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The use of opioids at the end of life: knowledge level of pharmacists and cooperation with physicians

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Abstract (241 words)

Purpose: What is the level of knowledge of pharmacists concerning pain management and the use of opioids at the end of life, and how do they cooperate with physicians?

Methods: A written questionnaire was sent to a sample of community and hospital pharmacists in the Netherlands. The questionnaire was completed by 182 pharmacists (response rate 45%).

Results: Pharmacists were aware of the most basic knowledge about opioids. Twenty nine percent of the pharmacists erroneously thought that life-threatening respiratory depression was a danger with pain control and 38% erroneously thought that opioids were the preferred drug for palliative sedation. One in three pharmacists did not think their theoretical knowledge was sufficient to advice about pain control. Most pharmacists had working agreements about euthanasia (81%), but fewer for palliative sedation (46%) or opioid therapy (25%). In the experience of most pharmacists (93%) physicians were open to unsolicited advice concerning opioid prescriptions. The majority of the community pharmacists (94%) checked opioid prescriptions most often only after dispensing, the majority of the hospital pharmacists (68%) most often did not check the prescriptions at all.

Conclusions: Although the basic knowledge of most pharmacists was adequate, there seemed to be a lack of knowledge in several areas, which may hamper them to improve the quality of care by giving advice to physicians and preventing or correcting mistakes if necessary. If education is improved, a more active role of the pharmacist might stimulate the quality of end-of-life pharmacotherapy.

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Introduction

Pain is one of the symptoms most frequently encountered at the end of life[1;2], although it can be controlled satisfactorily in most cases if health care professionals have adequate knowledge.[3] Possibilities to manage pain in patients at the end of life have increased in the past decade. These possibilities have been incorporated in handbooks and practice guidelines that were developed to support professionals in evidence-based practice [4-6].

However, the existence of professional guidelines does not guarantee that this knowledge is optimally used in daily practice. Several barriers have been identified concerning the prescribing and use of opioids that hamper the quality of pain management. First, there is still lack of theoretical knowledge about opioids among practicing physicians and nurses. [4;7-9] A systematic review of barriers hindering cancer pain management found that inadequate knowledge was one of the most reported barriers among physicians for adequate pain management.[10] The most reported misconceptions were the likelihood of opioid addiction and the belief that morphine dosage had an upper limit. Lack of theoretical knowledge also includes rare effects of opioids such as opioid induced hyperalgesia.[11]

Secondly, when health care professionals have sufficient theoretical knowledge about pain management guidelines, this does not necessary lead to adherence to these guidelines in daily practice. An example is that patients who clearly need opioids for pain frequently receive dosages that are too low.[12;13] Another example is prescribing laxatives concomitantly with opioids, a clinical rule that has been recommended in the WHO pain ladder[6] and almost all guidelines about pain management.[4;5;14] In daily practice, only about half of the patients are prescribed a laxative concomitantly.[15-17] Nearing end-of-life constipation can still be a problem, although the patient's deteriorating functional status can mean management of constipation has a lower priority. In the last days of life when patients are no longer able to receive oral treatment and consciousness diminishes, oral laxatives should be discontinued.[18]

Compared to physicians and nurses, surprisingly few studies have been aimed at the pharmacists' knowledge and experiences concerning pain management and opioid use. Among countries, pharmacists have different responsibilities in pharmaceutical care and hence their role in pain management might differ. In contrast with other countries[19], pharmacists are not allowed to prescribe in the Netherlands. Their primary task is to control the quality of prescribing, check for potential interactions and support prescribers and patients with optimal medication use.[20] Dutch hospital pharmacists frequently contact and advise clinicians, and an increasing number is present at wards for consultation and patient education.[21] In community pharmacy,

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patient education is common and there are regular pharmacotherapeutic audit meetings between pharmacists and general practitioners.[22] Characteristic for the Netherlands is that euthanasia and palliative sedation are legal options when suffering is unbearable and hopeless[23], and most pharmacies are prepared to fill prescriptions for euthanasia.[24]

Although not in the Netherlands, some studies investigated pharmacists' knowledge and attitude. They identified a general need for more knowledge and education in pain management.[25;26] Misconceptions were not only prevalent among physicians[10], but also among pharmacists.[27] Risk of addiction was no barrier to most pharmacists to dispense opioids, but conservative physicians and nurses, and concerns of pharmacists for adverse effects were experienced as barriers for opioid dispensing.[28] Hence, the few studies among pharmacists do not support the possible assumption that pharmacists' knowledge is sufficient for achieving optimal pharmacotherapy at the end of life. On the contrary, they suggest that the pharmacist might be a limiting factor in achieving optimal pharmacotherapy at the end of life. However, there have not been surveys performed among pharmacists recently, and the previous studies were all performed in the United States and had relatively low response rates.[27;28]

In end-of-life care, interdisciplinary cooperation among professionals is essential[29], and within this team approach the pharmacist has a responsibility in guarding and optimizing the quality of pharmacotherapy. Hence, it is important that the pharmacist has adequate and up-to-date knowledge of pain management and the medication involved. We aimed to study the level of knowledge of pharmacists in the Netherlands concerning pain management and the use of opioids at the end of life, how they cooperate with physicians and what barriers to good end-of-life care pharmacists experience.

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Methods

Design and population

Pharmacists working as health care provider in the Netherlands can specialize in community pharmacy or hospital pharmacy. Both community pharmacists and hospital pharmacists were approached to participate in this study, samples were taken from a national medical address guide. The medical address guide (BSL) is publicly available and holds addresses and basic characteristics of professionals working in Dutch health care. It is updated on a yearly basis. The random sample was taken per specialism: community pharmacists and hospital pharmacists. Inclusion criteria were: working in the Netherlands as a community or hospital pharmacist, not being in training. First all the names were ordered following postal code (region). Next every Nth case was sampled, N being the number in the sample frame divided by the desired number in the sample. The samples were representative for the Netherlands.

The questionnaire was sent in January 2009 followed by two reminders. With the second reminder a non-response questionnaire was enclosed for use in the non-response analysis. Respondents could complete the questionnaire on paper or online. The written questionnaire was anonymous. A separate answer card with the personal data of the respondent could be mailed to prevent further reminders. The online questionnaire was not anonymous, because it would otherwise not be possible to exclude the possibility that people who were not in the sample would complete the questionnaire. When the database was closed the questionnaires were anonymized.

In total 412 pharmacists were sent a questionnaire, 7 envelopes were returned to sender (respondent had moved in case of private address, or was no longer working at the institution in case of work address). Of the 322 community pharmacists, 147 completed the full questionnaire (response rate 46%). Of the 83 hospital pharmacists, 35 completed the full questionnaire (response rate 42%). The total response rate was 45%. Of the completed questionnaires, 70% were completed in writing and 30% were completed online. The non-response questionnaire was completed by 35 community pharmacists and seven hospital pharmacists.

After the closing of the data collection, a document with the correct answers to the knowledge statements was sent by e-mail to those who had indicated they were interested in receiving this.

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Developing the questionnaire and the pilot study

The questionnaire was developed by the authors who have expertise in end-of-life care, pharmacy, medicine, epidemiology and the development of questionnaires. We used previous studies of the knowledge or attitude concerning opioids and pain management at the end of life.[8;30] Questions were adapted and added to be able to answer the research questions, and to fit the specific situation in the Netherlands. For this purpose we used inter alia Dutch guidelines, original articles and review articles.[8;11;31-37] The questionnaire was piloted among GPs in training, elderly care physicians in training, and pharmacists. Opinions differed on the difficulty level of the knowledge statements in the questionnaire, but most respondents did not think the statements were unclear or too difficult; they sometimes even thought they were (too) easy.

The questionnaire consisted of three types of questions: 1) knowledge statements with three answering options: "true", "false" and "don't know" 2) experience and attitude questions with five answering options: "completely agree", "agree more than disagree", "neutral", "disagree more than agree" and "completely disagree" and 3) other questions, partly structured with four answering options: "often", "sometimes", "seldom" and "never" and partly semi-structured. Furthermore several background characteristics were asked, inter alia to grade one's own knowledge about opioids and pain management on a score of 1 to 10.

Analysis

We calculated descriptive statistics for the comparisons between community pharmacists and hospital pharmacists. Chi-square tests were used for comparing proportions between respondents and non-respondents, using linear by linear association for ordinal variables. Student´s *t*-tests were used for comparing means. For all tests p-values are presented. In Table 3, the categories "completely agree" and "agree more than disagree" were merged to the category "agree" versus the categories "neutral", and "(completely) disagree".

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Results

Background characteristics

In Table 1 the background characteristics of the respondents are shown per specialty. Hospital pharmacists were responsible for more patients to whom opioids were dispensed compared to community pharmacists. They also graded their own knowledge concerning opioids and pain management higher.

There was one significant difference in background characteristics between pharmacists who completed the non-response questionnaire (n=44) and pharmacists who completed the full questionnaire (n=182). Non-responders were more often fulltime employed (93%) than responders (74%, not in Table). The most important reasons for non-response were no time, too high workload and being understaffed.

Knowledge statements

In Table 2 the answers to the knowledge statements are shown per specialty. Of the 14 presented statements, community pharmacists gave on average between 9 and 10 correct answers. Hospital pharmacists answered more statements correctly (between 10 and 11). Knowledge questions with a low score of correct answers were 'opioids may cause or worsen pain' (statement is true, 11% correct answers), 'drug management of nausea in treatment with opioids is evidence-based' (statement is false, 19% correct answers), 'simultaneous prescription of a weak opioid (e.g. tramadol) and a strong opioid (e.g. morphine) is contra-indicated' (statement is true, 49% correct answers), 'opioids are the favoured drugs for palliative sedation' (statement is false, 61% correct answers) and 'life-threatening respiratory depression is a real danger when titrating morphine to control pain' (statement is false, 71% correct answers). Of the pharmacists, 74% knew that decreased renal function could raise plasma concentration of morphine and its active metabolite (morphine 6-glucuronide), and 82% calculated an example of opioid rotation correctly.

Attitudes, experiences and barriers concerning pain management

Pharmacists did not think that patients always indicate their pain to their physician (Table 3). The majority of the pharmacists (81%) stated that an opioid prescription should consist of both maintenance and as needed medication. Experienced barriers were opioid fear by the patient (79%) and family (72%), and underreporting of

For Peer Review

pain by patients (77%) and insufficient information about the pain (60%). Practical/logistic issues such as problems with manufacturing/availability, and problems with reimbursement were not often experienced as a barrier.

Attitudes and experiences concerning opioid rotation, tolerance, addiction, and checking prescriptions

Table 4 shows that almost 39% of the pharmacists found calculating of opioid dosages in case of opioid rotation difficult. Fear of addiction was seen as limiting factor for opioid use in daily practice (78%). The majority of the community pharmacists (94%) controlled opioid prescriptions most often after dispensing, the majority of the hospital pharmacists (68%) did not check opioid prescriptions personally. Community pharmacists were more frequently personally involved compared to their clinical colleagues;15% of the community pharmacists, and none of the hospital pharmacists reported to often have personal contact with the patient/caregiver.

Cooperation with physicians by working agreements, advice and contact about prescriptions

Table 5 shows cooperation between pharmacists and physicians. Working arrangements with physicians concerning euthanasia were more frequently reported by hospital pharmacists (97%) than by community pharmacists (77%). Working agreements concerning palliative sedation and opioid usage were less frequent. Community pharmacist were more often consulted by general practitioners, and hospital pharmacists by nursing home physicians and clinical specialists. Most pharmacists (93%) reported that physicians were open to unsolicited advice concerning the opioids prescribed by the physician. Almost all pharmacists (97%) would contact the physician if there was something wrong with the prescription. Most reported reasons to contact a physician in practice were laxatives not being prescribed (77%), administrative incompleteness (53%) and drug-drug interactions (52%). Most pharmacists contacted the physician when an opioid was prescribed without a laxative (63%). Reasons for not contacting the physician were that he/she might have had a good reason for not prescribing a laxative or that a laxative was not needed as the patient was terminal or being sedated. Other pharmacists dispensed a laxative to the patient according to working agreements, and some did not contact physicians about laxatives. Most pharmacist (96%) did not contact the physician when an opioid was prescribed without prescribing an anti-emetic drug.

Additional education

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About three quarters of the pharmacists (76%) indicated that they had enough options for additional education in subjects related to opioids and pain and symptom management at the end of life (not in Table). Others were very adamant that there were not enough options - neither in their region, nor non-commercial - or concerning information they could use in their daily practice to support physicians.

Subjects that were most often mentioned in which further education was wanted were opioid rotation (59%), pain and symptom management in general (52%), and palliative sedation (49%). The preferred methods to receive further education were literature in Dutch journals (65%), conferences (47%), courses on the internet (44%), and literature in international journals (41%).

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Discussion

The knowledge of the majority of the respondents was adequate on many points. We identified gaps in knowledge about some aspects of opioid use in a considerable part of the pharmacists. Pharmacists answered 71% of the knowledge questions correctly (10 out of 14) . Physicians scored between 31% and 68% correct answers in various studies[38-40], and pharmacists scored 46% correct answers in a single previous study.[25] The overall scores in different studies cannot be compared as such because other statements were used.

A point of concern was that only one in nine pharmacists was aware that opioids may cause or worsen pain. This is a rare effect and has not been known for a long time, so it is understandable that many pharmacists are unaware of this fact. However, the clinical effects can be significant if the dose of opioids is increased instead of decreased when a patient suffers from opioid-induced pain sensitivity.[11;41;42] Although the majority of the pharmacists stated that life-threatening respiratory depression is no real danger of opioids used for pain[36] control, 25% thought it was a real danger. Many studies have shown that this is not the case when titrated[35], even in patients with end-of-life COPD.[43]

Pharmacists could support physicians in preventing opioid over dosage in patients with renal failure, if they know that half-life of morphine itself and its active morphine 6-glucuronide is increased in the elderly and in patients with renal dysfunction.[44] However, only 74% answered this statement correctly, and for those who did, it is not known if they actually used this knowledge for prevention in practice. Pharmacists could also have a role in supporting physicians with opioid rotation. Opioid rotation is a complex aspect where the use of equianalgesic tables should always be accompanied by clinical judgement.[45] Half of the pharmacists are sometimes or often consulted by physicians with questions with regard to opioid rotation, and the majority of pharmacists sometimes or often advice physicians to rotate when pain control is inadequate or in case of side effects. However, 40% of the pharmacists indicated they found calculating the correct dosage difficult, and 18% were not able to calculate the correct dosage when asked to do so. Opioid rotation was also the subject that was most often mentioned by pharmacists as a subject in which they wanted further education (59%).

It is crucial that pharmacists involved in end-of-life care are aware that opioids are not the drug of choice for palliative sedation. About one in three pharmacists thought that opioids are the favoured drugs for palliative sedation. According to Dutch guidelines for palliative sedation, sedation with opioids should be considered malpractice.[31] Sedation was mentioned by half of the pharmacists as a subject in which they would want further education.

For Peer Review

Co-prescribing of laxatives is the most reported reason in this study for physician-pharmacist contacts, and 63% of the pharmacists reports that not prescribing a laxative when an opioid is prescribed, is a reason for contact. Although laxatives should not be prescribed in the last days of life, it is important that physicians should combine opioids with laxatives in most patients receiving palliative care.[18] Studies have found that many patients who are being prescribed opioids are not prescribed laxatives simultaneously[15;16] Although more evidence for the most effective laxative therapy in end-of-life care is needed[46], checking on concomitant use of laxatives can improve quality of pain management. Pharmacists in our study do seldom contact physicians for co-prescribing of anti-emetics for treatment or prevention of nausea during opioid therapy. Although nausea occurs in 15-30% of the patients receiving morphine for cancer, this is understandable as it is difficult to give advice when studies showing superiority of one anti-emetic drug over another are lacking.[32] As nausea is common at the start of opioid therapy[47], pharmacist-physician contact about nausea is most relevant at the initiation of opioid therapy.

Studies have shown that patients are concerned about using opioids for pain relief, and that these concerns may interfere with adherence to analgesic regimens.[48] Pharmacists in our study experience opioid fear of the patient as a barrier to good pharmacotherapy, and also identify this fear under family members of patients prescribed opioids. With most people with an incurable disease preferring to remain at home during the last part of their lives[49], education about pain management should not only be communicated to the patient, but also towards family caregivers.[50] Financial issues were seldom seen as a barrier, although they are acknowledged to be important at the end-of-life in a previous study in different Western countries.[51] With respect to medication this is not an issue as the costs of opioids are fully reimbursed in the Netherlands by the health care system. With a rather good coverage of pharmacies, availability and logistics are seldom experienced as problematic.

Most pharmacists had working agreements with their physicians about euthanasia (81%); the number of 97% of hospital pharmacists was substantially higher than 71% in 1994[52], reflecting euthanasia is becoming more incorporated in practice in the Netherlands. Working agreements were less common for palliative sedation (46%) and/or opioid prescribing (25%), and were more common in hospital pharmacy than in community pharmacy. In hospital as well as community settings, specific interventions of pharmacists have shown to contribute to the quality of care of patients at the end-of-their life.[53-55] As physicians were generally open to receive unsolicited advice from the pharmacist concerning opioid prescribing (93%), specific interventions can

For Peer Review

also be developed in the Netherlands. The open attitude of physicians might also be a start to develop local working agreements between pharmacists and physicians for palliative sedation and pain management.

It is usual in the Netherlands that community pharmacist checks all prescriptions after dispensing, whereas hospital pharmacist often only check prescriptions 'at risk', e.g. in case of drug-drug interactions. Our results show, however, that one might question whether current hospital practice is sufficient given the number of issues that warrant attention.

Strengths and limitations of this study

A strength of this study is that it is one of the first studies which maps the knowledge level of pharmacists about the use of opioids and pain management at the end of life. Studies like this are necessary to map strengths and weaknesses in the knowledge levels and experiences, and subsequently improve the (additional) education of pharmacotherapy at the end of life. A limitation of this study is that only a limited number of themes were assessed in which pharmacists should have adequate knowledge, and within those themes, not all aspects were studied. Another limitation is the relatively poor response rate of 45%, with other pharmacy studies reporting higher response rates.[56;57] Our initial sample was representative for pharmacists in the Netherlands, and the characteristics of responders and non-responders were comparable, except for full-time employment. This might have biased our results: full time pharmacists might have more experience and knowledge as they work more hours, and the actual knowledge in the population might be higher.

Another limitation is that some knowledge statements and their answer categories (true or false) leave room for interpretation. In retrospect, the statement that 'simultaneous prescription of a weak opioid (e.g. tramadol) and a strong opioid (e.g. morphine) is contra-indicated' may have been more ambiguous than we intended it to be. Technically speaking, this is not a true contra-indication as it is not a medical condition increasing the risk of a serious adverse drug reaction. However, the addition of tramadol to morphine is not a preferable treatment option, since it does not reduce pain and increases side effects.[58] Open interpretability also concerns the question whether management of nausea in treatment with opioids is evidence based. Anti-emetics are not licensed for opioid-induced nausea, and there is lack of knowledge about efficacy in end-of-life[59] , but there are best practices for opioid-induced nausea.[60] We do not know how pharmacists interpreted 'evidence based'. Although respondents of the pilot study did not make remarks with respect to interpretation, open interpretability is relevant to all questions - maybe most to those with a low score.

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Summarizing, the questions have not been validated and this leaves room open to interpretation. However, we believe these results give a good indication of the knowledge level of pharmacists.

Conclusion

Although the effects of a gap in the knowledge about opioids in clinical practice differ per subject, we can conclude that most of the knowledge questioned in our study should be part of the basic knowledge pharmacists should have, and that a gap in this knowledge can be a barrier to adequate care at the end of life. One in three pharmacists did not think they had sufficient knowledge to advise about pain control, but most were willing to follow additional education. Physicians were open to unsolicited advice from the pharmacist concerning opioid prescriptions. If education is improved, pharmacists could claim a more active role in communication with patients, caregivers and physicians to improve the quality in end-of-life pharmacotherapy.

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Conflict of interest

The authors declare they have no conflict of interest.

For Peer Review

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For Peer Review

Table 1 Background characteristics of respondents (n=182).

	Community pharmacists n=147 %	Hospital pharmacists n=35 %	Total n=182 %	*p*
Gender				
• Men	49	43	48	0.516[1]
• Women	51	57	52	
Age (years)				
• ≤40	47	46	46	0.705[2]
• 41-50	33	37	33	
• 51-60	19	17	19	
• ≥61	2	0	2	
Average age	42	41	42	0.818[3]
Employment				
• full-time	78	63	74	0.054[1]
• part-time	22	37	26	
Grade given for own knowledge before completing the questionnaire (1-10)				
• ≤6.5	24	11	22	0.002[2]
• 6.6-7.5	52	37	50	
• ≥7.6	24	51	29	
Average grade	(7.0)	(7.4)	(7.2)	0.003[3]
Number of patients to whom the respondent had dispensed opioids in 2008				
• None	0	0	0	0.000[2]
• 1-20	3	0	2	
• 21-50	25	0	20	
• ≥51	72	100	77	

[1] X-square.
[2] X-square for trend. Linear by linear association.
[3] Student's *t*.

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Table 2 Answers to the knowledge statements per specialty[1]

		Community pharmacists n=147 %	Hospital pharmacists n=35 %	Total n=182 %	*p* X-square
Mean number of correct answers		9.9	10.8	10.0	0.005
Pain					
1. In the management of pain it is important to differentiate between nociceptive and neuropathic pain	**% true**	**95**	**97**	**94**	0.517
	% false	2	3	2	
	% don't know	3	0	3	
2. Administration of opioids early on in the disease hampers good pain control later on	% true	13	3	11	0.311
	% false	**85**	**91**	**86**	
	% don't know	1	6	3	
3. Opioids may cause or worsen pain	**% true**	**9**	**24**	**11**	0.014
	% false	65	71	66	
	% don't know	26	6	23	
Prescribing opioids					
4. Once opioids have been started, other analgesics should be discontinued	% true	11	0	9	0.033
	% false	**89**	**100**	**92**	
	% don't know	0	0	0	
5. Opioids are only indicated for cancer patients	% true	0	0	0	-
	% false	**100**	**100**	**100**	
	% don't know	0	0	0	
6. Simultaneous prescription of a weak opioid (e.g. tramadol) and a strong opioid (e.g. morphine) is contra-indicated[2]	**% true**	**50**	**46**	**49**	0.675
	% false	44	54	45	
	% don't know	6	0	6	
7. Decreased renal function raises plasma concentration of morphine(-metabolites)	**% true**	**72**	**80**	**74**	0.196
	% false	15	14	14	
	% don't know	13	6	12	
8. Opioids have a maximum dosage	% true	11	3	10	0.163
	% false	**87**	**94**	**88**	
	% don't know	2	3	2	
Side-effects					
9. Life-threatening respiratory depression is a real danger when titrating morphine to control pain	% true	24	26	25	0.702
	% false	**71**	**74**	**71**	
	% don't know	5	0	4	
10. Drug management of nausea in treatment with opioids is evidence-based	% true	45	43	44	0.893
	% false	**19**	**17**	**19**	
	% don't know	36	40	37	
Opioid rotation					
11. You want to change a daily dosage of 60 mg oxycodon to an equivalent fentanyl patch. The strength of the patch is[3]:	**% 25 µg p/h[4]**	**43**	**65**	**47**	0.183
	% 50 µg p/h[3]	**37**	**24**	**34**	
	% false	11	3	9	
	% don't know	9	9	9	
Sedation and shortening of life by opioids					
12. Opioids titrated against pain, shorten life	% true	1	6	2	0.685
	% false	**97**	**94**	**95**	
	% don't know	3	0	3	
13. Opioids are the favoured drugs for palliative sedation	% true	36	23	34	0.087
	% false	**59**	**74**	**61**	
	% don't know	5	3	4	
14. Opioids are appropriate drugs to perform euthanasia	% true	4	0	3	0.078
	% false	**94**	**100**	**95**	
	% don't know	1	0	2	

[1] correct answer is printed in bold .
[2] a simultaneous prescription of a weak and a strong opioid is not a contra-indication in the true sense of the word. It is, however, for pharmacodynamic reasons in general not a sensible combination. This is why it is not advocated in the available guidelines for treatment of pain.
[3] respondents could circle the following options 12/25/50/75/100/125/150 µg per hour or "don't know". With this question 2 answers were considered correct, because different guidelines give different conversions, which leads to two different answers.

For Peer Review

Table 3 Attitudes, experiences and barriers concerning pain management

	Community pharmacists n=147 % agree	Hospital pharmacists n=35 % agree	Total n=182 % agree	*P* X-square
Pain				
• Good pain control is complex	84	83	84	0.981
• With the current medical expertise, pain is always controllable	45	46	45	0.958
• When a patient is in pain, he/she will always indicate this to his/her physician	26	17	25	0.490
• I have sufficient theoretical knowledge to advise about pain control	65	80	68	0.211
Prescribing opioids				
• An opioid prescription should always consist of a maintenance plus as needed medication (for break-through pain/escape)	81	83	81	0.913
Experienced barriers for good pain management				
• Fear for opioids by the patient	80	74	79	0.457
• Underreporting of pain by patients	77	77	77	0.941
• Fear for opioids by family	73	66	72	0.384
• Insufficient specific information about the pain	63	46	60	0.055
• Restrictive prescribing of opioids by physicians	54	57	54	0.721
• Insufficient knowledge by physicians	31	51	34	0.018
• Non-adherence	33	31	33	0.850
• Logistic problems (e.g. possibility to use an opioid-pump at home)	10	26	13	0.011
• Problems with reimbursement	7	14	8	0.156
• Problems with manufacturing	5	6	5	0.829
• Problems with availability of drugs	3	0	2	0.320

For Peer Review

Table 4 Attitudes and experiences concerning opioid rotation, tolerance, addiction, working arrangements with physicians and controlling prescriptions**

	Community pharmacists n=147 %often/ sometimes	Hospital pharmacists n=35 % often/ sometimes	Total n=182 % often/ sometimes	*P* X-square
Opioid rotation*				[1]
• Physicians consult me about opioid rotation	51	54	52	0.690
• I advice to rotate opioids if pain control is inadequate	64	82	67	0.111
• I advice to rotate opioids in case of side-effects	61	74	63	0.310
• I find calculating of opioid dosages when rotating difficult	42	26	39	0.248
Tolerance and fear of addiction**				[1]
• I think tolerance develops in the usage of opioids	84	97	87	0.055
• Tolerance hampers the usage of opioids in pain control	42	31	40	0.144
• Fear of addiction of patients themselves hampers the usage of opioids in practice	77	80	78	0.890
Checking opioid prescriptions and patient contact	**% always/ often/**	**% always/ often**	**% always/ often**	[2]
• I personally handle opioid prescriptions and have contact with the patient and/or his caregiver	15	0	12	0.017
• I check prescriptions before dispensing	27	9	24	0.000
• I check prescriptions after dispensing	94	47	85	0.000
• Prescriptions are checked and dispensed without being seen by me	8	68	20	0.016

* The following definition of opioid rotation was given in the questionnaire: "With the term "opioid rotation" we mean the replacing of one opioid by another opioid."

** The following definition of tolerance was given in the questionnaire: "By tolerance for a drug we mean that a patient needs a higher dose to reach the same pain relief while the pain stimulus remains the same. Tolerance has proven to be difficult to measure in practice, we are interested in your personal experience."

[1] Often/sometimes vs. seldom/never

[2] Always/often vs.sometimes/seldom/never

For Peer Review

Table 5 Cooperation with physicians by working arrangements, advice and contact about prescriptions

	Community pharmacists n=147	Hospital pharmacists n=35	Total n=182	*P* X-square
Do you have working arrangements with physicians about euthanasia and/or sedation and/or opioid usage?	**% yes**	**% yes**	**% yes**	
• Euthanasia	77	97	81	0.007
• Palliative sedation	40	71	46	0.001
• Opioid usage	20	46	25	0.003
• None of above	22	3	18	0.010
Are you being consulted by the next physcians:	**%often/ sometimes**	**% often/ sometimes**	**% often/ sometimes**	
• General practitioner	81	14	68	0.000
• Nursing home physician	17	66	27	0.000
• Clinical specialist	2	91	20	0.000
Unsolicited advice	**% yes**	**% yes**	**% yes**	
• Are physicians open for unsolicited advice concerning their opioid prescription	91	100	93	0.073
Contact with physician about prescription				
• I will contact the prescribing physician when I think there is something wrong with the prescription	95	97	96	0.602
Most frequently occurring reasons to contact the prescribing physician:				
• Laxative is not prescribed simultaneously	76	77	77	0.925
• Prescription writing is administratively incomplete	52	54	53	0.815
• Drug interaction with opioid	51	57	52	0.493
• Dosage too high	24	28	25	0.541
• Supposed opioid abuse by the patient	27	3	22	0.002
• Slow release preparation is not combined with immediate release	19	29	21	0.198
• Dosage is too low	22	14	20	0.338
• Anti-emetic is not prescribed simultaneously	7	11	8	0.376
Contact about co-prescribing of laxatives and anti-emetics				
When a physician prescribes an opioid without prescribing a laxative, I always contact the prescribing physician				
• Yes	61	71	63	0.303[1]
• Only for some physicians	4	12	6	
• No, that's not my usual practise	35	18	31	
When a physician prescribes an opioid without prescribing an anti-emetic drug, I always contact the prescribing physician				
• Yes	1	9	2	0.005[1]
• Only for some physicians	1	9	2	
• No, that's not my usual practise	99	83	96	

[1] Yes vs. only for some physicians/no

For Peer Review

The use of opioids at the end of life: knowledge level of pharmacists and cooperation with physicians

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Abstract (241 words)

Purpose: What is the level of knowledge of pharmacists concerning pain management and the use of opioids at the end of life, and how do they cooperate with physicians?

Methods: A written questionnaire was sent to a sample of community and hospital pharmacists in the Netherlands. The questionnaire was completed by 182 pharmacists (response rate 45%).

Results: Pharmacists were aware of the most basic knowledge about opioids. Twenty nine percent of the pharmacists erroneously thought that life-threatening respiratory depression was a danger with pain control and 38% erroneously thought that opioids were the preferred drug for palliative sedation. One in three pharmacists did not think their theoretical knowledge was sufficient to advice about pain control. Most pharmacists had working agreements about euthanasia (81%), but fewer for palliative sedation (46%) or opioid therapy (25%). In the experience of most pharmacists (93%) physicians were open to unsolicited advice concerning opioid prescriptions. The majority of the community pharmacists (94%) checked opioid prescriptions most often only after dispensing, the majority of the hospital pharmacists (68%) most often did not check the prescriptions at all.

Conclusions: Although the basic knowledge of most pharmacists was adequate, there seemed to be a lack of knowledge in several areas, which may hamper them to improve the quality of care by giving advice to physicians and preventing or correcting mistakes if necessary. If education is improved, a more active role of the pharmacist might stimulate the quality of end-of-life pharmacotherapy.

For Peer Review

Introduction

Pain is one of the symptoms most frequently encountered at the end of life[1;2], although it can be controlled satisfactorily in most cases if health care professionals have adequate knowledge.[3] Possibilities to manage pain in patients at the end of life have increased in the past decade. These possibilities have been incorporated in handbooks and practice guidelines that were developed to support professionals in evidence-based practice [4-6].

However, the existence of professional guidelines does not guarantee that this knowledge is optimally used in daily practice. Several barriers have been identified concerning the prescribing and use of opioids that hamper the quality of pain management. First, there is still lack of theoretical knowledge about opioids among practicing physicians and nurses. [4;7-9] A systematic review of barriers hindering cancer pain management found that inadequate knowledge was one of the most reported barriers among physicians for adequate pain management.[10] The most reported misconceptions were the likelihood of opioid addiction and the belief that morphine dosage had an upper limit. Lack of theoretical knowledge also includes rare effects of opioids such as opioid induced hyperalgesia.[11]

Secondly, when health care professionals have sufficient theoretical knowledge about pain management guidelines, this does not necessary lead to adherence to these guidelines in daily practice. An example is that patients who clearly need opioids for pain frequently receive dosages that are too low.[12;13] Another example is prescribing laxatives concomitantly with opioids, a clinical rule that has been recommended in the WHO pain ladder[6] and almost all guidelines about pain management.[4;5;14] In daily practice, only about half of the patients are prescribed a laxative concomitantly.[15-17] Nearing end-of-life constipation can still be a problem, although the patient's deteriorating functional status can mean management of constipation has a lower priority. In the last days of life when patients are no longer able to receive oral treatment and consciousness diminishes, oral laxatives should be discontinued.[18]

Compared to physicians and nurses, surprisingly few studies have been aimed at the pharmacists' knowledge and experiences concerning pain management and opioid use. Among countries, pharmacists have different responsibilities in pharmaceutical care and hence their role in pain management might differ. In contrast with other countries[19], pharmacists are not allowed to prescribe in the Netherlands. Their primary task is to control the quality of prescribing, check for potential interactions and support prescribers and patients with optimal medication use.[20] Dutch hospital pharmacists frequently contact and advise clinicians, and an increasing number is present at wards for consultation and patient education.[21] In community pharmacy,

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patient education is common and there are regular pharmacotherapeutic audit meetings between pharmacists and general practitioners.[22] Characteristic for the Netherlands is that euthanasia and palliative sedation are legal options when suffering is unbearable and hopeless[23], and most pharmacies are prepared to fill prescriptions for euthanasia.[24]

Although not in the Netherlands, some studies investigated pharmacists' knowledge and attitude. They identified a general need for more knowledge and education in pain management.[25;26] Misconceptions were not only prevalent among physicians[10], but also among pharmacists.[27] Risk of addiction was no barrier to most pharmacists to dispense opioids, but conservative physicians and nurses, and concerns of pharmacists for adverse effects were experienced as barriers for opioid dispensing.[28] Hence, the few studies among pharmacists do not support the possible assumption that pharmacists' knowledge is sufficient for achieving optimal pharmacotherapy at the end of life. On the contrary, they suggest that the pharmacist might be a limiting factor in achieving optimal pharmacotherapy at the end of life. However, there have not been surveys performed among pharmacists recently, and the previous studies were all performed in the United States and had relatively low response rates.[27;28]

In end-of-life care, interdisciplinary cooperation among professionals is essential[29], and within this team approach the pharmacist has a responsibility in guarding and optimizing the quality of pharmacotherapy. Hence, it is important that the pharmacist has adequate and up-to-date knowledge of pain management and the medication involved. We aimed to study the level of knowledge of pharmacists in the Netherlands concerning pain management and the use of opioids at the end of life, how they cooperate with physicians and what barriers to good end-of-life care pharmacists experience.

For Peer Review

Methods

Design and population

Pharmacists working as health care provider in the Netherlands can specialize in community pharmacy or hospital pharmacy. Both community pharmacists and hospital pharmacists were approached to participate in this study, samples were taken from a national medical address guide. The medical address guide (BSL) is publicly available and holds addresses and basic characteristics of professionals working in Dutch health care. It is updated on a yearly basis. The random sample was taken per specialism: community pharmacists and hospital pharmacists. Inclusion criteria were: working in the Netherlands as a community or hospital pharmacist, not being in training. First all the names were ordered following postal code (region). Next every Nth case was sampled, N being the number in the sample frame divided by the desired number in the sample. The samples were representative for the Netherlands.

The questionnaire was sent in January 2009 followed by two reminders. With the second reminder a non-response questionnaire was enclosed for use in the non-response analysis. Respondents could complete the questionnaire on paper or online. The written questionnaire was anonymous. A separate answer card with the personal data of the respondent could be mailed to prevent further reminders. The online questionnaire was not anonymous, because it would otherwise not be possible to exclude the possibility that people who were not in the sample would complete the questionnaire. When the database was closed the questionnaires were anonymized.

In total 412 pharmacists were sent a questionnaire, 7 envelopes were returned to sender (respondent had moved in case of private address, or was no longer working at the institution in case of work address). Of the 322 community pharmacists, 147 completed the full questionnaire (response rate 46%). Of the 83 hospital pharmacists, 35 completed the full questionnaire (response rate 42%). The total response rate was 45%. Of the completed questionnaires, 70% were completed in writing and 30% were completed online. The non-response questionnaire was completed by 35 community pharmacists and seven hospital pharmacists.
After the closing of the data collection, a document with the correct answers to the knowledge statements was sent by e-mail to those who had indicated they were interested in receiving this.

For Peer Review

Developing the questionnaire and the pilot study

The questionnaire was developed by the authors who have expertise in end-of-life care, pharmacy, medicine, epidemiology and the development of questionnaires. We used previous studies of the knowledge or attitude concerning opioids and pain management at the end of life.[8;30] Questions were adapted and added to be able to answer the research questions, and to fit the specific situation in the Netherlands. For this purpose we used inter alia Dutch guidelines, original articles and review articles.[8;11;31-37] The questionnaire was piloted among GPs in training, elderly care physicians in training, and pharmacists. Opinions differed on the difficulty level of the knowledge statements in the questionnaire, but most respondents did not think the statements were unclear or too difficult; they sometimes even thought they were (too) easy.

The questionnaire consisted of three types of questions: 1) knowledge statements with three answering options: "true", "false" and "don't know" 2) experience and attitude questions with five answering options: "completely agree", "agree more than disagree", "neutral", "disagree more than agree" and "completely disagree" and 3) other questions, partly structured with four answering options: "often", "sometimes", "seldom" and "never" and partly semi-structured. Furthermore several background characteristics were asked, inter alia to grade one's own knowledge about opioids and pain management on a score of 1 to 10.

Analysis

We calculated descriptive statistics for the comparisons between community pharmacists and hospital pharmacists. Chi-square tests were used for comparing proportions between respondents and non-respondents, using linear by linear association for ordinal variables. Student´s *t*-tests were used for comparing means. For all tests p-values are presented. In Table 3, the categories "completely agree" and "agree more than disagree" were merged to the category "agree" versus the categories "neutral", and "(completely) disagree".

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Results

Background characteristics

In Table 1 the background characteristics of the respondents are shown per specialty. Hospital pharmacists were responsible for more patients to whom opioids were dispensed compared to community pharmacists. They also graded their own knowledge concerning opioids and pain management higher.

There was one significant difference in background characteristics between pharmacists who completed the non-response questionnaire (n=44) and pharmacists who completed the full questionnaire (n=182). Non-responders were more often fulltime employed (93%) than responders (74%, not in Table). The most important reasons for non-response were no time, too high workload and being understaffed.

Knowledge statements

In Table 2 the answers to the knowledge statements are shown per specialty. Of the 14 presented statements, community pharmacists gave on average between 9 and 10 correct answers. Hospital pharmacists answered more statements correctly (between 10 and 11). Knowledge questions with a low score of correct answers were 'opioids may cause or worsen pain' (statement is true, 11% correct answers), 'drug management of nausea in treatment with opioids is evidence-based' (statement is false, 19% correct answers), 'simultaneous prescription of a weak opioid (e.g. tramadol) and a strong opioid (e.g. morphine) is contra-indicated' (statement is true, 49% correct answers), 'opioids are the favoured drugs for palliative sedation' (statement is false, 61% correct answers) and 'life-threatening respiratory depression is a real danger when titrating morphine to control pain' (statement is false, 71% correct answers). Of the pharmacists, 74% knew that decreased renal function could raise plasma concentration of morphine and its active metabolite (morphine 6-glucuronide), and 82% calculated an example of opioid rotation correctly.

Attitudes, experiences and barriers concerning pain management

Pharmacists did not think that patients always indicate their pain to their physician (Table 3). The majority of the pharmacists (81%) stated that an opioid prescription should consist of both maintenance and as needed medication. Experienced barriers were opioid fear by the patient (79%) and family (72%), and underreporting of

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pain by patients (77%) and insufficient information about the pain (60%). Practical/logistic issues such as problems with manufacturing/availability, and problems with reimbursement were not often experienced as a barrier.

Attitudes and experiences concerning opioid rotation, tolerance, addiction, and checking prescriptions

Table 4 shows that almost 39% of the pharmacists found calculating of opioid dosages in case of opioid rotation difficult. Fear of addiction was seen as limiting factor for opioid use in daily practice (78%). The majority of the community pharmacists (94%) controlled opioid prescriptions most often after dispensing, the majority of the hospital pharmacists (68%) did not check opioid prescriptions personally. Community pharmacists were more frequently personally involved compared to their clinical colleagues;15% of the community pharmacists, and none of the hospital pharmacists reported to often have personal contact with the patient/caregiver.

Cooperation with physicians by working agreements, advice and contact about prescriptions

Table 5 shows cooperation between pharmacists and physicians. Working arrangements with physicians concerning euthanasia were more frequently reported by hospital pharmacists (97%) than by community pharmacists (77%). Working agreements concerning palliative sedation and opioid usage were less frequent. Community pharmacist were more often consulted by general practitioners, and hospital pharmacists by nursing home physicians and clinical specialists. Most pharmacists (93%) reported that physicians were open to unsolicited advice concerning the opioids prescribed by the physician. Almost all pharmacists (97%) would contact the physician if there was something wrong with the prescription. Most reported reasons to contact a physician in practice were laxatives not being prescribed (77%), administrative incompleteness (53%) and drug-drug interactions (52%). Most pharmacists contacted the physician when an opioid was prescribed without a laxative (63%). Reasons for not contacting the physician were that he/she might have had a good reason for not prescribing a laxative or that a laxative was not needed as the patient was terminal or being sedated. Other pharmacists dispensed a laxative to the patient according to working agreements, and some did not contact physicians about laxatives. Most pharmacist (96%) did not contact the physician when an opioid was prescribed without prescribing an anti-emetic drug.

Additional education

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About three quarters of the pharmacists (76%) indicated that they had enough options for additional education in subjects related to opioids and pain and symptom management at the end of life (not in Table). Others were very adamant that there were not enough options - neither in their region, nor non-commercial - or concerning information they could use in their daily practice to support physicians.

Subjects that were most often mentioned in which further education was wanted were opioid rotation (59%), pain and symptom management in general (52%), and palliative sedation (49%). The preferred methods to receive further education were literature in Dutch journals (65%), conferences (47%), courses on the internet (44%), and literature in international journals (41%).

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Discussion

The knowledge of the majority of the respondents was adequate on many points. We identified gaps in knowledge about some aspects of opioid use in a considerable part of the pharmacists. Pharmacists answered 71% of the knowledge questions correctly (10 out of 14) . Physicians scored between 31% and 68% correct answers in various studies[38-40], and pharmacists scored 46% correct answers in a single previous study.[25] The overall scores in different studies cannot be compared as such because other statements were used.

A point of concern was that only one in nine pharmacists was aware that opioids may cause or worsen pain. This is a rare effect and has not been known for a long time, so it is understandable that many pharmacists are unaware of this fact. However, the clinical effects can be significant if the dose of opioids is increased instead of decreased when a patient suffers from opioid-induced pain sensitivity.[11;41;42] Although the majority of the pharmacists stated that life-threatening respiratory depression is no real danger of opioids used for pain[36] control, 25% thought it was a real danger. Many studies have shown that this is not the case when titrated[35], even in patients with end-of-life COPD.[43]

Pharmacists could support physicians in preventing opioid over dosage in patients with renal failure, if they know that half-life of morphine itself and its active morphine 6-glucuronide is increased in the elderly and in patients with renal dysfunction.[44] However, only 74% answered this statement correctly, and for those who did, it is not known if they actually used this knowledge for prevention in practice. Pharmacists could also have a role in supporting physicians with opioid rotation. Opioid rotation is a complex aspect where the use of equianalgesic tables should always be accompanied by clinical judgement.[45] Half of the pharmacists are sometimes or often consulted by physicians with questions with regard to opioid rotation, and the majority of pharmacists sometimes or often advice physicians to rotate when pain control is inadequate or in case of side effects. However, 40% of the pharmacists indicated they found calculating the correct dosage difficult, and 18% were not able to calculate the correct dosage when asked to do so. Opioid rotation was also the subject that was most often mentioned by pharmacists as a subject in which they wanted further education (59%).

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It is crucial that pharmacists involved in end-of-life care are aware that opioids are not the drug of choice for palliative sedation. About one in three pharmacists thought that opioids are the favoured drugs for palliative sedation. According to Dutch guidelines for palliative sedation, sedation with opioids should be considered malpractice.[31] Sedation was mentioned by half of the pharmacists as a subject in which they would want further education.

For Peer Review

Co-prescribing of laxatives is the most reported reason in this study for physician-pharmacist contacts, and 63% of the pharmacists reports that not prescribing a laxative when an opioid is prescribed, is a reason for contact. Although laxatives should not be prescribed in the last days of life, it is important that physicians should combine opioids with laxatives in most patients receiving palliative care.[18] Studies have found that many patients who are being prescribed opioids are not prescribed laxatives simultaneously[15;16] Although more evidence for the most effective laxative therapy in end-of-life care is needed[46], checking on concomitant use of laxatives can improve quality of pain management. Pharmacists in our study do seldom contact physicians for co-prescribing of anti-emetics for treatment or prevention of nausea during opioid therapy. Although nausea occurs in 15-30% of the patients receiving morphine for cancer, this is understandable as it is difficult to give advice when studies showing superiority of one anti-emetic drug over another are lacking.[32] As nausea is common at the start of opioid therapy[47], pharmacist-physician contact about nausea is most relevant at the initiation of opioid therapy.

Studies have shown that patients are concerned about using opioids for pain relief, and that these concerns may interfere with adherence to analgesic regimens.[48] Pharmacists in our study experience opioid fear of the patient as a barrier to good pharmacotherapy, and also identify this fear under family members of patients prescribed opioids. With most people with an incurable disease preferring to remain at home during the last part of their lives[49], education about pain management should not only be communicated to the patient, but also towards family caregivers.[50] Financial issues were seldom seen as a barrier, although they are acknowledged to be important at the end-of-life in a previous study in different Western countries.[51] With respect to medication this is not an issue as the costs of opioids are fully reimbursed in the Netherlands by the health care system. With a rather good coverage of pharmacies, availability and logistics are seldom experienced as problematic.

Most pharmacists had working agreements with their physicians about euthanasia (81%); the number of 97% of hospital pharmacists was substantially higher than 71% in 1994[52], reflecting euthanasia is becoming more incorporated in practice in the Netherlands. Working agreements were less common for palliative sedation (46%) and/or opioid prescribing (25%), and were more common in hospital pharmacy than in community pharmacy. In hospital as well as community settings, specific interventions of pharmacists have shown to contribute to the quality of care of patients at the end-of-their life.[53-55] As physicians were generally open to receive unsolicited advice from the pharmacist concerning opioid prescribing (93%), specific interventions can

For Peer Review

also be developed in the Netherlands. The open attitude of physicians might also be a start to develop local working agreements between pharmacists and physicians for palliative sedation and pain management.

It is usual in the Netherlands that community pharmacist checks all prescriptions after dispensing, whereas hospital pharmacist often only check prescriptions 'at risk', e.g. in case of drug-drug interactions. Our results show, however, that one might question whether current hospital practice is sufficient given the number of issues that warrant attention.

Strengths and limitations of this study

A strength of this study is that it is one of the first studies which maps the knowledge level of pharmacists about the use of opioids and pain management at the end of life. Studies like this are necessary to map strengths and weaknesses in the knowledge levels and experiences, and subsequently improve the (additional) education of pharmacotherapy at the end of life. A limitation of this study is that only a limited number of themes were assessed in which pharmacists should have adequate knowledge, and within those themes, not all aspects were studied. Another limitation is the relatively poor response rate of 45%, with other pharmacy studies reporting higher response rates.[56;57] Our initial sample was representative for pharmacists in the Netherlands, and the characteristics of responders and non-responders were comparable, except for full-time employment. This might have biased our results: full time pharmacists might have more experience and knowledge as they work more hours, and the actual knowledge in the population might be higher.

Another limitation is that some knowledge statements and their answer categories (true or false) leave room for interpretation. In retrospect, the statement that 'simultaneous prescription of a weak opioid (e.g. tramadol) and a strong opioid (e.g. morphine) is contra-indicated' may have been more ambiguous than we intended it to be. Technically speaking, this is not a true contra-indication as it is not a medical condition increasing the risk of a serious adverse drug reaction. However, the addition of tramadol to morphine is not a preferable treatment option, since it does not reduce pain and increases side effects.[58] Open interpretability also concerns the question whether management of nausea in treatment with opioids is evidence based. Anti-emetics are not licensed for opioid-induced nausea, and there is lack of knowledge about efficacy in end-of-life[59] , but there are best practices for opioid-induced nausea.[60] We do not know how pharmacists interpreted 'evidence based'. Although respondents of the pilot study did not make remarks with respect to interpretation, open interpretability is relevant to all questions - maybe most to those with a low score.

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Summarizing, the questions have not been validated and this leaves room open to interpretation. However, we believe these results give a good indication of the knowledge level of pharmacists.

Conclusion

Although the effects of a gap in the knowledge about opioids in clinical practice differ per subject, we can conclude that most of the knowledge questioned in our study should be part of the basic knowledge pharmacists should have, and that a gap in this knowledge can be a barrier to adequate care at the end of life. One in three pharmacists did not think they had sufficient knowledge to advise about pain control, but most were willing to follow additional education. Physicians were open to unsolicited advice from the pharmacist concerning opioid prescriptions. If education is improved, pharmacists could claim a more active role in communication with patients, caregivers and physicians to improve the quality in end-of-life pharmacotherapy.

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Conflict of interest

The authors declare they have no conflict of interest.

For Peer Review

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