Author's response to reviews

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Authors:

Isabel Dietz (Isabel.Dietz@helios-kliniken.de)
Andrea Schmitz (A.Schmitz@med.uni-duesseldorf.de)
Ingrid Lampey (lampey825@btinternet.com)
Christian Schulz (Christian.Schulz@med.uni-duesseldorf.de)

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Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review.

Isabel Dietz¹*, Andrea Schmitz²*, Ingrid Lampey²,³, Christian Schulz²

1 Clinic for Anaesthesiology HELIOS Clinic Wuppertal, University Witten/Herdecke, Germany

2 Interdisciplinary Center for Palliative Medicine, University Hospital Dusseldorf, Dusseldorf University, Germany

3 NELCS Northeast London (NHS) Community Services, London, United Kingdom

* these authors contributed equally to this work

Corresponding author: Isabel Dietz, MD
Department of Anaesthesiology I
Witten Herdecke University
Helios Clinic Wuppertal
Heusner Str. 40
42283 Wuppertal
Germany
Phone: 0049-2028961659
Email: Isabel.Dietz@helios-kliniken.de

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Abstract

Background: Levomepromazine is an antipsychotic drug that is used clinically for a variety of distressing symptoms in palliative and end-of-life care. We undertook a systematic review based on the question “What is the published evidence for the use of levomepromazine in palliative symptom control?”.

Methods: To determine the level of evidence for the use of levomepromazine in palliative symptom control and to discover gaps in evidence, relevant studies were identified using a detailed, multi-step search strategy. Emerging data was scrutinized using appropriate assessment tools. The strength of evidence was graded according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine. Used data sources were electronic databases (Medline, Embase, Cochrane, PsychInfo, OvidNursing), hand-searching and cross-reference searching.

Results: 33 articles including 9 systematic reviews met the inclusion criteria: 15 on palliative sedation, 8 regarding nausea and three on delirium and restlessness, one on pain and three with other foci. All publications varied largely in study design and sample size. Levels of evidence in those publications ranged from level 2b to level 5, most of them (n = 22) were level 3 (non-randomized, non-consecutive or cohort studies). Quality of reporting for the included articles was only low to medium.

Conclusion: Recommendations for the use of levomepromazine for diverse indications in palliative care have moderate to weak evidence. Levomepromazine has a broad range of beneficial effects in the terminal phase of many illnesses, resulting from its combined antipsychotic, anxiolytic, antiemetic and sedative actions. Prospective randomized trials are needed to support evidence-based guidelines.

Key words: levomepromazine, methotrimeprazine, palliative care, end of life care, symptom control, evidence, systematic review
Background

Patients with advanced disease approaching the end of life often suffer from symptoms that impair their own and their families quality of life.[1, 2] Alleviation of these symptoms, through a multi-dimensional and inter-professional palliative care approach, includes pharma-therapy as one essential component.

Common symptoms in the dying phase are pain, nausea and vomiting, agitation or restlessness and dyspnoea.[3] Pro re nata (PRN) prescription of drugs, as recommended in clinical pathways should cover these frequent symptoms, as well as rescue medication for possible emergency situations.[4, 5] Analgesics, antiemetics, sedatives and anxiolytics titrated to the individual patient’s level of need should be provided and drugs, which are not essential for symptom control, should be discontinued. Drug administration should preferably be via subcutaneous routes, and the amount of patient manipulation related to medication delivery, reduced to a minimum. In severe cases, where patients experience unbearable and/or refractory symptom burden, palliative sedation therapy [6] may be considered as an important and necessary therapeutic intervention.[7]

One drug widely used in the palliative care setting is levomepromazine in Europe and methotrimeprazine in the United States (trade names Neurocil, Nozinan, Nosinan or Levoprome). This aliphatic phenothiazine is a neuroleptic with low antipsychotic potency and was first used in psychiatry for treatment of schizophrenia.[8]

Levomepromazine acts as an antagonist at histamine type 1, muscarinic-cholinergic, dopaminergic 2, alfa1 and 5HT-2 receptor.[9, 10] Due to its half-life of 15-30 hours a once daily administration is practicable and it can be administered subcutaneously, intravenously or orally. Known adverse drug effects include postural hypotension, skin irritation, drowsiness, dry mouth, dystonia, neuroleptic malignant syndrome, Parkinsonism and epilepsy by lowering the seizure threshold.[11-13] Due to these side effects there are recommendations to best avoid its use in ambulatory palliative care patients.[14] Compared to the cost of some alternative drugs Levomepromazine is a cost effective option (e.g. in the UK 7 tablets with 24 mg of oral levomepromazine costs £1.69; http://www.cks.nhs.uk/).[15] Table 1 presents the essential pharmacokinetic data of the drug.
In palliative care, levomepromazine is predominantly used for the treatment of nausea and vomiting, and for severe delirium or agitation at the end of life. However, its effectiveness is mainly based on anecdotal evidence.[16, 17] More recently, its use as a sedative has become more frequent in the context of palliative sedation therapy, and analgesic properties are also described in some studies.[18, 19] For most of these indications the clinical use is off-label by application in many countries [20] and published evidence is scarce. The use of levomepromazine for symptom control in palliative care has been touched on in several published systematic reviews concerning individual symptoms, such as the treatment of nausea and vomiting [21], breathlessness [22] or sedation.[23] However, to date no systematic review has tried to establish the overall evidence base for using this interesting drug in the palliative care setting. The rationale for this investigation is levomepromazine’s broad-range applicability. Potentially, its properties are particularly beneficial in the treatment of several and diverse symptoms in end-of-life care. This review therefore aims to summarise and update the available evidence for the use of the “all-rounder” levomepromazine/ methotrimeprazine for patients in the palliative care setting, with a special focus on its utility in symptom control in end-of-life-care. This report follows the reporting standard of the PRISMA-Statement. Table 2 presents our research question according to the PICOS approach.[24]
Methods

A review protocol was developed and the trial was registered with the PROSPERO network for systematic review registration (registration number: CRD42012002390).

Study characteristics
Publications that met the inclusion criteria were those that 1) involved individuals treated in the palliative care setting, 2) included adults, 3) evaluated a pharmacological treatment of symptoms at the end of life with levomepromazine and 4) were characterized as randomized controlled trials, prospective trials, cohort studies, case series or case reports. Systematic reviews were also included and mostly were used for hand searches of references. Non-systematic or narrative reviews were excluded but collected as a separate category as proof of existing clinical knowledge. Our systematic review was limited to studies published in English or for which English abstracts were available. The period of review was from 1980 to April 2012.

Search strategy
The following five computerized online databases were searched in the second week of April 2012: Medline (1946 to April week 2 2012), Embase (1980 to 2012 Week 15), The Cochrane Library, PsychInfo (1806 to April week 3 2012), Ovid Nursing (1946 to April week 2 2012).

The automated search was conducted using two main components: The first component included several search terms for identification of literature relevant to palliative care based on a master search strategy developed for that specific concern [25] enlarged by some additional search terms. The second component contained the search terms for levomepromazine.

Search terms of the automatic search are the following:
exp advance care planning/ OR exp attitude to death/ OR exp bereavement/ OR death/ OR hospices/ OR life support care/ OR palliative care/ OR exp terminal care/ OR terminally ill/ OR palliat*.tw. OR hospice*.tw. OR “terminal care”.tw. OR terminally ill patient.mp. or exp terminally ill patient OR exp terminal care/ OR palliat*.tw. OR hospice*.tw. OR end of life care.mp. OR EOL care.mp. OR palliative therapy.mp. or palliative therapy/ OR terminally ill patient.mp. or terminally ill patient/
AND levomepromazine.mp. or levomepromazine/ OR methotrimetrazine.mp. OR neurocil.mp. OR nozinan.mp. OR levoprome.mp.

Table 3 shows the full electronic search strategy as performed in Embase.

Study selection
After conducting the search in all databases and de-duplication, as a first step, titles and abstracts of identified studies were screened for relevance to the topic and studies considered to be not relevant excluded. In a second step, full texts were sought for all studies, which appeared to meet the inclusion criteria. Conference abstracts were also included. Two independent researchers then separately reviewed all retrieved papers for relevance. Where a difference in results occurred, data was discussed and the discussion recorded. Final decisions were strictly based on reviewing the inclusion and exclusion criteria. If agreement could not be reached, full-text analysis using a relevant quality instrument was performed. Where there was still no agreement after thorough discussion, the study was included into the search and its relevance discussed in the publication.

Data extraction and assessment of studies
Relevant studies were extracted into a qualitative synthesis table and categorised according to the following items: author, title, year of publication, journal, study design, indication for levomepromazine, study population, setting, number of study participants, number of patients under treatment, mean dose, dose range, application, measurement of effectiveness, reported adverse effects, remarks, conclusion, main results from the quality analysis process, further comments. Studies were critically appraised and the evidence was graded based on the determinants of quality of evidence published by the Oxford Centre for Evidence-Based Medicine Levels of Evidence: Level 1: evidence from a systematic review of RCT; Level 2: evidence from a RCT; Level 3: evidence from a non-randomized controlled cohort studies Level 4: evidence from case-series or case-control or historically controlled studies D: expert opinion (should this be Level 5).[26] Study quality assessments were undertaken by using quality check-lists adherent to the standards gathered by the EQUATOR network.[27]
Results

Study selection
A total of 33 articles involving 9 systematic reviews met the inclusion criteria for research and reported data regarding patients treated with levomepromazine/methotrimeprazine in a palliative care setting. The search of the five databases provided 367 studies after de-duplication. After reviewing of titles and abstracts 270 of these papers were rejected as clearly not meeting the inclusion criteria. 19 additional records were identified through hand-searching and reference lists. Of the remaining 81 references full copies were retrieved and assessed for eligibility. Of those 48 papers met the inclusion criteria. After examination of these studies in more detail, 33 articles remained for data extraction. 27 out of these 33 papers were found via automatic database searches, five were found through reference tracking and two were obtained from the library of St. Christopher’s Hospice, London. Moreover we identified 23 reviews, other than systematic or narrative, which were not included in this review, but are regarded as relevant for clinical practice, and could beneficially be analysed with regard to that concern elsewhere. Figure 1 shows a flowchart of study selection process.

Study characteristics
The principal characteristics of the selected articles are presented in appendix 1. All relevant papers were published in peer-review journals between 1980 and 2011. Seven papers dealt with the topic of sedation, five with nausea and vomiting and one paper each with pain, delirium, several indications and side effects of levomepromazine. Regarding study design, we included six case reports, two survey studies, nine retrospective studies and seven prospective studies. Nine systematic reviews were also included.

Sedation
With 12 studies and three systematic reviews, papers on palliative sedation presented the largest group within the reviewed articles. Studies concerning the use of levomepromazine/methotrimeprazine in palliative sedation varied largely in study design and sample size. In a retrospective cohort study of 29 patients sedated at home, two had their medication changed from midazolam to levomepromazine, which was effective in both patients. In one of these patients the indication for...
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sedation was pain, in the other patient delirium was given as the rationale for use.[28] The other studies on sedation did not provide specific information on the background or indication for the use of levomepromazine in palliative sedation. The retrospective chart review of Stone et al. documented levomepromazine in 33 out of 115 reviewed patients (28.7%) in their last 5 days of life[29]. Stephenson et al. found that 51-58% of sedated patients received levomepromazine according to their chart review.[30] In a survey study by Chater et al. in 100 patients, reported by 61 selected palliative care experts, 30 (30%) had received levomepromazine for palliative sedation.[31] Sykes et al showed that levomepromazine was used in only 3 out of 114 patients (2.6%) receiving sedation in a English hospital setting, during their last week of life, but that this number increased to 30 patients (26%) in the last 24 hours.[32] Reutzel et al asked their respondents in a retrospective survey about one case of end-stage palliative sedation during the past 12 months; in 15 out of 312 reported cases (4.8%) levomepromazine was used.[33] In a multi-center, prospective, observational study on specialized palliative care units in Japan, in a sample of 102 patients the use of levomepromazine was documented in 2 cases (1.9%).[23] A retrospective chart review of Morita et al demonstrated the use of levomepromazine for sedation only in 2 out of 209 patients (0.97%) [34] and in a study comparing data from 97 sedated patients in three different countries (Israel, South Africa and Spain), only one received levomepromazine.[1]

One of the two case studies presented a patient suffering from motorneuron disease in which sedation was started for withdrawal of mechanical ventilation [35], the other case described sedation due to intractable seizures in a patient with metastatic insular thyroid cancer and brain metastases.[36]

In most of the cases presented in these studies, levomepromazine was given in combination with midazolam, only Alonso-Babarro changed to levomepromazine alone.[28] Relevant papers for the use of levomepromazine in palliative sedation with recommendations regarding doses and dose range and provided indications for sedation are shown in Table 4.

Effectiveness of sedation was measured in only some of these papers, mostly subjectively rather than with standardized tools.[1, 28, 31, 37] In the work of Alonso-Babarro, effective sedation was achieved with a level 5 or greater on the Ramsay scale and a lack of emergency calls during the process. In three studies survival was measured as main outcome criteria.[29, 32, 38]
Nausea and vomiting
Papers concerning the use of levomepromazine for nausea and vomiting represented the second largest group: we found six studies and two systematic reviews dealing with that topic. Eisenchlas et al. reported on a sample of 70 patients with digestive cancer treated in an open-label prospective study with levomepromazine for nausea and vomiting, in which sixty patients (86%) were categorized as responders. In that study, Pearson test revealed no association between levomepromazine dose and response to treatment, and no association between levomepromazine dose and degree of sedation.[13] In a quasi-experimental prospective study Kennett et al showed that levomepromazine is an efficient first line antiemetic in indeterminate patho-physiological causes of nausea and vomiting and second line for all other causes.[39] These findings were confirmed by a non-comparative prospective study conducted by Stephenson et al. in which, from a sample of 61 hospice patients with nausea, 27 (44%) received levomepromazine.[40] Moreover levomepromazine was proven to be effective as second line treatment in chemotherapy-induced nausea [41] and in carcinoid syndrome.[42] In a survey of 154 oncologists and oncology nurse prescribers levomepromazine was recommended for refractory chemotherapy-related nausea and vomiting as the second or even third-line treatment option.[43] One other paper did not focus on nausea and vomiting as a main issue, but reviewed the extent of drug use for unlicensed purposes in a palliative care unit and found that 8 out of 689 prescriptions (1,2%) were oral levomepromazine for nausea and vomiting, and 18 (2,6%) were subcutaneous levomepromazine.[44] In another systematic review on symptom management for the adult patient dying with advanced chronic kidney disease, levomepromazine was recommended as second line therapy for nausea and vomiting if haloperidol failed. The authors do not provide doses for levomepromazine in the renal failure population.[45]
Table 5 shows recommended doses and dose range of levomepromazine.

Delirium/ terminal restlessness
For the specific use of levomepromazine in delirious or restless patients three papers were included. One retrospective chart review found that, in 39 hospital patients with delirium during their last week of life, 7 patients (18%) were treated with
levomepromazine. A combined treatment of neuroleptics and benzodiazepines was used more often in that study.[46] Fainsinger at al. reported a case of agitated delirium that was treated with levomepromazine after haloperidol and lorazepam had failed. In that case the patient also failed to respond to the doses of levomepromazine that were used (20-60 mg/24 hours) and the presence of extrapyramidal side effects contributed to the decision to change treatment again, thus finally midazolam controlled delirium.[47] That case report is the only paper on levomepromazine included in the systematic review on the treatment of terminal restlessness performed by Kehl et al 2004 coming to the conclusion that there is little empirical evidence suggesting that a single medication or class of medications is superior over another for terminal restlessness.[48] One other paper did not focus on delirium as main issue, but reviewed the extent of drug use for unlicensed purposes in an English palliative care unit and found that 4 out of 689 prescriptions (0.6%) were subcutaneous levomepromazine.[44]

Other indications/ issues
The remaining three papers deal with different issues concerning the use of levomepromazine in palliative care. One study focuses on the analgesic quality of the drug. The authors report a case of a patient suffering from pain associated with lung cancer, which was sensitive to opioids and possibly related to bowel shutdown. This patient obtained adequate relief of abdominal pain with a dose of 10 mg levomepromazine i.m.. The authors used a conversion rate of 10 mg levomepromazine to 5 mg of morphine and preferred it because of a smaller effect on the gut and less respiratory depression.[49] Aside from this one case report, no further literature on the analgesic effect of levomepromazine was found. Another case report discusses the possible side effect of levomepromazine-induced lupus erythematosus in a patient with metastatic non-small cell lung cancer[50] and one conference abstract reported the use of levomepromazine in the management of terminal haemorrhage.[51] One systematic review on treatment of intractable breathlessness in patients with advanced cancer showed that there are no randomized controlled trials of phenothiazines in patients with cancer and that the use of these agents is predicated on evidence in COPD and healthy volunteers. The authors of that review recommend the use of levomepromazine in patients in whom anxiety becomes overwhelming or for palliative sedation therapy at the end of life.[22]
Effectiveness

Only 12 studies included information about effectiveness or reported information on measurement of effectiveness. In six of these studies, only specific effectiveness of the treatment with levomepromazine was provided, the summarized data is shown in Table 6.

Assessment of quality and risk of bias

The assessment of quality for the included studies was undertaken according to the standards gathered and regularly updated by the EQUATOR network. Risk of bias was assessed on the individual study level. The PRISMA checklist was used for the nine systematic reviews[24] and in 14 papers quality was assessed using the STROBE check-list for observational studies[53]. The six case reports included in the review were evaluated by the check-list recommended by Sorinola et al[54] and other four papers reporting survey research were evaluated as suggested by Kelley et al.[55] No one paper in any category covered all reporting or quality criteria as set out by their corresponding check-list. All survey studies were rated medium to high quality. All case reports had an averaged I medium quality. The quality of reporting for the systematic reviews and observational studies was only of low to medium quality.

Levels of evidence according to the Oxford Centre for Evidence-Based Medicine

Levels of Evidence ranged from level 2b (retrospective/individual cohort study) to level 5 (expert opinion). Most papers (n = 22) were categorized as level 3 (non-randomized, non-consecutive or cohort studies). Only three studies reached level 2: one concerning palliative sedation[28] and two on nausea[13, 39]. Details of quality assessments for every study are presented in appendix 1. Further information about the process of quality assessment and use of the check-lists can be obtained from the authors.

As no meta-analysis was conducted and the studies included in our systematic review showed large variations of study design, sample size and quality, no assessment of risk of bias across studies was undertaken.
Discussion
This review aimed to summarise and update the available evidence for the use of the “all-rounder” levomepromazine/methotrimeprazine for patients in the palliative care setting with a special focus on its utility in symptom control at the end-of-life.
That levomepromazine is a drug with broad-range applicability and effectiveness in the treatment of symptoms in end-of-life care had already been demonstrated in a study by Oliver et al in 1985.[37] However, since that study, which looked at the use of this particular drug for confusion and agitation, nausea and vomiting and pain as three main indications for use, no other work has considered levomepromazine in palliative care treatment “as a whole”. In that early work by Oliver et al., sedation was reported as a noted side effect of levomepromazine, whereas subsequent studies in the 1990th turned that side effect into a benefit and started to realize the value of the drug as a part of treatment where sedation was indicated and/or intended.[29, 31] Further researchers began to focus on the use of the drug in specific symptom control for individual symptoms in palliative care patients and an overall perspective on the multifaceted applicability of levomepromazine stepped into the background.
Multiple studies showed that levomepromazine, due to its broad-spectrum action on receptors involved in emesis, is effective as a first-line treatment for intractable pathophysiological causes and as a general second-line option for treatment of nausea and vomiting.[13, 39-43] Dose ranges vary slightly in the lower value but are stable in the upper one: only one study indicated doses up to 30 mg levomepromazine per day, all other studies indicated an upper value of no more than 25 mg per day. There exist a variety of non-systematic reviews and narrative articles recommending levomepromazine for nausea and vomiting in palliative care patients, which should be recognised and considered in practice, although they are mostly based on anecdotal evidence or expert opinion.[12, 16, 56-58] The two systematic reviews on nausea and vomiting included in our review provide very little information or data on dosage, which leaves them without much clinical utility. An expected Cochrane review evaluating the efficacy of levomepromazine for the treatment of nausea and vomiting in palliative care patients might be a useful step towards establishing recommendations for clinical practice.[59] However, we considered the bases for providing evidence-based recommendations on dosage and route of administration in nausea and vomiting is very small.
There is a large number of papers dealing with the use of levomepromazine in palliative sedation, most of them recommend the use in combination with midazolam or as second line drug for continuous sedation if midazolam is ineffective.[23, 28, 31, 35, 36, 60] Similar data are provided in non-systematic reviews.[29, 61-63] Again, we could not identify any consensus regarding dosage of levomepromazine for palliative sedation in the included papers: mean doses and dose ranges varied considerably between studies and we could not find evidence other than clinical expertise that substantiated the chosen doses.

The most common indication for the use of levomepromazine in sedation in the above named papers were terminal restlessness, especially in combination with neuropsychological symptoms such as confusion, anxiety, agitation or delirium. In the framework for the use of sedation in palliative care recommended by the European Association for Palliative Care (EAPC), one of the most recent and relevant papers, with significant clinical implications, levomepromazine is recommended for sedation of delirious patients as a first line choice based on the reason that benzodiazepines as an initial treatment for delirium may worsen rather than improve symptoms.[8] However, none of the systematic reviews on palliative sedation included in the present review provide strong evidence other than clinical expertise for the use of levomepromazine. Papers either provide no information about underlying evidence for recommendations on levomepromazine, or recommendations are limited to expert opinions, or data on levomepromazine is based on the same small group of low quality and low evidence studies, which we also found in our review.

Delirium was considered as a category of its own for the use of levomepromazine in palliative care patients in the present work. Unfortunately, papers that dealt with this indication were scarce and the reported data was highly heterogeneous. The spectrum of data ranged from levomepromazine being ineffective in a case study[47], or the statement that combined treatment of neuroleptics and benzodiazepines are often utilized to control delirium based on data of a retrospective chart review[46] to a systematic review including only two studies on levomepromazine, one of which was the case report named above, but nevertheless recommending neuroleptic medications in general as a first or second line pharmacological treatment of delirium.[48] As stated in a work by Caraceni et al and also mentioned in the EAPC-
framework, if control of delirium fails, sedation can be necessary and in these cases levomepromazine may be a choice.[7, 64] Thus, it seems that some authors seem to see a smooth transition between treatment of delirium and palliative sedation therapy, but to our knowledge there exist no studies as yet providing data about differences in dosages for delirium versus sedation, co-factors or co-morbidities influencing the choice of medication, or meaning of pathophysiologival causes of delirium in that context.

A Chochrane review conducted in 2010 about anti-psychotics for acute and chronic pain in adults, proposed levomepromazine for pain within the first 72 hours after acute myocardial infarction[19], and in chronic non-cancer pain management levomepromazine may be used supplementary to other drugs.[65] A couple of studies in the 1960th and 1970th reported levomepromazine to be effective in treatment of pain in cancer patients[66-68], and there even seems to be an accepted a conversion scale for morphine to levomepromazine of 1.5 : 1.[69] Our review included one case report published in 1987 and one study from 1985 underlining these previous findings[37, 49], but regrettably there seems to be absolutely no later published research on the use of levomepromazine for pain in palliative care or cancer patients.

Many studies mentioned side effects of levomepromazine, which mainly focused on sedation and hypotension, but also skin reaction or extrapyramidal side effects were reported.[13, 38, 47, 49] Incidences and co-factors of these side effects are not studied in detail, where such side-effects were reported, and no specific data for patients at the end of life seems to exist. The above-mentioned Chochrane review on the use of levomepromazine for the treatment of nausea and vomiting will also evaluate associated minor and serious adverse events.[59] Until then it seems that Levomepromazine needs to be considered for use in accordance to expert clinical knowledge and by establishing an indication for its use on ethical considerations, weighing the benefit and harm for an individual patient in clinical practice. Hypotension for example, which is a reported side-effect of Levomepromazine, is unlikely to be a problem in bed-bound patients with a low palliative performance status, and/or a situation in which active symptom control is the only means of providing quality at the end of life.[70] What is more, sedation as a side-effect could
be potentially useful and therefore incorporated in a holistic pharmacological regimen of end-of-life palliative care in some patients.

Limitations
Because of the limitations of available studies the overall evidence for the use of levomepromazine resulting from the present review remains weak. Findings mainly based on retrospective study designs, lack of control groups, missing randomisation and small sample sizes all lead to a weak level of evidence. More homogeneous prospective studies on larger number of patients, including measurement and reporting of outcome parameters, should be performed to provide more reliable data.

Our systematic review followed the steps considered good practice including the pre-investigation registration of our review protocol, adherence to the reporting standards and rigorous recording of decision pathways during the review process. However, some limitations apply. We did not perform any meta-analysis as the heterogeneous and low-quality data of the original studies included simply did not allow such a step. We did not apply risk-of-bias assessment tool across studies. What is more, we limited our review to published data deliberately excluding grey literature and non-published expert opinion, introducing a publication bias to our review.

Conclusion
As a consequence of this review we can summarize that there exists some low-grade evidence for the use of levomepromazine for several indications in the palliative care setting.
We emphasize, that we believe the amount of publications, which are at least mentioning levomepromazine, underlines, that there seems to be a clinical use and value for this drug’s use in symptom treatment in palliative care patients and this deserves further evaluation. Scrutinizing the published literature on levomepromazine it becomes clear, that today there is some low quality and low evidence literature available to support the use of levomepromazine in the palliative care setting. However, only a very limited number of experimental and scientific sound studies are available. Randomized controlled or even blinded trials on the topic are completely lacking. Even if that kind of research may be difficult to manage in the palliative care setting and in everyday clinical life[71, 72], we should strive for more high quality research. By generating a more solid evidence base for the use of the
Levomepromazine, its indications, impact and side effects in palliative care we could gain much needed empirical knowledge for the use of a drug that seems to be clinically effective and multi-factorial in application for end-of-life care. The promise of Levomepromazine as a medicament that can relieve more than one symptom with one dose exists, but has to be underpinned by further research, and most relevantly studies which have an experimental design.
Competing interests
All authors declare that they have no competing interests.
Authors’ contributions
ID and CS carried out the systematic literature review, coordinated the sequence alignment and drafted the manuscript. AS and IL participated in the sequence alignment and in the design of the review and helped to draft the manuscript. All authors read and approved the final manuscript.
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