvements in constipation specific QoL assessments with OXN PR. Overall, rates of **adverse drug reactions** were similar.	computerized randomisation power: 80% double-blind primary analysis (superiority testing) of BFI was performed in an intention-to-treat manner on the full analysis II population. dropout-rate: 27%	1+
Lauretti, BJC 2013 [104]	RCT, double-blind Power of 80% Aim: to evaluate the role of	n=72 (n=12/group) Drop-out=14	Aged 32 - 67 years; with a diagnosis of **cancer**, documented history of moderate/severe chronic cancer pain, classified as Tumour-Node-	Regular medication: oral morphine and oral amitriptyline (Oral mo regimen individually adjusted to a maximal oral dose of 80-90 mg per day, in order to keep the VAS score <4/10; oral	Daily: • Analgesia (Pain average - VAS) • Morphine consumption Weekly evaluation (yes/no) of side effects:	**Analgesia**: overall daily VAS scores <4cm in all groups **Morphine consumption**: • CG, DG and 2.5MetG: gradual increase in mo intake, without sign. difference between groups	Randomisation not clear described 19,4% drop-outs; no ITT-analysis described Study powered	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 SIGN
	epidural methadone-lidocaine in cancer pain combined or not to epidural dexamethasone.		Metastasis stage III or IV, requiring round-the-clock opioid Exclusion criteria: Clinically unstable; clinically significant gastro-intestinal disease, cyclic chemotherapy within 3 weeks before visit or planned during the core study; radiotherapy that would influence bowel function or pain, refusal, allergy to any of the drugs used or inability to ingest the oral rescue analgesic morphine	amitriptyline 25 mg at bedtime) Patients randomised to one of 6 arms if they complained of pain (VAS >=4/10): • Controll Group (CG): Epidural 40 mg lidocaine diluted to 10 ml volume with saline. • Dexamethasone group (DG): 40 mg lidocaine + 10 mg dexamethasone • 2.5 MetG: 2,5 mg epidural methadone + 40 mg lidocaine • 5MetG: 5 mg epidural methadone + 40 mg lidocaine • 7.5MetG: 7.5 mg epidural methadone + 40 mg lidocaine • 7.5Met-DG: 7.5 mg epidural methadone + 40 mg lidocaine + 10 mg dexamethasone	(1) daily somnolence (2) nocturnal insomnia (3) nausea (4) occurence of vomiting (5) constipation (6) diminished appetite (7) fatigue (8) sadness Follow-up during 21 days	• 5MetG and 7.5MetG: patients took 3±1 and 5±1 days, respectively, to restart oral morphine. • 7.5MetDG: patients took 14±2 to restart oral morphine (P<0.001). > shows dose-dependent effect of methadone and enhancement with dexamethasone **Adverse effects**: Daily somnolence and appetite improved in the 7.5MetDG during 2-week evaluation (P<0.005). Fatigue improved for both DG and 7.5MetDG during 2-week evaluation (P<0.005). By the third week of evaluation, all patients were similar.	The groups showed no differences regarding gender, weight, age and height , distribution of the primary site of the cancer pathology and incidence of metastasis	
Leppert, Int J Clin Pract 2010 [105]	RCT, cross-over Aim: to assess the impact of tramadol and	n=40 Drop outs=10 (n=5 in tramadol group and n=2 in DHC group dis-	opioid-naïve adult patients with nociceptive **cancer pain**, VAS>40 during non-opioids therapy	• 1st arm: Controlled release tramadol=TR (n=15) (starting dose: 100 mg b.i.d - max. dose: 600 mg/d)	• Analgesia (VAS), assessed daily • QoL (EORTC QLQ C 30), assessed weekly • Performance status (PS ECOG,	Mean daily doses on the 7th and on the 14th day: TR= 286.67 ± 157.35 mg; 256.20 ± 109.33 mg; DHC=138.87 ± 40.77 mg; 172.53 ± 95.19	No ITT-analysis No sample size calculation No description of concealment or randomisation	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 SIGN
	DHC treatment on quality of life (QL) and performance status (PS) of patients with cancer pain.	continued the study because of insufficient analgesia)	(NSAIDs, paracetamol, metamizol); mean age: 70.47 ± 8.97; 19 women and 11 men.	versus • 2nd arm: Controlled release dihydrocodeine=DHC (n=15) (starting dose: 60 mg b.i.d - max. dose: 360 mg/d) for 7 days, then cross-over	Karnofsky), assessed weekly • Adverse events (EAs) reported in another study • Patients' preferences	mg. • **Analgesia**: During all but 2 days, DHC analgesic effect sign. superior to TR. More patients in the tramadol group (12) than in the DHC group (8) used rescue analgesics. • **Preferences**: 19 patients preferred DHC treatment, 4 TR; 7 indifferent • **QoL**: **Functional scale**: TR: better emotional functioning; DHC: better global QL and cognitive functioning. **Symptom scale**: DHC: less fatigue, pain and sleep disturbances, less nausea and vomiting, better appetite. TR: less constipation, less financial problems • **Performance status**: ECOG and Karnofsky PS low in both groups • **AEs**: no serious adverse events reported.	No wash-out	
Mercadante, Clin J Pain 2010 [106]	RCT, Aim: According to experimental findings, oxycodone (OX) could have	n=60 Drop outs=21 (MO n=20; OX n=19)	**Pancreatic cancer** patients with a pain intensity of 4/10 requiring opioids	• 30 mg/d sustained release oral morphine (MO) versus • 20 mg/d sustained release oral oxycodone (OX) Opioids increased according to the clinical needs	• daily doses of opioids • pain intensity • symptom intensity recorded at admission (T0) and at weekly intervals for the subsequent 4 weeks (T1, T2, T3, and T4), with an extension at 8	**Pain and symptom intensity**: no sign. difference **OEI** at T4 and T8: no sign. difference	The experimental hypothesis that OX would be superior to MO in the clinical model of pancreatic cancer pain was not confirmed.	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 SIGN
	some advantages over morphine (MO) in clinical models of visceral pain. It was hypothesized that OX could have some advantages over MO in terms of efficacy and dose escalation in pancreatic cancer pain.				weeks (T8). • Opioid escalation index (OEI) as percentage (OEI %) and in mg (OEI mg)		Power Analysis: Sample Size Analysis: min 25 patients. Sample power dropped to 65% at the end of the study (4wk), limiting the statistical validity Blinding not possible Drop Outs: 35%; not clear if ITT-analysis. A certain number of patients developed bowel obstructions and could not continue to take the study drugs orally	
Mishra, Am J Hosp Palliat Med 2011 [107]	Double-blind, placebo-controlled RCT Aim: to evaluate comparative clinical efficacy of pregabaline with amitriptyline and pregabaline in neuropathic cancer pain	n=120	Patients with cancer and severe **neuropathic cancer pain**	• 1st arm: amitriptyline (AT) - 50mg/d (1st week), 75 mg/d (2nd week), 100mg/d (3rd week) • 2nd arm: gabapentine (GB) - 900 mg/d), 1200 mg/d (2nd week), 1800 mg/d (3rd week) • 3rd arm: pregabaline (PG) - 150 mg/d), 300 mg/d (2nd week), 600 mg/d (3rd week) • 4th arm: placebo (PL) • 30 patients each group	1.O.: Level of pain with Visual Analogue Scale (VAS 0-100) daily (ratings averaged over 7 days, i.e. results calculated once a week over 4 weeks) 2.O.: • Intensity of lancinating, dysesthesia, burning (NRS 0-10) • Global Satisfaction Scores (GSS) • Functional capacity (ECOG) • Adverse effects (AEs) (mild, moderate, severe) • morphine-sparing effect (%	**Pain intensity**: • Sign. decrease in mean VAS value in all 4 groups as compared to baseline. In all 4 groups, VAS sign. less in every visit as compared to previous visit. • PG: visit 3: mean VAS in group PG sign. less than in group AT (p=.003) and group PL (p=.024). Visit 4: mean VAS in group PG sign. less than in GB (p=.042). **Mo-sparing effect:** • PL: 100% of pts requiring mo in visits 2-4	No drop outs (or not described?) No sample size calculation Mo-sparing effect not described in 4th visit for PG. Data unclear. Nevertheless, the authors conclude that morphine-sparing effect is statistically and clinically significant with PG	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 SIGN
				• Oral morphine was used for rescue analgesic for continued pain • 4 weeks study period (4 visits)	patients requiring rescue morphine) – not described in protocole as outcome but measured	• Visit 3: AT 46,7%; GB 23,3%; PG 16,7%; PL 100% > all study drugs have mo-sparing effect • Mo. needs increased in AT and GB between visit 2 and visit 4. • PG: mo increment was minimum between visit 2 and visit 3. Mo needs in visit 4 not described. **Burning, lancinating pain, dysesthesia:** PL: Sign. higher reduction in burning, lancinating pain, and dysesthesia than in GB, AT and PL **ECOG-GSS:** max. improvement in PG group		
Moksnes, Eur J Cancer 2011 [108]	RCT, phase II trial, parallel groups, multi-centre Aim: We investigated whether patients switched to methadone by the stop and go (SAG) strategy have lower	n=42 Drop outs=7 (n=2 in 3DS group; n=5 in SAG group)	**Cancer** patients >18y, treated with morphine or oxycodone >1week and having increasing pain considered to be untreatable with further opioid titration and/or having opioid related adverse effects	Switch strategy from morphine or oxycodone to methadone: • Stop and Go (SAG) versus • switch over 3 days (3DS) The methadone dose was calculated using a dose-dependent ratio. Rescue dose: 1/6 of the baseline	1.O: Average pain intensity (PI) on day 3 (BPI) 2.O: • Average pain intensity (PI) on day 14 (BPI) • PI now on day 3 and 14 • Adverse events (AEs) on day 3 and 14 • Number of serious adverse events (SAEs)	Mean preswitch morphine doses: 900mg/d in SAG; 1330mg/d in 3DS; The two study groups had similar patients' characteristics except time on WHO step 3 opioids (SAG mean 9.1 months and 3DS 23.6 months, mean difference 14.4 (CI) 26.6 to)2.3)). **Average PI day 3/PI now**: no sign. difference, but trend of	The SAG group had sign. more dropouts and three SAEs (two deaths and one severe sedation). The SAG strategy should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone Sample size calculation, concealment and randomisation described.	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 SIGN
	pain intensity than the patients switched over three days (3DS), and whether the SAG strategy is as safe as the 3DS			opioid dose.		more pain in the SAG group **Mean AEs**: no sign. difference between groups **SAEs**: 3 in SAG (2 deaths, 1 severe sedation)	ITT-analysis?	

4.3. Metamizol

4.3.1.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Duarte Souza, Support Care Cancer 2007 [109]	RCT Double-blinded Cross-over Placebo controlled	34 Intention to treat 1 patient taking paracetamol+codeine during the study was not excluded	**Ambulatory cancer pts.** Presence of cancer pain for which analgesia with morphine was indicated. Exclusion criteria: Neuropathic pain, renal, hepatic failure, jaundice, additional analgesic co-medication	1.Morphine 6x10 mg p.o. + placebo 2.Morphine 6x10 mg p.o. + dipyrone 4x500 mg Crossover after 48 hrs Telephone interview at 48 hrs and 96 hrs.	1.O: Pain scores (VAS 0-10) at entry, 48 and 96 hrs. 2.O: • Preference of dipyrone versus placebo versus indifferent • Toxicities (not mentioned in the methods)	• **Pain scores** at baseline Mo+placebo: 7.31±0.29 Mo+ dipyrone: 6.88±0.28 (p=0.03) 48 hrs Mo+placebo: 7.06±0.32 Mo+ dipyrone:5.5±0.31 (p=0.001) 96 hrs Mo+placebo: 3.18±0.39 Mo+dipyrone: 1.94±0.37 (p=0.03) Dipyrone significantly adds to the analgesic effect of morphine. Pain control was still improved after 96 hrs after switch from dipy. to placebo. • **Preference** Dipyrone 28 pts. (85%) Placebo 4 pts. No preference 2 pts. (p<0.001) • **Toxicities** 48 hrs: n (%) Mo+placebo: 9 (56.2%) Mo+dipyrone: 7 (38.9%) 96 hrs: n (%) Mo+placebo: 15 (93.7%) Mo+dipyrone: 16 (88.9%)	The only study administrating dipyrone as co-medication to morphine. The co-medication to an opioid is the standard situation in clinical palliative care practice Randomisation: how? Power analysis? The significant results were only possible due to the low SD. Evaluation only by telephone interview Imbalance in pts. Characteristics Mo+placebo: higher proportion of visceral pain (p=0.02) Mo+dipyrone: higher proportion of bone pain (p=0.02) Higher proportion of pts. who had not yet received	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
						No agranulocytosis	oncological treatment (p=0.04)	
Rodriguez, Eur J Cancer 1994 [110]	RCT double- blinded parallel multi-center	149 pts. eligible, 121 analyzed Dropouts not mentioned, maybe these were 7 pts	**Pts. suffering from cancer pain** VAS ≥70 mm Karnofsky performance index >30% Exclusion criteria: Brain -, liver metastasis Gastric disorders, insufficient mental status, adjuvant therapy at the time of entering the study, radiotherapy or chemotherapy within 15 days prior to study	1. Dipyrone 3x1g oral + 3x placebo 2. Dipyrone 3x2 g oral + 3x placebo 3. Morphine 6x10 mg oral for 7 days dose escalation possible on day 4 rescue medication paracetamol+codeine	1.O: Degree of pain relief on VAS 0-100 2.O: • Number of pts. who decided to increase the dose on day • Grading of "tolerance" as excellent/ good on day 7 by pts. and observers • Side effects not mentioned in the methods but described I n the results	1.O: all groups had significant improvement in **cancer pain** But less pain relieve in dipyrone 1g compared to dipyrone 2g ($p<0.05$) + morphine (0.01) 2.O: • No difference in number of pts. who decided to increase the dose Dipyrone 1g: 17/31 (55%) Dipyrone 2g: 11/27 (41%) Morphine: 12/35 (35%) • Excellent / good tolerance graded by pts. / observers Dipyrone 1g: 77% / 77% Dipyrone 2g: 46% / 47% Morphine 62% / 62% • **Side effects** Dipyrone 1g: 52 side effects in 27 pts. Dipyrone 2 g: 63 bin 25 pts. Morphine: 92 in 34 pts. n.s. more severe side effects in the morphine group (21) than in dipyrone 1g (7) or dipyrone 2	Participating centers not mentioned, probably the institutions where the authors come from. Power analysis. No information about blinding procedure / appearance of medication. Seems to be liquid. No information on placebo. The taste of drugs allows unblinding. Dugs prepared by whom? Physicians are not explicitly mentioned as blinded. Who were the "observers"? = physicians? Or other persons, who were blinded? Definition of tolerance? In the results al lot of further comparisons between groups are preformed (e.g. grading of efficacy by pts. and observers) which have not been introduced in the method section. Statistics: Correction for multiple testing not mentioned. Investigation of 3 g	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
						g (14)	dipyrone /d does not make much sense (underdosing). It is clear that this cannot be equianalgesic to 60 mg morphine/ day.	
Yalçin, Acta Oncologica 1997 [111]	Cohort study Not randomised Not blinded Not controlled	50 pts. 25 per group No dropouts	**Cancer patients experiencing severe pain**. Inclusion criteria: no regular analgesic treatment before Exclusion criteria: significant impairement of brain, liver, kidney lung	1. 4x10 mg Ketorolac oral 2. 3 x 500 mg dipyrone oral	Not explicitly mentioned; according to the methods: 1.O: decrease in pain scores after 2 days compared to worst pain score for 24 hours before start of the study 2.O: number of patients with complete pain relief, incomplete relief and no benefit	1.O: Significant decrease in **VAS** scores in both groups with no difference between groups. ($p<0.05$) 2.O: **Complete pain relief** ketorolac n=13, dipyrone n=4 ($p<0.05$). **Partial** relief ketoroloac n=7, dipyrone n=17. **No** relief ketorolac n=5, dipyrone n=4	No ethics approval mentioned, No (written) informed consent mentioned No blinding, no randomisation, No statement whether it was a prospective study No power analysis Ketoroloac not available in Germany (due to severe side effects). Metamizol dose only 1.5 g/d No differentiation pain at rest / movement	2-
Yalçin, Am J Clin Oncol 1998 [112]	RCT not blinded cross-over	50 pts. included 3 dropouts (1 died, 2 lost to follow-up)	**14 different kind of cancer**, e.g. breast, lung, colorectal, stomach ca; Inclusion criteria: VAS score >5 - No history of long-term analgesic use -ECOG 0,1 or 2	1. Dipyrone 3 x 500 mg oral 2. Diflunisal 2 x 500 mg oral Both for 1 week followed by 1 day washout, then cross-over to the other drug for 1 week.	Not explicitly mentioned; 1.0 Decrease in pain scores after 7 days of treatment in the whole group and in subgroups with no metastasis, metastasis and bone metastasis 2.0 Side effects	1.O: **Reduction in VAS** scores: Diflunisal by a mean of 4.65 ± 3.10dipyrone by a mean of 3.25 ± 2.85 ($p < 0.001$) VAS scores in subgroups Pts. with no metastasis no difference, pts. with metastasis no difference, patients with bone metastasis diflunisal: VAS after treatment 5.0±3.9, dipyrone 6.2±3.3;	No ethics approval mentioned, No (written) informed consent mentioned No information on randomisation No power analysis No correction for multiple testing Only localization of pain described (extremities,	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			Exclusion criteria: renal or liver impairement, GI malabsorption, hemorrhagic diathesis, intracranial metastasis, active peptic ulcer			p=0.045 2.O: **Adverse events** Dipyrone 14.8% Diflunisal 17.02% n.s. In no pat. drug withdrawal necessary.	abdomen, face etc.) no characterization of pain (e.g. visceral, neuropathic, bone) Diflunisal not available in Germany Metamizol dose only 1.5 g/d No differentiation pain at rest - movement/ breakthrough pain	

5. Obstipation

5.1. Medikamentöse Therapie

5.1.1.1. 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	Comments	Level of Evidence SIGN (justification)
Bader, Schmerz 2012 [113]	SR (MA not possible)	10 studies (n=1136): 4 RCTs 6 controlled trials	Patients in end-of-life situations (most patients in these studies had cancer; n=994)	4 RCTs: 3 x methylnaltrexone vs. placebo 1 x naloxone/ oxycodone vs. placebo/ oxycodone 6 controlled trials: 1 x senna vs. lactulose 1 x Ayurvedic preparation (Misrakasneham) vs. senna 1 x Codanthramer vs. lactulose with senna 1 x senna vs. senna/ docusate 1 x naloxone 1 x polyethylene glycol (PEG), sodiumpicosulfate, lactulose	QoL reduction of symptoms frequency of defacation	Only for methylnaltrexone and naloxone evidence exists for opioid-induced constipation in patients with no risk of bowel perforation, which confirms the efficacy and safety of patients in palliative care settings. The studies on conventional laxatives approved the tolerance of lactulose, PEG, senna, sodiumpicosulfate and docusate in this population, but results of the included studies suggest, there is no evidence for the efficacy of one of these agents.	Evidence on medical treatment of constipation in palliative care is sparse and guidelines have to refer to evidence from outside of the palliative care setting and to expert opinions. Results from other studies with other patient groups can only be transferred with limitations to very ill patients at the end of life who might have a higher risk for potential side effects such was gastrointestinal perforation in case of abdominal tumour manifestation.	1+
Becker, Lancet 2009 [114]	SR; MA of McNicol included [115]	7 studies (with **methylnaltrone**; n=269): 5 RCTs 2 controlled trials	Studies with **methylnaltrexone**: Patients with incurable cancer or other end-stage disease n=133	Studies with **methylnaltrexone**; 5 RCTs: Placebo vs. morphine+placebo vs. morphine+methylnaltrexone	Effectiveness and safety of methylnaltrone and alvimopan: Transit time Time to bowel movement Proportion of patients that laxated within 4 h of first dose	**Methylnaltrexone** and alvimopan are better than placebo for reversal of opioid-mediated increase of gastrointensinal transit time and constipation.	• Alvimopan seems to have higher pharmacological potency than methylnaltrexone, but methylnaltrexone can be given via different	1+

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 SIGN (justification)
		12 studies (with **alvimopan**; n=4574) 12 RCTs	Healthy volunteers n=37 Patients with chronic methadone-induced constipation n=34 Patients with postoperative ileus n=65 Studies with **alvimopan** Healthy volunteers n=70 Patients with chronic methadone-induced constipation or opioid-induced bowel dysfunction n=765 Patients with postoperative ileus n=3739	Placebo vs. morphine vs. morphine+methylnaltreone 3xPlacebo vs. methylnaltrexone 2 controlled trials: methylnaltrexone in different doses: 0.64mg/kg vs. 6.4mg/kg vs. 19.2mg/kg) 0.3mg/kg vs. 1mg/kg vs. 3mg/kg Studies with **alvimopan** Placebo vs. morphine vs. alvimopan Alvimopan+morphine vs. placebo+morphine vs. placebo Morphine+placebo vs. morphine+alvimopan 10 x placebo vs. alvimopan in different doses	Colonic motility Time to recovery of gastrointestinal functions	Based on included MA of McNicol [115] gastrointestinal transit time in patients given methylnaltrexone was reduced by 52 min (95% CI inal transit time s at the en Placebo - Methylnaltrexone reduced the mean transit time to 93altrexone was reduced by 52 min (95% CI) **Methylnaltrexone** (intravenous doses of 0.3-0.45 mg/kg and oral doses up to 19 mg/kg) is well tolerated and able to relieve constipation in methadone dependent individuals and patients with advanced illnesses who need high doses of opioids. **Methylnaltrexone** should be used in patients with opioid-induced bowel dysfunction who do not have a response to a reasonable laxative regimen, in combination with the laxative regimen. Recommended dose: 8 mg (38-61kg); 12 mg (62-114 kg) every 2 days. Outside these weight ranges,:0.15mg/kg. Defaecation can be expected within 4 h after the first dose	routes, which might be beneficial for early postoperative or terminally ill patients, whereas alvimopan is available only orally. • External validity of the studies to the general population of patients is low.	

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 SIGN (justification)
						in about 50% of patients. **Alvimopan** is effective in patients with postoperative ileus at doses of 6 mg or 12 mg daily.		
Candy, Cochrane 2011[86]	SR; MA	7 RCTs (n=616)	• Participants at an advanced stage of disease (most participants had a cancer diagnosis). • Most common primary cancer site was the lungs. Participants with other diagnoses included advanced cardiovascular disease, AIDS and dementia. • Average age 61 to 72 years.	4 studies: laxatives lactulose, senna, co-danthramer, misrakasneham, magnesium hydroxide with liquid paraffinen 3 studies: methylnaltrexone	Change in frequency of defacation Ease of defacation Relief of systemic and abdominal symptoms related to constipation Change in quality of life Use of rescue laxatives	No differences in effectiveness were demonstrated between **lactulose** and **senna**, lactulose with **senna** compared to **magnesium hydroxide and liquid paraffin**, or between **misrakasneham and senna**. Between **lactulose and senna** versus **co-danthramer** was a significant difference, favouring the group who took lactulose and senna, in stool frequency. No significant difference between **lactulose and senna** compared with **co-danthramer** in participants' assessment of bowel function. All studies that compared different laxatives (one to three) participants suffered side effects. Most commonly reported events: nausea, vomiting, diarrhoea and abdominal pain. Subcutaneous **methylnaltrex-**	In studies comparing the different laxatives evidence was inconclusive. Evidence on subcutaneous methylnaltrexone was clearer Safety of subcutaneous methylnaltrexone is not fully evaluated. Large, rigorous, independent trials are needed. The study comparing lactulose and senna with magnesium hydroxide and liquid paraffin emulsion a participant from each group withdrew because of intolerable nausea and gripping abdominal pain. Participant preferences were only reported in two studies; one showed a preference for lactulose plus senna over magnesium hydroxide combined with liquid paraffin. The	1+

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 SIGN (justi-fication)
						one is effective in inducing laxation after 4 hours in palliative care patients with opioid-induced constipation and where conventional laxa-tives have failed compared to placebo. Rescue free laxation within 4 hours: OR 6.95 (95% CI: 3.83 to 12.6). Rescue free laxation within 24 hours: OR 5.42 (95% CI: 3.12 to 9.41)	other found no difference in preference.	

6. Depression

6.1. Screening, Diagnose und Assessment

6.1.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Meijer, PLoS ONE 2011 [116]	SR; no MA to evaluate the potential benefits of depression screening in cancer patients	19 studies (Sample size ranged from 16 to 361)	8 studies of patients with **breast cancer** patients. 11 studies of patients with **mixed cancer** sites across the spectrum of cancer stages. Number of cases of major depressive disorder (MDD) ranged from 6 to 74 (median=17).	Screening instrument vs. a valid MDD criterion standard ▪ HADS;-D ▪ EPDS	Assessing accuracy With: ▪ Sensitivity ▪ Specificity ▪ PPV ▪ NPV (95% CI)	• The main finding of this systematic review was that there are no RCTs that have evaluated whether screening for depression among cancer patients would improve depression outcomes. • The result shows that the recommendation statement of the NIH panel, IOM, clinical guideline of NCCN and NICE are not supported by evidence from RCTs that screening cancer patients for depression would improve patients' mental health beyond existing psychological services that are offered in oncology settings.		1-
Mitchell, J Clin Oncol 2007 [117]	SR, MA; Accuracy of distress thermometer (DT) and other ultra-short methods of detecting cancer-related	38 analyses about diagnostic validity studies	**Cancer** settings N=6414 patients	Ultra-short screening tools (DT, single-question, VAS) involving fewer than five questions	Utilizing an accepted psychiatric interview or a standardized ratings scale for assessing: ▪ Depression ▪ Anxiety ▪ Distress	Pooled ability of ultra-short methods to detect depression was given by: ▪ Sensitivity=78.4% ▪ Specificity=66.8% ▪ PPV=34.2% ▪ NPV=93.4% Thus these tools were very		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	mood disorders					good at excluding possible cases of depression but poor at confirming a suspected diagnosis. Their rule-in ability was poorer than their rule-out ability. Ultra-short methods cannot be used alone to diagnose depression, anxiety, or distress in cancer patients but they may be considered as a first-stage screen to rule out cases of depression.		
Mitchell, Brit J Cancer 2008 [118]	SR, MA; to examine the value of one or two simple verbal questions in the detection of depression	Seventeen analyses were found. Of these, 13 were conducted in late stage palliative settings.	**Cancer** settings	▪ Single depression question ▪ Single interest question ▪ Two questions (low mood and low interest)	The majority of studies defined depression using a psychiatric interview (applied in a semi-structured or clinical interview) but a minority utilised standardised rating scales.	(1) Single depression question (9 studies): prevalence of depression = 16%, sensitivity = 72%, specificity = 83%. PPV = 44%, NPV =94%. (2) Single interest question (3 studies): Prevalence=14%, sensitivity= 83%, specificity=86%, PPV= 48%, NPV =97%. (3) Two questions (5 studies): prevalence=17%, sensitivity= 91%, specificity= 86%, PPV = 57%, NPV =98%. Simple verbal methods perform well at excluding depression in the non-depressed but perform poorly at confirming depression. The 'two question' method is significantly more accurate than either single question but clinicians should not rely on		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						these simple questions alone and should be prepared to assess the patient more thoroughly.		
Mitchell, J Affect Disorders 2010 [119]	SR, MA; To examine the validity of the HADS in the identification of psychiatric complications of cancer, as defined by robust criterion standard	50 analysis	**Cancer and palliative setting**	50 analyses tested the HADS-S (depression), HADS-A (anxiety)or HADS-T (both) against syndromal (clinical) depression (n=22), syndromal anxiety (n=4) or any mental ill health/distress, all defined by semi-structured psychiatric interview.	1.O: Syndromal (clinical) depression defined by ICD10 or DSM-IV. 2.O: Syndromal anxiety disorder defined by ICD10 or DSM-IV. 3.O: Any mental ill health (usually distress or adjustment disorder) defined by ICD10or DSM-IV.	Overall it appeared to perform marginally better in non-palliative cancer settings. In the identification of depression the HADS-T, HADS-D and HADS-A had a pooled sensitivity and specificity of 82.0%, 77.0%; 71.6%, 82.6% and 80.5%, 77.8%, respectively. All versions performed poorly in case-finding but well in a screening capacity. For the identification of depression, anxiety or distress in cancer settings, the HADS (including subscales) is not recommended as a case-finding instrument but it may, subject to concerns about its length, be a suitable addition to screening programme.		1+
Mitchell, J Affect Disord 2012 [120]	SR, MA; To examine the validity of screening and case-finding tools used in the identification of depression as defined by an ICD 10/DSM-IV criterion standard	63 studies involving 19 tools	**Cancer** patients in ▪ **Palliative settings** ▪ Non-palliative settings	To examine the validity of screening and case-finding tools used in the identification of depression as defined by an ICD10/DSM-IV criterion standard. ▪ BDI ▪ BDI fast screen ▪ DT ▪ EPDS ▪ PHD ▪ PHQ-2	Validation of diagnostic accuracy with: ▪ Sensitivity ▪ Specificity ▪ I^2 ▪ Bayesian Plot (post-test and pre-test probabilities)	Across 16 analyses (n=4138) the weighted prevalence of depression in palliative settings was 19% (CI95% CI=17,5-19,5). In terms of case-finding, the two stem questions had level 1b evidence and one stem question had level 2b evidence. We gave both methods a grade B recommendation. Two	The main cautions are the reliance on DSM-IV definitions of major depression, the large number of small studies and the paucity of data for many tools in specific settings.	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	Plus panel recommendation of Depression in Cancer Care consensus group			▪ Two stem questions ▪ GHQ-12 and GHQ-24 ▪ CES-D ▪ Zung ▪ HADS ▪ HDS ▪ Several other tools		stem questions also had level 1b evidence in screening and also had high acceptability. For every 100 people screened in advanced cancer, the two questions would accurately detect 18 cases, while missing only 1 and correctly reassure 74 with 7 falsely identified.		
Nelson, J Clin Oncol 2010 [121]	SR;no MA To determine which depression instruments are appropriate	53 depression scales were identified, 8 tools were selected	**Geriatric cancer** patients	Patient reported scales ▪ BDI ▪ BSI-18 ▪ CES-D ▪ GDS-15 ▪ HADS ▪ PHQ-9 ▪ POMS-SF ▪ Zung SDS	▪ General properties: conceptual framework ▪ Instrument development ▪ Validation and psychometric properties ▪ Symptom profile analysis	We could not locate any validation or psychometric information of these measures specifically in elderly patients with cancer. The validation evidence for use of common depression instruments in geriatric patients with cancer is lacking.		1+
Vordermaier, Support Care Cancer 2011 [122]	SR, MA; to examine the scale's accuracy in assessing any type of clinically relevant mental disorder in cancer patients, as well as determining cut-off rates for clinical use.	28 studies	**Cancer** Mixed cancer sites: 10 studies, N=2828 Breast cancer: 8 studies, N=1407 Mixed cancer sites in palliative settings: 3 studies N=388 Lung cancer: 3 studies, N=219 Head and neck cancer: 2 studies, N=167 Laryngeal cancer: 1 study, N=250 Otolaryngologic cancer: 1 study, N=50	▪ HADS total and its subscale scores against ▪ semi-structured or structured clinical interview as a reference standard with regard to its screening efficacy for any mental disorders and depressive disorders alone	▪ Sensitivity ▪ Specificity on the HADS total and/or subscales and had any type of mental disorder and/or any type of depressive disorder as the criterion.	Respective thresholds for depression screening were 15 for the HADS total (sensitivity 0.87; specificity 0.88), 7 for the HADS depression subscale (sensitivity 0.86; specificity 0.81), and 10 or 11 for the HADS anxiety subscale (sensitivity 0.63; specificity 0.83). The HADS anxiety subscale performed worse than the total and the depression subscales for both indicators. Diagnostic accuracy varied widely by threshold but was consistently superior for depression screening than for screening of any mental disorder.		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Wasteson, Palliative Med 2009 [123]	SR ; no MA Assessment tools and classification systems	202 full-length articles: ▪ 128 observational study ▪ 61 prevalence studies ▪ 42 intervention studies (Depression outcome) ▪ 46 validation studies (depression assessment) ▪ 27 validations studies (other assessment) ▪ 15 intervention studies (other outcome) ▪ 18 other or not specified studies	**Palliative cancer care** patients	▪ What are the assessment methods that have been used according to the type of study, year of study, sample size and geographical region? ▪ In studies that report on depression cases, what are the classification systems that have been used to define caseness and how have the criteria of duration and functional consequences of symptoms been met?	▪ Assessment methods ▪ Type of study ▪ Sample size ▪ Geographical region ▪ Classification systems ▪ Duration and functional consequences ▪ Criteria modification	Large number of assessment methods in identified papers for depression (N=106), many of which were unique to one paper (N=65). The content of the assessment methods varied greatly and included different types (i.e. structured diagnostic interviews, specific questionnaires, general questionnaires). All together, the HADS was the most commonly used assessment method. There were regional differences: HADS dominated in Europe it was quite seldom used in Canada or in the USA. Few prevalence and intervention studies used assessment methods with an explicit reference to a diagnostic system. There were in total few case definitions of depression. Among these, the classifications were in general based on cut-off scores (77%) and not according to diagnostic systems. The full range of the DSM-IV diagnostic criteria was seldom assessed, i.e. less than one-third of the assessments in the review took into account the duration of symp-		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						toms and 18% assessed consequences and impact upon patient functioning. Although heterogeneity in assessments was expected the diversity in the reviewed papers was pronounced. Depression and distress are rarely conceptualized explicitly and it is often unclear why a given measure was chosen.		

6.2. Medikamentöse Therapie

6.2.1. Antidepressiva

6.2.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Rayner, Cochrane 2010 [124]	SR; MA to determine the efficacy of antidepressants in the treatment of depression in patients with a physical illness	51 RCTs included in qualitative analyses (n=3603; adults older than 18 years with depression in the context of a physical illness)	• 11 trials (stroke) • 7 trials (HIV/AIDS) • 6 trials (Parkinson's disease) • 4 trials (cancer) • 3 trials (COPD) • 3 trials (diabetes) • 3 trials (myocardial infarction	All types of antidepressants were eligible for inclusion in this review: • Selective serotonin reuptake inhibitors • Tricyclic antidepressants • Monoamine oxidase inhibitors • Serotonin noradrenaline	1.O: • Antidepressant efficacy at 6–8 weeks after randomisation • dichotomous outcome of individuals who attained a 50% improvement of depressive symptomatology at 6 to 8 weeks from randomisation (HDRS, MADRS, HADS)	1.O: • response to treatment: Odds of response were greater with antidepressants than with placebo (OR 2.33, 95CI 1.8 to 3.0, p<0.00001; 25 studies involving 1674) • Antidepressants were also more efficacious than pla-		1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
		44 studies (n=3372) contributed data towards the efficacy analyses included in quantitative synthesis of primary outcome	• 2 trials (renal failure) • 1 trial (rheumatoid arthritis) • 1 trial with: brain injury/ asthma/ coronary artery disease/ chronic heart failure/ epilepsy/ chronic prostatitis • 3 trials with mixed diagnoses Average age: 33-82 years	reuptake inhibitors • Noradrenergic specific serotonergic antidepressant • Serotonin2 antagonists • Noradrenaline reuptake inhibitor • Norepinephrine and dopamine reuptake blockers • Tetracyclic antidepressants • Heterocyclic antidepressants Control condition was placebo	• continous measures of depression expressed as mean values at 6 to 8 weeks from randomisation (HDRS, MADRS, HADS) 2.O: • Depression scores and symptomatology defined by validates measures • Number of drop-outs • Number of adverse events	cebo at the other time-points. • Mean depression score: Antidepressants were more efficacious than placebo in reducing depressive symptoms (SMD -0.66, 95% CI -0,94 to -0.38, p<0.00001; 22 studies involving 1214 patients). 2.O: • Mean depression score (4-5 weeks): Antidepressants were more efficacious than placebo in reducing depressive symptoms (SMD -0,46, 95% CI -0,88 to -0,04, p=0,03; 6 studies, n=365) • Number of drop-outs (4 to 5 weeks): Similar numbers of patients dropped out of the treatment and control group (OR1.11, 95% CI 0,48 to 2,57, p=0,86; 5 studies, n=365) • Tolerability: dizziness, dry mouth, headache, nausea, constipation, insomnia, sexual dysfunction, sedation, hypotension, appetite change.		
Rayner, Pall Med 2011[125]	SR; MA to determine the efficacy of antidepressants for the treatment	SR: 25 studies MA: 21 studies	• 7 trials (HIV/AIDS) • 6 trials (Parkison´s disease) • 4 trials (cancer) • 3 trials (COPD) • 2 trials (multiple sclerosis)	antidepressants vs. placebo in the treatment of depression in palliative care	1.O: • Efficacy assessed using dichotomous and continuous measures of depression: dichotomous outcome response to treatment' is defined con-	At each time-point antidepressants were more efficacious than placebo: 4-5 weeks odds ratio (OR) 1.93 (1.15-3.42) p=0.001; 6-8 weeks OR 2.25 (1.38-3.67)	• It is probable that the effect sizes yielded in this review overestimate the efficacy of antidepressants due to biases such as selective report-	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	of depression in palliative care		• 2 trials (renal failure) • 1 trial (chronic heart failure)		ventionally and widely reported as a 50% or greater improvement in depressive symptomatology according to a validated scale, such as the HDRS, the MADRS or the HADS. Continuous measures expressed as mean depression score values and standard deviations, according to a validated scale. Outcomes were assessed at three time-points: 4-5 weeks, 6-8 weeks and 9-18 weeks from randomization. 2.O: • Acceptability, tolerability, quality of life and functional status.	p=0.001; 9-18 weeks OR 2.71 (1.50-4.91) p=0.001. This review provides evidence that antidepressants are effective in treating depression in palliative care. Their superiority over placebo is apparent within 4-5 weeks and increases with continued use.	ing and publication. • the magnitude and consistency of the effect suggests genuine benefit.	
Ujeyl, Schmerz 2012 [126]	SR; MA Aim was to assess the evidence of the efficacy and safety of different classes of antidepressants depending on the type and severity of physical illness.	40 trials: • 35 doubleblind RCT´s • 3 doubleblind crossover RCT´s • 1 simpleblind RCT • 1 CT not blinded	• 3 trials (multiple sclerosis; n=133) • 6 trials (Parkisnon´s disease; n=187) • 7 trials (Alzheimer´s disease; n=625) • 8 studies (cancer; n=819) • 11 studies (HIV/AIDS; n=664) • 5 studies (COPD/CHF; n=568)	• Nonselective monoamine reuptake inhibitors (tri- and tetracyclics) • Selective serotonin reuptake inhibitors • mirtazapine • nefazodone • trazodone compared with placebo, other antidepressants, benzodiazepines, psychostimulants or psychotherapy	Outcomes: • response rate • change from baseline • remission rate	Due to heterogeneous study designs no conclusions can be drawn if efficacy or tolerability of AD is dependent on disease severity. In most cases, studies might have been too small to detect limited treatment effects. As a lack of superiority over placebo was predominantly shown in larger trials, publication bias might have been present. In most of the reviewed internal medicine diseases study results were heterogeneous. In contrast to the popularity of the treatment approach, results sug-	This review allows only limited conclusions concerning the use of antidepressants in physical illness at the end of life. The reviewed evidence does not allow direct conclusions to be drawn concerning the use of antidepressants in different disease severities and its benefits compared to other treatment options (psychotherapy, benzodiazepines etc.).	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						gest that SSRIs are not effec-tive in Alzheimer's disease. In Parkinson's disease, negative studies are too small to prove lack of efficacy of SSRIs as present in the majority of trials.		

6.2.2. Psychostimulanzien

6.2.2.1. 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	Comments	Level of Evidence SIGN
Abbasowa, Nord J Psychiatry 2013 [127]	SR /no MA Exploring the efficacy of psychostimulants (PS) in the treatment of major depressive disorder (MDD) to clarify the current empirically founded evidence for clinical approaches	18 RCTS (N=1407)	Patients suffering from ▪ MDD (n=1038) ▪ Bipolar depressed patients (n=342) ▪ Mixed samples of bipolar and unipolar patients (n=27)	▪ Modafinil ▪ Methylphenidate ▪ Dexamphetamine ▪ Methylamphetamine ▪ Pemilone were administered orally/intravenously, as monotherapy/adjunct therapy and in comparison to placebo (n=1311) or to antidepressants/mood stabilizers (n=96)	A priori defined efficacy measures (change and scores) of: ▪ HAM-D ▪ MADRS ▪ ESS ▪ IDS and non-predefined efficacy outcomes	▪ Two studies examining modafinil demonstrated significant ameliorating characteristics pertaining to symptoms of depression. ▪ No clear evidence for the effectiveness of traditional PS in the therapeutic management of MDD was found.	▪ In general the quality of included trials was poor since the majority was of short-term duration, comprising relatively small sample sizes and some, especially older studies, were methodologically flawed. ▪ Clearly larger well designed placebo-controlled studies with longer follow-up accompanied by evaluations of tolerance/ dependence are warranted before PS can be recommended in routine clinical practice for the treatment of MDD.	1-
Candy, Cochrane 2008 [128]	SR (24 RCTs); MA (13 trials) To determine the effectiveness of PS in the treatment of depression and to assess	24 RCTs • 15 parallel design • 9 cross-over design	Patients (>16 years) receiving psychostimulants as a treatment of depression (diagnosis was made according to any edition of DSM or ICD or when a clinician made the diag-	Psychostimulants (PS): • dexamphetamine • methylphenidate • methylamphetamine • pemoline • modafinil (trials using modafinil were evaluated separately)	1.O: Examine the effectiveness of PS on depressive symptoms or diagnosing using: • Continous measures (Hamilton Depression Scale or Montgomery Asberg Scale) • Dichotomous measures (proportion of people who re-	▪ 3 trials (n=62) demonstrated that oral psychostimulants, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.4, -0.33) with non-significant heterogeneity.	• 15 trials were performed over 20 years ago. • 4 trials declared pharmaceutical funding or interests. • Some evidence in the short-term, PS reduce symptoms of depression. Whilst this reduc-	1+

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 SIGN
	adverse events associated with PS.		nosis)	Main comparisons: • PS vs. monotherapy vs. placebo • PS vs. monotherapy vs. other treatment (medication, psychological therapy) • PS vs. other treatment as a adjunctive treatment	spond to treatment (categorisation of HAM-D score or any other validated depression scale into a 50 response or less. 2.O: • Changes in other symptoms associated with depression • Remission criteria • Social adjustment and functioning • HRQL • acceptability	▪ Similar effect was found for fatigue. ▪ No statistically significant difference in depression symptoms was found between modafinil and placebo.	tion is statistically significant, the clinical significance is less clear. • Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and to explore which PS may be more beneficial and in which clinical situations they are optimal.	

6.2.2.2. 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 SIGN
Kerr, J Pain Symptom Manag 2012 [129]	RCT, double-blind, placebo-controlled To evaluate the response of fatigue and depression in patients with advanced	n=34 4 drop-outs: • 3 died • 1 withdrew	hospice patients • 12 male; 18 female • diagnosis of terminal illness including cancer (n=26) and noncancer diseases (n=4) • absence of significant cognitive impairment	1st arm: 5mg methylphenidate twice a day 2nd arm: placebo Doses were titrated every three days according to response and adverse effects	Influence of methylphenidate on the symptom of fatigue on ▪ Piper-Fatigue-Scale (PFS) ▪ VAS-F ▪ ESAS and on depression with ▪ ESAS ▪ CES-D ▪ BDI-II	Fatigue: ▪ PFS: reduction of 66% (day 0 mean intensity of 6.2; day 14=2.1±2.5) ▪ VAS-F: reduction of 55% (day 0=4.9±2.7; day 14=2.2±3.1), although significant was noted until day 7 (P=0.05) ad day 14 (P=0.0007)		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 SIGN
	illness		• presence of fatigue for at least two weeks		from days 0-14	▪ ESAS: reduction of 64% from baseline index of fatigue (day 0=7.4±2.0 and day 14=2.7±1.3) Depression: ▪ ESAS: reduction of 35%, P=0.002 (day 0=2.9±3.1 and day 14=1.9±2.0) ▪ CES-D: reduction of 33%, P=0.002 (day 0=25.0, day 14=16.7±9.5 • BDI-II: reduction of 22%, P=0.028 (day 0=15.1, day 14=11.8±9.1)		

7. Kommunikation

7.1. Advance Care Planning – ACP (vorausschauende Versorgungsplanung)

7.1.1.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Bakitas, JAMA 2009 [130]	RCT	n=322 (279 included in primary outcome analysis, 322 included in survival outcome analyses)	▪ Patients with cancer of the gastrointestinal tract, lung, genitourinary tract and breast ▪ Patients with impaired cognition mini-mental state, an axis I psychiatric disorder or active substance use were excluded.	▪ Multicomponent, psychoeducational intervention conducted by advanced practice nurses consisting of 4 weekly educational sessions and monthly follow-up telephone sessions until death or study completion (n=161). The education manual contained 4 modules of problem solving, communication and social support, symptom management, advance care planning and unfinished business, and an appendix listing supportive care resources ▪ Usual care (n=161).	**1.0:** Higher scores for quality of life (p=0.02) in the intervention group as compared to the control group, no improvements in symptom intensity scores or reduced days in hospital or ICU or emergency department. **2.0:** Higher scores in mood (p=0.02 for all participants, p=0.03 for patients who died during the study)) in the intervention group as compared to the control group Post hoc, exploratory analyses demonstrated no statistically significant differences in survival between the intervention and the control group **Quality of life**: assessed with the Functional Assessment of Chronic Illness Therapy for Palliative Care **Mood**: assessed with the CES-D 2 sets of longitudinal, intention-	Estimated treatment effects (intervention minus usual care) for all subjects were 4.6 (P = 0.02) for QOL, −27.8 (P = 0.06) for symptom intensity, and −1.8 (P = 0.02) for depressed mood. Estimated average treatment effects in the sample of participants who died during the study were 8.6 (P = 0.02) for QOL, −24.2 (P = 0.24) for symptom intensity, and −2.7 (P = 0.03) for depressed mood. Compared with participants receiving usual oncology care, those receiving a nurse-led, palliative care-focused intervention addressing physical, psychosocial, and care coordination provided concurrently with oncology care had higher scores for quality of life and mood, but did not have im-	▪ ACP as part of a multicomponent, psychoeducational intervention	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
					to-treat analyses for all participants with baseline and 1 or more follow-up assessments using repeated measures analysis of covariance to examine the effect of the intervention on (1) the total sample in the year after enrollment and (2) the sample of participants who died.	provements in symptom intensity scores or reduced days in the hospital or ICU or emergency department visits.		
Clayton, Clin Oncol 2007 [131]	RCT / coder blinded / Parallel	174/4	Advanced **cancer** patients and their caregivers who were referred for palliative care. Inclusion criteria: 1) diagnosis of an advanced progressive life limiting illness, (2) English speaking, (3) older than 18 years of age, and (4) able and well enough to read QPL and complete questionnaires.	Provision of a question prompt list (QPL) with structured questions to patients before consultation /usual care consultation	**1.0** number of patient questions during consultation and topics of topics relevant to end-of-life care during consultations with a palliative care (PC) physician **2.0** total numbers of items discussed, patient concerns and caregiver questions/concerns, number of items discussed and patient/caregiver questions/concerns about nine individual topics covered by the QPL, achievement of patient information preferences, patient satisfaction with the consultation, patient anxiety, physician satisfaction with communication during the consultation, and consultation duration	Compared with controls, QPL patients and caregivers asked **twice as many questions** (for patients, ratio, 2.3; 95% CI, 1.7 to 3.2; P _ .0001), and patients discussed 23% more issues covered by the QPL (95% CI, 11% to 37%; P _ .0001). QPL patients asked **more prognostic questions** (ratio, 2.3; 95% CI, 1.3 to 4.0; P _ .004) and discussed more prognostic (ratio, 1.43; 95% CI, 1.1 to 1.8, P _ .003) and end-of-life issues (30% v 10%; P _ .001). Fewer QPL patients had unmet information needs about the future (_2 1 _ 4.14; P _ .04), which was the area of greatest unmet information need. QPL consultations (average, 38 minutes) were longer (P _ .002) than controls (average, 31 minutes). No	Well done study, intelligent design Intervention is a tool to facilitate ACP / encourage asking important q.s Prim. Outcome is difference of ACP consultation quality: contents: #, duration and content of questions No harm done in terms of anxiety etc., but also no clinical criteria Not about the clinical impact of ACP, but how to best realise ACP Ilicited questions re. caregiver that otherwise were not asked Setting: SAPV-Äquivalent	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
						differences between groups were observed in **anxiety** or **patient/physician satisfaction**		
Dyar, J Pall Med 2012 [132]	Initially designed as a randomized phase 2 Trial with a goal of accruing 100 patients with-metastatic cancer (50 patients per arm). Patients were randomized to either a control arm or an intervention arm.	Final questionnaire data could not be analyzed for eight patients, two in the intervention group and six in the control group. Two patients, both in the control group, were too ill to complete the baseline and follow-up questionnaires. Two participants withdrew because of lack of compliance with the required visits and consultations. One of them had expressed interest in the intervention arm and was not interested in participating in the control por-	See summary in table 1, keine signifikanten Unterschiede zwischen beiden Gruppen	The control group completed baseline and one month later (or at the time of hospice referral if that occurred earlier) hospice knowledge questionnaires (HKQ) and QoL tools, including the Functional Assessment of Cancer Therapy-General [FACT-G] and the Linear Analogue Self Assessment scale (LASA), but did not receive any mandatory palliative care intervention. These patients had access to palliative care consultations and hospice referrals as deemed indicated by their oncology team. Patients on the intervention arm, in addition to completing the questionnaires and QoL tools at baseline (pre-intervention) and one month later (post-intervention), had an initial and a one-month followup	Relevant endpoints included **change from baseline QoL and improvement in hospice knowledge.** Although an original primary endpoint of the study was to assess time to hospice referral in the two groups, the frequently prolonged period to hospice referral, relatively short study follow-up, and small sample size made it difficult to assess this outcome. By the same token, sense of abandonment upon hospice referral, which was a secondary endpoint of the study, could not be properly evaluated from the data collected. We set out to demonstrate that QoL outcomes can be improved with ARNP-directed education and follow-up. **Outcome measures:** Hospice knowledge questionnaires (HKQ) QoL tools, including the Func-	This study closed after the first 26 patients were entered in view of the finding of the positive effects of a nurse intervention in terminal cancers as reported by Bakitas and colleagues, and in view of the preliminary data analysis of the patients offered participation in this study that showed that many patients refused study participation as a result of the control arm and their desire to receive the ARNP intervention. There was a statistically significant improvement in the **FACT-G emotional domain** in the intervention group [Mean 1.2 (SD 2.94) vs. Mean -4.5 (SD 4.54) in non-interventional group] . None of the additional FACT-G domains had statistically significant differences between groups. **LASA scale**: The change from baseline mental QoL was	Endpoints klar definiert? Früher Abbruch wenige Patienten Differenzierung der Enpunkte? ACP hier nu rein Teil einer Intervention	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
		tion of the study after randomization. Four patients died prior to completing the followup survey (one in intervention group, three in control group).		consultation with an oncology ARNP who taught them about hospice, helped fill out the Five Wishes and living will forms, and assessed their psychological, physical, intellectual/ cognitive, social, and spiritual needs	tional Assessment of Cancer Therapy-General [FACT-G] Linear Analogue Self Assessment scale (LASA)	statistically improved. p = 0.0219		
Loberiza, Leukemia & Lymphoma 2011 [133]	prospective observational study	770 were found to be eligible, participation rate of 47% (364/770). The current analyses are focused on 293 (80%) participants who completed a preconsultation self-administered survey, a preconsultation interview and a postconsultation (after 3 months) interview, and had their consultation successfully audiotaped.	Lymphoma, Leukaemia or MDS, detailed characteristics see table 1, p.2344	In this study, we defined ACP in two ways. First, as used in our previous study [4], we ascertained the presence of written plans of ACP as those who responded " yes " to having both a living will and health care proxy, while patients with only one or neither were considered to have no ACP. Second, we also defined verbal ACP based on whether or not patients reported having discussions about life support with their family/friends and medical care team, based on clinical practice, which largely defers to orally communicated wishes over written documents	Keine Klare Zielkriterienbestimmung: Stepwise covariate selection was performed to identify psychosocial domains and patient characteristics (as listed in Table I) associated with having ACP. Physician estimate of life expectancy was also tested as a covariate in the all-model building. A separate logistic model was also constructed to evaluate whether the above factors were associated with discussing life support with family and/or physician (verbal plan). Covariates with an α of less than or equal to 0.05 were retained in the model.	Nur für „verbal ACP": As for factors associated with discussions about life support with family/friends and/or health providers (verbal plans), Table III also shows that lower physical component score of the SF-36 (OR 0.98, 95% CI 0.96 – 0.99, p _ 0.03); lower score on general health (OR 0.98, 95% CI 0.97 – 0.99, p _ 0.007); and lower physician estimate of life expectancy (OR 0.82, 95% CI 0.67 – 0.99, p _ 0.04) were the only factors associated with having discussed life support with family/friends and/or health providers.		2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
				Anmerkung: nur "verbal ACP" relevant für SR, wobei hier auch Situationen dabei gewesen sein könnten, in denen Patienten nur mit Angehörigen gesprochen haben:				
Loggers, JCO 2009 [134]	multisite, prospective, interview-based cohort study	Black (n _ 68) and white (n _ 234) patients. Of the 944 patients who were initially approached and confirmed to be eligible, 274 (29.0%) declined participation. Given the outcomes of interest, the sample was further limited to patients who had died (n_371) with complete information on location of death (n_370), self-reported black or	Patients with **stage IV cancer** and caregivers participated, September 2002 to August 2008. (Coping with Cancer study)	The following questions (with response options of "yes" or "no") were asked to assess having an EOL discussion, and having a DNR order, respectively: "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?";	**1.O.:** intensive EOL care defined as CPR and/or ventilation within the last week of life followed by death in an intensive care unit (ICU). Selection of this end point targets those receiving the most aggressive EOL care and eliminates consideration of individuals who, for example, received a brief trial of ventilation and then elected to die athomeor in hospice.	White patients who reported an EOL discussion or DNR order did not receive intensive EOL care; similar reports were not protective for black patients (aOR 0.53, P .460; and aOR 0.65, P .618, respectively)	Generalisability of ACP intervention that does only work with white patients?	2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
		white race (n _ 303, those excluded reported other racial or ethnic backgrounds, the majority being self-identified as Hispanic), and complete information on at least four of the five predictors of interest, resulting in a total of 302 patients						
Mack, JCO 2012 [135]	Cancer Care Outcomes Research and Surveillance Consortium, a population- and health system-based prospective cohort study, who died during	1231	patients with **stage IV lung or colorectal cancer** in the Cancer Care Outcomes Research and Surveillance Consortium, who died during the 15-month study period but survived at least 1 month	EOL discussions were identified if the patient or surrogate reported a discussion with the physician about resuscitation from patient and surrogate interviews for living patients) or hospice care (eg, "After your cancer was diagnosed, did any doctor or other health care provider discuss hospice care with you?" from all interview types, or "Was hospice recommended by any doctor or other health care provider?" from follow-up interviews.) EOL discus-	**Keine klare Benennung von primären/sekundären Zielkriterien:** After characterizing attributes of EOL care, bivariate logistic regression was used to investigate the association between attributes of EOL discussions (for the full sample, presence and source of EOL discussion; for MRA documented discussions, days between first EOL discussion and death, presence of medical oncologist, and inpatient discussion) and aggressiveness of EOLcare re-	Patients who had EOL discussions with their physicians before the last 30 days of life were less likely to receive aggressive measures at EOL, including chemotherapy (P = 0.003), acute care (P = 0.001), or any aggressive care (P = 0.001). Such patients were also more likely to receive hospice care (P = 0.001) and to have hospice initiated earlier (P = 0.001).	"End of life discussion" ist auch erfüllt, wenn über Wiederbelebung mit dem Arzt gesprochen wurde, oder wenn es in der Akte einen Hinweis auf eine Diskussion über Hospice oder palliative care gibt.	2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
				sions were identified in medical records if there was documentation of a discussion about advance care planning (do-not resuscitate order, hospice, palliative care, or not otherwise specified) or venue for dying (hospice, home, hospital, nursing home, or not otherwise Specified	ceived. Multivariable logistic regression models were fitted for each marker of aggressive EOL care and hospice. The attributes of EOL discussions were included in multivariable models regardless of significance. Patient characteristics were sequentially removed from models using backward selection until remaining characteristics had a significance level_.10.			
Mack, 2010 [136]	longitudinal multi-institutional cohort study	325	Patients recruited as part of the Coping with Cancer Study. Patients with **advanced cancer**. This report describes 325 patients recruited between October 2002 and September 2007 whose self-reported treatment preferences were available and who died during the course of the study	Patients were asked in "yes/no" format whether they and their physician had discussed any wishes about the care they would want to receive if they were dying.	**1.O.:** Measures Treatment preferences, EOL treatment received, Receipt of care consistent with preferences. **2. O.:** Measures Quality of life and distress. Survival.	Patients who reported having discussed their wishes for **EOL care** with a physician (39%, 125 of 322 patients) were more likely to receive care that was consistent with their preferences, both in the full sample (odds ratio [OR] _ 2.26; P = 0.0001) and among patients who were aware they were terminally ill (OR = 3.94; P = 0.0005). Among patients who received no life-extending measures, physical distress was lower (mean score, 3.1 v 4.1; P = 0.03) among patients for whom such care was consistent with preferences.		2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Stein, A J Clin Oncol 2013 [137]	RCT/	120/16 (primary outcome)/58 (secondary outcome)	diagnosis of **metastatic cancer**, no further curative treatment, estimated life expectancy of 3 to 12 months, awareness of prognosis, and English literacy.	Pamphlet and Discussion pamphlet and discussion with a psychologist (R.A.S.). The pamphlet was called "Living with Advanced Cancer" and contained five sections: "Communicating with the health care team," "Anticancer treatments," "Symptom management," "Psychological care," and "Planning for the future." The pamphlet was developed according to the CREDIBLE (Competently, Recently Updated, Evidence, Devoid of Conflicts of Interest, Balanced Presentation of Options, Efficacious) criteria19 for patient decision aids. During the development phase, it was reviewed by patients, oncologists, and allied health professionals. The discussion was based on a shared decision-making model. The aim was to encourage patients to consider their preferences and values toward the end of life. The discussion was semistructured with four	**1.0.**The primary outcomes were the place of death (in hospital or not), whether a patient had a DNR order, and the number of days between the earliest DNR order documentation and death. **2.0.** Depression and anxiety. The Hospital Anxiety and Depression Scale (HADS)21 assesses anxiety and depression. There is good evidence for its reliability and validity in oncology.22 Cronbach _ in this sample was 0.77 for anxiety and 0.80 for depression. Caregiver burden. The Caregivers Reaction Assessment (CRA)23 provides a measure of caregiver burden. It has five subscales: caregiver's selfesteem, family support, finances, disruption to schedule, and health. There is good evidence that the CRA has good validity and reliability in patients with metastatic cancer.23 The Cronbach _ in this sample was 0.82. Process measures: knowledge. The knowledge questionnaire was adapted from Kerridge et al.24 Patients indicate which, from a list of 10 procedures, are involved during CPR and estimate the success rates of CPR in	intention-to-treat analyses, neither remained significant (P = 0.06).In per-protocol analyses, DNR orders were placed earlier for patients who received the intervention (median, 27 v 12.5 days; 95% CI, 1.1 to 5.9; P = 0.03) and they were more likely to avoid a hospital death (19% v 50% (95% CI, 11% to 50%; P = 0.004). Differences between the groups over time were evident for estimates of cardiopulmonary rehabilitation (CPR) success rates (P _ .01) but not knowledge of CPR (P _ .2). There was no evidence that the intervention resulted in more anxious or depressive symptoms. Caregivers experienced less burden in terms of disruption to schedule if the patient received the intervention (P _ .05)		1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
				themes: (1) communicating with the doctor and family; (2) symptoms and their adverse effects; (3) psychological and palliative care; and (4) end-of life decision making and planning. Questions about end-of-life decision making included: "Have you been able to talk to people in your life and settle unfinished business?" "Have you thought about how you would like to say goodbye?" "Have you been able to talk about your wishes in the event that you become more unwell?" "Have you thought about decisions like whether you would choose to be resuscitated	different situations.			
Wright, JAMA 2008 [138]	prospective, longitudinal cohort study	n=332	▪ Patients with diagnosis of **advanced cancer** from 7 different outpatient sites in the USA ▪ age at least 20 years ▪ presence of an informal care-giver ▪ clinic staff and interviewer as-	In the baseline interview, patients were asked: "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?" Responses were coded as 1 for yes and 2 for no.	**1.O:** Aggressive medical care (eg, ventilation, resuscitation) and hospice in the final week of life. **2.O:** patients' mental health and caregivers' bereavement adjustment Mental health measures included the Structured Clinical Interview for DSM-IV , the Endi-	One hundred twenty-three of 332 (37.0%) patients reported having end-of-life discussions before baseline. Such discussions were not associated with higher rates of major depressive disorder (8.3% vs 5.8%; adjusted odds ratio [OR], 1.33; 95% confidence interval [CI], 0.54-3.32), or more worry (mean McGill score, 6.5	The findings are constrained by the limited information available on the end-of-life discussions. There is no information who initiated the conversation, when it happened, or what was said. the study does not include interviews with physicians or audiotaped	2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			sessment that patient had adequate stamina to complete interview Of the 917 eligible patients, 638 patients (69.6%) consented and enrolled in the larger study. Of the 279 patients who refused participation, 120 were not interested, 69 cited other reasons, and 37 patients' caregivers refused participation. For the analysis, the sample was restricted to the 332 patients who died to examine the medical care that patients received in the final week of life. The deceased cohort did not differ significantly by cancer type, psychological distress, or rates of psychiatric disorders.		cott Scale, and McGill Quality of Life psychological subscale. Patients' functional status and comorbid medical conditions were measured with the Karnofsky score and the Charlson Comorbidity Index, respectively. Quality of life was assessed with the McGill Quality of Life Index's physical health, symptom, and social support subscales.	vs 7.0; P=.19). After propensity-score weighted adjustment, **end-of-life discussions** were associated with lower rates of **ventilation** (1.6% vs 11.0%; adjusted OR, 0.26; 95% CI, 0.08-0.83), **resuscitation** (0.8% vs 6.7%; adjusted OR, 0.16; 95% CI, 0.03-0.80), ICU admission (4.1% vs 12.4%; adjusted OR, 0.35; 95% CI, 0.14-0.90), and earlier **hospice enrolment** (65.6% vs 44.5%; adjusted OR, 1.65; 95% CI, 1.04-2.63). In adjusted analyses, more **aggressive medical care** was associated with worse patient quality of life (6.4 vs 4.6; F=3.61, P=.01) and higher risk of major depressive disorder in bereaved caregivers (adjusted OR, 3.37; 95% CI, 1.12-10.13), whereas longer hospice stays were associated with better patient quality of life (mean score, 5.6 vs 6.9; F=3.70, P=.01). Better patient quality of life was associated with better **caregiver quality** of life at follow-up (=.20; P=.001).	conversations. Since there is no independent validation, the accuracy of patients' reported rates of discussions remains unknown. In addition, the study sample had disproportionately high rates of ethnic minority patients who were highly symptomatic and had poor performance statuses.	

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Zhang, Arch Intern Med 2009 [139]	prospective, longitudinal cohort study	n=603	▪ Patients with diagnosis of **advanced cancer** from 7 different outpatient sites in the USA ▪ age at least 20 years ▪ presence of an informal caregiver ▪ clinic staff and interviewer assessment that patient had adequate stamina to complete interview Of 875 patients approached for inclusion in the study and confirmed to be eligible, 627 patients (71.6%) were enrolled. The most common reasons for nonparticipation among 248 patients (28.3%) included "not interested" (n=118) and "caregiver refuses" (n=37). Compared with participants, nonparticipants were less likely to be of Hispanic race/ethnicity (5.5%	In the baseline interview, patients were asked: "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?" Responses were coded as 1 for yes and 2 for no.	**1.O:** Aggressive medical care (eg, ventilation, resuscitation) and hospice in the final week of life. **2.O** Secondary outcomes included patients' mental health and caregivers' bereavement adjustment Mental health measures included the Structured Clinical Interview for DSM-IV , the Endicott Scale, and McGill Quality of Life psychological subscale. Patients' functional status and comorbid medical conditions were measured with the Karnofsky score and the Charlson Comorbidity Index, respectively. Quality of life was assessed with the McGill Quality of Life Index's physical health, symptom, and social support subscales.	Patients with advanced cancer who reported having **EOL conversations** with physicians had significantly lower health care costs in their final week of life. Higher costs were associated with worse quality of death in the final week of life (Pearson production moment correlation partial =−0.17, P=.006).	The findings are constrained by the limited information available on the end-of-life discussions. There is no information who initiated the conversation, when it happened, or what was said. the study does not include interviews with physicians or audiotaped conversations. Since there is no independent validation, the accuracy of patients' reported rates of discussions remains unknown. In addition, the study sample had disproportionately high rates of ethnic minority patients who were highly symptomatic and had poor performance statuses.	2-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			vs 13.5%, P=.001). Otherwise, nonparticipants did not differ significantly from participants in age, sex, education status, or white, black, or Asian race/ethnicity. Of 627 patients enrolled, 603 (96.2%) responded to the question regarding prior EOL discussions that forms the basis for this study. Nonrespondents to the question did not differ significantly from respondents in cancer type, health status, recruitment site, or sociodemographic characteristics.					

8. Sterbephase

8.1. Das Sterben diagnostizieren

8.1.1.1. 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	Comments	Level of Evidence SIGN
Eychmüller, E J Pall Care 2013 [140]	SR; To provide an overview of evidence supporting timely recognition of entry into the dying phase of cancer patients	12 trials: • 11 Cohort Studies • 1 Cross-sectional • 10 prospective and 2 retrospective 2 explicitly conducted with the goal of identifying the dying phase through signs	younger patients (18 to 55 years) to predominantly geriatric patients studies: 7 cancer 2 non-cancer 3 mixed population	SR focused on two research questions (see col. outomes)	1.O: ▪ signs, symptoms, tools or other technologies that can identify (diagnose) the last days of life of a cancer patient 2.O: ▪ evidence that these signs, symptoms, tools or technologies can accurately identify (diagnose) that a cancer patient has entered the dying phase	1.O: Two out of the three studies found the following phenomena in common: ▪ fatigue (80 – 93% of patients) ▪ Dyspnoea (45 – 50%) ▪ Pain (> 40%) ▪ Confusion, reduced consciousness (25 – 50%) Other phenomena, described only in a single study are: ▪ Being totally bedbound ▪ Anxiety/dysphoria ▪ Feeling alone ▪ Nausea 2.0: one study addressed last days of life in cancer patients and integrated "significant factors for predicting dying" into a computer-assisted predicting model	▪ most important finding: the literature did not provide a basis for a systematic review: There is a need of more and better-designed studies to address the lack of data in the field. ▪ the seven-day limit may have excluded important phenomena, if dying is considered as a process that begins more than a week before death ▪ A bias might have been caused by the clinical background of all researchers, who favour the use of the Liverpool care pathway in the last days of life ▪ Based on this systematic literature search there is low evidence for both	1-

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 SIGN
							phenomena of approaching death in the literature, and for tools to diagnose the imminence of death, within a few days.	
Kehl, Am J Hosp Palliat Med 2012 [141]	SR; no MA to identify commonly occurring signs of impending death and symptoms that occur in the last 2 weeks of life and to estimate their overall prevalence.	12 peer-reviewed empirical studies which reported the prevalence of physical signs and symptoms in the last 2 weeks of life in multiple settings	Patients (n=2146) with physical signs or symptoms in the last 2 weeks of life	physical signs or symptoms in the last 2 weeks of life	1.O.: ▪ signs and symptoms ▪ documented and the overall prevalence of those signs and ▪ symptoms across the studies, both weighted and unweighted.	• In total, 62 signs and symptoms in the final 2 weeks of life were identified across all the studies. Of the 43 unique symptoms, symptoms with the highest prevalence are • dyspnea (56.7%) • pain (52.4%) • respiratory secretions/death rattle (51.4%) • confusion (50.1%)	4 signs and symptoms, agitation/ delirium/ restlessness (20.8%, range 5.8%-51%), anxiety (10.8 %, range 1.4%-45.5%), depression (8.3%, range 0.9%-38.6%), and sleep problems/insomnia (9.0%, range 3.2%-28.4%) were somewhat lower than previously reported ranges.	1-
Kennedy, BMJ, Support Pall Care 2014 [142]	SR; MA not possible	23 articles included: Findings on "characteristics of dying": 1 SR 7 retrospective chart reviews 2 qualitative studies 1 structured interview 1 quantitative study	Population due to findings "Characteristics of dying": Review included all research relevant to death, terminal care and bereavement; 2 studies focused on older people in nursing home setting; 4 studies focused on cancer; one study focused on stroke; 3 studies on cancer and	No interventions.	Findings on "characteristics of dying". Findings on "treatment orientation".	'characteristics of dying' involve dying trajectories that incorporate physical, social, spiritual and psychological decline towards death 'treatment orientation' where decision making related to diagnosing dying may remain focused towards biomedical interventions rather than systematic planning for end-of-life care.	SR about "diagnosing dying" but no interventions. Including retrospective and qualitative studies.	3

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 SIGN
		1 literature review 1 survey Findings on "treatment orientation": 2 case reviews 1 exploratory interview study 2 mixed methods 1 quantitative study 1retrospective cross-sectional survey of bereaved relatives 1 qualitative study 1 action research study 1 case review	long-term conditions, one on ALS and one on medical decision making at the end of life.			The findings of this review support the explicit recognition of 'uncertainty in diagnosing dying' and the need to work with and within this concept. Clinical decision making needs to allow for recovery where that potential exists, but equally there is the need to avoid futile interventions.		

8.1.1.2. Primärstudien

Study	Study Aim	Study type	Delphi group size	Rounds	Nature of Subjects	Scoring	Consens criteria	Response	Results	Level of evidence SIGN
Domeisen Benedetti, Support Care Cancer 2013	to provide expert consensus on phenomena for identifica-	Delphi Study; part of the OP-CARE9	252 in the first cycle; Second Cycle: N=36	3 cycles: Each cycle included: (1) development of the questionnaire, (2)	health care professionals, volunteers,	▪ Cycle 1: generated 194 different phenomena, perceptions and observations. ▪ Cycle 2_ these phenomena were checked for their specific ability to diagnose the last hours/days of life. Fifty-eight phenomena achieved more	▪ Cycle 1: The definitive decision on inclusion of phenomena was made by the synthesis group. ▪ Cycle 2: output 2 included phenomena that received more than 80 % expert consensus on agree-	▪ Cycle 1: response rate 100 % ▪ Cycle 2: response	The seven categories included after the third cycle were: "breathing", "consciousness/cognition", "emotional state", "general deterioration", "intake of fluid,	4

Study	Study Aim	Study type	Delphi group size	Rounds	Nature of Subjects	Scoring	Consens criteria	Response	Results	Level of evidence SIGN
	tion and prediction of the last hours or days of a patient's life	project	question-naires; Third cycle: 78 palliative care experts	distribution of the Delphi questionnaire and (3) review and synthesis of findings	public	than 80 % expert consensus and were grouped into nine categories. ▪ Cycle 3: these 58 phenomena were ranked by a group of palliative care experts (78 professionals, including physicians, nurses, psycho-social-spiritual support.)	ment ▪ Cycle 3 incorporated phenomena and respective categories that achieved more than 50 % expert consensus on "high relevance" in predicting that someone would die within the next few hours/days	rate 72%	food other", "non-observations/ expressed opinions/other" and "skin". The categories "mo-bility" and "communication" were discarded after this proc-ess.	

8.2. Therapie der häufigsten Symptome

8.2.1. Delir

8.2.1.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Boettger, Aust N Z J Psychiatry 2011, I [143]	Case control study	n=42	▪ Mean age 69.6, SD +/-11.9 yrs, range: 36-85) ▪ patients referred for delirium management to a Cancer Center Psychiatry Service ▪ Cancer diagnoses and etiologies were diverse in both groups and did not significantly differ (as by authors)	**Oral Aripiprazole (AR) vs. Oral Haloperidol (HP)** ▪ Cases: AR, Mean start dose: 15.2mg ▪ Controls: OZ, start dose: 4.9mg ▪ initial diagnosis of delirium (T1) and repeated at 2 - 3 days (T2) and 4 - 7 days (T3)	1.O: ▪ **Treatment efficacy** as measured by improvement in MDAS and delirium resolution (MDAS cutoff score <=10) 2.O: ▪ **Physical performance ability** measured by Karnofsky Performance Status Scale (KPS) ▪ **Side effects** as measured by Udvalg Kliniske Undersogelser Side Effect Rating Scale (UKU) scores	**Treatment efficacy:** ▪ No sign. difference between groups. ▪ MDAS scores declined from 18.1 at baseline to 10.8 at T2 and 8.3 at T3 in AR patients (Friedman: chi square 31.87, df = 2, p < 0.001); from 19.9 at baseline to 9.9 at T2 and 6.8 at T3 (Friedman: chi square 38.3, df = 2, p < 0.001) in HP patients. ▪ No sign. difference in the MDAS scores of AR and HP patients at T2 and T3. ▪ Resolution of delirium symptoms did not differ significantly between AR and HP patients at either subsequent observation point. **Physical performance ability** ▪ KPS scores improved from 28.1 at baseline to 35.2 at T2 and 41.0 at T3 in AR pa-	▪ No breakdown of cancer diagnoses and distribution ▪ population not clearly defined as "palliative"	2+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
						tients (Friedman: chi square 20.11, df = 2, p < 0.001) and 22.4 at baseline to 28.1 at T2 and 31.9 at T3 in HP patients (Friedman: chi square 20.83, df = 2, p < 0.001). ▪ No sign. differences between AR and HP at T2 and T3. ▪ greater frequency of EPS. **Side effects** ▪ No extrapyramidal side effects (EPS) were encountered in AR group. ▪ 19% of patients experiencing EPS in HP group. ▪ HP group: Parkinsonism in 19.0% and dystonia in 9%. ▪ HP group: hyperactive delirium with significantly higher doses of HP showed		
Breitbart, Am J Psychiatry 1996, I [144]	RCT, double-blind, parallel	n=30	▪ AIDS patients with treatment for AIDS-related medical problems ▪ Patients met DSM-III-R criteria for delirium and scored 13 or greater on the Delirium Rating Scale ▪ 77% men/23%	**Haloperidol (HP) vs. Chlorpromazine (CP) vs. Lorazepam (LO)** ▪ Three drug study utilizing dose level protocol. Assessment done every hour until stabilization. **Mean drug doses during the first 24 hours:** ▪ 1. Arm: HP 2.8 mg (SD =	1.O: ▪ **Efficacy of treatment** of delirium measured by ▪ Delirium Rating Scale [DRS] (0-32; >13=delirious) 2.O: ▪ **Cognitive status** as measured by MMSE: ▪ score of 28-30 = 0 (no deficits) on item 6 of the Delirium Rating Scale	▪ significant decrease in DRS scores from baseline to day 2 for the HP/CP groups but not for LO group ▪ HP: F=27.S0, df=1, 27, p<O.OO1 ▪ CP: F=37.02, df=1, 27, p<0.001 ▪ LO: F=0.23, df=1, 27, p<O.63). ▪ Cognitive functioning	▪ Placebo control group not included on ethical grounds ▪ All six patients who received LO developed treatment-limiting side-effects, including oversedation, disinhibition, ataxia, and increased confusion, leading to refusal to	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			women ▪ Mean age 39.2 yrs (SD=8.8, range=23-56) ▪ Mean Karnofsky Performance Status score n=30 was 52.3 (SD=21.3, range=10-90).	2.4) ▪ 2. Arm: CP 50 mg (SD = 23.1) ▪ 3. Arm: LO 3 mg (SD = 3.6) ▪ **Average maintenance doses:** ▪ HP 1.4 mg (SD = 1.2) ▪ CP 36 mg (SD = 18.4) ▪ LO 4.6 mg (SD = 4.7). ▪ LO arm stopped early due to adverse effects.	▪ score of 25-28 = 1 (very mild deficits) ▪ score of 20-24 = 2 (focal deficits) ▪ score of 15-19 = 3 (significant deficits) ▪ score of 15 or less = 4 (severe deficits) ▪ **Extrapyramidal Symptoms** as measured by ▪ Extrapyramidal Symptom Rating Scale (questionnaire, rating instrument and global impression rating)	(MMSE) improved significantly from baseline to day 2 for patients receiving CP, and trend toward a significant improvement for patients receiving HP. ▪ **DRS Scores:** ▪ ALL (n 30) baseline: 20.1 (SD 3.5, range 14 to 28) Day 2: 13.3 (SD 6.1, range 3 to 26) End of therapy: 12.8 (SD 6.4, range 3 to 26) ▪ HP (n 11) Baseline: 13.45 (SD 6.95) Day 2: 17.27 (SD 8.87) End of Therapy: 17.18 (SD 12.12) ▪ LO (n 6) Baseline: 15.17 (SD 5.31) Day 2: 12.67 (SD 10.23) End of Therapy: 11.5 (SD 8.69)	take the drug or requiring discontinuation.	
Breitbart, Am J Psychiatry 1996, II [144]						▪ **Extrapyramidal Symptom Rating Scale Scores:** ▪ CP (n 13) Baseline: 7.42 (SD 8.08) End of Therapy: 5.08 (SD 4.48) ▪ HP (n 11) Baseline: 7.0 (SD 6.8) End of Therapy: 5.54 (SD		

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
						6.76) ▪ LO (n 6) Baseline: 7.6 (SD 10.11) End of Therapy: 12.2 (SD 8.93)		
Breitbart, Psychosomatics 2002, I [145]	Cohort study, uncontrolled	n=82 dropout = 3	▪ Mean KPS score 37 (SD 9.9; range 20-85) ▪ Mean age = 60.6 yrs (SD 17.3; range 19-89) ▪ Cancer diagnoses: lung (21%, n = 17); gastrointestinal (18%, n =14); lymphoma (11%, n =9); breast (10%, n = 8); head and neck (6%, n = 5), ovarian (2%, n = 2), brain (2%, n = 2), sarcoma (2%, n = 2), and other cancers (25%, n = 20) ▪ stage of cancer: metastatic (80%, n = 63), localized (15%, n = 12), terminal (5%, n = 4) ▪ history of brain metastases (20%, n = 16) or a history of dementia (17%, n	**Olanzapine administered orally either as a single bedtime does or twice a day** Mean starting dose at baseline: 3.0 mg (SD 0.14; range, 2.5-10); Mean dose at T2: 4.6 mg (SD 0.27; range, 2.5-15); Mean dose at T3 or end of study: 6.3 mg (SD, 0.52; range, 2.5-20)	1.O: ▪ **Treatment efficacy** as measured by improvement in MDAS and delirium resolution (MDAS cutoff score <=10) 2.O: ▪ **Physical performance ability** measured by Karnofsky Performance Status Scale (KPS) ▪ **Side effects** (clinician documentation and rating)	▪ **Treatment efficacy:** Significant treatment effect Wilks A = 0.345, F (1, 78) = 53.1, P = 0.001. Mean baseline MDAS score (19.85, SD 3.79), significantly lower (improved) at T2 (12.73, 6.87), t (78) = 16.9, P = 0.001, even lower (more improved) at T3 (10.78, SD 7.31), t (78) = 17.6, P = 0.001. Mean MDAS scores between T2 and T3 were also significantly improved, t (78) = 8.6, P = 0.001 ▪ **delirium resolution:** 45% (n = 36) of patients at T2 and 76% (n = 57) of patients at T3 Age was the strongest predictor of treatment response (odds ratio [OR] = 171.5) (with patients age >70 yrs demonstrating sig-	▪ No control group/placebo ▪ No randomization ▪ no blinding ▪ population not clearly defined as "palliative" ▪ Only study so far which identifies predictors of treatment efficacy	2+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			= 14)			nificantly poorer response than patients age <70 yrs) subtype of delirium significant predictor of delirium treatment outcome (OR = 11.3): hyperactive delirium responding better to olanzapine treatment than hypoactive delirium		
Breitbart, Psychosomatics 2002, II [145]			▪ etiologies for delirium: opioid analgesics (63%, n = 50), corticosteroids (34%, n = 27), systemic infection (33%, n = 26), hypoxia (25%, n = 20), CNS spread of cancer (14%, n = 11), dehydration (11%, n = 9), other medications (2.5%, n = 2), and other (unclassified) etiologies (17%, n = 13) ▪ delirium mild 17% (n = 13) (MDAS <=15); moderate 61% (n = 48) (MDAS 15-22); severe 23% (n = 18) (MDAS >=			▪ **Side effects** most common: sedation (30% of patients reporting at T2 and T3) 1.3% (n=2 pts) olanzapine appeared to worsen delirium and was discontinued 3.8% of pts experienced other side effects of mild severity (rash, pruritus, nausea, stomach ache, dizziness, light headedness, blurring of vision, and headache)	▪	

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
			23) ▪ subtype of delirium: 46% (n = 36) ''hypoactive'' delirium; 54% (n = 43) ''hyperactive'' delirium (based on MDAS item 9) ▪					
Lin, J Intern Med Taiwan 2008 [146]	RCT, unblinded, parallel	n=30	▪ Patients from one hospice and palliative care center with advanced cancer who had been referred to the consultation-liaison psychiatry service ▪ Included pts had to meet DSM-IV criteria for delirium ▪ Mean age 61.13, SD +/-16.5 yrs, range: 23-87) ▪ Equal gender distribution	**Oral Haloperidol (HP) vs. Oral Olanzapin (OZ)** ▪ 1. Arm: HP, start dose: 5mg ▪ 2. Arm: OZ, start dose: 5mg Clinical Re-Evaluation after 24hours (T1), 48hours (T2) and 1 week (T3). Dosage titration by psychiatric specialist if no sign of improvement. Maximum dosage given for HP/OZ: 15mg orally.	1.O: **Treatment efficacy** as measured by improvement in MDAS-c (0-33) and CGI (Global Impression-Severity) scale 2.O: **Side effect** assessed by clinical records review and assessor observation	▪ **Treatment efficacy:** ▪ OZ: statistical sign. improvement on DRS-c at T3 (p=0.042); and CGI-S at T1 (p=0.040) ▪ HP: statistical sign. improvement on DRS-c at T1(p=0.008); T2 (p0.044); T3(p=0.043) and CGI-S at T1(p=0.012) ▪ No sign. differences between groups across time for DRS-c (T1, p=0.123; T2, p=0.240; T3, p=0.414) and for CGI-S (T1, p=0.581; T2, p=1.000; T3, p=0.618) ▪ **Side effects** No reported side-effects	▪ No blinding ▪ Selection bias (initial inclusion screening done by the same physician who titrated the antipsychotic drugs) ▪ No information on drop-outs ▪ No information on allocation concealment ▪ No information on cancer types ▪ No mention of side-effects	1-

8.2.2. Rasselatmung

8.2.2.1. 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	Comments	Level of Evidence SIGN
Pastrana, Schmerz 2012	SR (no MA)	6 studies (n=593): ▪ 4 RCTs (of which 1 phase-III RCT und 1 phase II pilot-RCT) ▪ 2 cohort studies	Adult patients with **cancer**	2 cohorts, 1 RCT: ▪ Scopolamine vs. glycopyrrolat 3 RCTs: ▪ Scopolamine vs. Placebo ▪ Scopolmaine vs. Butylscopolamine vs. atropine ▪ Scopolamine vs. octreotid	Effect on noisy breathing (not nearly specified) Adverse events	▪ Few studies ▪ Contradictory results in the cohort studies (once glycopyrrolat, once scopolamine more effective) ▪ Sign. results in only 1 RCT (glycopyrrolat more effective than scopolamine) ▪ Anticholinergic drugs seem to be more effective if applicated early	Insufficient evidence to support the administration of one or the other anticholinergic agent	1- (no adequate description of outcomes used; no information about the quality assessment of the studies)
Wee, Cochrane Rev 2008 [147]	SR (MA not possible)	4 studies (n=398): ▪ 4 RCTs	▪ **Cancer** patients in **terminal phase** (last 48-72 hours of life)	Hyoscine hydrobromide (HH) by any route: 4 RCTs: HH vs. other drugs ▪ 1st Arm: HH (4) ▪ 2nd Arm: normal Saline (placebo control) (1); Octreotide (1); Glycopyrronium (1); Atropine (1) ▪ 3rd Arm: Hyoscine butylbromide (1) 1 RCT with cross-over design	1.O: ▪ Any subjective or objective **change in noise intensity**. ▪ Complete **cessation of noise**. 2.O: ▪ The number of different types of interventions (including varying doses and types of anticholinergics) needed to achieve a reduction in noise intensity. ▪ The number of times an intervention has to be repeated to achieve or maintain a reduction in noise intensity.	▪ **Change in noise intensity:** no evidence that any intervention, be it pharmacological or non-pharmacological, was superior to placebo in the treatment of noisy breathing ▪ Higher efficacy (stronger decrease in death rattle) in the group of patients given glycopyrronium (n=6) compared to hyoscine hydrobromide (n=7), but not consistent over studies. ▪ No difference in effectiveness (37-42%) between sco-	▪ No Metaanalysis: insufficient data ▪ Small sample size for 3 out of 4 RCTs (n=13-31) ▪ Observer bias is a relevant limitation to the interpretation of results (scorer = involved palliative care nurse) ▪ blinding-bias through open label design in 1 RCT with the highest number of included participants, n=333	1+

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 SIGN
				▪ 1st Arm: HH followed by Octreotide ▪ 2nd Arm: Octreotide followed by HH	▪ Measurable documented **reduction in relatives' distress** relating to the noisy breathing (death rattle) and **reduction in patients' distress** relating to the noisy breathing (death rattle).	polamine (hyoscine hydro-bromide), atropine and hyoscine butylbromide after 1h ▪ **Patients' distress**: Statisti-cally significant reduction of pain in one placebo control study. No statistically sig-nificant reduction in rest-lessness. ▪ No data to support a **reduc-tion in relatives' distress**.		

8.2.3. Mundtrockenheit

8.2.3.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Davies, Palliat Med 2000 [148]	RCT, unblinded, cross-over	n=41 completed phase 1=30 completed phase 2=26 total dropout=15	▪ Inpatient and outpatient adults with malignant disease from two specialist palliative care institutions ▪ Estimated prognosis of more than 2 weeks ▪ Mean age = 66 yrs (range 32-87) ▪ 28% own teeth ▪ 37% partial set of dentures ▪ 26% full set of dentures ▪ 7% partial set of dentures but did not use them ▪ 2% no teeth/no dentures ▪ 84% receiving concomitant xerostomic drugs (M=2; range 0-4)	**Saliva stimulant versus saliva substitute** 1. Arm: **AS**+2 days washout+**CG** 2. Arm: **CG**+2 days washout+**AS** **AS**: 5 days artificial saliva spray (mucin-based Saliva Orthana) 4x/day (before meals+bedtime), **CG**: 5 days chewing gum (low-tack, sugar-free Freedent) 4x/day for 10mins (before meals+bedtime)	1.O: ▪ **Reduction of xerostomia** assessed by VAS mouth dryness (1 to 100) and xerostomia questionnaire 2.O: ▪ **patient preference** ▪ **adverse effects** ▪ both assessed by questionnaire	No statistically significant difference between treatments for **reduction of xerostomia** (Fisher's exact test; P = 0.33) ▪ 89-90% of participants felt that either intervention had helped their xerostomia ▪ 74% from AS group wanted to continue with it ▪ 86% from CG group wanted to continue with it ▪ No statistically significant difference for **patient preference** ▪ No statistically significant difference for **adverse effects**	▪ Population/patient characteristics not clearly depicted/no primary diagnoses ▪ Some risk of bias through missing blinding (not possible) ▪ potential selection bias (insufficient information about allocation concealment)	1-

8.3. Flüssigkeit/Ernährung

8.3.1.1. 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	Comments	Level of Evidence SIGN
Raijmakers, Ann Oncol 22: 1478-1486, 2011 [149]	SR / no MA Aim to address the following research questions: (i) how and how often are artifical nutrition (AN) and artificial hydration (AH) provided in the last week of life of cancer patients; (ii) what is the effect of AN and AH during the last week of life on symptoms, comfort and quality of life of cancer patients and (iii) does providing or not providing AN and AH hasten death or pro-	15 studies/design: • 9 prospective observational • 1 prospective observational • 5 retrospective observational Fokus of studies: • 4 papers on frequencies of AN in the last week of life • 7 papers on frequencies of AH in the last week of life • 4 papers on withholing/ withdrawing AN/AH in the last week of life • 1 paper about the effect of AN/AH on quality of life • 5 paper about the effect of AH on symptoms	**Cancer** patients (mean age > 54) in their last 7 days, or last 48 hours of life	• Artifical nutrition (AN) in the last week of life • Artifical hydration (AH) in the last week of life	• effects on symptoms and comfort/quality of life • effect on survival	• AH/AN are a substantial part of medical in the last week of cancer patients esp. in hospital up to 50-88%. • No significant relationship between AH and general comfort or quality of life measures. • ANH is not associated with any changes of comfort in 75% (n= 145 whole population) two days before death. • Effect of AH in the last week of life on quality of life: no significant effects in controlling several symptoms except for chronic nausea. No differences in pleural drainage or ascites in the latter studies. Two found more ascites in the AH group • Using AN/AH is not a significant determinant of survival.	Providing AN or AH to cancer patients who are in the last week of life is a frequent practice. The effects on comfort, symptoms and length of survival seem limited. Further	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 SIGN
	longe life?	• 1 paper about effect of AN/AH on survival						

8.3.1.2. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Bruera, JCO 2013 [150]	RCT, double blind hydration (n=63) placebo (n=66) (9 drop outs)	n = 129	▪ diagnosis of advanced cancer (i. e. locally recurrent or metastatic disease) ▪ > 18 years ▪ life expectancy >= 1 week	▪ parenteral hydration (normal saline 1l per day) ▪ placebo=PL (normal saline 100 ml per day) daily over 4 hours	1.O: • change in the sum of four dehydration symptoms (fatigue, myoclonus, sedation and hallucinations, 0 = best and 40 = worst possible) between day 4 and baseline 2.O: • Edmonton Symptom Assessment Scale (ESAS) • Memorial Delirium Assessment Scale (MDAS) • Nursing Delirium Screening Scale (NuDESC) • Unified Myoclonus Rating Scale (UMRS), • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) • Dehydration Assessment Scale • creatinine • urea • overall survival	• no significant differences between hydration and placebo for change in the sum of four dehydration symptoms(-3.3 v -2.8, P = 0.77) by day four • hydration at 1l per day did not improve symptoms, quality of life or survival compared with placebo. • ESAS (all non-significant) • MDAS (1 v 3.5, P = .084) • NuDESC (0 v 0, P = .13) • UMRS (0 v 0, P = .54) by day 4. • Results for day 7, including FACIT-F, were similar. • Overall survival did not differ between the two groups (median, 21 v 15 days, P = .83).	Intention-to-treat analysis was conducted to examine the change by day 4±2 and day 7±2 between groups ▪ Hydration at 1l per day did not improve symptoms, QoL, or survival compared with PL ▪ pts with severe dehydration were excluded because they tend to be acutely ill, making it difficult to obtain informed consent ▪ The power to detect statistical significance given the found values and sample sizes was 4.8%	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Nakajima, J Pall Med 2013 [151]	Descriptive; to explore the influence of hydration volume on the signs during the last three weeks of life in terminally ill cancer patients.	N=75	▪ Terminally ill cancer patients with abdominal incurable malignancies ▪ life expectancy estimated by a physician to be <3 months	▪ Hydration group (n=32) receiving 1000ml or more of artificial hydration per day, on and three wekks before death. ▪ Nonhydation group (n=43)	▪ dehydration and fluid retention signs in the last three weeks of life.	▪ percentage of patients with deterioration in dehydration score in the final three weeks was significantly higher in nonhydration group than in the hydration group (35% versus 13%, p = 0.027), while the percentages of patients whose symptom scores for edema, ascites, and bronchial secretion increased were significantly higher in the hydration group than in the nonhydration group (57% versus 33%, p = 0.040; 34% versus 14%, p = 0.037; 41% versus 19%, p = 0.036, respectively). ▪ There were no significant differences in the degree of pleural effusion or the prevalence of hyperactive delirium between these groups.	▪ The potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention signs.	3

9. Versorgungsstrukturen

9.1. Interventionen für Angehörige

9.1.1. Erste Suche

9.1.1.1. 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	Comments	Level of Evidence SIGN
Candy, Cochrane 2011 [152]	SR, MA	11 RCTs	Caregivers (CG)= Adults caring informally for a relative/friend with a disease in the terminal phase (n=1836) Most patients with cancer	Interventions providing support to the caregiver + usual care: Directly (9): support in the caring role (7), family life review (1), grief therapy (1) Indirectly via patients care (2)	1.O Psychological health (symptoms of depression/anxiety/ hopelessness, QoL, coping, ...) Physical health Service delivery Adverse outcomes 2.O Acceptability to CG CG's knowledge of patient's disease Perceived impact of care by patient CG bereavement Cost	Interventions supporting directly the CG: Low quality evidence that they significantly reduce psychological **distress** in the short term (8 trials: standardised mean difference (SMD) -0.15; 95% confidence interval (CI) -0.28 to -0.02). Low quality evidence that they in the short term may marginally improve **coping** skills and **quality of life**, but neither results were statistically significant (7 trials: SMD -0.05; 95% CI -0.24 to 0.14; 6 trials: SMD 0.08; 95% CI -0.11 to 0.26, respectively) 1 trial assessed **physical** outcome: no difference Indirect interventions:	Risk of bias unclear, as all trials underreported methods	1++

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 SIGN
						May reduce psychological **distress**, but not sign. No study assessing health service use or adverse outcomes.		
Harding, Pall Med 2003 [153]	SR (no MA due to heterogeneity)	22 studies (no design limit) Evaluation studies: 2 RCTs 2 prospective single-group 1 retrospective single-group 1 feed-back	CG = Adults providing informal care (including family members) for noninstitutionalized cancer and palliative care patients.	Interventions for CG specifically for CG (6) home nursing care (4) respite services (3) social network and activity enhancements (2) problem solving and education (3) group work (10)	Description or evaluation of intervention	The current evidence contributes more to understanding feasibility and acceptability than to effectiveness.	Small sample size Lack of evaluation design Use of untested measures	1- (English only, few databases, few RCTs)
Harding, Pall Med 2012 (update) [154]	SR (no MA due to heterogeneity)	33 studies (included are RCT, prospective, concurrent mixed-methods, qualitative, qualitative post-intervention data, before-after study): 10 (quasi-) experimental design	CG = Adults providing informal care (including family members) for noninstitutionalized cancer and palliative care patients. (24 studies with CG of cancer patients)	Interventions for CG: specifically for CG (17) 1 to 1 psychological models (8) Psychological interventions for patient/carer dyads (4) Palliative care/hospice (6) Information and training (3) respite (1) group interventions (10) physical (1)	Description or evaluation intervention	Group interventions (2 RCTs, 2 quasi-experimental studies): 2/4 sign. benefit 1 to 1 psych. interventions (3 (quasi) experimental studies): 2/3 positive effect; sign. treatment effect with respect to positive rewards of caring Pt/carer dyads (3 RCTs: 3/3 sign. effect (improved QoL, reduced stress…). No sign. effect on coping, hopelessness and uncertainty. PC/hospice (1 RCT out of 6 studies): n.s. on carer outcomes post-death	(Quasi-)experimental studies: moderate to good quality	1+ (English only, few databases)

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 SIGN
Lorenz, Ann Int Med 2008 [155]	SR (no MA due to heterogeneity). Comprehensive review to EoL care, with one chapter analysing caregiver burden.	8 SR 19 intervention studies (RCT, CCT)	EoL patients	Interventions for serving informal caregivers, including family, when patients are approaching EoL	CG outcomes (Burden relieve, Satisfaction)	Weak to moderate evidence suggests that caregiver interventions, especially when comprehensive and individually targeted, can relieve **burden**, although effect sizes are generally small. Moderate evidence suggests that palliative care interventions improve **satisfaction**. Because existing research focuses on dementia, evidence is moderate in dementia and weak in cancer. No evidence addressed caregivers in heart failure.	Most literature related to dementia, less to cancer	1++

9.1.2. Update

9.1.2.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Fegg, Psycho-Oncology 2013 [156]	RCT; parallel-group design (with equal randomisation 1:1)	n=160 (81 EBT; 79 control group) Dropouts=35	▪ 54.5+-13.2 years old; 69.9% were female ▪ Study participants were **informal caregivers (CG) of patients** receiving inpatient palliative care (**life expectancy≤6 months** according to the patient's physician) and post-death; minimum 21 years of age ▪ Patients' diagnosis: Cancer (82,7%), neurological disease (12,8%), other (4,5%) ▪ Only one relativeper patient took part with the next of kin being selected. ▪ Exclusion criteria: severe mental illness	Intervention: EBT (**Existential behavioural** therapy) treatment to **support** informal CG of palliative patients: Six group sessions totalling 22 h ▪ First meeting: Becoming acquainted and introduction into mindfulness. ▪ Second meeting: Death, bereavement and mindfulness ▪ Third meeting: Activating resources and finding meaning. ▪ Fourth meeting: Self-care and stress management. ▪ Fifth meeting: Personal values for (re-)orientation. ▪ Sixth meeting: Saying goodbye and new steps. Control group did not receive any special comparative treatment. However, they were free to use the spectrum of available support at the insti-	**1.O: mental stress and QOL** Severity of symptoms (Brief **Symptom Inventory** - BSI, sub-scales of; ▪ somatisation, ▪ depression ▪ anxiety Raw scores were transformed into gender-specific T-values (T≥60 is clinically striking). **QOL** ▪ Satisfaction with Life Scale (SWLS) assessing its cognitive aspects ▪ WHOQOL-BREF comprising QOL domains ▪ NRS on individual, overall QOL experience (QOL-NRS, range 0-10, 'How do you rate your quality of life at the moment?') (Data were collected at baseline, pre-treatment, post-treatment and follow-ups after 3 and 12 months.) **2.O:** ▪ changes in affect (Positive and Negative Affect Scale	▪ no sign. differences between both groups at baseline ▪ The multivariate model was significant for the pre-/postcomparison (p = 0.005) and the pre-/12-month comparison (p = 0.05) but not for the pre-/3-month comparison. ▪ Medium to large effects on **anxiety** (regression coefficient B (95% CI) =4,59 (1,34 to 7,85)) and **QOL** (SWLS: B (95% CI) =-0,39 (-0,69 to -0,10), WHOQOL-BREF: B (95% CI) =-3,68 (-6.34 to -1.02), QOL-NRS: B (95% CI) = -1,17 (-1,78 to -0,56)) were found at post-treatment; ▪ medium effects on **depression** (regression coefficient B (95% CI) =3,27 (0,15 to 6,39) and **QOL** (QOL-NRS: B (95% CI) =-1.18 (-1.90 to -0.45) emerged in the 12-month follow-up. ▪ **No adverse effects** of the	▪ Intention to treat analysis ▪ Powered study: 44 CG had to participate in the EBT to achieve a power of 0.8 at p = 0.05 ▪ Participants selected from different institutions, improving generalizability. ▪ A possible limitation is the heterogeneity of the sample. Participating informal CG had varying relationships to the patient, with partners being predominant. ▪ No reported calculation of overall effect of multivariate model ▪ No information about blinding	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
				tution or elsewhere	(PANAS) ▪ helpfulness ratings of specific intervention (0-4)	intervention were observed. ▪ 2.O: EBT participants had significantly less **negative affect** (regression coefficient B (95% CI) =0.29 (0.10 to 0.49) and a tendency towards more positive affect in the pre-/post-comparison. At 3-month follow-up, differences in the same direction but not significant (p=0.05). At 12-month follow-up, significantly less negative (regression coefficient B (95% CI) = 0.33 (0.11 to 0.54) and by trend more positive affect in EBT compared with controls.		
Hudson, Psycho-Oncology 2013 [157]	Phase III randomised parallel group (three-arm RCT)	n=298 (control: n=148; Intervention 1: n=57; Intervention 2: n=93) Drop-outs: 21 at Time 1; 137 at Time 2 (46%): patient no longer met the inclusion criteria (n = 22); patient died before time 2 (n	▪ primary **family caregivers** (CG) of patients with advanced **cancer** receiving home-based palliative care ▪ age > 18 years ▪ able to understand english ▪ exclusion criteria: confronted with significant emotional distress pre-	Intervention: The psycho-educational focus included tailored **information** and **resources** (primary written resource was a family CG guidebook) given to family CG to promote psychological well-being by preparing them for their role. Each CG was allocated a Family CG Support Nurse (FCSN) who assisted the local palliative care service. The intervention was delivered over 4 weeks and comprised	**1.O**: ▪ psychological distress (General Health Questionnaire (GHQ) **2.O**: Caregiving experiences prior to the patient's death ▪ caregiver competence scale (CCS) (4 questions scored 0-3) ▪ preparedness for caregiving scale (8 questions scored 0-4, 'total' score is the mean of valid responses)	▪ **Psychological well-being**: not sign. improved in intervention groups ▪ No significant reduction in **unmet needs** or improvements in positive aspects of caregiving amongst the intervention group were identified. ▪ significant improvement in **preparedness** and **competence** for Intervention 2: The difference in change between the two-visit	▪ Computer-gernerated randomization ▪ Research assistants blinded to group allocation to minimize response bias ▪ Selection bias: many relatives declines to participate ▪ Younger participants produced the higher scores (normally older people do) ▪ Attrition bias, with the	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
		= 9); or the carer withdrew from the study (n = 17). In the majority of circumstances (n = 80), the reason(s) were not identified.	cluding them from completing questionnaires. CG of patients with a nonmalignant diagnosis or a poor functional status (using a standardised measure) indicating likelihood of imminent death were excluded in order to reduce attrition.	the following: ▪ Step 1: preparing CG for the intervention. ▪ Step 2: assessing caregiver needs and preparing a care plan. ▪ Step 3: re-assessing needs and evaluating the care plan ▪ Step 4: assisting the family caregiver to prepare for their relative's death and to prepare for bereavement. Arm 1: 1visit and 3 phone calls Arm 2: 2 visits and 2 phone calls Arm 3: control (standard care)	▪ family inventory of need—part/scale B (20 questions scored 0-4) ▪ rewards for caregiving scale (10 questions scored 0-4) Measurement at: ▪ baseline (T1) ▪ 1 week post-intervention (T2) ▪ 8 weeks post-patient death (T3)	group and the control group was significant (p = 0.035). The effect sizes for the one-visit group, the two-visit group and the two groups combined relative to the control group were 0.14, 0.29 and 0.22 indicating small effects. The change between Times 1 and 2 in the two intervention groups combined versus the control group was significant (p = 0.03), as was the change in the two-visit group versus the control group (p = 0.04). The effect sizes of the changes in the one visit, two visits and both groups combined relative to the control group were 0.27, 0.33 and 0.30, respectively, indicating small effects.	biggest net loss between T1 and T2 ▪ no guarantee that implementation of the intervention was carried out routinely as intended (performance bias?)	
McLean, Psycho-Oncology 2011 [158]	Two-group RCT; couples randomly assigned to EFT or standard care (CTL) in a 1:1 ratio by statistician, no	N= 42 couples 22 couples for intervention group and 20 for control group Dropout=2 couples (one patient died of cancer	▪ Participants were recruited from Princess Margaret Hospital (PMH), Canada's largest comprehensive cancer center ▪ Metastatic **cancer**	Emotionally Focused Therapy (EFT), modified for the advanced cancer population versus standard care. Aim of the couple-based intervention: **support couples** facing death	**1.O:** ▪ marital functioning (Revied Dyadic Adjustment Scale = RDAS (standardized and validated 14-item self-report that is widely used to evaluate both individual and dyadic adjustments in dis-	▪ **Marital functioning**: At T1, sign. difference on the RDAS (p<0.0001), with the EFT having higher mean scores (better marital functioning) than the CTL group. Effect size for this difference: Cohen's d =	▪ Power analysis ▪ relatively small sample size. ▪ results limited to couples who were referred by their clinical team and met the RDAS cut-off for marital distress.	1+

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
	blinding of participants to their assignments. Study personal blinded to condition assignment	and one had progressive disease and was to ill to continue [both from CTL group])	▪ English speaking ▪ >= 18 years old ▪ In a romantic partnership of >= 1 year, endorsing marital distress (Revised Dyadic Adjustment Scale (RDAS) <= 47) in minimally one partner ▪ Not currently in couple therapy ▪ Patient Karnofsky Performance Status score of >= 60	EFT: ▪ 8-session EFT intervention adapted for use with couples where one partner has advanced metastatic cancer. ▪ 1-hour weekly couple sessions (M = 7.7, SD = 0.94, median = 8, mode = 8) were delivered by one EFT-trained psychologist (LM) and occurred over a 2-3-month period. Sessions took place at PMH clinical offices or at alternative locations in four of the INT group couples, including home (n = 2) and/or inpatient hospital room (n = 2), to accommodate needs and to maximize adherence. Control (CTL): ▪ standard care provided by the POPC department.	tressed relationships.)) **2.O:** ▪ Psychological Symptoms (Beck Depression Inventory-II (BDI-II) and Beck Hopelessness Scale (BHS)) ▪ CG's Burden (two subscales [Demand/Difficulty] of the Caregiver Burden Scale were used to access objective and subjective caregiving burden (CG only) ▪ Patient's perspective of CG empathic behaviour (10-item Relationship-Focused Coping Scale [RFCS]) Measures at ▪ baseline (T0) (before random assignment), ▪ immediately post-intervention (T1), 3-month post-intervention follow-up (T2).	1.00, which is in the large range. In both groups, patients showed a marginally higher mean score for marital functioning compared with CG [EFT: M= 56.3, standard deviation (SD) = 4.6 vs M= 54.3, SD = 4.5; CTL group: M= 43.4, SD = 10.3 vs M= 42.4, SD = 6.8, respectively]. At T2, results were maintained. ▪ **Psychological Symptoms**: no difference in BHS between groups. ▪ **Caregiver Burden and Patient-perceived empathic behaviour:** sign. higher mean scores at T1 for EFT patients, indicating higher patient perceived caregiver empathic behaviour (p = 0.02). There was no sign. difference (p = 0.09) between groups in CG subjective difficulty in caregiving for their ill spouses.		
Northouse, Psycho-oncology 2013 [159]	RCT, blinded (three-arm RCT)	N= 484 dyads (completed baseline assessment) N= 343 dyads completed Time 2 assessments	▪ advanced breast, colorectal, lung or prostate **cancer** (i.e., Stage III or IV), and were within a six-month window	Intervention: The original FOCUS Program was a home-based, dyadic intervention that provided **information and support** to cancer patients and CG to-	**1.O:** Quality of Life: General Functional Assessment of Cancer Therapy (FACT-G), assessing 4 domains: social, emotional, functional, physical well-being	▪ Significant Group by Time interactions showed there was improvement in dyads' ▪ **Coping** (F= 2.15, p = 0.013)**, self-efficacy** (F = 2.84, p = 0.024), and so-	▪ stratified randomization process ▪ sample size calculation > powered study ▪ only patients' risk status (i.e., high versus low)	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
		(70.9% retention); and N= 302 dyads completed Time 3 assessments (62.4% retention)	of having a new advanced cancer diagnosis, progression of their advanced cancer, or change of treatment for it. ▪ life expectancy ≥ 6 months, ▪ age 21 or older, ▪ living within 75 miles of participating cancer centers, and ▪ having a family caregiver willing to participate. ▪ CG were eligible if they were age 18 or older and identified by patients as their primary caregiver	gether, as the **unit of care**. We revised the original five-session program into Brief and Extensive versions. ▪ Arm 1: Brief FOCUS: 3 contacts (two 90-minute home visits and one 30-minute phone session). ▪ Arm 2: Extensive FOCUS: 6 contacts (four 90-minute home visits and two 30-minute phone sessions). ▪ Control: All study participants received usual care at their cancer center, consisting of the medical treatment of cancer and symptom management. Psychosocial support was provided occasionally, but was not delivered routinely to patients or CG.	**2.O:** Appraisals ▪ Appraisal of Illness and Caregiving (Appraisal of Illness Scale (patients) and Appraisal of Caregiving Scale (CG)) ▪ Uncertainty (brief version of the Mishel Uncertainty in Illness Scale) ▪ Hopelessness (Beck Hopelessness Scale) Resources: ▪ Coping: strategies (Brief Cope) and Healthy behaviors (researcher-developed scale to assess activities that were encouraged in the intervention) ▪ Interpersonal relationship: Dyadic support (modified family support subscale of the Social Support Questionnaire) and Communication (Lewis Mutuality and Sensitivity Scale) ▪ Self-efficacy (Lewis Cancer Self-efficacy Scale) Measures at: ▪ Hopelessness (Beck Hopelessness Scale) ▪ baseline (T1),	cial QOL (F = 4.28, p = 0.002), and in CG' emotional **QOL** (p<.05). ▪ Effects varied by intervention dose. ▪ Most effects were found at 3 months only. ▪ Risk for distress accounted for very few moderation effects. > Both brief and extensive programs had positive outcomes for patient-caregiver dyads, but few sustained effects. Patient-caregiver dyads benefit when viewed as the 'unit of care'.	were used as a stratification variable ▪ high drop out rate ▪ risk for distress measured instead of current distress	

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
					▪ 3 months after baseline (T2) ▪ 6 months after baseline (T3)			
Yun, J Clin Oncol 2011 [160]	RCT (two arms)	N=444	▪ primary family CG older than age 18 years ▪ patients of potentially eligible CG: were diagnosed with **terminal cancer,** older than age 18 years ▪ Korean speaking/reading	▪ DA (decision aid): professionally developed 20-minute take-home DVD and a companion 43-page workbook entitled *Patients Want to Know the Truth.* The material provided a protocol for informing patients about their terminal status and was aimed at **improving both communication** between patients and their families and **satisfaction with the decision-making process**. ▪ Control group received a Korean version of a US National Cancer Institute DVD of similar length on pain management entitled Controlling Cancer Pain: A Video for Patients and Families16 and 29-page educational book on pain control by the Korean Ministry of Health and Welfare entitled *Cancer Pain Can Be Controlled.*	**1.O**: ▪ CG decision to discuss a terminal prognosis with the patient **2.O:** ▪ Decision Conflict Scale (DCS): Total score, Support Score, Uncertainty score, Conflict Score, Informed Score, Value Clarity Score ▪ Hospital Anxiety and Depression Scale (HADS), ▪ Caregiver Quality of Life Index-Cancer (CQOL-C) Each completed by the caregiver at 0, 1, 3, and 6 months. ▪ Decision Regret Scale (DRS) at 1, 3, and 6 months (to measure decisional conflict and assessed conflict using personal perceptions of the level of uncertainty (uncertainty subscale), how well-informed patients felt about their choice (informed subscale), the clarity of personal values (values clarity subscale), and the support	▪ no difference in changes in the **decision to discuss terminal prognosis** between the two groups. ▪ **Conflict** (P=.003), **uncertainty** (P=.019), and **value clarity** (P=.007) subscale scores and total **DCS** score (P=.008) improved from baseline to 1 month significantly more in the DA than in the control arm. ▪ Over 6 months, the significant between-group differences continued for the **conflict** (P=.031), **uncertainty** (P=.014), and **value clarity** (P=.039) subscale scores and **total DCS** score (P .040).	▪ 80% power with min n=444 ▪ Descriptive statistics for estimation ▪ Analysis of covariances ▪ Analysis of baseline → no differences ▪ focus only on a family caregiver's prognostic disclosure to a terminally ill patient with cancer ▪ all study participants were Korean ▪ the outcomes we assessed were not typical end-of-life trial outcomes ▪ many CG were lost to follow-up	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
					they had in the decision-making process (support subscale)			

9.2. Interventionen zur Trauerbegleitung

9.2.1. Erste Suche

9.2.1.1. Systematic Reviews

Study (Author, journal, year)	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 SIGN
Gauthier, Clin Psychol-Sci Pr 2012 [161]	SR / no MA	8 studies (10 articles) : 2 RCTs 1 CBA (controlled before-after) 2 BA (before-after) 1 RCS (retrospective controlled study) 3 descriptive 1 quali	Bereaved spouses of patients with cancer. Most middle aged and women. (n=1366)	Bereavement interventions (4 studies, 6 articles): 3 BSG=bereave. support group (thereof: 1 RCT, 1 CBA) 1 relaxation training (BA) Prebereavement interventions (specialized EoL care) (4 studies, thereof 1 RCT)	Bereavement outcomes Prebereavement well-being (as factor for adjustement to bereavement)	Specialized EoL care: may impact favourably on bereavement **well-being** (1 RCT: distress sign. lower over 1 year, then no difference) Bereavement interventions (above all: BSG): little to no effect on psychological **well-being** (i.a. 1 RCT, 1 CBA) Studies did not include assessments of spouses' psychological well-being in the prebereavement period > effect of prebereavement well-being on spousal adjustement not measurable.	Body of evidence (1-): 2 RCTs without sample size calculation); 1 study fairly strong evidence; others weak evidence Few studies Because of no sample size calculation, it is difficult to determine whether the finding that bereavement interventions have little to no effect on psychological well-being is because of the effects of the interventions themselves or a result of insufficient power to detect an effect.	1++
Wittouck, Clin Psychol Rev 2011 [162]	SR / MA	14 RCTs: 9 RCTs: prevention of complicated grief (CG) 5 RCTs: treatment of (CG)	Adults who had lost a loved one through violent or non-violent death (n=1655; n=910 in the intervention group): 41 y mean age 70% female 4% of cancer survivors	Specific grief intervention to treat or prevent CG, initiated after the loss and non-psychopharmacological vs. control condition or an a-specific intervention (i.e. used for a variety of disorders) Number of sessions differed	(C)G: pre- and post- or follow-up-measurements, with a quantitative standardized questionnaire	Prevention: inconsistent support for the effectiveness of interventions. The meta-analysis of the interventions aiming at prevention of CG yielded a pooled standardized mean difference (SMD) of −0.03 (95% CI: −0.18−0.11; Z=0.47; p=0.64)	Body of evidence: unclear quality often due to lack of reporting methodology > intermediate to high level of evidence (1+) At the moment CG is not recognized as an official (DSM-) diagnosis. Neverthe-less, CG-symptoms have	1++ Only 2 data-bases searched Grey literature not

Study (Author, journal, year)	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 SIGN
				substantially among studies, with one to twelve sessions in preventive interventions and ten to sixteen sessions in treatment interventions.		at post-test and of 0.13 (95% CI: −0.08−0.33; Z=1.21; p=0.23) at follow-up. With regard to the outcome variable, studies were homogeneous in the post-test analysis (p=0.12) and heterogeneous in the follow-up analysis (p=0.07). Treatment: efficacious in the short- and long-term. Contrary to preventive interventions, the positive effect of treatment interventions increases significantly over time. Positive results reported for interventions employing cognitive-behavioral techniques. The meta-analysis of the interventions aiming at treatment of CG yielded a pooled SMD of −0.53 (95% CI: −1.00−−0.07; Z=2.23; p=0.03) at post-test and of −1.38 (95% CI: −2.08 to −0.68; Z=3.87; p=0.0001) at follow-up. With respect to the outcome variable, studies were heterogeneous (p=0.009) in the post-test analysis and homogeneous (p=0.87) in the follow-up analysis.	shown to be different from other symptoms and disorders, such as normal grief reactions, mood disorders and anxiety disorders Only 4% cancer survivors. Wide range of death causes (violent and non-violent)	searched, but MA

Study (Author, journal, year)	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 SIGN
						The difference among the pooled SMD's of preventive and treatment interventions at post-test was significant in favor of treatment interventions (χ^2=3.71; df=1; p=0.05). Heterogeneity among the studies was found (p=0.0006)		

9.2.2. Update

9.2.2.1. Primärstudien

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
Guldin, Family Practice 2012 [163]	RCT	N= 402 (drop-outs=107)	▪ >17 years ▪ registration with a Danish general practitioners (GP) and informed consent ▪ exclusion criteria: poor language (danish) skills or cognitive impairment	Information pamphlets were sent by mail after completion of the baseline questionnaire to GPs and patients. Pilot-tested pamphlets featured updated information on complicated grief (CG) symptoms, the dual-process model of adaptive coping and risk factors for the development of CG. GPs received information: results of the patient's baseline risk assessment based on the depression level 8 weeks post-loss; how to assess CG and simple suggestions; how to support the patient to ask about which reactions to grief the patient was experiencing and relate the reactions to the dual-process model of adaptive coping. Patients were encouraged to contact their GP if they showed signs of depression or CG or worried about their bereavement reaction. Questionnaires were mailed to the bereaved par-	1.O: ▪ bereaved relatives' score on the Beck's Depression Inventory II (BDI-II) and the Inventory of Complicated Grief-Revised (ICG-R) ▪ GP's clinical assessment of the relative's grief reaction ▪ relative's number of contacts with general practice ▪ Clinical grief assessment by the GP	▪ Larger improvements in **ICG-R** scores were found in the intervention group than in the control group. ▪ The sensitivity of the GP's ▪ assessment in the intervention group was 42.9% (95% CI: 21.8-66.0) and the specificity 73.8% (95% CI: 61.5-84.0); the positive predictive value was 34.6% (95% CI: 17.2-55.7) and the negative predictive value 80% (95% CI: 67.7-89.2). In the control group, sensitivity was 40% (95% CI: 19.1-63.9), specificity 83.7% (95% CI: 70.3-92.7), the positive predictive value 50% (95% CI: 24.7-75.3) and the negative predictive value 77.4% (95% CI: 63.8-87.7). ▪ In the intervention group, patients exhibiting **CG** symptoms were more likely to receive supportive care and to be referred to mental health practitioners,	▪ Computerized Randomization ▪ Sample size calculation > power good, but could have been higher ▪ Risk of systematic bias because of the recruitment procedure ▪ Men were underrepresented ▪ No Danish validation of ICG-R available	1-

Study (Author, journal, year)	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	Results	Comment	Level of Evidence SIGN
				ticipants 2, 6 and 13 month post-loss. If the bereaved participant was still in the study 13 months after the loss, a clinical assessment questionnaire was sent to the GP. Assessment battery consisted of BDI-II and ICG-R and sociodemographic questions.		whereas GP's in the control group more often prescribed psychotropic drugs for patients with symptoms of CG. ▪ The GP's ability **to identify CG** at 13 months did not seem to be better in the intervention group than in the control group. ▪ **Contact frequencies** with GPs were generally higher in the control group both before and after the loss. Compared with the control group, IRs were lower among bereaved relatives in the intervention group after the loss [IR = 4.68 (95% CI = 3.90- 5.62)/5.08 (95% CI = 4.33-5.96); IRR = 0.92 (95% CI = 0.72-1.17); P = 0.50]. ▪ Changes in sum score between the two groups did not reach statistical significance.		

9.3. SPV-Interventionen

9.3.1. Systematic Reviews

9.3.1.1. Systematic Reviews, die verschiedene Strukturen einschließen („SPV allgemein“)

Study (Author, journal, year)	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 SIGN
García-Pérez, Pall Med 2009 [164]	SR / no MA	6 SR 3 studies (4 publications) on effectiveness (1 RCT, 1 prospective cohort, 1 cross-sectional) 1 cost analysis	Terminally ill patients	Comparison of at least two different **specialised palliative care** programmes and/or their cost-effectiveness	• control of pain and other symptoms, • psychological symptoms, • health-related QoL, • well-being, • functional state, • satisfaction, • place • of death, • number of patients cared, • number of home visits, • number of days at hospital	All systematic reviews drew the conclusion that specialised palliative care is more effective than conventional care. The methodological limitations of the original studies and the heterogeneity of programmes did not allow to draw conclusions about whether a specific model of specialised palliative care is more or less effective or cost-effective than other.	SR of low quality studies RCT and cohort: good quality	1++
Higginson, Cancer J 2010 [165]	SR (meta-synthesis, but no MA)	8 RCTs, 32 observational or quasi-experimental studies	Patients with advanced cancer and their caregivers	**Specialist palliative care interventions** in the home, hospital or designated inpatient settings for patients with cancer	Pain, symptoms, QOL, use of hospital services, anxiety	Home, hospital, and inpatient specialist palliative care significantly improved patient outcomes in the domains of **pain** and **symptom control, anxiety**, and reduced hospital **admissions**. The results suggest that specialist palliative care should be part of care for cancer patients.	We were able to identify and include a wide range of robust literature, focusing more closely on specialist palliative care services and overcoming some of the weaknesses of earlier reviews that included specialist and nonspecialist services. Our review was still weakened by the wide range of outcomes measured.	1++

Study (Author, journal, year)	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 SIGN
Higginson, J Pain Symptom Manag 2003 [166]	SR / MA where possible	44 studies, mostly lower quality (retrospective, observational, cross-sectional studies). Anecdotal and case reports were excluded.	Patients with a progressive life threatening illness and their caregivers	Comparison of palliative care or hospice team (**PCHCT**) and conventional care. (Teams: home care (22), hospital-based (9), combined home/ hospital care (4), inpatient units (3), and integrated teams (6))	Pain and symptom control QOL and quality of death Patient and family satisfaction/ morbidity pre- and post-bereavement	Meta-regression (26 studies) found slight positive effect (0.1) of PCHCTs on **patient outcomes**, independent of team make-up, patient diagnosis, country, or study design. Meta-analysis (19 studies) demonstrated small benefit on patients' **pain** (odds ratio [OR]: 0.38, 95% confidence interval [CI]: 0.23-0.64), other **symptoms** (OR: 0.51, CI: 0.30-0.88), and a non-significant trend towards benefits for **satisfaction**, and therapeutic interventions. Data regarding **home deaths** were equivocal. Metasynthesis (all studies) found wide variations	First study to quantitatively demonstrate benefit from PCHCTs	1++
Thomas, Can J Aging 2006 [167]	SR / no MA	23 RCTs	Patients terminally ill, near death or dying	PC interventions	Effect of PC provided by community teams: QoL, manag. of symptoms Satisfaction with care Duration of care and place of death Effect of specific interventions (ACP, held records, etc...) Costs of PC compared to conventional care	Effect of PC provided by community teams: **QoL** and manag. of **symptoms**: Some improvement in 6 studies, no improvement in 3 studies **Satisfaction** with care: higher satisfaction of patient (1 study) and caregivers (2); no increase in 2 studies **Duration** of care and **place of death**: 4 studies schowed no increase of death at home. 1	RCTs mostly published in the late 1990s or early 2000s and mostly single-site studies with small sample sizes. 10 included a power computation.	1+ (poor description of inclusion criteria, and interventions)

Study (Author, journal, year)	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 SIGN
						RCT found it, as well as shorter survival		
Zimmermann, JAMA 2008 [168]	SR (no MA due to the hetero-geneity of the studies	22 RCTs	Patients receiving specialized PC (the majority were cancer patients) USA, UK, Canada, Norway	**Specialized palliative care** (11 in a home setting, 5 at outpa-tient clinics, 1 in a nursing home, 1 in a combined inpa-tient and home setting, 4 assessed patients)	QOL Satisfaction with care Economic cost	The existing evidence does not conclusively support specialised palliative care programmes. **QoL** (13 RCTs): 9 RCTs showed no significant differ-ence between specialist pallia-tive care and control treat-ments, one favoured the control and three favoured the intervention. **Symptoms** (14 RCTs): 1 RCT demonstrated significant benefits for the palliative care group for any measured single symptom, while three found a benefit of palliative care for reduction of symptom distress but not symptom severity. Patient **satisfaction** with care (10 RCTs): 1 RCT showed a significant difference between groups in favour of the inter-vention at 30 days but not at 60 days.	Most of the studies were small and likely to be un-derpowered.	1++

9.3.1.2. Palliativstation und Konsildienst

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 SIGN
Evans, Cochrane Review (Protocole - Ref. folgt)	SR (MA if possible)	RCTs, CCTs, CBA (controlled before and after studies), ITS (interrupted time series analyses with min 3 data collection points before and 3 after the intervention)	Adults patients with advanced malignant or non-malignant disease and their caregivers, receiving support from SPCT	Effectiveness of SPCTs (specialist palliative care teams) in **in-patients** settings Control: general hospital/oncology services or usual care	1.O: pain control 2.O: symptom control, depression, satisfaction with care, time spent in hospital, caregiver burden/strain/distress, professionals' adherence to guidelines, prescribing rationale			

9.3.1.3. Home-care Programme

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 SIGN
Candy, Int J Nurs Stud 2011 [169]	SR (MA not possible because of heterogeneity)	18 comparative studies (thereof 2 RCT) 4 qualitative studies	Patients and their family in the final phases of a terminal disease	Specialist hospice care provided at **home**, in **nursing home** or in **hospice** Control (quantitative studies): usual generalist healthcare	▪ symptom management ▪ pain assessment and other aspects of patient care ▪ satisfaction with services family carer well-being such as care burden and bereavement/grief ▪ health service use ▪ costs ▪ place of death	Hospice care at home reduced general health care use and increased family and patient satisfaction with care	Mostly limited quality of quantitative evidence Low concordance of identified studies in comparison with other SysRev (e.g. Gomes 2013), what raises the question of the accuracy of the search strategy and selection process	1-

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 SIGN
Gomes, Cochrane Review 2013 [170]	SR and MA	16 RCTs (6 high quality), 4 CCTs, 2 CBA (controlled before and after studies), 1 ITS (interrupted time series analyses)	Adults patients and/or caregivers in receipt of a home palliative care service (n=37.561, 4.042 caregivers; majority cancer)	**Home** specialist palliative care service Control: usual care Reinforced home specialist PC Control: home specialist PC	1.O: death at home 2.O: time spent at home, satisfaction with care, pain/ other symptoms control, physical function, QOL, caregiver outcomes, costs and cost-effectiveness measures	Sign. increase of **death at home** (Meta-analysis for dying at home (7 trials, 3 of high quality): odds ratio (OR) 2.21, 95% CI 1.31 to 3.71; P value = 0.003) Small but sign. reduction of **symptom burden** for patients No effect on caregiver grief **Cost-effectiveness**: inconclusive results		1++
Hall, Cochrane Review 2011 [171]	SR (MA not possible because of heterogeneity)	2 RCTs and 1 controlled before-and-after study included	Residents of care homes for older people (care home = institutional settings where care is provided 24 hours a day, 7 days a week)	Palliative care service delivery interventions for **residents of care homes for older people** (referrals to external palliative care services and/or palliative care training for care home staff)	We extracted all measures reported as outcomes for individual residents, including process of care (e.g. completion of advance care plans and place of death)	One study reported higher **satisfaction** with care and the other found lower observed **discomfort** in residents with end-stage dementia (mean [SD] 218.10 [142.10] and 368.88 [168.30] respectively, t = 3.80, difference in means = 150.78, 95% CI for difference = 77.38 to 230.18. Two studies reported group differences on some **process measures**. Both reported higher referral to hospice services in their intervention group (,enrolment to hospice within 30 days of the intervention (21/107 [20%] compared with 1/98 [1%]) and (24/346 [6.8%] compared with 2/113 [2%]), one found fewer hospital admissions and days	Few studies identified, and all were in the USA	1++

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 SIGN
						in hospital in the intervention group , (0.28 [range 0-4] compared with 0.49 [range 0.4] and 1.2 [range 0-18] compared with 3.0 [range 0-29] respectively) the other found an increase in do-not-resuscitate orders and documented advance care plan discussions . (225/346 [65%] compared with 50/113 [44%], chi-square = 15.32, absolute risk reduction = 20.78%, 95% CI = 10.34% to 31.23%, NNT = 5, 95% CI for NNT = 3.2 to 9.7)		
Shepperd, Cochrane Review 2011 [172]	SR and MA Aim: To determine if providing home-based end of life care reduces the likelihood of dying in hospital and what effect this has on patients' symptoms, QoL, health service costs and caregivers	4 RCT (thereof 1 cluster-RCT)	Adults at the end of life and requiring terminal care	End of life care at home Control: inpatient hospital or hospice care	▪ Place of death ▪ Patients' preferred place of death ▪ Control of symptoms (pain, breathlessness, nausea and vomiting, constipation, terminal agitation) ▪ Delay in care (medical, nursing or domiciliary care) from ▪ point of referral to intervention (end of life home care/hospice at home or inpatient care) ▪ Family or care giver stress ▪ Family or care giver unable to continue caring	**Place of death**: patients receiving home-care sign. more likely to die at home (RR 1,33, 95% CI 1,14 to 1,55, P=0,0002 - 2 trials, n=652) No sign. differences for **functional status**, **psychological well-being**, **cognitive status** **Hospital admission**: high variation between studies, no conclusion possible Some evidence of increased **satisfaction** with home-based end of life care	Moderate quality of included studies, due to lack of power by high mortality, unblinded trials and difficulty in measuring symptoms in a way that permits comparability.	1++

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 SIGN
	compared with inpatient hospital or hospice care.				▪ Patient anxiety ▪ Family/care giver anxiety ▪ Unplanned/precipitous admission or discharge	Little evidence of the impact of home-care on **caregivers**		

9.3.1.4. Tageskliniken

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 SIGN
Davies, Support Care Cancer 2005 [173]	SR /no MA	12 studies in 15 publications (any design, only English) : 1 CBA (prospective) 6 observational (no comparision) 5 qualitative	Adults receiving care from specialist palliative day-care services	Specialist day-care services with reported information on service structure, care processes or outcomes	Service structure: • Funding, organization and management of services • Staff skill mix and interventions offered to patients and relatives Care processes: • Referral, allocation of places to patients and discharge • Uptake of interventions by patients and relatives Patient outcomes: • symptom control, • health related quality of life • social and psychological support • patient or relative satisfaction with care	**Service structure**: Most services are nurse-led, but varied in the facilities, staff mix, care models, activities and places they offered. **Process**: Patients attending seemed a selected group of those already receiving palliative care who were mostly white, aged over 60 years and retired, with needs for emotional and social support and pain control. **Patient outcomes**: insufficient studies to provide conclusive evidence of improved symptom control or health related quality of life, but all qualitative studies found evidence for high satis-	Low grade of evidence of most studies	2++ (no RCTs, CCTs)

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 SIGN
						faction in the social, psychological and spiritual domain		
Stevens, Pall Med 2011 [174]	SR /no MA	35 studies in 36 publications (any design, only English): 4 reviews 2 controlled cohort studies Others observational not controlled or qualitative	Population attending PDS (no more description)	PDS (palliative care day services)	Outcomes of PDS utilizing the perceptions of attendees/other stakeholders Outcomes of PDS using validated measures	some quantitative evidence showing that PDS had an impact on attendees' **quality of life** or wellbeing	• less than half of the studies could be fully analysed for quality • Fewer studies utilized validated outcome measures to determine the effect of PDS on attendees' wellbeing • Small sample sizes combined with high attrition rates influenced the significance of some the results.	2- (unclear question and results)

9.3.2. Primärstudien

Im Folgenden werden Interventionsstudien dargestellt, die aus Systematic Reviews zu SPV identifiziert wurden (zur Methodik, siehe Leitlinienreport). Ergänzend zu den eingeschlossenen Primärstudien sind Begleitstudien (weitere Publikation derselben Studie) in hell-grau dargestellt. Obwohl diese Begleitstudien die Einschlusskriterien nicht erfüllen, wurden sie extrahiert mit dem Ziel, ergänzende Informationen zu den Interventionsstudien darzustellen.

SEKTORENÜBERGREIFENDE SPV-STUDIEN (Hiermit werden Studien verstanden, die SPV-Interventionen untersuchen, deren Setting strukturenübergreifend ist. Das sind Interventionen, die mindestens zwei SPV-Versorgungsstrukturen einschließen (Palliativstation, Home-Care-Programme, etc…) und diese in den Ergebnissen nicht unterscheiden.

Study characteristics

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justific
Dunt, Palliative Medicine, 1989 [175]	The cost-effectiveness of the citymission Hospice Porgramme Melbourne	quasiexperimental	to examine costeffectiveness, according to costs and clinical benefit, of hospice care in comparison to standard care.	known histologically confirmed diagnosis of cancer and terminal phase (less than six months)	single center	Australia	2-
Kane, The Lancet, 1984 (part 1) [176]	A randomised controlled trial of hospice care	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-
Kane, JAMA 1985 (part 2) [177]	Hospice Effectiveness in controlling pain	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care on pain	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-
Kane, J Chron Dis, 1986 [178]	The role of hospice in reducing the impact of bereavement	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-
Wales, J, Medical Care, 1983 [179]	UCLA Hospive Evaluation Study	RCT	to establish robust methodology		single center	USA	1-
Zimmermann, Lancet, 2014 [180]	Early palliative care for patients with advanced cancer:a cluster-randomised controlled trial	Cluster-Randomised Controlled Trial	To evaluate if, compared with standard cancer care, early intervention (clinical prognosis of 6–24 months) by a palliative care team would be associated with improved patient quality of life, symptom control, and satisfaction with care, and less difficulty with clinician–patient interactions.	Age > 18 years, stage IV cancer breast or prostate cancer refractory to hormonal therapy: patients with stage III cancer and poor clinical prognosis were included at the discretion of the oncologist); an estimated survival of 6–24 months (assessed by their main oncologist); and ECOG-performance status of 0, 1, or 2 (assessed by their main oncologist).	24 clinics randomized, stratified by clinic size and tumour site (4 lung, 8 gastrointestinal, 4 genitourinary, 6 breast, 2 gyn.). 8 oncologists had clinics in 2 tumour sites (randomised to 2 clusters); 5 oncologists had their 2 clinics randomised within same trial group, 3 to	Canada	1++

Patients' characteristics at baseline / Informal caregivers' (CG) characteristics at baseline

Author, Journal, Year	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	CG: Number of CG / Drop outs	CG: Female / Male (n/n)	CG: Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	CG: Others
Dunt 1989 [175]	n = 120 (65 intervention, 55 control) creating 271 patient and 195 caregiver interviews	intervention: 33/32, control: 26/29	less than 60 interv. 21 and control 16 ; age not otherwise specified	100%	intervention: 1. Lung (n=14), Breast (n=8), colorectum (n=11), Other (n=32); control lung (n=7), Breast (n=9), colorectum (n=6), others (n=33)	Karnofsky Perfromance Status(<40): intervention: n = 25; control: n= 9	intervention/control: usual pain: pain severity(n=4/12), pain duration (n=19/30), pain frequency (n=15/23), worst pain: sevrity (n=18/24), duration (n=25/29), shortnessof breath (n=4/8), insomnia (n=6/9), weakness (n=23/22), bowel complaints (n=10/4), nausea/vomiting (n=3/5), worst symptom (n=37/33), anxiety (n=11/16), depression (n=16/15);; dissatisfaction with casre socre (n=6.9/7.5), QL index (n=3.5/4.0), perceived dependency (n=11/15), pleasure		intervention 61 / control 53	not mentioned	not mentioned	anxiety (n=17/11), depression (n=5/5), fatigue (n=17/9), difficulty in CG role /(n=18/10), dissatisfaction with pateint´s care scor (7.0/7.3)	none
Kane 1984 [176]	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	73% of partiens had FCG; 95% gave consent; 6% withdrew consent	not specified	not specified	not specified	not specified
Kane 1985 [177]	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-93	100%	2. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. terminal phase	not specified	not specified	none	none	not specified	not specified	not specified	not specified
Kane 1986 [178]	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase	not specified	not specified	none	n = 152 (83 inv = hospice, 69 controls = regular care)	72 female in intervention / 56 in control	58 (SD 12) years in interv, 56 (14) in control	anxiety, depression bereavement	20 chronic health problems (list)
Wales 1983 [179]													
Zimmermann 2014 [180]	24 Clusters (clinics) randomised: 12 clinics allocated to control group and 12 clinics allocated to intervention group n=233(control) NO=24 NO=17 n=228 (intervention) NO=12; NO=15	Intervention: 136/92, control: 125/108	Intervention: 61,2 (SD 12,0) Control: 60,2 (SD 11,3)	100%	Cancer: 1. stage IV 2. stage III cancer and poor clinical prognosis were included at the discretion of the oncologist 3. estimated survival 6-24 month	ECOG= 0, 1 or 2 (assessed by the patients main oncologist) Intervention ECOG=0 61 (26,8%) ECOG=1 149 (65,4%) ECOG=2 18 (7,9%) Control: ECOG=0 76 (32,6%) ECOG=1 143 (61,4%) ECOG= 2 14 (6,0%)	Intervention: FACIT-Sp (n=443) 101 (SD 20,3) QUAL-E (n=436) 73 (SD 11,1) ESAS (n=461) 28 (15,5) FAMCARE-P16 (n=449) 64 (9,7) CARES-MIS (n=448) 4·7 (5,6) Control: FACIT-Sp (n=443) 105 (18,8) QUAL-E (n=436) 74 (11,5) ESAS (n=461) 23 (15,7) FAMCARE-P16 (n=449) 68 (9,7) CARES-MIS (n=448) 3·9 (5,4)						As an exploratory substudy, we also collected data from caregivers; these data will be reported separately

Needs assessment / Needs complexity / Intervention characteristics (structure and process quality criteria), part 1

Author, Journal, Year	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation: How	Referral criteria / allocation of place
Dunt 1989 [175]	trained interviewers	monthly after baseline until death	Levels of symptoms and other outcome variables: 5 point VRS (none, mild, moreate, severe, very severe), measures of QL included dissatisfaction with care, the Spitzer QoL index, Tunstall's social contact score, functional dependency: KPS	not specified	not specified	hospice programme (CMP = Citymission Hospice Programme)	conventional care	inpatients and outpatients (home care prgramme)	Medical care was provided jointly by two RMH oncologists (on a part-time basis), both with a special interest in palliative care, as well as other senior sessional medical staff, typically with physician training and also with special interest in palliative care. (Medical establishment - 1.0 full-time equivalents approx.) The remainder of the CHP staff consists of an administrator, secretary, inpatient and home-care nurses, chaplain, coordinator of volunteers, sessional pharmacist, other patientcontact staff and a corps of volunteers.	10-bed inpatient facility, with a 50-bed nursing home for the frail aged. It also provides a home care programme, servicing up to 25 patients with an on-call afterhours system ensuring a 24-hour, seven-day cover.	not specified	The Citymission Hospice Programme was funded as a joint initiative of the WK Kellogg Foundation, the Australian Federal Government and several Australian philanthropic trusts.	not specified	not specified	not specified	clinical judgement and geographical area
Kane 1984 [176]	not specified	regular interviews (7 cohorts = 18 weeks) Methodology outlined separetly in Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	Pain scores (Melzak: presence or absence of pain; intensity); Symptom Scale adapted from California Pain Assessment Profile; depression scale adapted from Nat. Institute of Mental Health's Center for Epidemiologic Studies' scale; anxiety derived from General Well-Being Measure; satisfaction (interpersonal care scale adapted from the Ware scale, physical environment scale based on McCaffree and Harkins); involvement-in-care questions adapted from Nat. Cancer Institute's Hospice	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	2 physicians, 19 nurses, a social worker, a chaplain, and about 30 volunteers for 11 beds; a homecare programme serving about 25 patients at any given time; a consultation service for patients awaiting admission	11 beds, about 25 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis
Kane 1985 [177]	not specified	referal to methodology being published elswhere:Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	tools Pain scores according to Melzak	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds, 30 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis
Kane 1986 [178]	not specified	additional interviews 6weeks, 6, 12 an 18 months after death	anxiety measure: Rand Health Insurance Study; depression: CES-D Scale, sequelae of bereavement: participation in social activities and social contacts, smoking habits and alcohol consumption, use of medication, bed disability days, work loss days, restricted activity days, hospitilisation,	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis
Wales 1983 [179]																
Zimmermann 2014 [180]						palliative care team. The core intervention was consultation and follow-up in the oncology palliative care clinic by a palliative care physician and nurse	standard cancer care	The Princess Margaret Cancer Centre palliative care service consists of an outpatient oncology palliative care clinic, a 12-bed palliative care unit, and an inpatient consultant team. 24 clinics randomized (16 medical oncologists)	a palliative care physician and nurse	outpatient oncology palliative care clinic, a 12-bed palliative care unit, and an inpatient consultant team.	n/a	n/a a cost analysis is underway, and will establish the economic implications of implementing this model.	n/a	n/a	n/a	

Intervention characteristics, part 2

Author, Journal, Year	Description of intervention: Schedule/Frequency	Description of intervention: Content (clinical/non-clinical)	Description of bereavement intervention: Schedule/Frequency	Bereavement: Content	Description of control intervention	Coodination of intervention: Who	Coodination: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration: How	Others
Dunt 1989 [175]	not specified	all the services usually associated with hospice care, including thorough-going symptom relief, emotional support, whole-patient care and, where appropriate, whole-family care either in the patient's home or in a home-like institution	not specified		Standard care: Medical care of these patients was provided variously by oncologists, general specialists or GPs.	not specified	not specified			Thus while symptom control, with the emphasis on emotional or social support, is introduced after entry into the programme, some aspects of the patient's previous care continue, e.g. chemotherapy, hospital inpatient care, general practitioner medical care in the home.	
Kane 1984 [176]	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none
Kane 1985 [177]	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none
Kane 1986 [178]	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none
Wales 1983 [179]											
Zimmermann 2014 [180]		Consultation and follow-up in the oncology palliative care clinic by a palliative care physician and nurse, consisting of: • comprehensive, multidisciplinary assessment of symptoms, psychological distress, social support, and home services, within 1 month of recruitment (60–90 min duration); • routine telephone contact from a palliative care nurse 1 week after the fi rst consultation, and thereafter as needed; • monthly outpatient palliative care follow-up (20–50 min); and • a 24-h on-call service for telephone management of urgent issues. • Ancillary Interventions depending on the status of the patient, included: arrangement of home nursing care services; transfer of care to a home palliative care physician (when the patient's ECOG performance status was 3 or worse, or when requested); and admission to the Princess Margaret Cancer Centre palliative care unit for urgent symptom control or terminal care.			no formal intervention, but palliative care referral was not denied, if requested. Participants in the control group referred to the palliative care service received the same care as patients in the intervention group, but did not have the same standardised monthly follow-up.	Princess Margaret Cancer Centre, a comprehensive cancer centre and part of the University Health Network in Toronto, ON, Canada.	n/a	n/a	cancer care center with palliative care team		

Outcomes / Results / Comments

Author, Journal, Year	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Dunt 1989 [175]	physical and emotional symptoms of patients satisfaction with care/quality of life of the patient emotional difficulties of the caregiver cost	yes	**physical and emotional symptoms of patients:** 1st assessment: control had higher ususal pain duration (OR 2.5: CL 1.0-6.4). No other sign. Results last assessment: control had higher levels of usual pain severity (OR 9.9: CL 2.1-45.8), worst pain severity (OR 5.0: CL 1.0-24.5), shortness of breath (OR 11.9: CL 1.1-131.0), insomnia (OR 5.4: CL 1.1-27.0) **emotional difficulties of the caregiver** last assessment control caregivers had lower levels of difficulty in their roles as CG (OR 0.3: CL 0.1-0.9)o further sign results **Satisfaction**: The nonhospice group had significantly higher dissatisfaction with care scores **Place of death**: % of patients dying at home identical in both groups (22%).	emotional difficulties of the caregiver last assessment control caregivers had lower levels of difficulty in their roles as CG (OR 0.3: CL 0.1-0.9)o further sign results	methodologically flawed: no defintion of intervention, no blinding, relevant differences in baseline results (KPS!) shadowed in results!
Kane 1984 [176]	differences in pain, symptoms, activities of daily living (functional status) and affects satisfaction (patients) satisfaction (carers) utilisation of services (hospitalisation, therapeutic procedures…) costs	yes	differences in….: no sign. effects Satisfaction (pts): sign better (for interpersonal care in 5 cohorts (3): p<0,02; (4):p< 0,001, (5):p< 0,003; (6): p< 0,002; (7): p<0,004 for involvement in care (4):p<0,02; (5):p<0,05; (6):p< 0,003; (7):p<0,003 utiltisation of services: no sign difference costs: no sign difference	satisfaction equally improved	presumably bias due to gender, intervention not clearly defined
Kane 1985 [177]	differences in pain scores, correlation with other symptoms use of analgeics	no	no sign effects	none	intervention not clearly defined; exactly the same study and the same results reportes as in Lancet 1984
Kane 1986 [178]	differences in anxiety scale, CES-D Depression Scale, health scale score and items of the sequelae bereavement list	no	no sign effects between the two groups	no sign effects	intervention not clearly defined; exactly the same study gender bias, methodology remains vague
Wales 1983 [179]					no real figures given, re-test reliablilties based on assumptions (24hours), the gaps in applied methodology of the main studies are not explained by this article despite it being referenced as the relevant
Zimmermann 2014 [180]	**1.O.**:Change score for FACIT-Sp (Functional Assessment of Chronic Illness Therapy—Spiritual Well-Being; [measures Quality of Life]) at 3 months. **2.O:** Change score for FACIT-Sp at 4 months. Change scores for other scales at 3 months and 4 months: Quality of Life at the End of Life [QUAL-E] scale, symptom severity: Edmonton Symptom Assessment System [ESAS], satisfaction with care: FAMCARE-P16, and problems with medical interactions: Cancer Rehabilitation Evaluation System Medical Interaction Subscale [CARES-MIS]	ongoing cost analysis, that will establish the economic implications of implementing this model.	**1.O.:** At 3-months, there was a non-significant difference in change score for **FACIT-Sp** between intervention and control groups (3,56 points [95% CI –0,27 to 7,40], p=0·07) **2.O.: At 4-month** for **FACIT-Sp:** differences in change scores were significant (+2,46 [15,47] vs –3,95 [14,21], p=0,006), QUAL-E (+3,04 [8,33] vs –0,51 [7,62], p=0,003), and ESAS (–1,34 [15,98] vs +3,23 [13,93], p=0,05) **At 3-month:** a significant difference in **QUAL-E** (2,25 [0,01 to 4,49], p=0,05) and **FAMCARE-P16** (3,79 [1,74 to 5,85], p=0,0003), and no difference in **ESAS** (–1,70 [–5·,26 to 1,87], p=0,33) or **CARES-MIS** (–0,66 [–2,25 to 0,94], p=0,40)	n/a	Power: initial sample size estimation showed that 380 patients (190 per group) would provide 80% power at the two-sided 5% level of significance to detect a between group difference in FACIT-Sp of 0•45 SD (medium effect size) by the primary endpoint of 3 months. Intention to treat analysis computer-generated sequence Randomization: computer-generated sequence Selection bias, which is common in cluster-randomised studies because of randomisation of clusters before consent of individuals. Single-blind; patients knew about the treatment, but were not informed about the existence of another group. Results of the single clinics not reported separately. Unclear what "early" means - no definition is reported.

Author, Journal, Year	Study characteristics: Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification
PALLIATIVSATION							
Greer, J Chron Dis 1986 [181]	An alternative in terminal care: Results of the national hospice study	quasi experimental study	1. What is the difference between hospice and conventional care? 2. What is the differential impact of hospice and conventional care on the quality of life of patients and their families? 3. What is the impact of hospice on the health care costs incurred by terminal cancer patients?	cancer patients served in HC or HB hospices or in CC settings; cancer; remote metastasis (except for lung, brain, and pancreatic cancer); presence of a primary care person (PCP), generally a family member in the household (this excluded all nursing home patients); age 21 or older; CC patients only: Karnofsky Performance Status (KPS) of 50 or less	multicentric (40 hospices and 14 conventional oncological care settings; 26 hospices received special Medicare demonstration waivers allowing payment for normally non-covered services))	USA	2+ (some risk of bias because only patients with cancer and with a primary care person were inlcuded, i.a. patients living alone excluded)
Greer, J Chron Dis 1983 [182]	National hospice study analysis plan	Analysis Plan	(1) What is the differential impact of hospice on the QoL of terminal patients and their families, as compared to "conventional" care? (2) What are the differential costs of caring for comparable terminally ill patients? (3) What are the differences in the services? (4) What is the likely impact of Medicare reimbursement on the organizational structure? (5) What are the likely national cost implications of reimbursed hospice care?"			USA	
Morris JN, J Chron Dis, 1986b [183]	The effect of treatment setting and patient characteristics on pain in terminal cancer patients: a report from the National Hospice Study	subanalysis	Relationship between measures of pain. Comparison of prevalence and severity of pain among TCPs served in different settings. Description of shifts in the prevalence and severity of pain as patients approach death	idem	idem	idem	
Morris JN, J Chron Dis, 1986a [184]	Last days: a study of the quality of life of terminally ill cancer patients	secondary analysis	Behavior of a number of Quality of Life measures gathered from two samples of terminal cancer patients over the last weeks of their lives are reported.	idem plus additional study (only results or NHS study participants reported in the following)	idem	USA and Canada (only results or NHS study participants reported in the following)	
Birnbaum HG, AJPH 1984 [185]	What Does Hospice Cost?	subanalysis (cost analyis)	To address the question: What is the cost of hospice? (…) a second question: Does hospice care provided to Medicare beneficiaries cost less than conventional methods of caring for terminally ill cancer patients?	idem	idem	idem	
Mor 1990 [186]	A comparison of hospice vs conventional care in the terminally ill cancer patient	review/narrative report	n.d.	idem	idem	idem	
Powers JS, Public Health Reports 1988 [187]	Terminal Care Preferences: Hospice Placement and Severity of Disease	secondary analysis	National Hospice Study data for 1981-82 were used to predict the location of care for terminal cancer patients.	idem	idem	idem	
Reuben DB, Ann Internal Med 1988 [188]	Clinical symptoms and leangth of survival in patients with terminal	secondary analysis	questioned wheather the assessment of clinical symptoms in addition to performance status might improve our	all patients with complete information on symptoms, function, cancer type and survival			

Author, Journal, Year	Patients' characteristics at baseline: Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Informal caregivers' (CG) characteristics at baseline: Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others
Greer, J Chron Dis 1986 [181]	n=1754 (833 HC, 624 HB, 297 CC) / drop out: 4.4% with no differences across settings / n.d.*	% female (HC vs. HB vs. CC): 51.3 vs. 51.8 vs. 52.7	means n.d.; HC vs. HB vs. CC in %: 21-54 years 10.3 vs. 9.3 vs. 26.6, 55-64y: 21.5 vs. 14.3 vs. 30.6, 65-74y: 42.4 vs. 44.8 vs 28.3, ≥75y: 25.8 vs. 31.6 vs. 14.5	100%	1. lung, breast, prostate, colorectal cancer; 2. metastatic at diagnosis: HC 49.6 vs. HB 50.4 vs. CC 47.6%; 3. "terminally ill"/"terminal cancer"	HC vs. HB vs. CC: least functional (10-30): 45.8 vs. 49.8 vs. 67.7 % most functional (40 and over): 54.2 vs. 50.2 vs. 32.3%	Patient awareness at initial interview comparable (full mental capacity HC vs. HB vs. CC): 48.9 vs. 49.9 vs. 54.3%;	non-white (% HC vs. HB vs. CC): 1.5 vs. 4.7 vs. 8.1; *Only patients who died during the study period were included in the final analytic samples since outcomes were assessed in relation to proximity to death;	same as patients (study describes sample of patients with a primary caregiver (=PCP)	n.d.			PCP was the patient's spouse or child in 4 out of 5 cases; In HC hospices the PCPs were significantly less likely to be employed at the time of hospice entry. At the onset of the disease, a higher percentage (46%) of all PCPs were employed; those with patients entering hospice were only slightly less likely to be employed at this juncture
Greer, J Chron Dis 1983 [182]													
Morris JN, J Chron Dis, 1986b [183]	idem	idem	idem	idem	idem plus additional information: **HC vs. HB vs. CC:** Primary breast cancer: 13.4 vs. 11.1 1vs. 3.0 %, Primary lung cancer: 25.7 vs. 22.6 vs. 25.3%, brain metastases: 18.6 vs. 14.8 vs. 18.5%, bone metastases: 35.5 vs. 34.1 vs. 36.0%	idem	at study entry, 12.1% of patients reported "horrible" or "excruciating" pain (PCP reported "frequent" or "persistent" pain in 82% of the cases); 31% of patients reported that pain was "not present" (8.8% of patients were "free of pain" according to the PCP)		idem	n.a.	n.a.	n.a.	
Morris JN, J Chron Dis, 1986a [184]													
Birnbaum HG, AJPH 1984 [185]													
Mor 1990 [186]													
Powers JS, Public Health Reports 1988 [187]	idem	idem	**64.1 years; HB=65.4 HC=64.0 vs. CC= 61.7**	idem	idem	idem					**total=57.5 (SD n.d.); HB=57.9 HC=48.5 vs. CC=53.9**		
Reuben DB, Ann Internal Med 1988 [188]	1592												

Author, Journal, Year	Needs assessment: Who assesses	When	How (tool)	Needs complexity: Categories	Process of categorisation (needs > complexity)
Greer, J Chron Dis 1986 [181]	**Patient outcomes:** Primary care person assessed patients' overall and social quality of life and pain and symptoms; patients themselfs rated satisfaction with care; **PCP outcomes:**	**patients needs:** Personal interviews with the patient and PCP were conducted at study entry; first followup contact 7 days later and then repeated every 14 days thereafter until the patient's death; **PCP needs:** initial interview; bereavement interview 90-120 days after the patient's death		Functional performance: least functional (10-30) vs. most functional (40 and over); aggressive treatment (no/yes); severe pain reported (no/yes)	
Greer, J Chron Dis 1983 [182]	<u>caregivers</u> **needs (PCP):** family secondary morbidity (psycho-social distress, role loss, and dysfunctional symptoms); Family satisfaction with care received; Subjectively reported grief reaction	idem	idem plus decribed more detailed in Tab.6, p.754		
Morris JN, J Chron Dis, 1986b [183]	Pain was reported by the patient when able to respond and by the patients' primary care person (PCP) during repeated interviews until death.	idem (prospective interview stream was converted retrospectively into fixed periods prior to death. The last measure (TI) included interviews that occurred within 14 days of death and averaged 7 days. The penultimate (T2) and pre-penultimate (T3) interviews averaged approximately	**Patient:** Pain was measured via a direct self-reported question; **PCP** was asked to characterize the patient's pain on a scale of 4 to 1	categories "pain free" and "persistent pain"	"categories "pain free" and "persistent pain" because these are felt to be clinically the least ambiguous categories"
Morris JN, J Chron Dis, 1986a [184]	idem	idem	s. outcomes	1.) % of patiens whose QL data are impoving/deteriorating/beeing stable over a 6-week time period, means at each of 9 successive time periods as death is approached, and 2.) the proportion of patients in the "worst" and "best" categories of the measures	
Birnbaum HG, AJPH 1984 [185]					
Mor 1990 [186]					
Powers JS, Public Health Reports 1988 [187]					
Reuben DB, Ann Internal Med 1988 [188]					

Author, Journal, Year	Intervention characteristics (structure and process quality criteria): Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management: How	Referral criteria / allocation of place	Description of **intervention**: Schedule/Frequency	Content (clinical/non-clinical)	Description of **bereavement intervention**: Schedule/Frequency	Content	Description of **control** intervention	Coodination of intervention: Who	How	Discharge criteria	Integration of oncological and palliative structures: Who	How	Others
Greer, J Chron Dis 1986 [181]	hospice programm (hospices classified as those with beds (hospital based, HB) and those without beds (home care, HC));	conventional (oncological) care	home care and inpatient facilities (hospices with beds (hospital based, HB) and without beds (home care, HC), conventional ocological care)		home care hospices: 14 demonstration, 6 non-demonstration facilities; hospital based hospices: 11 demonstration, 8 non-demonstrationfacilities	n.d.	Medicare; Twenty-six (26) of the hospices received special Medicare demonstration waivers allowing payment for normally non-covered services (home care hospices: 14 demonstration, 6 non-demonstration facilities; hospital based hospices: 11 demonstration, 8 non-demonstrationfacilities)	-	small volunteer-dominated community programs caring for a handful of patients to large institutions and agencies with major commitments to hospice care;			not scheduled	hospices with beds (hospital based, HB) and those without beds (home care, HC); hospice model treats the patient and family caregiver(s) as a unit	bereavement interview was conducted with the PCP 90-120 days after patient's death	conducted to assess PCP outcomes and to summarize records of utilization of hospital, physician, and home health services that the PCP had maintained while the patient was alive. In addition to the patient interviews, at each contact the PCP provided data on his own condition and attitudes, presented a record of all health services utilized by the patient, and reported on the patient's condition.	"conventional care" = all health care received by terminal cancer patients not enrolled in hospice. "Access points" were located and used to identify terminal cancer patients not receiving hospice care. The NHS selected conventional care (CC) settings representing, in the opinion of knowledgeable area physicians. "good" oncological care. Fourteen such access points ultimately participated in referring patients who. although identified in an outpatient setting, may have used a different inpatient	US hospices?					
Greer, J Chron Dis 1983 [182]			Hospices classified into 3 types: (a) Hospital-based; (b) Home health agency-based; (c) Freestanding. **Hospital-based** hospices have inpatient facilities by definition. **Freestanding hospices** may or may not have an inpatient facility. **Home health agency based** hospices are affiliated with existing home care agencies.	**CC group:** Customary care sites were selected using the following criteria: (i) Appropriate representation of major categories (a) University medical center care, supervised by academic oncologists or (b) Community-based oncological care. (ii) Ease of access to patients (e.g. cancer registry or center). (iii) Conditions conducive to follow-up (e.g. integrated records). (iv) Willingness of key providers to participate. (v) Proximity to regional management centers.								idem, see diagramm page 746 for additional information	characteristic of hospice programs: (a) Health care and services are provided to terminally ill. (b) The patient,.family, and other persons essential to the patient's care comprise the unit of care. The "hospice patient's family" refers to the patient's immediate relatives; individuals with significant personal ties may be designated as the patient's "family" by mutual agreement among the patient, the individual, and the hospice organization. (c) Inpatient and home care services are closely integrated to ensure continuity and coordination of care. (d) Care is available 7 days a week, 24 hours a day. (e) Care is planned and provided by a medically supervised interdisciplinary team composed of several individuals with appropriate skills. The team members work together to plan and provide services that will secure the physical, emotional and spiritual welfare of the patient and his/her family. (f) Palliative and supportive cure is directed at allaying the physical and emotional discomfort associated with terminal illness. (g) Bereavement services are provided which			customary / conventional care: (a) University medical center care, supervised by academic oncologists; (b) Community-based oncological care; involves multiple programs and sites and, often, several physicians; terminal cancer care is directed by oncologists, either as attending physicians or consultants.						
Morris JN, J Chron Dis, 1986b [183]																						
Morris JN, J Chron Dis, 1986a [184]																						
Birnbaum HG, AJPH 1984 [185]	hospital based hospice (HB): "either as part of a hospital or freestanding organizations with their own inpatient beds"																					
Mor 1990 [186]													As much a philisophy of care as an istitutional entity, hospices stresses: palliative rather than curative care; the patient and family as the unit of care; the administration of care by an interdisciplinary team whose members are geared toward meeting the unique needs of terminally ill patients and their families									
Powers JS, Public Health Reports 1988 [187]																						
Reuben DB, Ann Internal Med 1988 [188]																						

Author, Journal, Year	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Greer, J Chron Dis 1986 [181]	impact in 4 areas: • **pattern of care: % of patients receiving medical and social service interventions in the last weeks of life (data obtained from PCP and Medicare/reimbursement records whenever feasible)**: Intensive medical services (= Radiation therapy, surgery, chemo or hormonal therapy, thoracentesis), Diagnostic tests (=Blood tests, X-rays, or scans), Oxygen or respiratory therapy, Social services at last week of life (=Counseling, financial or legal assistance, paperwork, service referrals, training in patient self-care) • **patient outcomes:** overall and social QoL* (QL-Index), pain and symptoms* (McGill questionnaire; California pain assessment profile), satisfaction with care (medical interview satisfaction scale); * = assessed by primary care person. More details on QoL see Morris et al 1986a, more details on pain see Morris et al 19986b. • **family outcomes** (PCP): perceived axiety while the patient was alive (EITS Manual for the Profile of Mood States); emotional distress following patients death (Manual for the Grief Experience Inventory); morbidity during the bereavement	Hospice inpatient and home care unit cost coefficients were developed using 1982 cost report data compiled either by HCFA or evaluation staff accountants. Cost reports separately allocated all pertinent agency costs to a hospice cost center. All inpatient costs were nationally adjusted based on Medicare hospital reporting data; hospice home care costs were not nationally adjusted since national standards did not exist. (See Birnbaum and Kidder [46] for a description of the approach to calculating the cost of utilization	QoL similar in hospice and CC systems with the exception of pain and symptom control, which may be better in the inpatient hospice setting (HB). Hospice patients are less likely to receive diagnostic tests, X-rays, and aggressive anti-tumor therapy in the terminal period, and they are more likely to receive social service support than CC patients. • pattern of care: • <u>patient outcomes:</u> **overall QoL:** similiar, **social quality of life: Hours of direct care** provided to the patient sig. higher for HC patients than HB or CC patients (p=n.a.), **hours of social visiting (=other than PCP) 3 weeks prior to death:** HC sign. higher than CC, difference between HC and HB n.s.; **pain and other symptoms:** for pain see Morris et al. 1986, **other symptoms (nausea, dry mouth, constipation, dizziness, feverishness, dyspnea):** 3 weeks before death: HB fewer symptoms than HC or CC, 1 week prior to death: same but stat. sign. in the HB-CC comparison, only. for details on pain see Morris et al. 1986b • **satisfaction with care:** No sig. differences, "uniformly high in all settings" • <u>Costs:</u> **Total cost per study day:** substantially lower in HC than in HB or CC ($101 (SE=9.1) vs. $146 (SE=10.0) vs. §149 (SE=11.7) p=n.d.); These differences were related to utilization patterns; **Inpatient and physician**	Families appeared to tolerate the stress of terminal illness and bereavement better than expected. Consistent with their greater burden, HC PCPs reported more emotional distress than HB PCPs during bereavement but were not more likely to report secondary morbidity. • **satisfaction with care:** HB PCPs higher satisfaction with the patient's care than CC PCPs (before and after death of patient); PCPs in both types of hospices satisfied with where the patients died (despite marked differences in places) however, both hospice PCP groups were more satisfied with where the patient died than were CC PCPs. HC PCPs were significantly more likely than HB and CC PCPs to report that the patient had been able to remain at home as long as he/she wanted. • **perceived caretaking burden:** small sign. difference (HC PCP perceiving higher burden than HB / CC) • **modified mood state scale (measuring anxiety and depression):** no sign. differences among the three PCP groups; • increased absenteeism from work: 4% overall, differences n.s.; **regret concerning the medical tratment the patient received:** 11%	• **thoughts on generalizability:** conducted within closed-system managed care settings; as a result, it may be less generalizable to all healthcare settings, and the relative cost savings may not be realized across other settings; the sample is only patients with a primary care person, i.e. patients living alone (a proxy for no PCP) are not included in the analysis • **high levels of satisfaction with care in all three settings**: may reflect self-selection, but could also be the result of the extremely high level of informal support which is mobilized in the presence of terminal illness and which may leave little room for incremental improvement from professional sources; small but significantly higher level of satisfaction reported by HB family members may be a reflection of their reduced sense of burden. • **costs:** HC model is less costly than HB or CC largely because HC substitutes home care for inpatient care, relying on family members to provide up to 12 hours a day of direct care. HB hospice appears to be less costly than CC for patients during the last
Greer, J Chron Dis 1983 [182]		The cost analysis includes: "Costs" of those services for which standard techniques of computing cost exist are compared for hospice and non-hospice patients. Charges for services for which standard costing techniques are not available are compared separately. These include physicians' services, drugs, supplies and other expenses.			
Morris JN, J Chron Dis, 1986b [183]	<u>pain</u> • 1.O: relationship between measures of pain obtained from the patient and from a familial informant, • 2.O: prevalence and severity of pain among TCPs served in different settings, • 3.O prevalence and severity of pain as patients approach death, as well as the medical and demographic correlates of pain		Twenty to thirty per cent of patients are pain free during their final weeks of life, and this proportion remains fairly stable as death approaches; no sign. differences in the proportion of pain-free patients by setting at either measure preceding death; Controlling for medical characteristics, pain at study entry, and other health factors, HB hospices appear to meet pain control goals best; • **1.O** correlation between the patient and the PCP reports was 0.43 (p < 0.001) with PCP more likely to report the presence of pain than patients (18.8% of patients were "free of pain" according to the PCP, while 31% of patients reported that pain was "not present").; • **2.O** at the last measure prior to death (T1) HB patients were sign. less likely than CC (p< 0.001) or HC (p< 0.01) patients to be in persistent pain while at T2 only the HB vs. CC comparision remained significant (p<0.01); mean (SE) of % of patients in persistent pain (HC vs. HB vs. CC): at second to last measure (T2): 7% (0.02), 3%(0.02), 14%(0.04) and at last measure (T1): 13%(0.02) vs. 5%(0.02) vs. 22%(0.05); mean (SE) % patients pain free at second to last measure (T2): 7% (0.02), 12%(0.02), 9%(0.04) and at last measure (T1):	n.a.	• different outcomes of the two studies suggest caution in accepting the generalizability of either and clearly merit further exploration • Schmerzratings bezieht sich auf die Fremdbewertung durch die primary care person (PCP), nicht der Patienten selbst; dies ist der Fall, da die meisten Patienten kurz vorm Lebensende besonders stark funktional/psychisch beeinträchtigt waren und keine Befragung druchgeführt werden konnte, zu Studienstart gab es für ca. 70% der Patienten eine Eigenbewertung - diese wird aber nicht klar dargestellt, nur grob bei Vergleich der Übereinstimmung mit den Proxy-Schmerzratings der PCP
Morris JN, J Chron Dis, 1986a [184]	<u>**1.O: QoL described by the following measures**</u> • Karnofsky Performance Index with operational specifications for use by nonclinical staff • Spitzer QL Index (also present in the McGill Data Set) -a multifaceted functionally based index • HRCA-QL Index (where the item "mobility" is substituted for "activity" in the original QL Index: Activity/) • Spitzer Uniscale QL Index-a broad based overall quality of life measure • integrated Pain and Discomfort Index (constructed by HRCA using items from Spitzer's Multiscale). • Emotional QL (created by Morris, Wright and Sherwood from HRCA) • Awareness (adapted from Spitzer scale) • social QoL		declines in quality of life varied as a function of the patient's proximity to death, rapid decline being limited to the last few weeks of life while pain was most discrepant; increasing deterioration in quality of life, with accelerated deterioration between 3 and I week of death. Pain follows a somewhat different pattern than other measures. More patients are in either of the extreme categories at an earlier point in time than found for other measures. and there are fewer changes as death is approached. Finally, about 20% of the patients do not fall into extremely low quality of life categories, even in the week prior to death; only a minority of patients remain in the same QL categories over the 6-week time period: from a high of 40% (for the Pain Index) to a low of 16-18% (for the QL Index and the HRCA-QL). Change is the norm, stability the exception.		• important: as noted, the Pain Index was the most independent of the QL measures studied, and cannot be easily "proxied" by any of the other measures. Pain is a crucial QL measure in terminal cancer studies and must be separately measured. • authors believe that these data demonstrate the need to employ a number of different quality of life measures in studies of terminal cancer patients; if one had to choose a single measure to capture the change curve of initial gradual deterioration with a greater loss in quality of life as death is approached, we would recommend the HRCA-QL Index. •
Birnbaum HG, AJPH 1984 [185]		**Hospice Cost Sample** is used to estimate the cost of hospice to Medicare; it includes all demonstration Medicare hospice patients admitted in the first year of the demonstration. **The Terminal Cancer Cost Sample** is limited to patients with diagnoses of terminal cancer; it is used to estimate the cost savings of hospice to Medicare for cancer and excludes patients with noncancer terminal diagnoses.	<u>Costs:</u> HC hospice costs are lower than conventional care costs regardless of length of stay. However, HB costs seem lower than conventional care costs only for patients with lengths of stay less than two months. Hospice and conventional care patients appear to differ with respect to predisposition toward intensive health care utilization. **Total costs per day:** HB hospice costs per day are 44 % higher than home care (HC) hospice costs per day ($95 versus $66, respectively). In addition, per patient hospice costs are 24 per cent more for patients enrolled in HB than in HC hospices ($5,890 versus $4,758, respectively). proportional costs: HB and HC in cost per patient is smaller than the cost per day difference due to the shorter average HB length of stay, 62.3 days compared to 72.5 days for HC. • <u>hospice costs:</u> **per patient: HC**=$4758 vs. HB=$5890; <u>**Unit Costs of Service (HC vs. HB):**</u> **Inpatient (Hospital and Hospice)** Total Costs/Total Days of Inpatient Care $278 vs. $218; Median Cost for Inpatient Days: 259 vs. 195; **Homes Services (excluding Continuous Care)** Total Costs/Total Days at Home 46 vs. 43, Median Cost for Home Daysc 37 vs. 27, **Continuous/Home Respite**		**• fact that, regardless of setting, hospice saves less on average for long stays than for stays of less than two months reflects both a tendency toward lower savings in all time intervals for long-stay patients and a tendency for hospice to cost more than conventional care immediately after intake for patients with stays of greater than two months!** • Medicare hospice costs in the future will probably be greater than those found in the NHS because NHS conventional care comparisons do not include noncancer patients or patients discharged alive from hospice, entry of patients with a primary care person (PCP) into study, only (…) • "To the extent that hospitals and hospices work together as an integrated system, at least informally, well-managed hospice care should be financially viable. In an era of increasing hospital rate regulation, hospitals will need to develop arrangements
Mor 1990 [186]			Hospice patients are less likely to receive aggressive interventions in the two weeks prior to death (p<0.001 for surgery, chemo- or hormone therapy, radiation therapy; n.s. for thoracentesis)		#WERT!
Powers JS, Public Health Reports 1988 [187]			location of care was best explained by the patient's functional capacity; location of care was found to be poorly explained by extent of organ involvement or specific symptoms; only some examples extracted here: • Patients receiving conventional care were more disabled than other patients according to the modified ADL (Activities for Daily Living) Scale of Katz (16) and the Karnofsky Performance Status Scale (p<0.05) and used more intravenous support systems and catheters than hospice patients • Hospice home care patients survived longer and were older and more often married than conventional care patients (p<0.05) • HC patients lost more weight, had a greater appetite change, and had more cold sweats than patients receiving CC, but were calmer and happier and less lonely, frightened, and hopeless (p<0.05) • No significant differences among groups were found regarding quality of life, level of awareness, and therapy for depression • HC patients and their PCP were closer and reported being happier despite more burdensome patients and	PCP of patients under hospice home care experienced more stress but reacted no differently when compared with PCP at other care sites	Home hospice care is not a panacea for treatment of the elderly with chronic or terminal disease. We need both good home services and good institutional care alternatives for humane and effective care. Deciding how to use these alternative resources most effectively will take considerable additional thought and inquiry
Reuben DB, Ann Internal Med 1988 [188]					not extracted because no comparison of treatment settings

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)																						Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description		Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)	Funding		Organisation / Management related to structures		Referral criteria / allocation of place	Description of **intervention**		Description of **bereavement intervention**		Description of **control** intervention	Coodination of intervention		Discharge criteria	Integration of oncological and palliative structures		Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs			
																										Intervention	Control					Who (source)	How much	Who	How		Schedule/Frequency	Content (clinical/non-clinical)	Schedule/Frequency	Content		Who	How		Who	How						
PALLIATIVSTATION (Fortsetzung)																																																				
Goldberg RJ, J Chron Dis 1986 [189]	Analgesic use in terminal cancer patients: report from the National Hospice Study.	subanalysis	This paper presents data on the use of analgesics among terminal cancer patients in the United States, including which analgesics were used, how they were used (in terms of dose, route, and scheduling), and who used them. (…) This paper presents data concerning differential analgesic use patterns among conventional care, hospital based	random subsample: Medication prescription and consumption information was recorded at each interview contact for every third CC patient and every tenth hospice patient enrolled in the study.	idem	idem		181		range 21 to over75years (58% >65y)	idem																																					**1.O Medication prescription and consumption information** (recorded at each interview contact for every third CC patient and every tenth hospice patient enrolled in the study. The interviewer recorded the name, dosage, route, and schedule for each medication prescribed that matched one)		Patients in hospital based hospice programs were more likely than other patients to have an analgesic prescription and to have consumed analgesics. Patients in hospice settings were more likely to consume analgesia orally and less likely to have "prn" (as needed) analgesic prescriptions. The amount of analgesic consumption was inversely related to age. • HB patients were significantly more likely than patients in other settings to have analgesics prescribed (p < 0.01 df = 2) at the last period prior to death. n.sign at the earlier period allthough the direction of the relationship is similar • oldest patients were significantly less likely (p < 0.05) to have an analgesic prescribed at TI than were the youngest patients • no statistically significant differences by setting for the level of analgesic consumed		
Wallston KA, Medical care 1988 [190]	Comparing the quality of death for hospice and non-hospice cancer patients.	secondary analysis	In performing a secondary analysis of data collected for the NHS, we questioned whether the measurement methods used to compare hospice and non-hospice care adequately captured the impact of hospice care.	subset of patients participating in the NHS who 1) died of cancer within 6 months of entering the study and 2) whose principal care provider (PCP) participated in a bereavement interview between 90 and 120 days after the death of the patient.	idem	idem								n.a.							Primary care provider (PCP)	The weights were derived from the interviews of all patients when they were admitted into the study; QOD data collected retrospectally from PCP rated QOD data for last three days of life of patient	Quality of death (QOD) was defined in this study as experiencing in the last 3 days of life feelings and events that terminally ill patients reported they desired; The weights were derived from the interviews of all patients when they were admitted into the study. A single open-ended question, "What would you like your last 3 days of life to be like?"; **more:**																									**1.O Quality of death (QOD)** (defined in this study as experiencing in the last 3 days of life feelings and events that terminally ill patients reported they desired; QOD, is a weighted sum of 13 situational elements, which the PCP reported were either present or absent during the last 3 days of the patient's life as reported by the PCP; • People he/she would have wanted were there; • Physically able to do what he/she wants to do, • free of pain; • Participatein normala ctivitiesl ike any other day • Able to stay at home as long as he/she wanted • Feel at peace with God • Die in sleep, without awareness • Stay mentally alert etc. • Complete tasks he/she wished to do • Able to accept death • Know ahead of time that death is imminent • Live until a key event occurred		sign. main effect for mode of care (P < .03). The QOD for those receiving conventional care was lower (Mcc = 72.5) than those in either type of hospice (MHB = 81.5; MHC = 80.4). No sig. differences between the two types of hospice; For the subsample of patients studied (N = 880), the QOD scores ranged from 1.4 to 136.1 with a mean of 79.4 (SD = 21.8).	n.a.	results support the impression that hospice care optimizes the QOD of the terminally ill patient. Major limitation: NHS used retrospective reports by primary care providers as the best available means of assessing whether a given situational element
Kane, The Lancet, 1984 (part 1) [176]	A randomised controlled trial of hospice care	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	73% of partiens had FCG; 95% gave consent; 6% withdrew consent	not specified	not specified	not specified	not specified	not specified	regular interviews (7 cohorts = 18 weeks) Methodology outlined separetly in Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	tools: Pain scores according to Melzak; Symptom Scale adapted from the California Pain Assessment Profile; depression scale adapted from the National Institute of Mental Health's Center for Epidemiologic Studies' scale; anxiety derived from a section of the General Well-Being Measure; satisfaction measures included the interpersonal care scale adapted from the Ware scale, physical environment scale and involvement-in-care questions adapted from the National Cancer Institute's Hospice Study; functional status assessed by	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	2 physicians, 19 nurses, a social worker, a chaplain, and about 30 volunteers for 11 beds; a homecare programme serving about 25 patients at any given time; a consultation service for patients awaiting admission	11 beds, about 25 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in pain, symptoms, activities of daily living and affects satisfaction (patients) satisfaction (carers) utilisation of services costs	yes	differences in….: no sign. effects Satisfaction (pts): sign better (for interpersonal care in 5 cohorts (3): p<0,02; (4):p< 0,001, (5):p< 0,003; (6): p< 0,002; (7): p<0,004 for involvement in care (4):p<0,02; (5):p<0,05; (6):p< 0,003; (7):p<0,003 utiltisation of services: no sign difference **Costs:** no sign difference	satisfaction equally improved	presumably bias due to gender, intervention not clearly defined
Kane, JAMA 1985 (part 2) [177]	Hospice Effectiveness in controlling pain	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care on pain	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-93	100%	2. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase	not specified	not specified	none	none	not specified	not specified	not specified	not specified	not specified	referal to methodology being published elswhere:Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	tools Pain scores according to Melzak	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds, 30 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in pain scores, correlation with other symptoms use of analgeics	no	no sign effects	none	intervention not clearly defined; exactly the same study and the same results reportes as in Lancet 1984
Kane, J Chron Dis, 1986 [178]	The role of hospice in reducing the impact of bereavement	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to	not specified	not specified	none	n = 152 (83 inv = hospice, 69 controls = regular care)	72 female in intervention / 56 in control	58 (SD 12) years in interv, 56 (14) in control	anxiety, depression bereavement	20 chronic health problems (list)	not specified	additional interviews 6weeks, 6, 12 an 18 months after death	anxiety measure: Rand Health Insurance Study; depression: CES-D Scale, sequelae of bereavement: participation in social activities and social contacts, smoking habits and alcohol consumption, use of medication, bed disability days, work loss days, restricted activity days, hospitilisation,	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in anxiety scale, CES-D Depression Scale, health scale score and items of the sequelae bereavement list	no	no sign effects between the two groups	no sign effects	intervention not clearly defined; exactly the same study gender bias, methodology remains vague
Wales, J, Medical Care, 1983 [179]	UCLA Hospive Evaluation Study	RCT	to establih robust methodology		single center	USA	1-																																													no real figures given, re-test reliablilties based on assumptions (24hours), the gaps in applied methodology of the main studies are not explained by this article despite it being referenced as the relevant methodology section

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)																						Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
Author, Journal, Year	**Title**	**Type of study / Design**	**Aim of study**	**Inclusion criteria**	**Centre (single - multicentric)**	**Coun-try**	**Level of Evidence =LoE (SIGN) / Justific**	**Number of patients / Dropouts (DO) / Dropouts through death (DO†)**	**Female / Male (n/n)**	**Age (mean, SD)**	**% of patients with cancer**	**1. Diagnosis 2. stage/grade 3. phase of illness**	**Perform-ance status (ECOG, ...)**	**Patients' needs (psychosocial, spiritual, etc...)**	**Others**	**Number of CG / Drop outs**	**Female / Male (n/n)**	**Age (mean, SD)**	**CGs'needs (psychosocial, spiritual, etc...**	**Others**	**Who assesses**	**When**	**How (tool)**	**Categories**	**Process of categorisation (needs > complexity)**	**Overall description**		**Setting**	**Health care providers: Total, n/profession or qualification**	**Number of places/ beds**	**Equipment (incl. drugs, EDV, setting/ room/ housing)**	**Funding**		**Organisation / Management related to structures**		**Referral criteria / allocation of place**	**Description of intervention**		**Description of bereavement intervention**		**Description of control intervention**	**Coodination of intervention**		**Discharge criteria**	**Integration of oncological and palliative structures**		**Others**	**Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)**	**Costs**			
																										Intervention	Control					Who (source)	How much	Who	How		Schedule/Frequency	Content (clinical/non-clinical)	Schedule/Frequency	Content		Who	How		Who	How						
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG																																																				
Ahlner-Elmqvist, PallMed 2004 [191]	Place of death: hospital-based advanced home care versus conventional care	CCT, non randomized	to evaluate HRQL of patients, with cancer in palliative stage, receiving either hospital-based advanced home care (AHC)	above 18 years of age, had a histological verified malignant disease, were informed about their diagnoses and were in a palliative care situation (life expectancy 2-12months)	single center	Sweden	1- (CCT)	n= 722 (targets), recruited 297, intervention 119, control 178	56/61 (interv.) and 88/75 (control)	Interv (mean): 67 Control: 68yrs, SD not mentioned, range intervention (38-88), control (28-85)	100%	primary cancer (interventional group/control): lung (16/38) (p=0.007)!, prostate (10/5), gastrointestinal (43/73), breast (9/18), urogenitalia (16/11), others (23/18)	KPS > 70 interventional group 55%, control group 71% (p=0,007)	nor assessed		not assessed	not assessed	not assessed	not assesed							AHC Programme (regional palliative care programme, 24/7 on call, complementary to conventional care)	conventional care	AHC: 25 housebound patients at a time (3 backup beds)	The staff included a team of nine experienced nurses, an oncologist, a physiotherapist, a social worker and a secretary. A priest was associated on a consultation basis. All the professionals had long experience from advanced cancer care, but had no formal	25 outpatients (3 backup beds)	not specified	The hospital-based AHC service was affiliated to the Department of Oncology at Malmo¨ University Hospital.	not specidfied	hospital based home care team		clinical judgement--> proposal for refferal, patient preference	AHC 24/7 care	not specified	none	none								1. place of death 2. days spent in hospital 3. differences in sociodemographic prerequisites	no	1. place of death: more home deaths in the AHC (interventional) group: 53/17 (p<0.001) 2. time spent in hospital: AHC 18% of time; Control 31% of time (p<0.005) 3. sociodemographic data associated with place of death: Living situation (living with someone) p=0.0014, OR 2.4 in both groups	none	no defined intervention, bias due to preferred care, bias in baseline data!
Ahlner-Elmqvist, J Pain Sympt Manage, 2008 [192]	Characteristics and Quality of Life of Patients Who Choose Home Care at the End of Life	prospective, non randomized	to evaluate HRQL, sociodemographic data and medical data of patients, with cancer in palliative stage, receiving either hospital-based advanced home care (AHC)	above 18 years of age, had a histological verified malignant disease, were informed about their diagnoses and were in a palliative care situation (life expectancy 2-12months)	single center	Sweden		n= 722 (targets), recruited 297, intervention 119, control 179	56/61 (interv.) and 88/75 (control)	Interv (mean): 67 Control: 68yrs, SD not mentioned, range intervention (38-88), control (28-85)	100%	primary cancer (interventional group/control): lung (16/38) (p=0.007)!, prostate (10/5), gastrointestinal (43/73), breast (9/18), urogenitalia (16/11), others (23/18)	KPS > 70 interventional group 55%, control group 71% (p=0,007)	measured in both groups		not assessed	not assessed	not assessed	not assesed																													HRQL (symptom presence and severitiy: EORTC QLQ-C30, psychological distress: IES, social: five questions of Mc Adam´s questionnaire, general well being: Norwegian Health Survey)	no	**HRQL:** **EORTC QLQ-C30 significantly poorer in AHC group for (ONLY SIGN RESULTS FEATURED)** Physical (AHC/CC) 29/51 p<0.001 Role (AHC/CC) 17/37 p<0.001 Emotional (AHC/CC 50/63 p<0.001 Cognitive (AHC/CC) 58/73 p<0.001 Social (AHC/CC) 45/58 p=0.001 Global health (AHC/CC) 35/44 p=0.003 **Symptom Scales** Fatigue 77/56 <0.001 Pain 53/41 0.002 **Single items** Dyspnea 56/40 <0.001 Appetite loss 53741 0.009 **IES mean** Intrusion 16/13 0.008 **Mc Adam´s Questionnaire** Worried about families future 54/34 0.001 Share feelings with others 77/71 0.009 **General wellbeing (comparison with normative data)** AHC (being "Tired and worn out" or "Very tired and worn out") (69%) CC patients (48%) (P < 0.001) Overall, both groups of patients reported reduced physical and psychological well-being compared with data from a Norwegian population study	none	results are more related too different phases of disease than to specific interventional features; possibly more a study for needs than SAPV
Ringdal, Pall Med , 2004 [193]	Health-related quality of life (HRQOL) in family members of cancer victims: results from a longitudinal intervention study in Norway and Sweden	longitudinal intervention study (In the Norwegian site a cluster randomized experimental design was adopted, whereas a nonrandomized controlled design was applied in the Swedish site.)	to compare the health-related quality of life (HRQOL) of family members of patients who participated in a program of palliative care with those in conventional care (control family members); based on two hypothesis:H1: The respondents' HRQOL scale scores will decrease from the inclusion in the study and reach a low point a few months after the death of the cancer victim, and thereafter show an increase. H2: The trajectories of the HRQOL scale scores for the intervention and the control groups will show an increasing difference over time in quality of life in favor of	incurable malignant disease,over 18 years, predicted survival time of two to nine months.	two centres	Norway and Sweden		n= 183/130 (interv/control) in Norway und n= 102/102 in Sweden (n= not patients but enrolled caregiver!)			100%	Almost half of the patients suffered from gastrointestinal cancer. Other common cancer diagnoses in the sample were lung, breast/female genitalia, prostate and urological cancer				183/130 N and 102/102 in Sweden at baseline	128/55 in interv. N, 87/41control N and 72/30 interv. S and 59/43 control in S	median age was 67/69 years	by SF36				CGs were mailed a questionnaire to their home address every second month. The family members who consented to continue after the death of the patient received questionnaires at one, three, six, and 13 months after the time of death.If the questionnaires were not returned after two weeks, a reminder was given, and if still no answer was received, the family member was regarded as a drop-out and the distribution of subsequent questionnaires was																									HRQOL measured by the short-form (SF-36) health survey questionnaire, including eight subscales	no	sign differences found for subscales at different time points (very complex statistical construction) the scale scores varies across time according to H1; The group by time interaction is, however, only statistical significant at the 0.05 level for the role limitation, emotional scale and the mental health scale.	highly complex methodological approach - almost too complex to follow. Bias due to different ways of recruitment and gender imbalnace very likely. Intervention not clearly explained. Whether the detected statistical differences are related to clinically relevant effects remians very dubious	
Axelsson 1998 [194]	Evaluation of a hospital-based palliative support service with particular regard to financiel outcome measures	CCT	financial assessment of a hospital-based palliative support service	incurable cancer patients, treated at the Department of General Surgery (DGS)	single canter	Swedish	1-	41 / 2 drop-out(1 because death one day after including in the study, 1 because of lack of care-giver, no wish to live at home)	48/34	median 72 (58-87)	100%	5 criteria: 1. symptomatic, incurable cancer disease; 2. a cancer disease within the realm of general surgery; 3. living within 40 km of the Country hospital; 4. wish to stay at	60 (10-90)		median survival time from diagnosis to death 23 month											Palliative Support service, 0.5 physician (surgeon) and a full-time nurse	control group: usual care, reference group: fullfilling the inclusion criteria but living beyong the radiau of the DGS	inpatients								recruitment in hospital before referral	first contact in hospital, nurse visited patients at home if needed.	coordination of care, communication with GP´s, management of infusions, catheters, nutrition e.g. at home when needed			usual care							duration of terminal hospitalization, ratio of days at home / to toal inclusion days; days at home during the last two month of life, economic advantages	palliative support team defrayed ist own costs and saved another SK17.000 / patient (=US$2.500)	intervention group significant less duration of terminal hospitalization (p=.005); ratio days at home / inclusion days higher (p=.001); more days at home (p=.001)		
Bakitas; JAMA, 2009 [130]	Effects of a Palliative Care Intervention on Clinical Outcomes in Patients With Advanced Cancer The Project ENABLE II Randomized Controlled Trial	RCT	To determine the effect of a nursing-led intervention on quality of life, symptom intensity, mood, and resource use in patients with advanced cancer	prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver	single center, rural area	USA	1++	n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	100%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/21	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed	not assessed	not assessed	not assessed	not assesed	n	questionnaire	baseline, 1 months after baseline, follow up every three months				psychoeducational intervention	conventional care		nurses (special qualification)								4 weekly sessions; monthly follow-up	A multicomponent, psychoeducational intervention (Project ENABLE [Educate, Nurture, Advise, Before Life Ends]) conducted by advanced practice nurses consisting of 4 weekly educational sessions and monthly follow-up sessions until death or study completion										PO patientreported quality of life, symptom intensity and resource use. (assessed with the Functional Assessment of Chronic Illness Therapy for Palliative Care), symptom intensity (assessed with the ESAS), and resource use by chart review SO mood (assessed with CES-D)	no	Longitudinal intention to-treat analyses for the total sample revealed higher quality of life (mean [SE],4.6 [2]; P=.02) (Functional Assessment of Chronic Illness Therapy for Palliative Care scores and CES-D mood score p=0.02 no further sign results	robust methodology, straight forward.Simply a well done and important study.	
Bakitas; Palliative and supportive care, 2009 [195]	The project ENABLE II randomized controlled trial to improve palliative care for rural patients wiht advanced cancer: baseline findings, methodological challenges and solutions			prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver	single center, rural area	USA	2	n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	200%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/22	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed						questionnaire	baseline, 1 months after baseline, follow up every three months							nurses (special qualification)																							does not add any information regarding evidence for interventional effects	
O´Hara , Palliative and Supportive Care 2010 [196]	Impact on caregiver burden of a patient-focused palliative care intervention for patients with advanced cancer	RCT	to determine the effect of a nursing-led intervention on quality of life and burden of caregivers	prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver	single center, rural area	USA		n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	300%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/23	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed	n= 220 (interv 106, control 116)	not specified	not specified	not specified		questionnaire	baseline, 1 months after baseline, follow up every three months; in case of death ADI for caregivers							nurses (special qualification)																			Montgomery Borgotta Caregiver Burden Scale; After Death Bereaved Familiy Memeber Interview (ADI), no caregiver centered intervention, simply monitoring effects of patient centered intervention on caregivers	no effects shown			
Brumley, JAGS 2007 [197]	Increased Satisfaction with Care and Lower Costs: Results of a Randomized Trial of In-Home Palliative Care	RCT, parallel,	to test an in-home palliative care model at two sites using a randomized, controlled design; Standard care compared with standard care plus an in-home palliative care program to determine the program's ability to improve patient outcomes and reduce the costs of medical care at the end of life; hypothesized that the program would increase patient satisfaction, reduce costs of medical care, and increase the proportion of terminally ill patients dying at home.	primary diagnosis of CHF, COPD, or cancer; life expectancy ≤12 months*; ≥1 visit of emergency department or hospital within previous year; ≤70% on the Palliative Performance cale; * primary care physician was asked "Would you be surprised if this patient died in the next year?"	multicentric (2 sites)	USA (Colorado, California, Hawaii)	1+ (not blinded, endpoints not clearly defined, some risk of bias)	n=310 randomized (n=155 IG / CG) / drop out: n=13 / n=8 died before intervention	146/151	IG: 73.9 (11.1), CG: 73.7 (13.0), total: 73.8 (12.1)	IG: 44%, CG 49%, total: 47%	CHF, cancer, COPD; "terminally ill" (≤12months)	Palliative Performance Scale score mean (SD): IG=57.8(13.1), CG= 58.5(12.0), total=58.2(12.5)	Reid-Gundlach Satisfaction with Services instrument - mean(SD): 40.1(5.7); Palliative Performance Scale (mesuring severity of illness) - mean (SD): 58.2(12.5)	37% ethnic minority: 18% Asian/Pacific Islanders, 13% Hawaiian, 4% Latino, 2% other						Undergraduate- and graduate-level research assistants, blinded to group assignments, were recruited and trained to conduct telephone interviews with the patient or, if the patient was unable to participate, the primary caregiver	within 48 hours of study enrollment and every 30, 60, 90, and 120 days	Reid-Gundlach Satisfaction with Services instrument; Palliative Performance Scale	satisfaction with service: total score of ≥37 categorized as very satisfied; suprise question - answer "no"		standard care plus an in-home palliative care (IHPC) program	standard care	two group-model, closedpanel, non-profit health maintenance organizations (HMOs) providing integrated healthcare services in Hawaii and Colorado	**Colorado site:** ≥500 physicians, all medical specialties and subspecialties, HMO contracts with outside providers for emergency department, hospital, home health, and hospice care to serve its 477,000-person membership; **Hawaii site:** 317 medical group physicians provide care; "Intervention providers": core care team consisting of the patient and family plus a physician, nurse, and social worker with expertise in symptom management and biopsychosocial intervention.	**Colorado site:** 16 separate ambulatory medical offices, HMO contracts with outside providers for emergency department, hospital, home health, and hospice care to serve its 477,000-person membership; **Hawaii site:** 217-bed medical center, has an internal home health agency, accepting referrals from hospital- and clinic-based medical group physicians.		HMOs		palliative care physician	Patients are assigned a palliative care physician who coordinates care from a variety of healthcare providers, including specialists and the patients' primary care physician, thus preventing the service fragmentation that often occurs in healthcare systems.		referral guidelines expanded: to target patients earlier in their disease process, with an estimated 12-month life expectancy (compared to hospice programs based on 6-months prognosis); admission: team assesses the physical, medical, psychological, social, and spiritual needs of the patient and family; initial assessments from physicians, nurses, and social workers. Additional team members (spiritual counselor or chaplain, bereavement coordinator, home health aide, pharmacist, dietitian, volunteer, physical therapist, occupational therapist, and speech therapist) join the core care team in service provision as needed; team convenes to develop a care plan in accordance with the wishes of the patient and the family. Frequency of subsequent medical visits is based on the individual needs of the patient. Physicians conduct home visits, available along with nursing services on a 24-hour on-call basis; advanced care planning is provided that involves patients and their families in making	interdisciplinary home-based healthcare program designed to provide treatment with the primary intent of enhancing comfort, managing symptoms, and improving the quality of a patient's life; team provides education, support, and medical care to the patients and their families; patients and families are trained in the use of medications, selfmanagement skills, and crisis intervention in the home with the goal of stabilizing the patient and minimizing excessive emergency department visits and acute care admissions;	spiritual counselor or chaplain, bereavement coordinator (...) join the core care team in service provision as needed; advanced care planning is provided that involves patients and their families in making informed decisions and choices about care goals and end-of-life care.		standard care to meet the needs of the patients and followed Medicare guidelines for home healthcare criteria; various amounts and levels of home health services, acute care services, primary care services, and hospice care; Patients treated for conditions and symptoms when they presented them to attending physicians; ongoing home care when they met the Medicare-certified criteria for an acute condition.	palliative care physician; core care team (=patient and family plus a physician, nurse, and social worker with expertise in symptom management and biopsychosocial intervention)	palliative care physician: coordinates care from a variety of healthcare providers, including specialists and the patients' primary care physician; core care team (=patient and family plus a physician, nurse, and social worker): responsible for coordinating and managing care across all settings and providing assessment, evaluation, planning, care delivery, follow-up, monitoring, and continuous reassessment of care.	palliative care until death or transfer to a hospice program. (For more information on this model, see17,18.)				1.O: medical care costs; 2.O: • satisfaction with care (Reid-Gundlach Satisfaction with Services instrument); • sevice use • proportion of terminally ill patients dying at home	Service costs= actual costs for contracted medical services (services provided by non-HMO contracted facilities) + proxy cost estimates for all services provided within the HMO; costs for: emergency + physician office visits + home health and palliative care visits + cost for each discipline's reimbursement rate; **total cost variable** constructed by aggregating costs for physician visits, emergency department visits, hospital days, skilled nursing facility days, and home health or palliative days accumulated from the enrollment until the end of the study or death.	• **cost of care:** sign.lower in IG vs CG: overall costs IG 33% less (P=.03; 95% CI= $12,411 to $780; R2=0.16), mean costs per patient $12,670 ±$12,523 vs. $20,222 ±$30,026 (p<.001), average per day $95.30 vs. $212.80 (p=.02); • **satisfaction with care:** no sig. difference at 60days after enrollment (OR=1.79; 95% CI=0.65–4.96; P=.26); signif.increased in IG at 30 days (OR=3.37, 95% CI=1.42–8.10; P=.006) and 90 days (OR=3.37, 95% CI=0.65–4.96; P=.03) after enrollment; 93% vs. 81% patients very satisfied with care at 90 days after enrollment; •**service use:** 20% vs. 33% went to emergency departement (P=.01), 36% vs. 59% hospitalized (P<.001); •**site of death:** 71% vs. 51% died at home (p<.001), IG 2.2 times as likely to die at home OR=2.20 (CI= 1.3-3.7; R2=0.27, p<.001)		* primary vs. Secondary endpoints not clearly defined; power calculation based on medical care costs; • satisfaction with care: potential of bias since analysis is based on comparison of percentages satisfied at each time-point - instead of analysing "change" (satisfaction with services was different at study entry, thus likely to stay better over all timepoints???) • conducted within closed-system managed care settings; as a result, it may be less generalizable to all healthcare settings, and the relative cost savings may not be realized across other settings • use of proxycosts of care calculated from aggregated patient records limits the ability to generalize findings across settings • Relying on death at home as a measurement of patient preferences for site of death

SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG (Fortsetzung)

Study characteristics

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Coun-try	Level of Evidence =LoE (SIGN) / Justification
Brumley, J Pall Med 2003 [198]	Effectiveness of a Home-Based Palliative Care Program for End-of-Life	CCT (nonequivalent comparison group)	1) to provide documentation of the effectiveness of a home-based palliative care model through the following research hypothesis: total medical service use during the last months of life will be less under the palliative care model than under the traditional model of care; 2) to determine if patients enrolled in the palliative care program were more satisfied with their care compared to those receiving traditional care.	IG: life-threatening disease (primary COPD, CHF, or cancer) and a prognosis of approximately 1 year or less to live; CG: diagnosis of COPD, CHF, or cancer, two or more emergency department visits or hospitalizations in the last year, and a prognosis of less than 24 months to live	multicentric but one site (three Kaiser permanente medical centres)	USA (southern California)	1- (no randomization, nonequivalent samples, high risk of bias)
Buckingham Death Educ 1978 [199]	A Guide to Evaluation Research in Terminal Care Programs	CCT	to find evidence for or against the thesis, that a hospice home care program provides effective care to ist terminal patients	hospice patients (cancer) with min. 14 days survival after introduction of hospice service vs nonhospice patients of the same physician, stratified to age, sex and disease site characteristics of the hospice group, not reside within the	single center	USA	1-
Casarett, JAMA 2005 [200]	Improving the Use of Hospice Services in Nursing Homes	RCT, nonblinded	To examine whether promoting communicatin about hospice care can increase hospice enrollment and improve quality of care for nursing home residents	Nursing home residents and their surrogates from 3 nursing homes seleceted for the diversity of their resident population; residents who were not admitted for a respite stay; not already receiving hospice care; not too cognitively impaired; availability of a surrogate	multicentric (3 sites)	USA	1+ (RCT with some risk of systematic bias, no blinding, selection of nursing homes)
Cummings, Arch intern Med 1990 [201]	Cost-effectiveness of Veterans Administration Hospital-Based Home Care (VA HBHC)	RCT	to determine whether VA HBHC is more cost-effective than customary follow-up care alternatives	severely disabled (having ≥ 2 impairments in activities of daily living functionning) or terminally ill (life expectancy ≤ 6 months; by primary physician) inpatients of Hines VA Hospital; presence of available caregiver; residence within the HBHC 48 km catchment area;	single center	USA	1- (high risk of bias due to little information on intervention and control intervention; method of randomization unclear)
Hughes, Health Services Research 1991 (Begleitstudie) [202]	A Randomized Trial of the Cost Effectiveness of VA Hospital-Bases Home Care for the Terminally Ill	RCT?		terminally ill (life expectancy < 6 months; by primary physician) inpatients of Hines VA Hospital; presence of available caregiver; residence within the HBHC 30mile catchment area;	idem	idem	
Grande, BMJ 1999 [203]	Does hospital at home for palliative care facilitate death at home? Randomised controlled trial	RCT, parallel, nonblinded	To deteminde whether hospital at home enabled more patients to remain at home until death	> 16 years; any disease with prognosis of two weeks or less (estimated by clinicans); respite care for patients with cancer, MND , AIDS	single center	UK	1- (high risk of bias as there is no clear difference between the study intervention and the control intervention)
Grande, Journal of Palliative Care 2004 (Begleitstudie 1) [204]	Caregiver Bereavement Outcome: relationship with hospice at home, satisfaction with care, and home death	RCT, parallel, nonblinded	to investigate the impact of hospice at home on caregiver bereavement outcome	bereaved informal carers of terminally ill patients who took part in the study	idem	idem	
Grande, Palliative Medicine 2000 (Begleitstudie 2) [205]	A randomized controlled trial of a hospital at home service for the terminally ill	RCT, parallel, nonblinded	to test whether Hospital at Home differs from standard care in terms of perceived symptom control, adequacy of care and patients' ability to remain at home during their final 2 weeks	> 16 years; any disease with prognosis of two weeks or less (estimated by clinicans); respite care for patients with cancer, MND , AIDS	single center	UK	
Greer, J Chron Dis 1986 [181]	An alternative in terminal care: Results of the national hospice study	quasi experimental study	1. What is the difference between hospice and conventional care? 2. What is the differential impact of hospice and conventional care on the quality of life of patients and their families? 3. What is the impact of hospice on the health care costs incurred by terminal cancer patients?	cancer patients served in HC or HB hospices or in CC settings; cancer; remote metastasis (except for lung, brain, and pancreatic cancer); presence of a primary care person (PCP), generally a family member in the household (this excluded all nursing home patients); age 21 or older; CC patients only: Karnofsky Performance Status (KPS) of 50 or less	multicentric (40 hospices and 14 conventional oncological care settings; 26 hospices received special Medicare demonstration waivers allowing payment for normally non-covered services))	USA	2+ (some risk of bias because only patients with cancer and with a primary care person were inlcuded, i.a. patients living alone excluded)
[Begleitstudien von Greer: s. unter Palliativstation]							

Patients' characteristics at baseline

Author, Journal, Year	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Perform-ance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others
Brumley 2003 [198]	IG n=210, CG n=348 enrolled; analyzed: subgroup of patients who died: IG n=161, CG n= 139; / drop out: n=73 (13%) refused to participate in the interview	female IG=50.9%, CG=55.4%	IG: 70 (n.d.), CG: 74 (n.d.)	IG: 60.9%, CG 39.1%	CHF, COPD cancer; life expectancy of ≤12 vs. 24months	PPS mean (SD n.d.): IG 46.94, CG 52.5	mean days on service: IG 102, CG 159; PPS mean: IG 46.94, CG 52.5 (SD n.d.); Reid-Gundlach Satisfaction with Services instrument mean(SD): n.d., Text info: high for both groups (mean >40)	Ethnicity (% IG vs. CG): White 65.6vs. 52.5, Latino 17.4 vs. 16.5, African American 9.4 vs. 18.7, Asian 6.3 vs. 10.1
Buckingham 1978 [199]	35	no data	no data	100%	no data	no data	Symptom checklist 90, Social Adjustment Self-Report, Zuckerman Adjective Checklist	
Casarett 2005 [200]	205	153/52	84y(54-102)	9%	not defined	ADL, Charlson Score, MMSE	goals for care: single question adapted fro the SUPPORT study; needs for symptom management: Global Distress Index (GDI) of the Memorial Symptom Assessment Scale	Assessment of the residents` appropriateness for hospice care if either the resident or the surrogate: (1) expressed goals for care that focused on comfort; (2) refused both resuscitation and ventilation; (3) identifie at least 1 need for palliative care
Cummings 1990 [201]	n=244 severely disabled n=175 terminally ill/drop outs n=15/drop outs through death 44%	no numbers given; majority men	Interv (mean): 66.0±10.6 Control: 66.8±9.6	Interv: 29.4 Control: 32.6	1. cancer, heart disease; < 10% other diseases 2. - 3. for terminally ill: life expectancy ≤6 months	Bartels-ADL (0-100): Interv 66.0±30.4 Control 68.9±26.3; Cognitive status (0-10): Interv 8.1+2.1 Control 8.1+2.0;		Morale (1-2): Interv 1.5±0.2, Control 1.5±0.3; Satisfaction with care (1-3): Interv 2.6+0.3, Control 2.6+0.3;
Hughes 1991 [202]	n=175/n=4	65 % male	Interv (mean): 65.73±10.9 Control: 63.26±8.0	Interv: 73 Control: 80	1. cancer, diseases of genitourinary system, other respiratory diseases 2. - 3. life expectancy < 6 months	Bartels-ADL (-5-100): Interv 71.7, Control 71.8; Cognitive status (0-10): Interv 8.3, Control 8.2;		Satisfaction (1-3): Interv 2.65, Control 2.61;
Grande 1999 [203]	n=241/n=12 excludes (still alive at the end of the study)	115/114	Interv : 72.6 (13,6) Control: 72.1 (11.3)	Interv: 87 Control: 86	1. cancer (gastrointestinal 31%, genitourinary 21%, breats 9%, lung 8%) non-cancer conditions (14%) 2. - 3. prognosis ≤ 2 weeks			
Grande 2004 [204]	n=96	47/49	Interv: 72.4 (14.6) Control: 69.9 (12.4)	Interv: 83.3 Control: 83.3				
Grande 2000 [205]	n=241/n=12 excludes (still alive at the end of the study)	115/114	Interv : 73 (14) Control: 72 (11)	Interv: 87 Control: 86	3. prognosis < 2 weeks			
Greer 1986 [181]	n=1754 (833 HC, 624 HB, 297 CC) / drop out: 4.4% with no differences across settings / n.d.*	% female (HC vs. HB vs. CC): 51.3 vs. 51.8 vs. 52.7	means n.d.; HC vs. HB vs. CC in %: 21-54 years 10.3 vs. 9.3 vs. 26.6, 55-64y: 21.5 vs. 14.3 vs. 30.6, 65-74y: 42.4 vs. 44.8 vs 28.3, ≥75y: 25.8 vs. 31.6 vs. 14.5	100%	1. lung, breast, prostate, colorectal cancer; 2. metastatic at diagnosis: HC 49.6 vs. HB 50.4 vs. CC 47.6%; 3. "terminally ill"/"terminal cancer"	HC vs. HB vs. CC: least functional (10-30): 45.8 vs. 49.8 vs. 67.7 % most functional (40 and over): 54.2 vs. 50.2 vs. 32.3%	Patient awareness at initial interview comparable (full mental capacity HC vs. HB vs. CC): 48.9 vs. 49.9 vs. 54.3%;	non-white (% HC vs. HB vs. CC): 1.5 vs. 4.7 vs. 8.1; *Only patients who died during the study period were included in the final analytic samples since outcomes were assessed in relation to proximity to death;
[Begleitstudien von Greer]								

Informal caregivers' (CG) characteristics at baseline / Needs assessment / Needs complexity

Author, Journal, Year	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…)	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)
Brumley 2003 [198]	-					data from telefone interviews: undergraduate and graduate-level research assistants with either the patient or the primary caregiver if the patient was unable to participate; Pain=care team	Interviews were conducted via telephone at 7 days after enrollment in either palliative care or the comparison group and every 60 days thereafter; Pain is assessed at each visit.	Palliative Performance Scale (PPS) (11 categories that are measured in 10% decrements ranging from fully ambulatory to death); tool for pain assessment n.a.	-	
Buckingham 1978 [199]										
Casarett 2005 [200]	173	126/47	57(23-91)y			2 research assistants, interviews with resident in person and with surrogate by telephone	baseline interviews after rucruitment; when residents dies within 6 months follow-up, interviews with surrogates were carried out 2 months after the resident`s death	items adapted from the Toolkit Afterdeath Survey		
Cummings 1990 [201]	n=244 severely disabled n=175 terminally ill/drop outs through death of the patient 44%	no numbers given; majority women	Interv (mean): 66.8±13.4 Control: 58.4±13.6		Morale (1-2): Interv 1.6+0.3, Control 1.6+0.3; Satisfaction with care (1-3): Interv 2.6+0.3, Control 2.7+0.3;					
Hughes 1991 [202]	n=175/n=4		Interv (mean): 55.5±15.0 Control: 56.4±13.1		Morale (1-2): Interv 1.64+0.3, Control 1.58+0.3; Satisfaction with care (1-3): Interv 2.65+0.3, Control 2.61+0.3;	research staff (no further details)	health diary information retrieved monthly; interviews at one and six-month	health diary oer 6-months period, interviews (at patient's current location)		
Grande 1999 [203]										
Grande 2004 [204]	n=198 informal carers identified (for 86% of the patients); n=143 returned questionnaire after 1 month, n=95 after 6 months; n= 85 returned both	59/37	Interv: 62.3 (13.0) Control: 63.6 (8.3)	bereavement outcome, eneral health		researcher, questionnaire	six weeks and six months post bereavement	interview, TRIG (Texas Revised Inventory of Grief), The Physical Component Summray (PCS) and the Mental Component Summary (MCS) of the SF-36 Health		
Grande 2000 [205]	198					informal carers, GPs, district nurses	within 6 weeks of patients death	postal questionnaire with three-point scale for need of support; 4-point scale for symptom severity		
Greer 1986 [181]	same as patients (study describes sample of patients with a primary caregiver (=PCP)	n.d.			PCP was the patient`s spouse or child in 4 out of 5 cases; In HC hospices the PCPs were significantly less likely to be employed at the time of hospice entry. At the onset of the disease, a higher percentage (46%) of all PCPs were employed; those with patients entering hospice were only slightly less likely to be employed at this juncture	Patient outcomes: Primary care person assessed patients' overall and social quality of life and pain and symptoms; patients themselfs rated satisfaction with care; PCP outcomes:	patients needs: Personal interviews with the patient and PCP were conducted at study entry; first followup contact 7 days later and then repeated every 14 days thereafter until the patient's death; PCP needs: initial interview; bereavement interview 90-120 days after the patient's death		Functional performance: least functional (10-30) vs. most functional (40 and over); aggressive treatment (no/yes); severe pain reported (no/yes)	
[Begleitstudien von Greer]										

Intervention characteristics (structure and process quality criteria) – Teil 1

Author, Journal, Year	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management related to structures: How	Referral criteria / allocation of place
Brumley 2003 [198]	Palliative Care Program (interdisciplinary, home-based)	usual care	interdisciplinary home-based system of health care	n: n.d.; professions: home visits from the palliative care physician; nurse, and social worker with expertise in symptom management and biopsychosocial intervention	n.d.; total member enrollment of 675,000 (=patients)	TriCentral Service Area is comprised of three KP medical centers and provides home health care and hospice services for all medical centers through a central Continuing Care Department. (...) Telephone support and after-hours home visits available 24 hours per day, 7 days per week as needed. The after-hours line is staffed by a nurse who provides guidance based on established treatment guidelines, obtains physician orders,	Kaiser Permanente Garfield Memorial Fund	-	care team	coordinating and managing care across all settings and providing assessment, evaluation, planning, care delivery, follow-up, monitoring and continuous reassessment of care. The team also provides patient and family education (...)	IG: various sources including physicians, discharge planners, home health nurses, and social workers, liason nurses; CG: identified on enrollment in home health services and received standard KP health care in response to patients' needs (services included various amounts and levels of home health services, acute care services, primary care services and hospice care)
Buckingham 1978 [199]	hospice service	usual care	outpatients								hospice
Casarett 2005 [200]	structured interview with residents and their surrogates to identify residents appropriate for hospice care. If residents were identified as appropriate for hospice care, in the intervention group, the residents` physicians were informed about the interview results and asked to auhorize a hospice informational visit.	In the control group, hospice appropriateness was assessed in the same way, but the physicians were not informed about the interview results. Residents received usual care.	Nursing homes	nursing home staff and phycicians providing usual care for residents, hospice organizations		3 nursing homes	principal investigator received funding from the Dep. Of Veterans Affairs and a Paul Beeson Phycician Faculty Scholars Award				nursing home residents (3 sites)
Cummings 1990 [201]	Hospital based home care with interdisciplinary team	not specified	home care	physician, nurse, social worker, dietician, physical therapist, health technician; number and qualification not stated;			Departement of Veterans Affairs		HBHC physician also manages the inpatient intermediate care unit;		inpatients of Hines VA hospital who were severely disabled (having > 2 impairments in activities of daily living functionning) or terminally ill (life expectancy < 6 months; by primary physician); screening within 5-8 days after admission/no details on allocation of place
Hughes 1991 [202]	idem	customary care	home care	one physician, nurses, one social worker, one dietician, one physical therapist, health technicians; number and qualification not stated;	refering VA Hospital: 1100 inpatient beds				HBHC physician also manages the inpatient intermediate care unit;		all inpatient of Hines VA hospital with life expectancy < 6 months (by primary physician) with informal caregiver and within catchment area/no details on allocation of place
Grande 1999 [203]	Intervention: standard care + practical nursing care	Control: standard care	home care, outpatients, inpatient facilities	Intervention: 6 qualified nurses, 2 nursing auxiliaries, 1 nurse coordinator	100 patients/year		Elizabeth Clark Charitable Trust, NHS research and developement primary/secondary care interface programme		Who	How	> 16 years; any disease with prognosis of two weeks or less (estimated by clinicans); respite care for patients with cancer, MND , AIDS/random numbers
Grande 2004 [204]	idem	idem	idem	idem	idem		idem				idem
Grande 2000 [205]	Intervention: standard care + practical nursing care	Control: standard care	home care, outpatients, inpatient facilities	Intervention: 6 qualified nurses, 2 nursing auxiliaries, 1 nurse coordinator (all with specific interest in palliative care)	100 patients/year		Elizabeth Clark Charitable Trust, NHS research and developement primary/secondary care interface programme		Hospital at Home office at the same site as Marie Curie nursing service and inpatient hospice; administratively under same palliative care manager	run as separate service with separate funding.	
Greer 1986 [181]	hospice programm (hospices classified as those with beds (hospital based, HB) and those without beds (home care, HC));	conventional (oncological) care	home care and inpatient facilities (hospices with beds (hospital based, HB) and without beds (home care, HC), conventional ocological care)		home care hospices: 14 demonstration, 6 non-demonstration facilities; hospital based hospices: 11 demonstration, 8 non-demonstrationfacilities	n.d.	Medicare; Twenty-six (26) of the hospices received special Medicare demonstration waivers allowing payment for normally non-covered services (home care hospices: 14 demonstration, 6 non-demonstration facilities; hospital based hospices: 11 demonstration, 8 non-demonstrationfacilities)	-	small volunteer-dominated community programs caring for a handful of patients to large institutions and agencies with major commitments to hospice care;		
[Begleitstudien von Greer]											

Intervention characteristics (structure and process quality criteria) – Teil 2

Author, Journal, Year	Description of intervention: Schedule/Frequency	Content (clinical/non-clinical)	Description of bereavement intervention: Schedule/Frequency	Content	Description of control intervention	Coodination of intervention: Who	Coodination of intervention: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration of oncological and palliative structures: How	Others
Brumley 2003 [198]	program structure is similar to the Hospice Medicare benefit with modifications to provide care over longer periods of time; purpose= to provide an improved model of care combining care modalities and cost savings from the Hospice Model with curative care; (...) By including restorative therapy (...) "hospice philosophy" may be introduced without the negative connotation of "giving up" that is often associated with hospice (...) care team is responsible for coordinating and managing care across all settings (...) Telephone support via a toll-free number and after-hours home visits are available 24 hours per day, 7 days per week as needed by the patient.	• alleviating the physical, emotional, social, and spiritual discomforts of an individual with a terminal illness who is in the last phases of life; • patients may elect to continue restorative treatment (=ameliorative, referring to treatment that will not cure their disease, but will maintain and sustain a reasonable quality of life). • symptom control, patient education (self-management and crisis intervention in the home), and psychosocial services • training staff, patients, and families on use of medications • patient and family education and support	-		standard Kaiser Permanente TriCentral Service Area care and follows Medicare guidelines for home health care criteria.	central care team (patient and family, physician, nurse, and social worker with expertise in symptom management and biopsychosocial intervention)	responsible for coordinating and managing care across all settings and providing assessment, evaluation, planning, care delivery, follow-up, monitoring and continuous reassessment of care		-		
Buckingham 1978 [199]		hospice care, not more desscribed									
Casarett 2005 [200]	structured interview with residents and their surrogates to identify residents appropriate for hospice care. If residents were identified as appropriate for hospice care, in the intervention group, the residents` physicians were informed about the interview results and asked to auhorize a hospice informational visit.				standard care (physicians were not informed if residents were assessed as appropriate for hospice care)	research assistants			in-house hospice programs and outside hospice organizations		
Cummings 1990 [201]	HBHC service including medical, nursing, social work, physical therapy, and dietetic care including physicians home visits, pharmaceuticals, and supplies. Inividual patient-care plans developed by the team.				Mediacare home health care (no details)	HBHC manager					
Hughes 1991 [202]	HBHC program (develops goal-oriented, interdiciplinary patient care plans , schedules visits according to individual patient needs, involment of informal caregivers, timely communication about patients across team members)				traditional community home care service	HBHC manager					
Grande 1999 [203]	standard care (in hospital, hospice or care home with input from general practice, district nursing, Marie Curie nursing, Macmillan nursing, evening district nursing, social services, flexible care nursing service, or private care)+ practical nursing care for up to 24 h a day for up to two weeks provided by qualified nurses, nursing auxiliaries, nurse coordinator, agency nurses as required				standard care (in hospital, hospice or care home with input from general practice, district nursing, Marie Curie nursing, Macmillan nursing, evening district nursing, social services, flexible care nursing service, or private care)	Hospital at home coordinator					
Grande 2004 [204]	idem				idem						
Grande 2000 [205]	standard care (in hospital, hospice or care home with input from general practice, district nursing, Marie Curie nursing, Macmillan nursing, evening district nursing, social services, flexible care nursing service*, or private care)+ practical nursing care for up to 24 h a day for up to two weeks provided by qualified nurses, nursing auxiliaries, nurse coordinator, agency nurses as required ; *same as Marie Curie nursing but funded by community				standard care (in hospital, hospice or care home with input from general practice, district nursing, Marie Curie nursing, Macmillan nursing, evening district nursing, social services, flexible care nursing service, or private care)	Hospital at home coordinator				Standard care provided by e.g. Marie Curie Nurses and Macmillan Nursing	
Greer 1986 [181]	not scheduled	hospices with beds (hospital based, HB) and those without beds (home care, HC); hospice model treats the patient and family caregiver(s) as a unit	bereavement interview was conducted with the PCP 90-120 days after patient's death	conducted to assess PCP outcomes and to summarize records of utilization of hospital, physician, and home health services that the PCP had maintained while the patient was alive. In addition to the patient interviews, at each contact the PCP provided data on his own condition and attitudes, presented a record of all health services utilized by the patient, and reported on the patient's condition.	"conventional care" = all health care received by terminal cancer patients not enrolled in hospice. "Access points" were located and used to identify terminal cancer patients not receiving hospice care. The NHS selected conventional care (CC) settings representing, in the opinion of knowledgeable area physicians. "good" oncological care. Fourteen such access points ultimately participated in referring patients who. although identified in an outpatient setting, may have used a different inpatient	US hospices?					
[Begleitstudien von Greer]											

Outcomes / Results / Comments

Author, Journal, Year	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Brumley 2003 [198]	outcomes not clearly defined; as apparent from context: 1.O: sevice use (utilization data from KP mainframe database: number of emergency department visits, physician office visits, hospital days, skilled nursing facility days, home health and palliative visits, and days on hospice) and costs of care 2.O: • patient satisfaction with care (Reid-Gundlach Satisfaction with Services instrument); • severity of illness (Palliative Performance Scale (PPS)) • proportion of patients dying at home	calculated based on the 1999 cost of staff time associated with the care. Medication, facility, and administrative costs were not included in the calculations. As a result, the estimates of the costs of care are very conservative. Application of these costs to a nonmanaged care environment would be expected to reveal even greater cost savings.	• cost of care: average IG= $7,990, CG=$14,570 (programm reduced medical costs of care by 45%, p<0.001); • service use (IG vs. CG; mean(SD), p): Physician visits 5.335 (13.97) vs. 11.089 (13.81), p=0.001, Hospital visits 2.359 (10.96) vs. 9.352 (10.82) p<0.001, Emergency department visits 0.930 (2.51) vs. 2.297 (0.92) p<0.001, Skilled nursing care visits 0.851 (11.0) vs. 4.575 (10.87), p=0.005, Total home health visits 35.048 (31.83) vs. 13.247 (31.44) p<0.001; • satisfaction with care: at 60 days following enrollment: IG: "significantly higher satisfaction than at baseline (t=-2.57, p<0.01)", IG: satisfaction remained the same for comparison group members (t=-0.5, p=0.6) (mean(SD) n.d.); • site of death: IG 90%, CG 57% of patients died at home	-	• The reduction in use of emergency care, hospital, skilled nursing facility, and physician office visits for the palliative care group while concomitantly increased home health service use demonstrates the palliative care program's ability to effectively transfer end of life care from high-cost acute care services to a lower cost home based arena that allows patients to die in the comfort of their homes. • significant increase in level of satisfaction with services of palliative care patients from baseline to 60 days after study enrollment supports the transfer of care into the home environment; replication of this model may hold implications for a shift in care paradigms for chronically ill populations as well as those nearing end of life; • potential bias and confounders: comparison group design; PPS was used by telefone interviewers instead of trained medical professionals; conducted within a closed-system managed care organization in southern California area = doubtful ability to generalize this model to other organizational systems, populations, and communities; costs: Medication, facility, and administrative costs were not included
Buckingham 1978 [199]	depression, anxiety and social adjustment		hospice patients exhibited lower level of anxiety and depression and higher levels of social adjustment		limitied because of missing information about statictical details.
Casarett 2005 [200]	1.O: (1) hospice enrollment within 30 days of the intervention and (2) families`ratings of the quality of care for residents who died during 6-months-follow-up (items adapted from Toolkit Afterdeath Survey). 2.O: acute care admissions, days in acute care settings		(1) Hospice enrollment: Intervention residents were more likely to enroll in hospice (21/107 (20%) vs 1/98 (1%); P<0,001, Fisher exact test); (2) quality of care: Families of intervention residents rated the resident`s care more highly than did families of usual care residents, 4.3(2-5) vs 2.2(1-5), P=0.04. 2.O: Acute care admissions: Intervention 0.28(0-4) vs. 0.49(0-4), P=0.04. Days in hospital: Intervention 1.2 vs. 3.0, P=0.03		important findings for elderly patients living in nursing homes (simple intervention, highly efficient) but limiting generalization of the results to patients with cancer
Cummings 1990 [201]	Assessment at baseline, 1-month, 6-month: Functional status (Barthels Self Care Index; modified version) Cognitive Status (Short Portable Mental Status Questionnaire) Morale (Philadelphia Geriatric Center Morale Scale) Satisfaction of Care	use of health care services	Health care utilization: 100% of intervention group with at least one home visit, 63% of control patients; intervention group more likely to also receive visits from other profession of the interdisciplinary team (13,6 vs. 1,4 visits, p<0,0001); HBHC more continuous and longer (control group: longer delay until the start of service, shorter time on the program. Mean length of stay: effect size t=2,66, p=0,01); almost the same number of service visits in general in both groups. No sig. differences in hospitals days: Interv patients had fewer outpatient clinic visits. Significant more home care visits in intervention group. Interv. Total costs significantly lower Functional status: no differences Cognitive status: no differences Morale: no differences Satisfaction with care: Interv significant higher satisfaction at one month (0,1 on a 3-points scale,	Morale: no differences Satisfaction with care: Interv significant higher satisfaction at 1 and 6 months compared to control	multiple comparisons affect level of significance; no details on randomization process; No information regarding qualification of the team members. Little details on intervention and control intervention, no generalisability.
Hughes 1991 [202]	Assessment at baseline, 1-month, 6-month (carers: if patient dies between 1-month and 6-month, an interview was conducted within one month after the patients' death): Functional status (Barthels Self Care Index; modified version) Cognitive Status (Short Portable Mental Status Questionnaire) Morale (Philadelphia Geriatric Center Morale Scale) Satisfaction of Care	Utilization of health care services (within the VA system and the private sector); costs calculated based on US $ in 1985	Health care utilization: 98% of intervention group with at least one home visit from a HBHC staff member, 52% of control patients received some community-based home health care service; Interv group: average of 19.25 visits during study period, control group 13.64 (p< .05); Interv group lengths of stay on home care 67.9 d vs. control group 46.1 (p< .05);control group rarely received visits from disciplines other than nursing, intervention group more likely to also receive visits from other profession of the interdisciplinary team; no differences in readmissions to hospital, no differences in deaths at hospital; significant higher numbver of clinic visits for control group. HBHC costs more than double of control group ($1001 vs $343), VA hospital costs reduced by almost 50% for HBHC patients ($1798 vs. $3434); total costs of institutional care significantly lower for HBHC group. patients: no effect of group assignement on ADL, cognitive status, or morale; significant higher satisfaction with care in intervention group at one-month, higher but		no details on randomization process; sample size at six-month insufficient for regression model
Grande 1999 [203]	1. place of death/death certification		1. place of death: no sign. difference between the two groups in the likelihood of dying at home (interv.: 124/186, 67%; control: 25/43, 58%); patients who were actually admitted to hospital at home (not only allocated) were more likely to die at home than controls (78% vs. 58%)		Intention-to-treat analysis: only 113 (61%) of the patients allocated to hospital at home eventually got admitted to the service; 4:1 randomisation ratio to ensure that the service runs at capacity --> propable dilution of treatment effect. Initially planned study period had to be reduced from 22 to 15 months due to redesign of the trial to retrospective data collection --> loss of power due to lower number of patients that could parcipate. Standard care already seems to be quite comprehensive in the study area --> other input can contaminate results + generalisability is limited + high risk of
Grande 2004 [204]	1. bereavement outcome and carers satisfaction 2. relation of bereavement outcome to place of death		1. no difference in bereavement outcome between careres of intervention or control group 2. better early bereavement response für carers of patients who died at home, no difference after 6 months		high number of statistical tests. no details on who conducted the interviews (qualification?) or how these were conducted.. collection of a lot of data.
Grande 2000 [205]	1. informal carers need for support (three point scale; rated by GPs, district nurses and informal careres) 2. patient's symptom severity (four point scale; rated by GPs, district nurses and informal careres) 3. time spend at home during last 2 weeks of life (GPs, district nurses) 4. Visits made by the GP in the last two weeks of life		1. Intention-to-treat (ITT)- no difference in need for support for patient or carer between groups (carers rating); for patients who actually did spent time at home (per protocol; PP)- district nurse rating: significant more need for support by night nursing (support for patient) and looking after patient (support or carer) in the control group 2. ITT- carers: significant higher ratings for pain in the control group. c PP- carers: significant higher ratings for pain and nausea/vomiting in the control group; GP: significant higher ratings fordepression and anxiety in the control group 3. no significant difference in proportion who spent time		Intention-to-treat analysis: only 113 (61%) of the patients allocated to hospital at home eventually got admitted to the service and did spend time at home; second analysis for patients who actually did spend time at home differs in some results compared to the intention-to-treat analysis. Ratings of GPs and district nurses in the intention-to-treat analysis are not mentioned in detail. retrospective data collection as patients were to ill to complete questionnaires primary/secondary outcomes not clearly defined
Greer 1986 [181]	impact in 4 areas: • **pattern of care: % of patients receiving medical and social service interventions in the last weeks of life (data obtained from PCP and Medicare/reimbursement records whenever feasible)**: Intensive medical services (= Radiation therapy, surgery, chemo or hormonal therapy, thoracentesis), Diagnostic tests (=Blood tests, X-rays, or scans), Oxygen or respiratory therapy, Social services at last week of life (=Counseling, financial or legal assistance, paperwork, service referrals, training in patient self-care) • **patient outcomes:** overall and social QoL* (QL-Index), pain and symptoms* (McGill questionnaire; California pain assessment profile), satisfaction with care (medical interview satisfaction scale); * = assessed by primary care person. More details on QoL see Morris et al 1986a, more details on pain see Morris et al 19986b. • **family outcomes** (PCP): perceived axiety while the patient was alive (EITS Manual for the Profile of Mood States); emotional distress following patients death (Manual for the Grief Experience Inventory); morbidity during the bereavement	Hospice inpatient and home care unit cost coefficients were developed using 1982 cost report data compiled either by HCFA or evaluation staff accountants. Cost reports separately allocated all pertinent agency costs to a hospice cost center. All inpatient costs were nationally adjusted based on Medicare hospital reporting data; hospice home care costs were not nationally adjusted since national standards did not exist. (See Birnbaum and Kidder [46] for a description of the approach to calculating the cost of utilization episodes.)	QoL similar in hospice and CC systems with the exception of pain and symptom control, which may be better in the inpatient hospice setting (HB). Hospice patients are less likely to receive diagnostic tests, X-rays, and aggressive anti-tumor therapy in the terminal period, and they are more likely to receive social service support than CC patients. • pattern of care: • <u>patient outcomes:</u> **overall QoL:** similiar, **social quality of life: Hours of direct care** provided to the patient sig. higher for HC patients than HB or CC patients (p=n.a.), **hours of social visiting (=other than PCP) 3 weeks prior to death:** HC sign. higher than CC, difference between HC and HB n.s.; **pain and other symptoms:** for pain see Morris et al. 1986, **other symptoms (nausea, dry mouth, constipation, dizziness, feverishness, dyspnea):** 3 weeks before death: HB fewer symptoms than HC or CC, 1 week prior to death: same but stat. sign. in the HB-CC comparison, only. for details on pain see Morris et al. 1986b • **satisfaction with care:** No sig. differences, "uniformly high in all settings" • <u>Costs:</u> **Total cost per study day:** substantially lower in HC than in HB or CC ($101 (SE=9.1) vs. $146 (SE=10.0) vs. §149 (SE=11.7) p=n.d.); These differences were	Families appeared to tolerate the stress of terminal illness and bereavement better than expected. Consistent with their greater burden, HC PCPs reported more emotional distress than HB PCPs during bereavement but were not more likely to report secondary morbidity. • **satisfaction with care:** HB PCPs higher satisfaction with the patient's care than CC PCPs (before and after death of patient); PCPs in both types of hospices satisfied with where the patients died (despite marked differences in places) however, both hospice PCP groups were more satisfied with where the patient died than were CC PCPs. HC PCPs were significantly more likely than HB and CC PCPs to report that the patient had been able to remain at home as long as he/she wanted. • **perceived caretaking burden:** small sign. difference (HC PCP perceiving higher burden than HB / CC) • **modified mood state scale (measuring anxiety and depression):** no sign. differences among the three PCP groups; • increased absenteeism from work: 4% overall, differences n.s.; **regret concerning the medical tratment the patient received:** 11%	• **thoughts on generaliizability:** conducted within closed-system managed care settings; as a result, it may be less generalizable to all healthcare settings, and the relative cost savings may not be realized across other settings; the sample is only patients with a primary care person, i.e. patients living alone (a proxy for no PCP) are not included in the analysis • **high levels of satisfaction with care in all three settings**: may reflect self-selection, but could also be the result of the extremely high level of informal support which is mobilized in the presence of terminal illness and which may leave little room for incremental improvement from professional sources; small but significantly higher level of satisfaction reported by HB family members may be a reflection of their reduced sense of burden. • **costs:** HC model is less costly than HB or CC largely because HC substitutes home care for inpatient care, relying on family members to provide up to 12 hours a day of direct care. HB hospice appears to be less costly than CC for patients during the last
[Begleitstudien von Greer]					

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)																						Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justific	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Perform-ance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description		Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding		Organisation / Management related to structures		Referral criteria / allocation of place	Description of intervention		Description of bereavement intervention		Description of control intervention	Coodination of intervention		Discharge criteria	Integration of oncological and palliative structures		Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs			
																										Intervention	Control					Who (source)	How much	Who	How		Schedule/Frequency	Content (clinical/non-clinical)	Schedule/Frequency	Content		Who	How		Who	How						
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG (Fortsetzung)																																																				
Harding, J Pain Sympt Manag 2004 [206]	Evaluation of a Short-Term Group Intervention for Informal Carers of Patients Attedning a Home Palliative Care Service	Controlled before-after-study	to measure uptake of the group, to discover which carers access to the model, to determine processes of the group, to measure carers outcome	adult informal unpaid carers of patients atteding two palliative care services, fluency of spoken English, staff prognostication that the patient would be alive for a minimum of 3 wks	two centers	GB	2+	n.r.	n.r.	65 (16.3)	n.r.	1. cancer 63, HIV 4, motor neuron disease 2, Bechet´s disease 1, congestive heart failure 1, Liegh´s syndrome 1, Parkinsonßs 1	n.r.	n.r.	n.r.	170 CG, 40 agreed to participate in the intervention, 4 no data collection = 36 as intervention and 37 as control group = 73 (not balanced for employment, ECOG-PS)	50 / 23	59.2 (13.3)	psychological support, anxiety reduction, information giving, short term coping:	relation to patient (wife/partner 24, husband/partner 21, daughter 10, parent 8, son 3, friend 2, ex-partner 1, sibling 1 other family 2), daily hours (mean 15.4, median 17 hrs) and months of caring (mean 27.3 madian 17 months), employment	research staff	baseline (t1), post-intervention (=t2 about 8 wks from t1) and follow-up (=t3 about 5 months from t1)	Palliative Outcome Scale (POS), ECOG-PS, Zarit Burden Inventory (ZBI), Coping Response Inventory (CRI), General Health Questionnaire-12 (GHQ-12), State Anxiety Scale (SAI) - short version,	?	?	90 minutes group meeting, weekly for 6 times	usual care	Group meeting	24h home access to specialist nursing, advice, and support	max. 12 per group	n.r.	NHS	n.r.	n.r.	n.r.	n.r.	6 times, weekly: 15 min: opening, catch up oof the week; 30-40 min. speaker presenting a topic, 35-45 min: expanding of the topic, group discussion, preparation of next week; 15 min: closure and goodbyes	welfare benefits advice, occupational and physical therapy, clinical nurse specialist, aromatherapy	n.r.	n.r.	usual care of palliative home care service	facilitator	n.r.	not applicable	n.r.	n.r.		Carers beiing in employment was significantly associated with worsening patient psychological scores. A significant association was identified for increasing daily hours of caring and burden increase. The significant effect for daily hours of caring was also found for worsening role strain. A significant association was found for increasing months of caring and improving role strain. Greater age was associated with a reduction in overall burden, increasing state anxiety and problem-focused coping response.	n.r.	not clearly mentioned		no clear data regarding to differences between intervention and control in time course
Harding, J Palliat Care 2002 [207]	A Multi-Professional Short-Term Group Intervention for Informal Caregivers of Patients Using a Home Palliative Care Service	prospective observational study combining quantitative and qualitative methods, no control	to present the developement, content and delivery of a short-term multidisciplinary information and support group for carers of patients assessing home palliative care; to identify the most appropriate evaluation meth...	adult informal carers of patients atteding two palliative care services	two centers	GB	2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	160 addressed, 40 participated, 21 included in t	n.r.	n.r.	n.r.	to meet people with similar problems, to reduce feelings fo isolation, to share troubles, ideas and advices	research team	t1, t2, t3	semistructured interview	n.r.	n.r.	90 minutes group meeting, weekly for 6 times	not applicable	Group meeting	n.r.	max. 12 per group	n.r.	NHS and Kings College	n.r.	n.r.	n.r.	n.r.	6 times, weekly: 15 min: opening, catch up oof the week; 30-40 min. speaker presenting a topic, 35-45 min: expanding of the topic, group discussion, preparation of next week; 15 min: closure and goodbyes		n.r.	n.r.				not applicable	n.r.			reported benefits: (1) reasons for attending (see above), (2) format (90 good length, no of session 6 o.k., size of group max. 12), (3) group participation (friendly atmosphere, (4) content and information gained (valued weekly topic), (5) reported benefits (meeting other carers, (6) heterogeneity of members (was seen as a difficulty, e.g. different diseases, late and earlier stage), (7) facilitatrors' perspective: focus on themselves (carers) was possible, light guidance, difficulties were to stop discussions and to find a	n.r.	not applicable	qualitative analysis	
Jordhoy, Lancet 2000 [208]	A palliative-care intervention and death at home: a cluster randomised trial	RCT (cluster randomization)	to enable patients to spend more time at home and die there if they prefer	patients with (a) uncurable malignant disease, (b) aged 18+, (c) life expectancy of 2-9 months	single center	Norway	1+	434 / 395: 16 withdrew (6 vs. 10)	204 /230	median 69 (SD n.r.)	100%	1. GI-Tract 181; Lung 52; breast / female genitals 67; prostate / male genitals 41; kidney / vesica / urether 29; lymphoma 13; skin 12; others 39; 2.distant metastasis 343, regional / localized disease 91; 3. n.r.	KPS 90-100 = 153; 60-80 = 250; <=50 = 31	not addressed	local, regional and distant disease, living situation, working status, education	not addressed	not addressed	not addressed	not addressed	not addressed	Patients	at baseline	1. in- and outpatient service at the PCU, unless required elsewhere for medical reasons, 2. team of PCU served as link to the community, 3. predefined guidelines, 4. educations program for community professionals;	n.r.	n.r.	program of palliative care	standard care: family physician, home care nursing, nursing homes, 24h home-care service, night service is limited to short visits and telephone consultation,	outpatients	PCU 12 beds, outpatients clinic, consultant team in and out the hospital, including a palliative-care nurse, a social worker, a priest, a nutritionist, a part time physiotherapist, 3 full time physicians, with one in charge for the consultant service. The team worked daytime	12	n.r.	Norwegian Cancer Society - Public health care	n.r.	Palliative Medicine Unit (PMU) of the University Hospital of Trondheim;	n.r.	n.r.	The patients' family physician and a community nurse were defined as the main professional caregivers. After trial entry, the patients were referred to the Palliative Medicine Unit and plans for the treatment or care were set up in a joint meeting of the patient, the informal caregiver or caregivers, the family physician, the community nurse, and a consultant nurse or physician from the unit. Thereafter follow-up consultations by the community staff were set up as routine. The Palliative Medicine Unit team coordinated care and was available for supervision and advice and to join visits at home. Hospital service was offered on request. Discharge from the inpatient unit was planned jointly with the patients, the family, and the community service. Multidisciplinary staff meetings were arranged weekly. For referral and admission to nursing homes, conventional routines were followed. The educational programme for community staff included bedside training and 6–12 h of lectures every 6		n.r.		standard hospital and community care, including services from general practitioners, home care nurses, and nursing homes			n.r.	n.r.			place of death; time spend in institutions in the last months of life; median survival	n.r.	death at home n=54 (25% - intervention) vs. n=26 (15% - control) p=0.02; nursing home death n=19 (9% - intervention) vs. n= 36 (21% - control) p<0.01); similar proportion of hospital death; nursing home admission in the last month of life n=28 (13% - intervention) vs. n=42 (24% - control) p<0.01; time spend in nursing home (proportion of days) mean 3.0 (intervention) vs. 7.4 (control) p<0.05) / in the last months 7.2 vs. 14.6; time spend in hospital (proportion of days) 32.2 vs. 29.8 / in the last months 45.5 vs. 45.3; median surivival 99 days (intervention) (95% CI 79-119) vs. 127 (control) (95% CI 88-166);	not applicable	high percentage of patients dying in instututions and not at home. Criteria for integration of patients in the study not well defined. Number of patients in both study arms unequal.
Jordhoy, J Clin Oncol 2001 [209] (main study2) [207]	Quality of life in palliative cancer care': results from a cluster randomized trial	RCT (cluster randomization)	to improve HRQOL especially pain control, physical and emotional functioning and psychological distress	patients with (a) uncurable malignant disease, (b) aged 18+, (c) life expectancy of 2-9 months	single center	Norway	1+	434 (Baseline) / 16 / 395	204 /230	median 69 (SD n.r.)	100%	1. GI-Tract 181; Lung 52; breast / female genitals 67; prostate / male genitals 41; kidney / vesica / urether 29; lymphoma 13; skin 12; others 39; 2.distant metastasis 343, regional / localized disease 91; 3. n.r.	KPS <= 70 170; KPS > 70 264	not addressed	living situation, residence, education, wks from diagnosis to inclusion	n.r.	n.r.	n.r.	n	n.r.	Patients	monthly	EORTC-QLQ-C30; IES; 5 social support items, 3 items of general well-being	n.r.	n.r.	program of palliative care	standard care	outpatients	Palliative Medicine Unit (PMU) with inpatient unit - 18 nurses, 2 physicians -, outpatient clinic and a multidisciplinary consultant team - palliaitve care nurse and physician -	12 beds	n.r.	Norwegian Cancer Society - Public health care	n.r.	Palliative Medicine Unit (PMU) of the University Hospital of Trondheim;	n.r.	n.r.	A predefined intervention program including detailed guidelines for the interaction between the PMU and the community was initiated by the opening of the trial. The patients' general practitioner (GP) and a community nuse were defined as the main professional caregivers. When entering the program, the patients were referred to the PMU. Individual treatment plans were set up in a joint meeting of the patient, the informal caregiver, the GP, the community nurse, and a consultant nurse or physician from the PMU. Follow-up consultations by the GP and the community nurse were arranged according to the patients' needs and predefined minimum standards.Hospital service was offered on request and always at the PMU, that is, unless otherwise required for medical reasons (eg, surgery). The PMU consultant team participated in the inpatient care, handled the PMU outpatient clinic, coordinated the follow-up, and was available to the community staff for supervision and advice and to join visits in the patient's home. An educational program for the community		n.r.	n.r.	GPs, home care nurse, nursing home, no inpatient treatment on PMU but on other wards, no multidisciplinary team, ad hoc outpatient consultation, mainly addressing physical needs, principal caregiver and hospital contacts seldom clearly defined, none care consultation, adhoc treatment plan, no joint meetings, home care and GP visits ad hoc, hospital admittance on request, hospital discharge ad hoc routines, no assistance with community service, no palliative care training for inpatient and community staff		n.r.	n.r.	n.r.	n.r.	n.r.	QoL including: - physical and emotional functioning, - pain, - psychologic distress assessed monthly by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) questionnaire and Impact of Event scale (IES)	n.r.	No significant differences on any of the quality-of-life scores were found. At later assessments and for scores that were made within 3 months before death, there was also no consistent tendency in favor of any treatment group on the main outcomes or other EORTC QLQ-C30 scales/items	not applicable	no relevant difference in QoL scores defined.
Jordhoy et al. 2003 [210]	Which cancer patints die in nursing homes? Quality of life, medical and sociodemographic characteristics	retrospective cohort study	to define characteristics associated with death in nsursing homes	patients with (a) uncurable malignant disease, (b) aged 18+, (c) life expectancy of 2-9 months	single center	Norway	2-	395 (death of 434 in the primary study)	184 / 211	n.r.	100%	GI-Tract = 168, Lung = 48, Breast and female genitals = 57, Prostate and male genitals 36, others 86	KPS <= 70 = 161; > 70 = 234	not addressed	living situation, education, metastases, no patients with living in the nursing home at study entry	not addressed	not addressed	not addressed	not addressed	not addressed	not applicable	not applicable	not applicable	n.r.	n.r.	program of palliative care by PCI in close co-operation with the comunity service (intervention)			PCU, University Hospital of Trondheim, GP, home care nursing, nursing homes					nursing home placement is decided in the nursing office, responsible for home care and nursing home servive	n.r.	based on the overall evaluation of the patient´s medical and social situation	nursing home placement is normally used when frequent or continuous attention is needed while spezialized hospital care is not required		n.r.					n.r.	n.r.			characteristics associated with death in nursing home	n.r.	patients dying in nursing home (compared to hospital or home) were older (median 77 yrs vs. 69 and 65), often living alone (58% vs. 30 and 20), and female (66% vs. 44 and 41), poor KPS = <=70 (73% vs. 39 and 26); in-patient care 57% all and 88% of last months for those dying in nursing homes vs. 42% and 60% (death in hospital) and 14% and 17% (for home death), median survival 129 days (nursing home death), 75 days (hospital death) and 111 (home death) p=0.66 (log rank); factors in multivariate analysis for outcome death in nursing home: age (OR 1.88 per 10 yrs), KPS >=70 (OR 0.33), conventional care (OR 2,73), living with spouse (OR 0.43); results of HRQOL: no baseline differences, but poorer results in all functional scale and in	not applicable	
Ringdal et al. 2002 [211]	Family satisfaction with End-of-Life Care for Cancer Patients in a Cluster Ranomized Trial	retrospective comparision between two groups of family members of an RCT	difference of close family member´s satisfaction with care between the intervention and control arm of an RCT on Palliative Care	patients with (a) uncurable malignant disease, (b) aged 18+, (c) life expectancy of 2-9 months	single center	Norway	2-	434 patients,426 with family members, 312 included, 183 completed questionnaires one months after death	87 / 96	68 (median)	100%	GI-Tract = 85 Lung = 26 Breast / female genitals 20 Prostate 16 others 36	n.r.	n.r.	education, time from inclusion to death, place of death	183	125 / 58	57.6 (median) intervention arm 53.9 (median control arm)	not addressed	relation to patient, children living at home, education, work	questionnaire filled in by the family members	one months after death	FAMCARE Scale	n.r.	n.r.																							satisfaction with care, response rate	n.r.		response rate: 49% intervention group, 36% control group; death at home 27% intervention group, 14% control group. In all but 2 of 20 items the intervention group had better results than the control group. Results were significant in 10 out of 20 items (Table 3). The relationship to the deceased was signifikant related to satisfaction with care, as was the sex of the deceased (higher satisfaction in male than in female patients), if patients dyed at home, satisfaction of care was higher compared to death in nursing	
Ringdal et al. PSC 2007 [212]	Does social support from family and friends work as a buffer against reactions to stressful life events such as terminal cancer	secondary data analysis of a cluster randomized trial	to axamine the relationship between social support and emtional functioning and stress reaction	patients with (a) uncurable malignant disease, (b) aged 18+, (c) life expectancy of 2-9 months	single center	Norway	2+	434 / 198	204 / 230	median 69 (SD n.r.)	100%	1. GI-Tract: 181; Lung 52; Breast / femal genitals 67; Prostate 41; Urological 29; others 64; 2. n.r.; 3. n.r.	KPS 40-60 86; 70 84; 80 111; 90 107; 100 46	not addressed	Eduction	n.r.	n.r.	n.r.	n.r.	n.r.	Patients	baseline in the hospital, than via mail, reminder 2 wks later	social support questions, emotional functioning subscale of the EORTC-QLQ-C30; subjective stress by the Impact of Event Scale (IES) subscale intrusion and subscale avoidance	n.r.	n.r.	program of palliative care	standard care	outpatients	Palliative Medicine Unit (PMU) with inpatient unit, outpatient clinic and a multidisciplinary consultant team in close collaboration with the community health care service.	12 beds	n.r.	Norwegian Cancer Society	n.r.	Palliative Medicine Unit (PMU) of the University Hospital of Trondheim;	n.r.	n.r.	follow up consultations by the community professionals as a routine, PMU and was available for supervision, advice and to join in home visits, hospital service was offered on request, the family was encouraged to participate in all consultations.	Indentification of familty doctor and community nurse as the principal professionals, treatment plan estbalished with patients and relatives, PMU and community professionals. PMU consultant team coordinated the care, and the discharge from the inpatients unit was planned jointly with the pateints, family and community service.	n.r.	n.r.	standard hospital and community care, including services from general practitioners, home care nurses, and nursing homes	follow up consultations by the community professionals as a routine, PMU and was available for supervision, advice and to join in home visits, hospital service was	n.r.	n.r.	n.r.	n.r.		1st pts who report a high degree of social support will experience fewer stress reactions and better emotional functioning than pts with a low degree of social support at baseline 2nd at 2 months follow up	n.r.	pts with high social support report better emotional functioning and less serious stress reactions than pts with less social support	n.a.	secondary data analysis, not preplaned, effect of structured PC compared to usual care not analysed
McCorkle et al, Cancer 1989 [213]	A Randomized Clinical Trial of Home Nursing Care for Lung Cancer Patients	RCT, nonblinded	to test the effects of three treatment regimens on the psychosocial well-being of patients with lung cancer	(1) patients registered in the Cancer Surveillance System program with lung cancer (squamous cell, adenocarcinoma, small cell, or giant cell), and classified as stage II lung cancer or higher; (2) resided in King County, Washington, USA; (3) met the Medicare criterion of being homebound; (4) capable of cooperating with the requirements of the study, informed consent	multicentric (recruitment at 19 hospitals and 1 outpatient facility, data collection at patients` homes)	USA	1- (RCT with high risk of systematic bias, no blinding, no sample size calculation, no intention-to-treat analysis)	900 eligible patients, 166 patients included in final analysis; 66% (n=111 patients) died or withdrew from the study during study period/before completion of 5 interviews; 78 patients who completed 4 interviews were used to complete the substantive analysis. The 5th occasion data (5th interview) were not included because of the	61/105	18-89 years	100%	stage II lung cancer or higher (squamous cell, adenocarcinoma, small cell, or giant cell)									research assistants	5 times at 6-weeks intervals: 2; 3,5; 5; 6,5 and 8 months after diagnosis				(1) specialized oncology home care program (OHC); (2) Standard home care program (SHC) .	office care (OC) program	home care	intervention groups: nurses with master's degrees trained to give personalized care to persons with advanced cancer and to their families; registered nurses, physical therapists, home health aides, medical social work, occupational therapist, and a speech pathologist. Control group: patients` physicians			?	?	?	?		2 intervention groups over a period of 6 months: (1) specialized oncology home care program (OHC) delivered by nurses with master's degrees trained to give personalized care to persons with advanced cancer and to their families. (2) Standard home care program (SHC) provided by an interdisciplinary team of health professionals (registered nurses, physical therapists, home health aides, medical social work, occupational therapist, and a speech pathologist).				standard home care provided by the patient's physicians (traditional treatment, office care group (OC))						Each patient was interviewed on 5 occasions over a 6-months period; first occasion after a preliminary consent interview (within 8-10 weeks after initial diagnosis of lung cancer); remaining 4 interviews occurred at 6-week-intervals.	• Pain (McGill-Melzack Pain Questionnaire) • Mood disturbance 8 Profile of Mood States, POMS) • Concerns (Inventory of Current Concerns, ICC) • Symptom distress (Symptom Distress Scale) • Functional status (Enforced social dependency Scale) • Health perception (General Health Rating Index) • number of hospitalization, length of hospital stay	ns	**Pain, concerns, mood, number of hospitalization, length of hospital stay:** not significant **Symptom Distress:** significant difference (p=0.03, F=5,01) between the time profiles of the two home care nursing groups and the office care group. All groups experienced increased symptom distress over time, but the OC group (control group) experienced elevated symptom distress a full occasion sooner (6 Weeks sooner) than the intervention groups. **Functional status:** All groups experienced increased dependency at occassion 4, but patients receiving home care remained independent for a longer period of time than the Office Care group (p=0.02, F=5,72). **Health perception:** OC group reported rather steadily reported Health Perceptions over time, whereas the two treatment groups reported worse Health Perceptions (P=0.05, F=4,06).		Results suggest that home nursing care may help lung cancer patients to deal with distress from symptoms and maintain their independency longer in comparision to no home care. However, patients receiving home care may rather acknowledge the reality of their situation. Despite its limitations, this study published in 1989 seems important and demonstrates that new, rather simple home care models may maintain quality of lifefor a longer time period in severly ill patients with respect to some relevant outcomes.
McCorkle et al, Nursing Research 1998 [214]	The effects of home nursing care for patients during terminal illness on the bereaved´s psychological distress	secondary analasis of data from the RCT (main study, described above)	To determine whether specialised oncology home care services provided to terminally ill patients positively influences bereavement psychological distress	Spouses of the patients included in the main study (patients criteria described above)	..	..		..								Of the 100 persons enrolled, 91 completed the baseline interview (=constituting the final spouse sample). Of the 91 persons, 34 were not included in the final analysis because the patient remained alive at the completion of data collection, were lost to follow up, or refused to participate. In addition, data were incomplete for 11 persons. Therfore, the	predominantly female	mean age 58 years			..	spouses were interviewed at the same times as the patients while the patients remaned alive (5 times at 6weeks intervals; see above). If a patient died, spouses were then interviewed at 6 weeks and at 6 months after the patient`s death.	spousal psychological distress was measured using the Brief Symptom Inventory (BSI)			..	..	..	..								..											..			Significant mean group differences on the subscales of depression (F/2,43)=4.67, p=0.015) and paranoid ideation (F(2,43)=3.66;p=0.034) after the patients' death. On all measures, the distress levels of the bereaved spouses in the OHC group were on average lower than the other towo groups. Statistically significant (P<0.05) differences between the OHC group and the OC group at these points of time: 6 weeks on depression and psychoticism; 6 months on hostility, paranoid ideation, and psychoticism; and 13 months on hostiliuty, paranoid ideation and GSI. However, there were no significant differences between any of the groups at 25 months.	The data suggest that the bereavement course among survivors can be positively influenced based on the model of nursing care provided during the patients' terminal phase of illness. Oncology home care may reduce the overall level of distress among patients` spouses compared to office care or standard home care. However, the study has relevant limitations e.g. the small sample size, no intention-to-treat analysis and the data should be interpreted with caution.

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justific	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management related to structures: How	Referral criteria / allocation of place	Description of intervention: Schedule/Frequency	Description of intervention: Content (clinical/non-clinical)	Description of bereavement intervention: Schedule/Frequency	Description of bereavement intervention: Content	Description of control intervention	Coodination of intervention: Who	Coodination of intervention: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration of oncological and palliative structures: How	Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)																						Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG (Fortsetzung)																																																				
McKegney, Gen Hosp Psychiatry 1981 [215]	Prediction and Management of Pain in Patients with Advanced Cancer	CCT	The major hypothesis of the study was that visits in the home by trained oncology nurse practitioners would result in improved quality of life for an experimental group of patients, compared with a carefully matched control group of patients who did not receive such home visits but whose care was otherwise the same as that of the experimental group. Multiple psychosocial and biological variables were also studied, as they might identify those patients with predictably greater difficulties in pain management over their last months of life.	terminal cancer; mental competente; a minimum age of 16 years; a signed informed consent; and an expected survival of greater than three months but less than one year as judged by an experienced oncologist	multicetric? (multiple health providers, home patients, but one site coordinated study/intervention)	USA, Vermont	1- (no randomization, high risk of bias)	n=199 patients (intervention group n=98, control group n=101) included, thereof n=139 had died during the study and thereof 38 intensive and 45 non-intensive patients had a sufficient number of pain ratings (=were analyzed)*	IG: n=21/19, CG: 27/16	IG mean (SD): 58.7 (1.7); CG: 56.1 (2.2)	100%	1. types of cancer n patients included: IG: lung=20, breast=6, GI=8, other=6; CG: lung=14, breast=6, GI=9, other=14; 2. n.d., "varying stages of their illness"; 3. terminal cancer patients (expected survival of greater than three months but less than one year as judged by an experienced oncologist)	s. Yates et al. 1977	• pain: not reported for initial assessment; • CMI: 23/55 patients had initially a mild to severe emotional disturbance ("high CMI" group). • Rotter Lotus of Control (I-E) Scale: 34/55 initially gave 4 or more "external" responses on the 8-item I-E scale ("high I-E" group), and 21 patients gave 0-3 external responses ("low I-E" group)	* no data on drop out but improtant hint: Of the 139 patients who died during the study, 38 intensive and 45 non-intensive patients had a sufficient number of pain ratings (three or more) to compare the effectiveness of pain management over time in the two groups.	-					trained independent raters (non medical observers); nurse in pain assessment?	same frequency as the nurses' visits (beweekly in patients with an expected survival of less than three months and monthly in those expected to live longer)	structured interviews in the patients' homes, done at the same frequency as the nurses' visits: • "Pain Estimate" score by Sternbach (0-100 self-report of pain) • modified Rotter Lotus of Control (1-E) scale (internal-external expectation of control) • Cornell Medical Index (CMI) M-R scales (psychological symptoms) • initial research data base (IRDB) (medical, nutritional, physical, psychosocial, and religious status)	• Cornell Medical Index (CMI): "High CMI" = 6 or more "yes" responses on the M-R section of the CMI, indicating a mild to severe emotional disturbance vs. "low CMI"= 0-5 yes responses • Rotter Locus of Control (I-E) Scale: "high I-E"= ≥4 'external' responses on the 8-item I-E scale; "low I-E"= 0-3 'external' responses on the 8-item I-E scale	• CMI: "cut score" of 6, slightly above the customary 4 or 5, was chosen in order to increase the accuracy of positive prediction; • Rotter Lotus of Control (1-E) scale: n.d.	standardized home visits by a nurse practitioner acting as an extension of a multidisciplinary team; multidisciplinary care at the MCHV and/or from their private physicians	multidisciplinary care at the MCHV and/or from their private physicians without home visits	home care, rural setting	nurse was chosen as the interface between the multidisciplinary team and patients receiving palliative therapy, since normal activities for nurses encompass many of the skills carried out by individual team members. Nurse practitioners with extensive experience in care of the patients with advance cancer; Regular participants in the multidisciplinary team consisted of medical and radiation oncologists, psychiatists, social workers, physical therapists, nutritionists, occupational therapists, enterostomal therapists, and clergymen.			NIMH Training Grant MH08057 17 and NCI grant 17868	-	Vermont Regional Cancer Center (VRCC) at the University of Vermont; major medical center, the Medical Center Hospital of Vermont (MCHV), responsible for most of the region's cancer surgery, radiation therapy, and chemotherapy.		All new patients seen by radiation therapy and medical oncology were eligible for accession to the study.	the visit rarely exceeded 30-45 minutes; Patients with an expected survival of less than three months were visited by nurses biweekly and those expected to live longer were visited monthly.	The home visit by the nurses was primarily focused on attending to the needs of the patient, and interactions with family members were incidental to that task. In addition to providing physical care, much of the nurse's time was spent in talking with the patient about their illness and its implications. The nurse frequently mobilized family and other social resources to meet the patient's needs and also coordinated with the patient's local physician. These nurses thus served in the well-known public health, or visiting nurse, role, with the differente that the project nurse had the benefit of a multidisciplinary health care team back-up resource.	-		patients received only multidisciplinary care at the MCHV and/or from their private physicians, without home visits by the nurse	Nurse practitioners with extensive experience in care of the patients with advance cancer; multidisciplinary health care team back-up resource	A "Protocol for Management of Pain" was developed by the team and used by the nurses as part of their wide range of physical treatments and psychosocial interventions. This protocol was based upon sound pharmacological principles, many of which are often ignored (i.e. oral methadone is an effective and longer lasting analgesic than other narcotics, and was used extensively in this program);		Medical Center Hospital of Vermont (MCHV), multidisciplinary team, local physicians	Medical Center Hospita1 of Vermont (MCHV), responsible for most of the region's cancer surgery, radiation therapy, and chemotherapy; nurse was chosen as the interface between the multidisciplinary team and patients receiving palliative therapy.		1.O: pain as a reflection of quality of life ("Pain Estimate" score described by Sternbach, a 0-100 self-report of pain at the present time) 2.O: • expectation of control (modified Rotter Lotus of Control (1-E) scale) • psychological symptoms (Cornell Medical Index (CMI) M-R scales, a 51-item self-report measure) • overall health status (Kamofsky Performance Status (KPS) scale) • patient's medical, nutritional, physical, psychosocial, and religious status	-	*means not reported for the single time-points; means are only presented in figure and the following information available in the text:* • **pain control:** with nearing death, mean pain scores in intervention ("Intensive") group were significantly lower than in the control ("Non-intensive") group in the last period (0-30days before death); in the last 90 days before death mean pain scores in the non-intensive group of patients continued to rise until death, whereas the mean pain scores in the intensive group of patients plateaued; the two groups had essentially the same mean pain scores until the last 90 days before death; • **CMI:** "High CMI" group (n=34) had higher mean pain scores than the "Low CMI" group (n=21) in the last 120 days before death; this differente being statistically different in the last 60 days before death (P < 0.05) • **Rotter Locus of Control (I-E) Scale:** High 1-E group had significantly higher mean pain scores than did the Low 1-E group in the 180-120-day and 120-60-day periods before death (P < 0.05). This differente persisted in the last 60 days before death but was no longer statistically significant at the 0.05 level. Mean pain scores in the High and Low 1-E groups not different in the 240-180-day period.	-	• **potential bias: 1. incomplete data:** problems in gathering complete initial data bases: the observer-scored IRDB, and the patient-completed Cornell Medical Index, Pain Estimate and Lotus of Control scales because of a) patient factors: serious physical illness and the presence of mild mental confusion, b) observer factors: discomfort with asking upsetting questions about patients' disabilities and unhappiness, and a reluctance to impose yet another burden on patients with progressive illness; **2. observer effect:** Early in the study, it became apparent that home observers could not restrain themselves from offering help to patients and families when their needs became apparent in the process of data gathering. Although personnel changes were made later in the study, the human contact between the research observers and the patients in the home may have reduced differences in quality of life outcomes between the intensive and non-intensive groups (…) supported by the fact that the major difference between the two groups was in pain management, the one problem which the nurses could address, but which
Kassakian, Nurse Practicioner 1979 [216]	The Cost and Quality of Dying: A Comparision of Home and Hospital	retrospective chart review (preliminary subanalysis of main CCT study)	assessing the financial aspects of health care in the last month of life for 71 patients (who participated in the CCRRS(="Cancer Care and rehabilitation in a Rural Setting" study) team project - this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)!	over 16 years, histologically proven cancer and prognosis of less than one year	see above	USA, Vermont	3 (retrospective subanalysis of patients included in the CCT study repoted by McKengney et al.)	n=71 (subsample of patients who died with information of their place of death)	28/43	*	100%	*	n.a.	place of death: "home"/"home-hospital" n=23, nursing home n=11, hospital n=37	aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! description of subsample of patients who died with information of their place of death, only; characteristics (age) are presented for time of death; all patients included were expected to die and were no longer receiving chemotherapy or raqdtiation therapy								• activity and disease status (Karnofsky Performance status scale); • psychosocial impact of dying assessed by questions which measure areas of concern on a five point scale (instruments not reported): "social activities"(0=none to 4=full), "hobbies and crafts"(0=none to 4=full), "difficulty walking"(0=dependent to 4=independent), bathroom activity (0=dependent to 4= independent), pain with activity (0=incapacitated to 4=functional), "future planning" (0=very realistic to 4= very unrealistic)	• classifications made according to the place of death • social acitiviies / hobbies and crafts: "none" = 0, "some"=1-4 • difficulty walking / bathroom activities: "dependent"=0, "independent"= 1-4 • pain with acitvity: "incapaciated"= 0, "some to none"=1-4 • future planning: "unrealistic"=0-1, "realistic"=2-4		idem	diem	idem	cancer rehabilitation team and oncology nurse practitioner		for evaluation of these activities, statistical and data manegement personnel are also inlcuded in the team sessions; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home			Vermont regional cancer center;	team sessions, including statistical and data manegement personnel;		no further information		-		no further information	multidisciplinary team (see above)	weekly team conference; team nurse practitioners keep the local physicians well informed of the patients' status and collaborate with local physicians when confronted with complex medical problems; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home		members of the "Cancer Care and rehabilitation in a Rural Setting (CCRRS)" study	weekly team conference; team nurse practitioners keep the local physicians well informed of the patients' status and collaborate with local physicians when confronted with complex medical problems; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home	this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)!	• 1.O **financial impact of dying** (average cost per patient in each "place of dying" group for the last month of life) • 2.O **psychosocial impact of dying:** assessed by questions which measure areas of concern on a five point scale (instruments not reported): "social activities"(0=none to 4=full), "hobbies and crafts"(0=none to 4=full), "difficulty walking"(0=dependent to 4=independent), bathroom activity (0=dependent to 4= independent), pain with activity (0=incapacitated to 4=functional), "future planning" (0=very realistic to 4= very unrealistic)	cost factors examined were: visiting nurse visits (oncology nurse practicioner visits included in the category), home health aide visits, hospital days, home visits made by physicians, physicians office visits, hospital visits made by physicians and nursing home costs	this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! In addition, presentation of results (numbers/means) is in figure / tables, only. As results do not relate to the intervention but another research question, only some relevant inforamtion (cost data, description of psychosocial impact of dying) data are extracted here: • 1.O **financial impact of dying** (relative cost per patient in each "place of dying" group for the last month of life): home (n=15) $45013; hospital-home (n=7) $56100, "hospice (projected)" $104297, "nursing home" (n=11) $149636, "hospital" $189631 • 2.O: **psychological impact of dying (% in the home / nursing home/ hospital group)**: **social activities** comparable between groups; **hobbies/crafts** pursued more by those at home than among institutionalized patients (% of patients answersing 1-4 respresenting "some"= 38/10/25; **difficulty walking** - % "independent" (answers1-4): 65/45/46; **bathroom activity** - % "independent" (answers 1-4): 65/45/46; **pain with activity** - % "some to none" (answers 1-4). 73/100/100; **future planning** - % realistic (ansers 0-1): 60/14/45, % unrealistic (2-4) 40/38/36, unable to evaluate: 0/48/18.		• this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! • intransparent presentation of methods and especially data used for this subanalysis; also intransparent and sparse presentation of results (numbers/means in figure / tables, only) and especially of costs; • due to sprase information given on data collection, risks of bias unclear / intransparent
Mulligan CA, University of Wales 1989 [217]	An evaluation of a specialist home care service	CBA (doctor thesis)	The central aim of the present study is the evaluation of a specialist home care team for the terminally ill. The service aims to provide good terminal care in the manner described above as effective.	patients referred to St. Patricks Foundation (see referral criteria); Those living in two boroughs of Gwent were included. Among these patients, some were excluded from the study for a number of reasons: a) if they were first seen by a Foundation nurse while they were in hospital; b) if they were seriously confused and had no key relative; c) if the patient was very near to death at the time of the referral; d) if for any other reason it was considered inappropriate to ask families to complete	single center	UK (Wales, Gwent)	2+	119 (63 patients in group A, 42 in group B, and 14 in group C)	55/64	median(range) = 65 (25-87)	98%	1. cancer sites: ca. 30% respiratory system cancer (lung/bronchus), ca. 16% Upper Digestive System, ca. 14% Male & Female Reproductive System, ca. 13% breast cancer, ca. 10% Lower Digestive System, ca. 5% Lympho-reticular disorders ….; non-cancer: n=1 terminal respiratory disease, n= 1other from longstanding poliomyelitis and diabetes; 2. n.d.; 3. "terminally ill"	n.d.								5 nurses, 1 researcher	study entry, 2-4 weeks later, and then at approximately 2 month intervals where possible	• **pain:** Site of pain ; intensity (10cm VAS) • **symptoms** (13 item checklist of principal symptoms) • **psychological distress patients** (Scale B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **psychological distress relatives** (Scale A (Somatic Symptoms), B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **Distress in Bereavement:** General distress ;			**Home Care service** Foundation Group A: Patients in this group are those referred to the Foundation from one borough in the catchment area which has received a service from the Foundation for some years. Foundation Group B: Patients in this group are those referred to the Foundation from a borough in the catchment area where the Foundation had only been offering a service for a few	no specialist service for the terminally ill operating	home care, St. David's Foundation, registered charity, South Wales industrial valleys (Newport, Gwent)	nine nurses operated throughout the county of Gwent; no medical practitioner of its own, close conjunction with General Practitioners and District Nurses			funding from a variety of sources, including a substantial amount from local fundraising activity		team of nine nurses operated throughout the county of Gwent; a day centre was open for two days a week in Newport;	operates in close conjunction with General Practitioners and District Nurses	The referral criterion for people with cancer is that the presence of metastases must have been diagnosed. This criterion is waived in the case of people having primary tumours with particularly poor prognostic implications, for instance some lung and brain tumours. Referral criteria for other conditions are the loss of the swallowing reflex for neurological conditions, and the point when inevitable disease progression changes from chronic to acute for other conditions.	twenty four hour call service, so that a patient or relative can speak to a nurse at any time of day or night, and receive a visit if necessary; limited night nursing service is also available to give relatives involved in fulltime caring the possibility of a full night's sleep at least every few days;	• Home Care Nurses provide advice with regard to pain and symptom control, and counselling and emotional support patients and their families; provides a service to people with a variety of potentially terminal conditions, although the vast majority are cancers; • volunteers who will sit with patients for relatives to go out, or who will take patients to the Foundation's day centre or to hospital appointments; • one of its aims: to enable more people to die at home rather than in hospital; • •	All relatives are visited at least once after the death, and some many times. All are invited to attend coffee mornings a few months after bereavement	support to families after bereavement, although this is often limited in practice due to pressure of work; All are invited to attend coffee mornings a few months after bereavement at which most of the nursing team as well as several volunteers are present, and many attend these. When people appear to have persisting difficulty in coping they are referred to Cruse, which has several counsellors in Gwent. However a problem commonly expressed by the home care nurses is that their workload is such that there is less time than they would like for bereavement support.	This group is drawn from a nearby area (in Mid Glamorgan) where there was no specialist service for the terminally ill operating. The General Practitioners involved in the project were asked to refer patients to the study who would meet the referral criteria for St. David's Foundation.							**1.O: pain:** Site of pain; intensity (10cm VAS), type (McGill Pain Questionnaire) **2.O symptoms** (13 item checklist of principal symptoms commonly experienced by people with terminal illness; dichotomous response) • **psychological distress patients** (Scale B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **psychological distress relatives** (Scale A (Somatic Symptoms), B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **Distress in Bereavement:** General distress (s.psychological distress relatives); Resolution of grief (Expanded Texas Inventory of Grief (TIG));		Pain: sign. more pain if patients referred 2 weeks or less before dying		
Ventafridda, Tumori 1985 [218]	The importance of a Home Care program for patients with advanced cancer	CCT	To show the effect of a multimodal Home Care Service for patients in Milan and their families	Patients with far advanced cancer, who could no longer be treated in an out-patient cancer clinic and received assistance at home	single center	Italy	1-	30 pts with Home Care Service, 17 pts without , 2 dropouts because of +	no demographic data	no demographic data	100%	no data	no data	LASA Scale		Home Care Service Team										Family Support and Home Care Team in Milan(32 pts)	Family Support	outpatients (ambulant)	no description	not relevant	not described	no statement		Volunteer Group Coordinator ?			Schedule/Frequency				Home Care Sevice in Milan - no clear descriptioin				Home Care Service, Outpatient Clinic, Palliative Care Unit, Pain Ambulance	regular or on needs		• • Pain (Integrated Pain Score) • Performance Status (Karnofsky) • Quality of life (QLI Spitzer) • Weakness, mood anxiety, side-effects (Linear Analogue Scale Assessment = LASA) At week 0, 2 and 6	no results	Integrated **Pain** Score decreased for both groups during the period running with statistically significant difference in favor of the Home Care group. No difference in the **Performance** (Karnovsky Index) during the 6-weeks investigation period. **Quality of life** (Spitzer Index) remained unchanged in the Home Care group and deteriorated progressively in the Control group monitored by their families with statistically significant difference (p<0.02) at the 6th week. Feelings of **weakness, anxiety, mood and magnitude of side effects** (evaluated by Linear Analogue Scale Assessment LASA) showed signs of improvement in the Home Care group with statistically significant differences in week 2 and 6. Anxiety and Mood in family members measured LASA showed better results in the Home Care groupresults for family. Partially significant better results for the parameters pain, QoL, feelings of anxiety, weakness and side-effects measured over a 6-weeks period of 32 patients treatd by		A nice early study to show the importance of a Home Care setting but with limited generalization as the two groups and the kind of family caring was not examined
Ventafridda, Tumori 1989 [219]	Comparison of Home and Hospital Care of advanced incurable Cancer Patients with	CCT	To show the difference in the care of patients cared by multimodal Home Care Service compared to a sample of patients hospitalised with Palliative Care	Patients with incurable cancer and painful symptoms who needed palliative care assistance at home or in hospital			1-	30 pts in Home Care Service, 30 pts hospitalised supported by the Pain and Palliative Care Service	48 males, 22 females	59 yrs in both samples	100%	incurable cancer, no radio- or chemotherapy,	Karnofsky 30 - 70	Integrated Pain Score, Spitzer Quality of Life Index		Home Care Service Team vs. Pain & Palliative Care Service in hospital										weekly assessment of 30 pts in hospital palliative care vs 30 pts in outdoor Home Care		inpatients vs. Outpatiens	Outpatients: Home Care Service Team (9 physicians,9 nurses, 1 social worker, 1 psychologist, 43 voluteers Inpatients: hospitalised in various wards cared by Pain Therapy and Palliative Care Service of the hospital (Palliative Consultation Team?)	not relevant	not described	Floriani Foundation		not described		Any type of painful advanced neoplastic disease, both sexes between 20 & 70 yrs., no more anticancer treatment, patients treatable according WHO Guideline adapted to individual needs.	Daily recording of clinical and behavioural data on pain, hrs of sleep, side effects and therapies using integrated pain score and Spitzer Index											• Pain (Integrated Pain Score: integrates intensity and duration of pain in a single score) • Hours of sleep, hours standing, sitting and lying • Performance Status (Karnofsky) • Side effects • QoL (Spitzer QoL index and social care records) • Costs	yes	Only week 1 and week 2 could be compared. Afterwards no comparison possible because of dropouts (discharges and deaths) . No sign. difference in the two samples except for education (higher in the home care group), no significant difference in survival time. Home care group showed better **performance status** at T14 (Anova H 7.062, p=0.01, otherwise no significant difference in **pain** intensity or **sleep** Significant difference in **QoL** (better at T14 in the Home Care group: F=11.473, p=0.001) None of the hospitalised pts fully aware of illness, while 26.7% at home were fully aware p< 0.05. Mean daily **costs** of care calculated for hospitalised pts: 261,4 $, for the Home Care pt: .37,4 $ The results showed that Home Care produced significant better results for psychological and social parameters (Spitzer Score at T14) patients satisfactiion und costs, while clinical parameter (survival, pain,activity showed no		A nice study to show the importance of a Home Care setting especially for psychosocial well-being and lower costs without increasing suffering compared to inpatient treatment. The dropout rate of the two samples was quite high because of discharges and deaths in both groups, so only the first two weeks (of intended 6) were compared. Description of Home Care Team
Ward, Community Medicine 1987;9 (1): 47 54 [220]	Home Care Services - an alternative to hospices?	prospective cohort study (PCS)/CBA randomised pts with interviews	to show differences in outcome and places of deaths in pts treated by Home Care Services attached or not attaches to Inpatient hospices in GB	957 pts with advanced cancer newly reffered to 8 Home Care Services followed up till death or one year after 1st enrollment	eight services (4 attached to inpatient hospice, 4 not attached to inpatient hospice)	GB	2+	n=957	29% widowed no demographic data	no data	no data on diagnosis but mostly cancer pts. (MacMillan Nurses)	no data	no data	no data		McMillan Nurses					Nurses completed forms, research workers collected data, more detailed interviews with a sample of 40 pts selected from a sample					Nr of visits/pts of home care nurses		outpatients (ambulant)																				O1: In the four centres attached to an in-patient hospice 29% of pts died at home compared to 65% treated by the four services not so linked, O2 Compared to the periods before the inception of Home Care Services the proportion of home deaths decreased slightly in regions with hospice based services and increased slightly in districts served by home care only services				A study with an interesting well founded result, that the implementation of an inpatient hospice based home Care service decreases home deaths while services not based to an hospice increase the proportion of patients dying at home, but probably this result is difficult to generalize for Germany becaus of the different health system.

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity	
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justific	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)
PALLIATIVDIENST IM KRANKENHAUS (KONSIL)																									
Gade, J Pall Med 2008 [221]	Impact of an Inpatient Palliative Care Team:	RCT	to measure the impact of an interdisc. palliative care service (IPCS) on patient satisfaction,clinical outcomes, and cost of care	18 or more years of age, hospitalized, and whose attending physician indicated they would not be surprised if the patient died within 1 year	multicenter	USA	1+	N=517; 5 drop-outs (withdrew their consent)	283/329	IPCS: 73,6/ Usual Care: 73,1	27.3% bzw. 34.4%	1. cancer, CHF, MI, other heart disease, COPD, other pulmonary disease; ESRD; organ failure; stroke, dementia	ECOG Score:IPCS: 2; usual care: 2; Quality of Life (Physical area scale; Emotional/relationship area scale; self reproted quality of life. All measured on a 11-point scale). No differneces in both groups.												
Hanks, British Journal of Cancer (2002) [222]	The imPaCT study: a randomised controlled trial to evaluate a hospital palliative care team	blinded RCT	asses the effectiveness of a hospital palliative care team on physical symptoms and health related quality of life(HRQoL): compare outcomes symptom control, health-related quality of life, duration of hospital admission, rate of re-admission)	initially only patients with cancer, later on all diagnostic groups (since they represent ~10% of the total)	single center	Bristol, UK	1 ++	684 / 261 left for randomisation	119/142 (= study patients)	68,4	93% / 88%	cancer or non-cancer	-	-	-	-	-	-	-	-	specialist physician and/or nurse	q1w, for 4 weeks	Symptoms (EORTC QLQ30, VA, MPAC, WONCA scale)	-	-
Jack, European Journal of Cancer Care 2006 [223]	Improving cancer patients' pain: the impact of the hospital specialist palliative care team	non-equivalent control group design /CBA	measuring symptom control and effectiveness of a hospital palliative care team	confirmed diagnosis of cancer	single center	UK	2-; the non-equivalent control group design clearly impairs comparability, and intervention was not described	n=100, control group n=50/ n=5/ n=0 intervention n=50 /n=19/ n=16	42/58 total control: 13/37 intervention: 29/21	-	100	Confirmed diagnosis of cancer, intervention group with referral to PCT, control group without PCT; primary sites: 27% colon/rectum CA 24% lung	PACA tool	physical:pain	-	-	-	-	-	-	self-reported assessment PACA tool	3 times (1st, 4th, 7th day)	PACA (Palliative Care Assessment) tool	symptom scoring: 0-3	
Norton, Crit Care Med 2007 [224]	Proactive palliative care in the medical intensive care unit: Effects on length of stay for selected high-risk patients	prospective pre/post nonequivalent control group design, performance improvement study /CBA	examine the effect of proactive palliative care consultation on length of stay for high-risk patients in the medical intensive care unit	MICU patients at high risk of dying werde screened within 72h of admission: a) intensive care admission following a current hospital stay of >/= 10days; b) age >80yrs in presence of >/= 2 life-threatening comorbidities; c)diagnosis of an active stage IV malignancy; d)status post cardiac arrest; e) diagnosis of an	singlecenter	USA	2+ (sequential, non-randomized observational design)	Usual care: n=65/ - / n=36 (55,4%) death in hospital; intervention: n=126/ -/ n=75 (59,5%) death in hospital;	Usual Care: (32/33) intervention: (69/57)	Usual Care: 68,75 intervention: 66,31	Usual Care: 7 (10,8%) intervention: 26 (20,6%)	see "inclusion criteria"	mainly two outcome measures: days in MICU; total days in hospital	-	-	-	-	-	-	-	MICU nursing and physician leaders	within 72h of admission	identification of patients who benefit best from PC intervention: developing screening inclusion criteria	-	-
SUPPORT principal investigators, JAMA 1995 [225]	A Controlled Trial to Improve Care for Seriously Ill Hospitalized Patients	prospective observational cohort study (phase I) plus RCT (phase II)	improving end-of-life decision making, reduce frequency of mechanically support painful, prolonged process of dying	adults, hospitalized with ≥1 of nine life-threatening diagnoses; an 47% overall death mortality rate	multicenter (five Hospitals)	USA	1 -	n=9105 [phase I: n=4301; phase II: n=4804 in two groups: n(intervention)= 2652 and n(control)=2152	I = 1849/2452 II = 2128/2676	I = 65 II = 65	I = 16.9% II = 14.4%	acute organ system failure (I/II= 42,9%/49,6%) (acute respiratory failure, multiple organ system failure with sepsis, multiple organ system failure with malignancy), chronic disease(I/II= 34,4%/28,8%) (severe COPD, cirrhosis, congestive heart failure), non-traumatic coma (I/II= 5,7%/7,3%, Cancer (I/II= 16,9%/14,4%(metastatic colon cancer, NSCLC)	ADL (I/II=1,6/1,5) APS of Apache (I/II= 33/32)		length: phase I: 2years, phase II: 2years						nurse	medical record based data (days 1,3,7,14,25). Interview (patient ~day12, surrogate: 4-10week postmortem)	medical record based data (concurrent, retrospective). Interview (patient or surrogate)	"measures: -incidence and timing of written DNR orders -patient-phyisician Agreement on CPR-Preferences -Days in an ICU, Comatose or Receaving Mechanical Ventilation Before Death -pain -hospital resource use	
Rabow, JAMA 2004 [226]	The Comprehensive Care Team. A Controlled Trial of Outpatient Palliative Medicine Consultation	CCT (randomisation of primary care physicians (not patients))	We compared physical, psychological, social, and spiritual outcomes between an intervention group of patients receiving a multifaceted, outpatient, palliative medicine consultation intervention plus usual primary care and a control group receiving only usual primary care.	adult patients with diagnoses of cancer, advanced COPD, or advanced CHF, whom they believed had a life expectancy of 1 to 5 years and who were not yet ready for hospice care. We excluded patients with nonmelanoma skin cancers, dementia, or psychosis; those enrolled in hospice care; and those unable to complete a written survey in English or Spanish.	single center	USA	1-	intervention group/comparison group: N=50/40 enrolled / drop outs: 15/9 / deaths:10/5	37/13 and 21/19	The mean age of study participants (N = 90) was 68.6 years (no diff between groups)	26%/42%	CHF 34%/35%; COPD 40%/20%. Mean baseline forced expiratory volume in 1 second for patients with COPD was 1.29 (SD, 0.32), and the mean baseline ejection fraction for those with CHF was 46.9% (SD, 13.0), with no significant difference between groups (*P* = .85 and *P* = .40, respectively).	There was no significant group difference (*P* = .15) in baseline mean functional status on the Rapid Disability Rating Scale (27.5 [SD, 6.2] for the intervention group; 25.1 [SD, 7.8] for the control group).	University of California, San Diego Shortness of Breath Questionnaire; Brief Pain Inventory; Sleep quantity and quality were assessed using 6 sleep items from the Medical Outcomes Study; Anxiety: 5-point Likert scale Profile of Mood States; depression: 20-item Center for Epidemiological Studies Depression Scale; 20-item Spiritual Well-Being Scale; Multidimensional Quality of Life Scale–Cancer Version; Group Health Association of America							social worker	baseline	see tool in "O"		
Rabow JPM 2003 [227]	The Comprehensive Care Team: A Description of a Controlled Trial of Care at the Beginning of the End of Life	Survey (quantitative descriptive/observational). The paper does summarize feedbacks, experiences and observations during the study without being a formal survey.	This paper presents a basic description of the CCT project and research program. In addition, it outlines the major challenges, successes, and lessons learned in the course of developing and implementing this outpatient palliative care intervention.	see above	see above	see above	3	see above	see above	see above	see above	see above	see above	see above	More details in page 492, Table 1										
Temel, NEJM 2010 [228]	Early palliative care for patients with metastatic NSCL cancer	RCT, parallel, nonblinded	to examine the effect of early PC integrated with standard oncologic care	pathologically confirmed metastatic NSCL within previous 8 weeks; ECOG 0-2, not receiving PC	single center	USA	1++ (no blinding but otherwise high quality)	n=151 / drop outs n=43 († 27)	78/73	Interv (mean): 64.98±9.73 Control: 64.87±9.41	100%	Newly diagnosed metastatic NSCL cancer (26-31% brain metastases)	ECOG 1 (n=81) ECOG 2 (n=14)	HADS-Anxiety: 33-36% HADS-Depres-sion: 22-25% PHQ-9 (major depr. Synd-rome) 12-17%								Within 8 weeks after diagnosis	Performance (ECOG), Mood (HADS, PHQ-9), QoL (FACT-L, TOI)		
Yoong, JAMA Intern Med 2013 [229]	Early Palliative Care in Advanced Lung Cancer	Qualitative (content analysis on health records)	to (1) identify key elements of early PC clinic visits, (2) explore the timing of key elements, and (3) compare the content of PC and oncologic visit notes at time points of clinical deterioration / radiographic disease progression.	idem	idem	idem		n=20 from PC intervention group (5 patients from 4 survival groups: < 3 months, 3-6 mth, 6-12 mth, 12-24 mth)	12. Aug	Mean: 68 (47-84)	idem	Survival: < 3 months (n=5), 3-6 mth (n=5), 6-12 mth (n=5), 12-24 mth (n=5)	-	-	-	-	-	-	-	-	-	-	-	-	-

Author, Journal, Year	Intervention characteristics (structure and process quality criteria): Overall description – Intervention	Overall description – Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding – Who (source)	Funding – How much	Organisation / Management related to structures – Who	Organisation / Management related to structures – How	Referral criteria / allocation of place	Description of intervention – Schedule/Frequency	Description of intervention – Content (clinical/non-clinical)	Description of bereavement intervention – Schedule/Frequency	Description of bereavement intervention – Content	Description of control intervention	Coodination of intervention – Who	Coodination of intervention – How	Discharge criteria	Integration of oncological and palliative structures – Who	Integration of oncological and palliative structures – How	Others
Gade, J Pall Med 2008 [221]	interdisciplinary palliative care service (IPCS)	usual hospital care (UC)		palliative care physician PC nurse hospital social worker chaplain	Denver (383), Portland (225), San Francisco (102)		Garfield Memorial Fund					All teams provided care in accordance with key palliative care components which were adapted from Weismann. The teams assessed patients' needs for symptom management, psychosocial and spiritual support, end-of-life planning, and posthospital care. All of the team's efforts were based on the patient's individual goals of care.										
Hanks, British Journal of Cancer (2002) [222]	usual care + PCT care	usual care + telephone-PCT	university teaching hospital with PCT	normal health care, intervention + PCT(2,5 full-time equivalents)	- (United Bristol healthcare Trust: 433 beds)	-	NHS National Cancer R&D Programme (Grant number NCP/J01)	-	Debbie Ashby, Helen Jones;	administration of the study:	-	full service PCT versus telephone PCT	telephone and in-person consultation by full-PCT: (two clinical academic consultants, one specialist registrar, three clinical nurse specialists) having close links with clinical psychologist, a local hospice and community based PC-Services; access to social workers, rehabilitation staff and chaplaincy in the hospital,	-	-	telephone-PCT: no direct contact between PCT, patient and family; telephone consultation between senior medical member of PCT&referring doctor, PCT nurse specialist&involved nurse,	-	-	unable to give informed consent, unable to undertake baseline assessment, unaware of their diagnosis, likely to die or to be discharged within 24h, insist on Palliative Care Team, put family or ward staff in "extreme stress"	-	-	-
Jack, European Journal of Cancer Care 2006 [223]	confirmed diagnosis of cancer and referral to PCT; specialist hospital palliative care team intervention	confirmed diagnosis of cancer but no referral to PCT; traditional care	university hospital with PCT	4 clinical nurses specialists, PC consultant, specialist registrar	1/ 1300 beds	-	-	-	-	-	hospital inpatients distributed on wards	specialist hospital palliative care team intervention	individualized assessment, psychological support, symptom control and evaluation	-	-	standard care	B. Jack	consecutive recruitment and data collection	unable to give informed consent; unrelated medical problem	-	-	
Norton, Crit Care Med 2007 [224]	proactive care: palliative care consultations	usual care	seventeen bed adult MICU	-	17, (~1100 patients per years)		supported, in part, by the Fraser-Parker Foundation, Atlanta, GA					review of chart, brief history, discussin symptom control, goals of care and others with MICU team, discussing results with attending, written statement				improving patient's quality of life by providing excellent pain and symptom management, goal clarification, assistance with medical decision making and support						
SUPPORT principal investigators, JAMA 1995 [225]	11 groups. 1. physician received estimates of the likelihood of 6m-survival for every day up to 6m.,outcomes of CPR, and fuctional dicability at 2m. 2. specially trained nurse had contact to all involved people to elicit preferences, improve understanding for outcomes, envourage attention to pain control, and facilitate advance care planning and patient-physician	16 groups,	Hospital	special SUPPORT-criteria nurses, hospital staff	5 different hospitals in 27 Physician Groups		Robert Wood Johnson Foundation			discuss phase II intervention based on phase I findings		Phase I: Describe Outcomes, Develop Prognostic Models, Identify Shortcomings of Care, Establish Adjustment Methods, Design Intervention Phase II: Apply Intervention to 4804 Patients Randomized by 27 Physician Groups Adjusted Analyses of Intervention vs control for Five Outcomes	Phase II Intervention aimed to improve communication and decision making by: providing timely and reliable prognostic information, eliciting and documenting patient and familiy preferences, understanding disease prognosis and treatment and by providing a skilled nurse to help carry out the needed discussions, convene the meetings, and bring to bear the relevant information.			"usual care"			Exclusion: <18,discharge, death within 48h, were admitted with a scheduled discharge within 72h, did not speak English, were admitted to psychiatric ward, had acquired immunodeficiancy syndrome, pregnancy, sustained acute burn or head or other trauma,			
Rabow, JAMA 2004 [226]	See paper page 84 "The comprehensive care team intervention" (7 main components) = newly developed 1-year program	usual care	The study was performed within the 70-physician general medicine practice of a tertiary care, university medical center located in a large urban setting and serving an ethnically diverse population.	Social worker, chaplain, nurse, pharmacists, psychologists, art therapists, volunteer coordinator and 3 physicians (all but volunt coord had palliative care expertise)	-	not reported	Study funding: Robert Wood Johnson Foundation		main done by social worker		Referral by primary care physician	See paper page 84 "The comprehensive care team intervention" (7 main components): social worker did assessment and present results to the CCT meeting > recommendations to the primary care physician; at 3 points: study entry, midway, and study completion	The program integrated PCP consultation, case management, volunteer and group support, chaplaincy consultation, and artistic expression.	not explicit stated		usual care by primray care physician	social worker	meetings and directly	not explicit stated	structures: intervention and primray care physicians (not oncologists)	recommendations that were offered to the patient's PCP via a written letter and e-mail	
Rabow JPM 2003 [227]													Table 2 (page 493): Outpatient interdisciplinary palliative care team consultation; Social worker case management; Medication management; Volunteer patient advocacy; Family caregiver support; Chaplain consultation; Patient artistic expression; Institutional advocacy "Thank God It's Friday" luncheon									
Temel, NEJM 2010 [228]	Early PC integrated with standard oncologic care	Standard oncologic care alone	outpatients (ambulant)	board-certified palliative care physicians and advanced-practice nurses							patients with newly diagnosed metast. NSCL and ECOG 0-2	1st visit: within 11 weeks after diagnosis Next visits: at least monthly thereafter until death. Additional visits with the palliative care service were scheduled at the discretion of the patient, oncologist, or palliative care provider.	Adapted guideline for palliative care (National Consensus Project): Assessing physical and psychosocial symptoms Establishing goals of care Assisting with decision making regarding treatment Coordinating care on the basis of the individual needs of the patient.			Standard oncologic care; no meeting with the PC team, unless wish of the patient, the family or the oncologist					Integration of a PC team in a outpatients oncologic structure; parallel attendance	
Yoong, JAMA Intern Med 2013 [229]	idem	-											• Addressing symptoms and coping: the most prevalent components of the PC clinic visits. • Initial visits focused on building relationships and rapport with patients and their families and on illness understanding, including prognostic awareness. • Discussions about resuscitation preferences and hospice predominantly occurred during later visits • Comparing PC and oncologic care visits around critical time points, both included discussions about symptoms and illness status; however, PC visits emphasized psychosocial elements, such as coping, whereas oncologic care visits focused									

Author, Journal, Year	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Gade, J Pall Med 2008 [221]	**1.O**: symptom control, levels of emotional and spiritual support, patient satisfaction and total health services costs at 6 months postindex hospitalization. **2.O**: survival, number of advance directives (ADs) at discharge and hospice utilization within the 6 months postindex hospitalization (hospitalization during which study enrollment occured).	Total mean health costs for the IPCS group were lower by $6,766 per patient compared to UC patients (IPCS: $ 14,486 ; UC: $21,252, p 0.001). After sub-tracting the cost of staffing the IPCS ($1,911 per patient), the net savings was $4,855 per patient. Cost savings were largely driven by a significant difference in hospital readmission costs (IPCS: $6,421 per patient versus UC: $13,275 per patient, p 0.009). No difference in the number of hospital readmissions but IPCS patients had significantly fewer ICU stays on readmission (IPCS: 12; UC: 21, p 0.04).	**1.O:** Physical area scale (standard deviation): IPCS (study enrollment(SE): 5.2; hospital discharge (HD): 4.0); UC (SE: 5.1; HD: 4.1); Emotional/relationship area scale: IPCS: (SE: 6,3; HD: 7.0) UC: (SE: 6.5; HD: 6.2); Spiritual area scale: IPCS (SE: 6.8; HD: 6.6); UC: (SE: 6.5; HD: 6.2); Self-reported quality of life: IPCS (SE: 4.1; HD: 6.4); UC: (SE: 4.1;HD: 6.3) . **There were no differences between groups for any scale** 2.O: **no difference in survival** between IPCS and UC. Median post enrollment survival was 30 days for IPCS and 36 days for UC (p 0.08), and 173 IPCS patients (63%) and 132 UC patients (56%) died during the study period (p 0.08). Significantly more IPCS patients (17.1%) died during their index hospitalization compared to UC patients (8.0%; p .002). Satisfaction: The IPCS group reported higher mean satisfaction for both the Place of Care Environment scale (IPCS: 6.8; UC: 6.4, p=001.) and the Doctors, Nurses/Other Health Care Providers Communication scale (IPCS: 8.3; UC: 7.2, p 0.001)		patients reported relatively low physical symptoms at study enrollment; the average index hospitalisation LOS after study enrollment was 4.9 days, a shorter time for the IPCS team to manage complex physical symptoms compared to studies with longer interventions.; patient population survived for a longer period of time indicating they might be earlier in their disease state than other inpatient palliative care patients. Lack of some measurable process measures, e.g., what symptoms and issues were helped by which components of the IPCS. Participants in this study were members of a health plan with an integrated medical delivery system which may limit generalization of study outcomes in other settings.
Hanks, British Journal of Cancer (2002) [222]	**1.O:symptom control** (severity measured by VAS and mood by the Memorial Pain Assessment Card (MPAC); and extent to which emotional problems had been a bother by the WONCA scale) , **HR QoL** (measured by EORTC QLQ-C30= questionnaire) , > measures of HRQoL and symptoms were repeated at weekly intervals for 4 weeks. **hospital stay** (length of the index admission] and **rates of readmission** until the patient´s death or study closure; **2.O: satisfaction/dissatisfation with care** of patients, family carers and primary health care professionals; and **use of health service resources**.	Hospital resource use (number of diagnostic images, diagnostic tests, visits from other hospital therapists) was very similar in the two groups (data not shown).	1.O:Both interventions lead to better outcomes, and full PCT non-significantly more than telephone PCT; there was a highly significant improvement in scores for all items in the 'full-PCT' group and for some items in the 'telephone-PCT' group. However, comparison of the mean scores at 1 week adjusted for the baseline scores revealed no statistically significant differences between the groups. The improvements in scores for symptom severity, mood, emotional problems and HRQoL, which were apparent at 1 week, were, amongst survivors, sustained and increased over the subsequent 3 weeks.There was very little difference in the length of hospital stay or rates of readmission between the two groups. **2.O:** Patients in both treatment groups expressed high levels of satisfaction with their hospital care and there were no apparent differences between the groups; Hospital resource use (number of diagnostic images, diagnostic tests, visits from other hospital therapists) was very similar in the two groups.		Randomisation was undertaken by a non-clinical administrator with no involvement in patient recruitment or assessment.; full-scope RCT. No PCT-free control, but telephone group. Cost reduction not shown. It has failed to show a significant difference between the 'full-PCT' and 'telephone-PCT' in respect of the primary outcome measures, and particularly symptoms and HRQoL. The lack of a significant difference between the two interventions may be a false negative in that there is a difference but we have failed to show it.
Jack, European Journal of Cancer Care 2006 [223]	Pain, patient insight and symptom control for anorexia, constipation and insomnia, pain (tool: the four-point scale Palliative Care Assessment (PACA) tool), measured at day 1, day 4 and day 7)		At the Before-After Comparison there was no difference between the groups (P=0.198). This indicates that all the patients (intervention and control) demonstrated an improvement in their reported pain scores. However, the patients who received hospital specialist palliative care team intervention had a greater improvement. At the second and third assessments there was a between-group difference of P=0.029 (mean 1.42 vs. 1.78) and P<0.01 (mean 1.00 vs 1.74) respectively. This amounted to a 0.36-point difference between the groups and at time three a 0.74-point difference on a four-point scale.An improvement that amounted to 0.74 difference at the final assessment between the palliative care and traditional care groups on a four-point scale		The selection bias, nonequivalent groups and lack of blinding are major weaknesses of this study and therefore the results have to be interpreted with caution. Furthermore, the precise interventions made by the palliative care team and its effect upon pain is unclear. The groups were different in the relation of sexes. According to the authors this did not have an effect on the results.
Norton, Crit Care Med 2007 [224]	**1.O**: patients length of stay in the MICU; patients length of stay in the entire hospitalization; patients length of stay from the MICU admission to hospital discharge **2.O:** mortality rates, discharge disposition		**1.O**: Patients ins the proactive palliative care group had significantly shorter MICU-stay (difference in days: -7.32 [-6,5], p=0.0001), but similar length of stay within hospital and in length of stay from MICU admission to hospital discharge **2.O:** There were no significant differences between the usual care and proactive palliative care intervention groups in respond to discharge disposition, mortality (and age, gender, race, screening criteria)		sequential design, no randomisation, but clear-cut intervention; A pre/post intervention design has limitations. Although there were no concurrent MICU initiatives targeting our sample, the changes in MICU length of stay could have been related to other factors, which were not considered. No differentiation between the baseline usual care group by their level of PC needs. This curtailed the ability to examine additional subgroup relationships between complete and basic PC consultation requirements and length of stay. Patients receiving only basic PC consultation were not followed throughour their entire hospitalization subsequent to their MICU stay. This likely diluted any potential effect of our intervention on length
SUPPORT principal investigators, JAMA 1995 [225]	1) Incidence and timing of written DNR orders; 2) patient-physician Agreement on CPR Preferences; 3) days spent at ICU, comatose, or Receiving Mechanical Ventilation Before Death; 4) frequency and severeity of pain; 5) hospital ressource use	intervention did not reduce use of hospital resources	Phase I observation: documented shortcomings in communication, frequency and aggressive treatment and the characteristics of hospital death: only 47% of physicians knew when their patientes preferred to avoid CPR; 46% of do-not-resuciate (DNR) orders were written within 2 days of death; 38% of patients who died spent at least 10 days in an intensive care unit (ICU); and for 50% of conscious patients who died in the hospital, family member reported moderate to severe pain at least half of the time; Phase II intervention: patients experienced no improvement in patient-physician communication or in the five targeted outcomes		nurse-driven intervention; physicians (and patients) had to comply voluntarily; half of AD's during 2 last days of life. Did NOT validate this approach positively; power > 90%; Because Patients were assigned to intervention and control based on a limited number of speciality group, the resulting cohorts might be unbalanced in patient baseline risk factors.
Rabow, JAMA 2004 [226]	Physical (**Functional status**: Rapid Disability Rating Scale-2 ; **Dyspnea**: University of California, San Diego Shortness of Breath Questionnaire, **Pain**: Brief Pain Inventory; Sleep: 6 sleep items from the Medical Outcomes Study), Psychological and well-being (**Anxiety**: 6-item anxiety scale from the Profile of Mood States; **Depression**: Center for Epidemiological Studies Depression Scale; **Spiritual well-being**: Spiritual Well-Being Scale; **QoL**: Multidimensional Quality of Life Scale–Cancer Version; **Health care satisfaction**: Group Health Association of America Consumer Satisfaction Survey). **Advance care planing** (yes/no) ; Health care utilisation	basic charge (not a formal cost-benefit analysis)	Groups were similar at baseline. Similar numbers of patients died during the study year (*P* = .63). After the intervention, intervention group patients had less **dyspnea** (F= 7.06, p = .01) and **anxiety** (F= 4.09, p = .05) and improved **sleep quality** (F= 4.05, p = .05) and **spiritual well-being** (F= 8.21, p = .007), but no change in **pain** (F0 0.69, p = .41), **depression** (F= 1.19, p = .28), **quality of life** (F= 0.65, p = .43), or **satisfaction with care** (F= 1.31, p = .26). Few patients received recommended analgesic or antidepressant medications. Intervention patients had decreased **primary care** (*P* = .03) **and urgent care visits** (*P* = .04) without an increase in **emergency department visits, specialty clinic visits, hospitalizations**, or **number of days in the hospital**. There were no differences in **charges** (*P* = .80): intervention: $47211 (SD73009); control: $43338 (SD 69647). **Conclusions** Consultation by a palliative medicine team led to improved patient outcomes in dyspnea, anxiety, and spiritual well-being, but failed to improve pain or depression. Palliative care for seriously ill outpatients can be effective, but barriers to implementation must be explored.	-	A really complex intervention. For this, quite a small sample size (although sample size calculation was done). Randomsation of physicians not patients (might be a limitation and a benefit).
Rabow JPM 2003 [227]			**For further research**: improve recruitment (see page 497, Table 5); more authority/decision about therapy by intervention physician. **Recommendations**: 1. Communication least expensive but most effective; 2. Team member support important because of very ill pts; 3. Extra sensitivity and caution to initiate discussion about eol - but pts appreciate these discussions. The majority of patients (63%) listed the CCT **social worker** as the most important; however, more than 10% identified the volunteer advocates as most important. Many CCT recommendations were **not implemented by PCPs**. Patients found **discussing advance care planning** difficult (66%), but desired these conversations (66%) (see page 494, table 3).	Participating family caregivers were appreciative of the benefits to patients as well as the services provided directly to the family.	Palliative care consultation was acceptable to outpatients with serious illness, and was feasible in a general medicine practice. Despite financial and staffing challenges, patients received a variety of clinical, psychological, social, and spiritual services. Although some patients were originally reluctant to enroll in the project, once participating, they expressed appreciation for the services provided by the project and reported improved satisfaction resulting from these services. **Ultimately, most patients expressed the desire to discuss difficult topics and the wish to have participated in such a program earlier in the course of illness.** Families and PCPs expressed appreciation for the CCT services. **However, physicians did**
Temel, NEJM 2010 [228]	1.O: change in QoL at 12 weeks (TOI = Trial Outcome Index, FACT-L) 2.O: • Mood (HADS, Patient Health Questionnaire-9) • Health care use (incl. aggressive EoL-care, medication prescription, emergency visits…) • Documentation of patients' resuscitation preferences • Median survival		• **QoL:** sign. better QoL for intervention group (mean score on the FACT-L scale 98.0 vs. 91.5; P = 0.03) • **Mood:** sign. fewer patients in the intervention group had depressive symptoms (16% vs. 38%, P = 0.01) • **Aggressive EoL-care**: fewer patients in the intervention group received aggressive end-of-life care (33% vs. 54%, P = 0.05) • **Median survival**: longer among patients receiving early palliative care (11.6 months vs. 8.9 months, P = 0.02)		limiting generalization of the results to other care settings or patients with other types of cancer.
Yoong, JAMA Intern Med 2013 [229]			Early PC clinic visits emphasize managing symptoms, strengthening coping, and cultivating illness understanding and prognostic awareness in a responsive and time-sensitive model. During critical clinical time points, PC and oncologic care visits have distinct features that suggest a key role for PC involvement and enable oncologists to focus on cancer treatment and managing medical complications.		

Study characteristics								Patients' characteristics at baseline							
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Perform-ance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others
TAGESKLINIK															
Goodwin, JPSM 2003 [230]	Effectiveness of Palliative Day Care in Improving Pain, Symptom Control, and Quality of Life	Prospective comparative study (cohort study)	This analysis aims to evaluate the effectiveness of palliative day care in improving pain, symptom control, and QoL.	The day care patients were consecutive new referrals to the five centers. Eligibility criteria for both groups of patients were: over 18 years of age, well enough to be interviewed (for approximately 35–45 minutes), and no obvious confusion /not severely cognitively impaired.	5 day care centers in the UK.	UK	2-	intervention group/comparison group: N=120/53: first interview 102/47 / drop outs: 88/29 / deaths ?	first interview 50/52 (interv) 23/24 (comparison)	interv (mean): 64.39±13.17 Control: 69.98±10.62 (p=0.009)	99%	Lung cancer 24 (23.5%)/14 (31.8%); Gastrointestinal 20 (19.6%)/8 (18.2%); Breast 18 (17.5%)/3 (6.8%); Genitourinary/Prostate 20 (19.6%)/12 (27.2%); Gynae 16 (15.5%)/5 (11.4%); Other cancer 4 (3.9%)/2 (4.5%)	nn	There was a marginally significant baseline difference for the POS item 'pain control' (P 0.053), where the comparison group had more severe/overwhelming scores.	
Higginson, Support Care Cancer 2010 [231]	Does a social model of hospice day care affect advanced cancer patients' use of other health and social services? A prospective quasi-experimental trial	CBA (quasi-experimental trial)	to evaluate the effect of a new HDC (Hospice Day Care) on the use of health and social services	• >18 y • advanced cancer • receiving palliative care (included in hospice programm)	single center	GB	2- (high drop out rate)	163 (HDC:37, Standard: 50, before: 76) 104 drop-outs (death or too ill)	Male: HDC: 62% Standard: 52% Before: 40% Female: HDC:38% Standard:48% Before: 60%	70,5-75,7	100%	1. Cancer 3. Advance		**POS** (Palliative Outcome Scale): mean 7.9-8.4, similar in all groups **HHI** (Hope): lower in HDC group at baseline	**General health status** (EQ-5D VAS 1-100): 60.2-64.7; similar in all groups
Sviden PM 2009 [232]	Palliative day care – a study of well-being and health-related quality of life	controlled cohort study (matched controls 2:1 re age, gender and functional status) - only after-measurements	to study the outcomes of palliative day care, in terms of health-related quality of life and the emotional well being of cancer patients participating in a palliative day-care programme for a period of 5 weeks, compared with a group of patients in palliative care but not participating in day care.	cancer; no confusion - recruitment between 2003 and 2005	two day care centers	Sweden	2-	Included: 31/17; completed: 23/12	female: 25/14	Majority between 50-69 y	100%	not reported	between 50-70 Karnofsky	not reported	
STATIONÄRES HOSPIZ (keine Studien identifiziert)															

	Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)					
Author, Journal, Year	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)
Goodwin, JPSM 2003 [230]						Researcher	1. baseline; 2. 6-8 weeks; 3. 12-15 weeks	POS	siehe POS	siehe POS	day care (palliative/hospice): For the purpose of this study, palliative day care was defined as day care in a hospice setting; it did not include attendance at day care for outpatient appointments.	without day care: All patients received the usual palliative care services (home care, in-patient sevices, and outpatient services), but the comparison group did not attend day care.	day care at day care centers: Five palliative day care centers in the UK provided facilities for medical and nursing assessment of all patients. At each center, there was a variety of social, recreational, and therapeutic activities. The centers often employed specialists, such as art	At each center, there was a variety of social, recreational, and therapeutic activities. The centers often employed specialists, such as art therapists and aromatherapists.		
Higginson, Support Care Cancer 2010 [231]						trained interviewers					Hospice Day Care (HDC) in addtion to standard palliative care	1. Before group (historical group, recruited before HDC unit was built) 2. Standard palliative care group	Hospice programm in South East England (HDC, in-patients, home care)		HDC: 10-15 places/day, opened 3 days/week	
Sviden PM 2009 [232]											palliative day care settings in Sweden could be described as applying a social model of care placed within a medical context, providing an environment for social and therapeutic activity.	no day care (but could have had home palliative care)	hospital-based outpatient service	Occupational therapists and nurses managed the programmes, and a multiprofessional team comprising of a physiotherapist, a physician, a social worker and a chaplain was available for the participants if required.	8 to 10	not reported

	Intervention characteristics (structure and process quality criteria)																Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
Author, Journal, Year	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management related to structures: How	Referral criteria / allocation of place	Description of **intervention**: Schedule/Frequency	Description of **intervention**: Content (clinical/non-clinical)	Description of **bereavement intervention**: Schedule/Frequency	Description of **bereavement intervention**: Content	Description of **control** intervention	Coodination of intervention: Who	Coodination of intervention: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration of oncological and palliative structures: How	Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs			
Goodwin, JPSM 2003 [230]					The reasons for referral to day care given by the health care professionals included: social support (49%), time out of home (20%), symptom management (14%), therapeutic intervention (12%), psychological support (2%), respite for caregiver (4%).												1. QoL (McGill Quality of Life Questionnaire); 2. POS (single items (symptom control) + overall (QoL)) at each interview time point		The comparison group had marginally more severe pain at baseline (p= 0.053) and more severe **symptoms** at second assessment (p= 0.025). Both patient groups maintained overall **health-related quality of life** during the three months of the study (p= 0.065). Palliative day care was not found to improve overall health-related quality of life. (effect sizes not mentioned)		Limitations related to difference at baseline (characteristics/pain, number of pts) and the lack of randomisation.
Higginson, Support Care Cancer 2010 [231]					Reasons for referral to HDC included: • social support (37%) • respite for carer (22%) • social and • psychological support (19%) • social and medical support (15%) • time out of home (7%)	usually 1 day a week, 10am-3pm	Mainly social content: • lunch, tea, coffee, social activities, including discussion and art and craft, supported by volunteers • aromatherapy, massage, or reflexology, offered individually • If required, patients could see a physiotherapist or a nurse • Volunteer transport was available to take patients to and from the day unit			1. **Before group**: Patients who were receiving hospice services (home care or in-patients) and lived in the catchment region of the planned day hospice were recruited. As soon as the day unit opened, recruitment to this group ceased. 2. **Standard palliative care group:** Home care palliative nursing teams of the hospice. They were not receiving day care usually because of choice or convenience (travel distance).							Patient outcomes: • Overall health status (EQ-5D, VAS 1-100) • Self-assessment of patients' hope (Herth Hope Index, HHI, Likert 1-4) • Palliative needs (POS, Palliative Outcome Scale, Likert 0-4) Difference in use of following services: • Community (GP, district nurse, …) • Hospice (PC doctor or nurse) • Social care support (social worker, home help, melas, priest) • Hospital (cancer specialist, other doctor or nurse) • Therapist (occupational, dietician, physiotherapist, chiropodist) Time of measures: • Baseline • 6-8 weeks • 12-15 weeks		Patient outcomes: • **Overall health status**: n.s. • **HHI:** sign. improvement compared to Before group at 1st follow-up (mean change, 2.2 versus −1.0; p=0.050, F= 4.19) • **POS:** n.s Difference in **use of services**: • At baseline: patients in the HDC group used almost all services, except for hospital services, more than the standard care (P=0.004, Wilk's λ=0.74, F5,57=4.00) and before groups, although the difference with the latter (P=0.07, Wilk's λ=0.87, F5,81=2.18) was not significant. • Baseline -> 1st follow-up: sign. change of therapist service use between HDC and standard group (adjusted P=0.003). The change was in the opposite direction, with a reduction in the HDC group and an increase in the standard care group (mean change±SD, 0.1±0.5; 95%CI, −0.1 to 0.3). • None of the other baseline or service change differences reached significance level.		Limitations: • Sample size calculation but high rate of dropouts (total: 63%; HDC: 70%; Standard: 60%; Before: 63%) -> limited power. • the before group was slightly different from the HDC and standard care groups—in particular comprising more patients with breast cancer. Breast cancer has a longer survival than many other cancers and it may be that the before group comprised longer surviving patients who had been 'waiting' for HDC to start. This may explain some of the differences in baseline service use. Findings: • The lack of particular trends towards differences suggests that if HDC does have an effect, it is small. Indeed it is usual that non-randomized studies find a greater effect than randomized studies. Our findings support the proposal of Hopkins and Tookman of a move away from the social model of HDC to a more therapy-based model. • Our data appear to suggest that HDC supplements existing services.
Sviden PM 2009 [232]	not reported	not reported	occupational therapists and nurses		not reported	The participants visited the day care setting one to three times a week, depending on their situation, needs and desires. There were about 8–10 participants attending each day, spending between 2 and 5 h in the setting.	The programme aimed to enhance well-being and quality of life. The main focus of the programme was to offer opportunities to participate in creative and social activities. Included in the programme were different activities, like arts and crafts, gardening, physical exercise, outings and gathering around for coffee and lunch. Activities were organised both on a group and on an individual basis. The goal and the content of the two different facilities were the same.	-		no day care service; usual care (including home palliative care services)	occupational therapists and nurses		not explicit stated	not explicit stated			weekly during 5 weeks. Quality of life/symptoms (EORTC QLQ-30) + emotional weel-being (Mood Adjective List (MACL))	-	Higher levels of emotional well-being for the day-care-group (but not statistical sign). Same levels for QoL/symptoms	-	Limitations: only after-measurements; lack of information about pts characteristics (e.g. cancer diagnosis etc.); no sample size calculation

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