

RESEARCH ARTICLE

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

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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 then scrutinized using appropriate assessment tools, and the strength of evidence systematically graded in accordance with the Oxford Centre for Evidence-Based Medicine’s ‘levels of evidence’ tool. The electronic databases Medline, Embase, Cochrane, PsychInfo and Ovid Nursing, together with hand-searching and cross-referencing provided the full research platform on which the review is based.

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 six with other foci. The studies varied greatly in both design and sample size. Levels of evidence ranged from level 2b to level 5, with the majority being level 3 (non-randomized, non-consecutive or cohort studies $n = 22$), with the quality of reporting for the included studies being only low to medium.

Conclusion: Levomepromazine is widely used in palliative care as antipsychotic, anxiolytic, antiemetic and sedative drug. However, the supporting evidence is limited to open series and case reports. Thus prospective randomized trials are needed to support evidence-based guidelines.

Keywords: 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 pharmacotherapy as an essential component.

Common symptoms in the terminal phase are pain, nausea and vomiting, agitation or restlessness and dyspnoea [3]. Pro re nata (PRN) prescription of drugs, as

recommended in clinical pathways aim to cover these common symptoms, as well as to provide stand-by medication for possible emergency situations [4,5]. Analgesics, antiemetics, sedatives and anxiolytics titrated to the individual patient’s level of need should be prescribed and any medication, which is not essential for symptom control, discontinued. Drugs administration is preferably via subcutaneous routes, and the amount of patient manipulation related to medication delivery, reduced to a minimum. In severe cases, where patients experience an unbearable and/or refractory symptom burden, palliative sedation therapy may be considered as an important and necessary therapeutic intervention [6,7].

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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 first used in psychiatry for the treatment of schizophrenia [8]. Levomepromazine acts as an antagonist at histamine type 1, muscarinic-cholinergic, dopaminergic 2, alpha-1 adrenoceptor and 5HT-2 receptors [9,10], and due to a half-life of 15–30 hours makes once daily administration practicable. 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]. As a result of the potential impact of some of these side effects on safe mobilisation 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]. In clinical practice, its use as a sedative has also become more frequent as part of palliative sedation therapy, and the analgesic properties of levomepromazine are described in some of the studies [18,19]. For most of the above indications the clinical use of levomepromazine 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 considered in several published systematic reviews concerning individual symptoms, such as the treatment of nausea and vomiting [23], breathlessness [24] or sedation [25]. However, to date no systematic review has tried to collate 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 at the end-of-life. The report follows the reporting standard of the PRISMA-Statement. Table 2 presents our research question according to the PICOS approach [26].

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 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 but were primarily 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/practice. 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 purpose [27], 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 methotrimeprazine.mp. OR neurocil.mp. OR nozinan.mp. OR levoprome.mp.

Table 1 Pharmacokinetic data of levomepromazine [21,22]

Bioavailability	20-40% p.o.
Onset of action	30 min.
Maximum serum concentration (t_{max})	p.o.: 2–3 h i.m.: 30–60 min
Half life ($t_{1/2}$)	15-30 h
Duration of action	8 h

Table 2 PICOS approach in our systematic review according to the PRISMA guideline [26]

P	patients	patients at the end of life
I	intervention	pharmacological treatment with levomepromazine
C	comparison	none
O	outcome	symptom control with levomepromazine
S	study design	randomized controlled trials, prospective trials, cohort studies, case series, case reports, systematic reviews

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 being 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 adherence to 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 for 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 Level 5: expert opinion [28]. Quality assessments were undertaken by using quality check-lists adherent to the standards gathered by the EQUATOR network [29].

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 initially 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 84 references full copies were retrieved and assessed for eligibility. Of those 48 papers met the inclusion criteria. After further examination of these studies in more detail, 33 articles remained for data extraction. 25 out of these 33 papers were found via automatic database searches and eight were found through reference tracking or hand searching. Moreover we identified 23 reviews, other than systematic or narrative, not included in this review, which could be regarded as relevant for clinical practice, and beneficially be analysed in a separate review elsewhere. Figure 1 shows a flowchart of the study selection process.

Study characteristics

The principal characteristics of the selected articles are presented in the Additional file 1: Appendix. 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

The 12 studies and four systematic reviews on palliative sedation presented the largest group within the reviewed articles [30–45]. 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 sedation was pain, in the other patient delirium was given as the rationale for use [31]. 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

Table 3 Electronic search strategy performed in Embase

No.	Search term	Results
1	exp advance care planning/	448482
2	exp attitude to death/	8692
3	exp bereavement/	5150
4	death/	92098
5	hospices/	6053
6	life support care/	77969
7	palliative care/	40548
8	terminal care/	20376
9	terminally ill/	5136
10	palliat\$.tw.	54515
11	hospice\$.tw.	8617
12	terminal care.tw.	1478
13	physician-patient relations/	74874
14	prognosis/	385402
15	quality of life/	193187
16	survival rate/	119505
17	treatment outcomes/	0
18	attitude to health/	70459
19	palliative care.mp.	17299
20	exp terminal care/	40896
21	exp terminally ill patient/	5298
22	terminally ill.mp.	8305
23	exp palliative therapy/	52501
24	EOL care.mp.	307
25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1405466
26	levomepromazine.mp.	4195
27	levomepromazine/	4103
28	methotrimeprazine.mp.	127
29	methotrimeprazine/	4103
30	neurocil.mp.	206
31	nozinan.mp.	480
32	levoprome.mp.	34
33	26 or 27 or 28 or 29 or 30 or 31 or 32	4223
34	25 and 33	499
35	limit 34 to english language	364
36	limit 35 to yr = "1980 -Current"	363

chart review of Stone et al. documented levomepromazine in 33 out of 115 reviewed patients (28,7%) in their last 5 days of life [40], Stephenson et al. found that 51–58% of sedated patients received levomepromazine according to their chart review [33]. In a survey study by Chater et al. of 100 patients, reported on by 61 selected palliative care experts, 30 (30%) had received levomepromazine for

palliative sedation [39]. 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 [35]. 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 [34]. 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%) [44]. A retrospective chart review of Morita et al. demonstrated the use of levomepromazine for sedation only in 2 out of 209 patients (0,97%) [37] and in a study comparing data from 97 sedated patients in three different countries (Israel, South Africa and Spain), only one received levomepromazine [38].

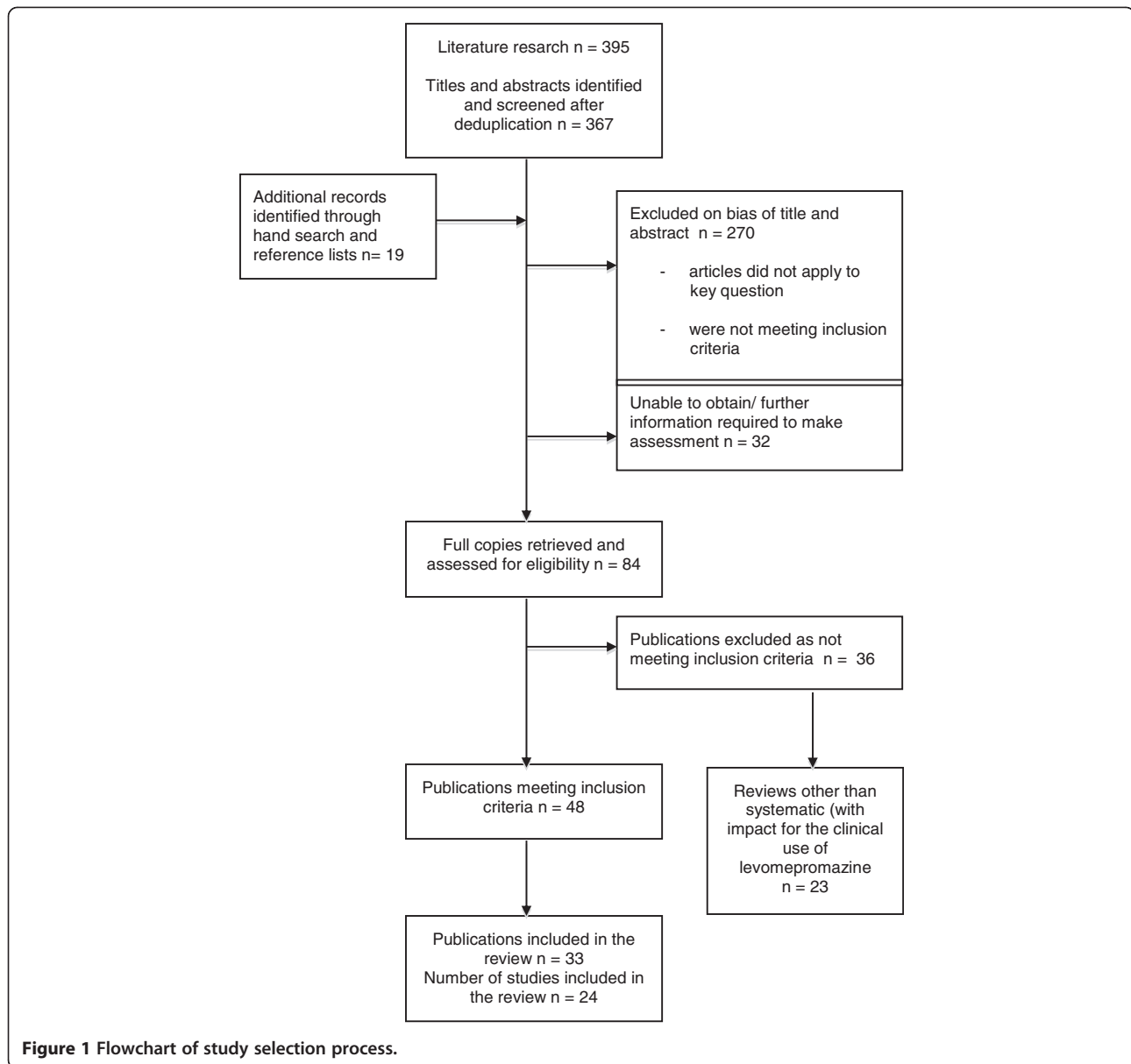
One of the two case studies presented a patient suffering from motor-neurone disease in which sedation was started to allow withdrawal of mechanical ventilation [30], the other case described sedation due to intractable seizures in a patient with insular thyroid cancer and brain metastases [32].

In most of the cases presented in these studies, levomepromazine was given in combination with midazolam, only Alonso-Babarro changed to levomepromazine alone [31]. 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 the papers, mostly subjectively rather than with standardized tools [31,38,39,41]. 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 [37,40,46].

Nausea and vomiting

Papers concerning the use of levomepromazine for nausea and vomiting represented the second largest group: we found six studies [13,47–51] and two systematic reviews [23,52] 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, the 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



[50]. 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 [48]. Moreover levomepromazine was proven to be effective as second line treatment in chemotherapy-induced nausea [51] and in carcinoid syndrome [49]. 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 [47]. 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 [53]. 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 [54].

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 [56–58]. One retrospective chart review found that, in 39 hospital patients with delirium during their last week of life, 7

Table 4 Recommended doses and dose ranges for levomepromazine in palliative sedation (data refer to subcutaneous application)

Author	Year	Study design	Mean dose (mg/24 h)	Dose range (mg/24 h)	Findings
Lebon [30]	2010	case study	25	25-100	levomepromazine in combination with midazolam
Alonso-Babarro [31]	2010	retrospective cohort study	125	100-150	indications: pain, delirium
D'Cruz [32]	2009	case report	no data	no data	indication: agitation/delirium
Stephenson [33]	2008	retrospective chart review	9.4 75	2.5-75 25-150	2006 1996 levomepromazine was often used first line, 2006 midazolam was used first line and levomepromazine as an adjunct
Reuzel [34]	2008	survey study	no data	no data	most common indications: pain and dyspnoea
Sykes [46]	2003	retrospective case-control study	125	125-200	indication: continuing agitation
Gambles [36]	2001	descriptive retrospective study	no data	6.25-12.5	indication: agitation/restlessness
Morita E [37]	2001	prospective study	50	50	
Fainsinger [38]	2000	prospective observational multicenter study	no data	no data	most common indication: delirium
Chater [39]	1998	survey study	100	50-250	
Stone [40]	1997	retrospective chart review	64	no data	levomepromazine was usually prescribed in combination with another sedative
Oliver) [41]	1985	retrospective chart review	no data	37.5-300	indications: confusion/agitation, pain, vomiting (not palliative sedation as main indication)
Mercadante [42]	2011	SR	no data	100-150	based on [39]
DeGraeff [43]	2007	SR	64	25-250	based on [39] [40,45,46]
Morita T [25]	2005	SR	no data	5-12,5	guideline is based on a Delphi process conducted by the Sedation Guideline Task Force
Cowan [45]	2001	SR	64	48-600	based on [40,41]

patients (18%) were treated with levomepromazine. A combined treatment of neuroleptics and benzodiazepines was used more often in that study [56]. Fainsinger et al. reported a case of agitated delirium that was treated with levomepromazine after haloperidol and lorazepam had failed. In that case the patient equally 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, with midazolam the final agent effectively controlling the delirium [58]. 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, which concluded that there is little empirical evidence suggesting that a single medication or class of medications is superior to another for terminal restlessness [57]. One final paper, which did not focus on delirium as main issue, but was reviewing the extent of drug use for unlicensed purposes in an English palliative care unit, found that 4 out of 689 prescriptions (0,6%) were subcutaneous levomepromazine [53].

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 [59]. 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 [60] and one conference abstract reported the use of levomepromazine in the management of terminal haemorrhage [61]. 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 non-the-less recommend the general use of levomepromazine in patients in whom anxiety becomes overwhelming, or for palliative sedation therapy at the end of life [24].

Effectiveness

Only 12 studies included information about effectiveness or reported information on measurement of effectiveness [13,31,35,37–41,48,50,51,58]. 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 an individual study level. The PRISMA checklist was used for the nine systematic reviews [26] and in 14 papers quality was assessed using the STROBE check-list for observational studies [62]. The six case reports included in the review were evaluated by the check-list recommended by Sorinola et al. [63], and the four papers reporting survey research were evaluated as suggested by Kelley et al. [64]. 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. The case reports averaged medium quality, and 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 [31] and two on nausea [13,50]. Details of quality assessments for every study are presented in Additional file 1: Appendix. 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 symptom control at the end of life.

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 [41]. 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 1990^{es} 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 [39,40]. Further researchers began to focus on the use of the drug in specific symptom control for individual

Table 5 Recommended doses and dose ranges for levomepromazine in nausea and vomiting

Author	Year	Study design	Mean dose (mg/24 h)	Dose range (mg/24 h)	Findings
Molassiotis [47]	2010	survey study	no data	no data	second or third line for refractory chemotherapy-related nausea and vomiting
Stephenson [48]	2006	non-comparative prospective study	no data	6.25–25	first line in indeterminate pathophysiological causes and second line for all other causes of nausea and vomiting
Eisenchlas [13]	2005	open-label prospective study	6.25	3.12- 25	second line
Amesbury [49]	2004	case report	no data	12.5 -25	first line indication: 5HT2 antagonist property of levomepromazine is used because large amounts of circulating 5-HT are present in carcinoid syndrome
Kennett [50]	2004	quasi experimental prospective study	no data	6.25-25	second line or for indeterminate pathophysiological causes
Higi [51]	1980	prospective study	no data	16-30	second line in chemotherapy induced nausea
Davis [23]	2010	SR	no data	no data	based on [13,49,50]
Glare [52]	2004	SR	no data	no data	based on one study [55] (not available)

Table 6 Studies reporting effectiveness and measurement of effectiveness of levomepromazine

Indication	Reference	Number of patients under study	Number of patients receiving levomepromazine	Effect
sedation	Alonso-Babarro [31]	29	2	100% (defined as symptom control was achieved, consciousness (consciousness was 5 or greater using the Ramsay scale and no emergency calls during the PS process)
nausea	Eisenclas [13]	70	70	86% (categorized as responders if NRS score decreased by 6+ from the baseline score)
nausea	Kennett [50]	65	65	62.3% (14 patients met the definition of a complete response and 19 a partial response)
nausea	Higi [51]	113	113	62% (fully protected from nausea and vomiting)
nausea	Oliver [41]	675	15	86% (no data about how effectiveness was measured)
nausea	Twycross [55]	29	29	83% (no data about how effectiveness was measured, study not included in our review)
delirium	Fainsinger [38]	1	1	0% (ineffective in treating the patient's delirium and thus discontinued after 48 hours)
agitation	Oliver [41]	675	49	67% (no data about how effectiveness was measured)
pain	Oliver [41]	675	16	94% (no data about how effectiveness was measured)

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 patho-physiological causes and as a general second-line option for treatment of nausea and vomiting [13,47–51]. Dose ranges vary slightly at the lower value but are stable in the upper; only one study indicated doses up to 30 mg levomepromazine per day, all other studies stated 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 [12,16,56–58,65,66]. The two systematic reviews on nausea and vomiting included in our review provide very little information or data on dosage, which leaves them short on clinical applicability [23,52]. However, an expected Cochrane review evaluating the efficacy of levomepromazine for the treatment of nausea and vomiting in palliative care patients may in future, when completed and published, provide some useful guidance towards establishing recommendations for clinical practice [67]. At present, we consider the research foundation for evidence-based recommendations on dosage and route of administration in nausea and vomiting to be very small.

There are a large number of papers dealing with the use of levomepromazine in palliative sedation, most of them recommend its use in combination with midazolam or as a second line drug for continuous sedation if

midazolam is ineffective [25,30–32,39,42]. Similar data can be found in non-systematic reviews [40,46,68,69]. 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 found no evidence other than clinical expertise to underpin the choice of dosage and/or level.

In all the above named papers the most common indication for the use of levomepromazine as a sedative agent is in relation to terminal restlessness, especially where this occurs in combination with neuro-psychological symptoms such as confusion, anxiety, agitation or delirium. In the framework for the use of sedation in palliative care published 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 rationale that benzodiazepines, as an initial treatment for delirium, may worsen rather than improve symptoms [7]. However, neither the systematic reviews, nor the studies on palliative sedation, included in this review provide robust evidence, other than clinical expertise for the use of levomepromazine. Papers either provide no information about underlying evidence for recommendations, or recommendations are limited to expert opinions, or findings are based on the same small group of low quality and low evidence studies.

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 [58], or the statement that combined treatment of neuroleptics and benzodiazepines are often utilized to control delirium based on data from a retrospective chart review [56] to a systematic review, that included 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 [57]. 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 [7,70]. Thus, it seems that some authors see a smooth transition between treatment of delirium and palliative sedation therapy, but to our knowledge there exist no studies as yet which provide data on dosage levels for delirium versus sedation, or differential co-factors/co-morbidities which would influence the choice of medication, or the meaning of patho-physiological causes of delirium in this context.

A Cochrane 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 [71]. A couple of studies in the 1960es and 1970es reported levomepromazine to be effective in treatment of pain in cancer patients [72–74], and there even seems to be an accepted conversion scale for morphine to levomepromazine of 1.5:1 [75]. Our review included one case report published in 1987, and one study from 1985 underlining these previous findings [41,59], 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 skin reactions and extrapyramidal side effects were also reported [13,44,58,59]. Incidences and co-factors of these side effects are not studied in detail, and where such side-effects were reported no specific data for patients at the end of life seems to exist. The above-mentioned Cochrane review on the use of levomepromazine for the treatment of nausea and vomiting will also evaluate associated minor and serious adverse events [67]. 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 [76]. 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, and 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, and 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. Beneficial effects of levomepromazine are widely reported in the palliative care literature; it's role in symptom control therefore 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 few experimental and scientifically sound studies are available. Randomized controlled or even blinded trials on the topic are completely lacking, and although that kind of research may be difficult to manage in the palliative care setting and in every day clinical life [77,78], 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 pharmacological tool, capable of relieving more than one symptom with one dose, exists but needs to be underpinned by further research, and most importantly, studies of experimental

design, providing a firmer research base with which to guide future clinical practice.

Additional file

Additional file 1: Appendix 1. Principal characteristics of the included articles.

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.

Acknowledgements

We acknowledge Constanze Rémi from the Interdisciplinary Centre for Palliative Care in Munich, Germany, for her input from the pharmaceutical background. ID is funded by the Dr. Werner Jackstädt foundation, for the manuscript preparation no funding was obtained.

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Received: 16 October 2012 Accepted: 15 January 2013

Published: 19 January 2013

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doi:10.1186/1472-684X-12-2

Cite this article as: Dietz et al.: Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review. *BMC Palliative Care* 2013 12:2.

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