Journal of Geriatric Oncology 12 (2021) 1193–1199

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

# Development of criteria for identifying potentially inappropriate prescribing in older adults with cancer receiving palliative care (PIP-CPC)

Cathal A. Cadogan [a,*], Melanie Murphy [b], Sarah McLean [c], Kathleen Bennett [d], Carmel M. Hughes [e]

[a] School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland
[b] School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin, Ireland
[c] St Vincent's Private Hospital, Merrion Road, Dublin, Ireland
[d] Division of Population Health Sciences, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin, Ireland
[e] School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Belfast, United Kingdom

ARTICLE INFO

*Article history:*
Received 11 November 2020
Received in revised form 3 May 2021
Accepted 10 June 2021
Available online 16 June 2021

*Keywords:*
Cancer
Geriatric oncology
Older adults
Aged
Palliative care
Prescribing
Delphi

ABSTRACT

*Objectives:* To develop criteria for identifying potentially inappropriate prescribing of medications for symptomatic relief in older adults (≥65 years) with cancer who are receiving palliative care and have an estimated life expectancy of <1 year.
*Materials and methods:* A two-round Delphi exercise was conducted using web-based questionnaires. A panel of 18 expert stakeholders with expertise in palliative care, oncology and/or geriatric medicine across Ireland and the United Kingdom rated their level of agreement with each statement using a 5-point Likert scale and had the option of adding free-text comments throughout the questionnaire. A priori decision rules were used to accept or reject criteria.
*Results:* Twenty-eight criteria were presented in Round 1. Group consensus was achieved for 15 criteria which were included in the final set of criteria. Following a review of the panel's ratings and additional comments for the remaining 13 criteria, four criteria were removed from Round 2. Group consensus was achieved for all nine criteria included in Round 2. The final set comprised 24 criteria relating to: anorexia-cachexia ($n = 1$); anxiety ($n = 2$); constipation ($n = 5$); delirium (n = 1); depression ($n = 3$); diarrhoea (n = 1); dyspnoea/breathlessness ($n = 1$); fatigue ($n = 2$); insomnia (n = 2); nausea and vomiting (n = 2); pain (n = 3); duplicate drug classes (n = 1).
*Conclusion:* A consensus-agreed set of prescribing criteria has been developed for identifying potentially inappropriate prescribing of medications for symptomatic relief in older adults with cancer who are receiving palliative care and have an estimated life expectancy of less than one year. Future studies should examine the application and validity of these criteria.


## 1. Introduction

The global burden of cancer is increasing, partly driven by population ageing, and by 2038, it is expected that more than half of all new cancer diagnoses will occur in older adults (≥65 years) [1]. At diagnosis, adults with cancer often have existing health conditions. Population-based studies have reported that the estimated prevalence of multimorbidity (two or more chronic conditions) in this patient cohort varies according to cancer type with higher prevalence rates amongst older age groups [2,3]. These pre-existing health conditions can necessitate the use of polypharmacy, which is commonly defined as the prescribing of five or more medications [3–5]. The reported prevalence of polypharmacy in older adults with cancer ranges from 2% to 80% [6,7]. For those who subsequently engage with palliative care services, the number of medications prescribed often increases between referral and death due to the continuation of medications for co-morbid conditions and the addition of medications for symptomatic relief (e.g. analgesics, laxatives) [8,9].

Polypharmacy in older adults with cancer poses the risk of potentially inappropriate prescribing and the potential for adverse outcomes [6,7]. Potentially inappropriate prescribing refers to various suboptimal prescribing practices, including over-prescribing (potentially inappropriate medications) and under-prescribing (potential prescribing omissions) [10]. Optimising medication regimens in older adults with cancer requires clinicians to consider whether each medication is appropriate in relation to patients' treatment goals and life expectancy [11]. Based on studies conducted to date, it is evident that medicines optimisation does not always occur in older adults with cancer and with palliative care needs. For example, preventative medications for existing

* Corresponding author.
*E-mail address:* cathal.cadogan@tcd.ie (C.A. Cadogan).

https://doi.org/10.1016/j.jgo.2021.06.003

conditions are often continued, even though they may no longer be clinically beneficial [8,12,13]. This poses increased risk of medication-related harm (e.g. drug-drug interactions) [14]. There is also evidence of under-prescribing of key palliative care medications required for optimal symptom control towards end of life, such as appropriate analgesia [15,16].

Targeted action is needed to improve medication prescribing in older adults with cancer, particularly at the end-of-life [17]. Others have developed standardised, objective screening tools to identify inappropriate or unnecessary medications in patients with cancer receiving palliative care [18,19]. For example, the OncPal deprescribing guideline [19] consists of nine medication classes which are potentially suitable targets for discontinuation in patients with advanced cancer. While these types of tools can help to identify potentially inappropriate medications, they do not assess under-prescribing of medicines for symptom control, which has been found in palliative care populations [15,16].

There is a need for the robust development, validation and evaluation of criteria for identifying potentially inappropriate prescribing for symptomatic relief in older adults with cancer receiving palliative care. This could help to improve symptom control and, ultimately, enhance patients' quality of life. The aim of this study was to develop criteria for identifying potentially inappropriate prescribing of medications for symptomatic relief in older adults (≥65 years) with cancer who are receiving palliative care and have an estimated life expectancy of <1 year.

## 2. Materials and methods

A Delphi consensus technique was used to develop the prescribing criteria. The Delphi technique is an accepted method that is widely used for achieving convergence of opinion from experts within a particular area [20]. This approach was particularly suited to achieving the study aim, as there is a recognised lack of robust evidence regarding the safety and effectiveness of drug treatments in palliative care populations [21,22]. There are a multitude of reasons for this, including ethical, economic, and practical constraints of conducting clinical trials or largescale observational studies in palliative care settings. The Delphi technique, therefore, allows the opinions and experiences of expert stakeholders to be captured as part of a consensus-building exercise [22].

The development of the criteria was overseen by a Project Steering Group consisting of a palliative care consultant, academic and research pharmacists and an epidemiologist. Project Steering Group members were based in the Royal College of Surgeons in Ireland (RCSI), St Vincent's Hospital, Dublin, Ireland and Queen's University Belfast, United Kingdom. The methods outlined below were based on those used previously by members of the Project Steering Group in developing prescribing criteria for other patient cohorts [23,24] and are reported in accordance with guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care [22]. Ethical approval was granted by the RCSI Research Ethics Committee (REC1681).

### 2.1. Development of a draft list of criteria

A scoping review was undertaken to help inform the development of a draft list of criteria for inclusion in the Delphi exercise [25]. The scoping review sought to characterise prescribing in patients receiving palliative care for any life-limiting illness and identify methods used to evaluate prescribing practices. The following electronic databases were searched from inception to October 2018: PubMed, EMBASE, CINAHL and Web of Science. Search terms included 'palliative care', 'end of life' and 'prescribing'. Standard methodology was followed in terms of screening articles based on title and abstract, assessment of full-text articles and data extraction [26]. Eligible study designs comprised observational studies examining prescribing practices and patterns for patients receiving palliative care (i.e. cross-sectional, case–control and cohort studies). Studies were eligible for inclusion if they aimed to examine medication prescribing for adult patients receiving palliative care for any life-limiting illness in any setting. Following deduplication, 12,874 unique citations were reviewed and 45 studies met inclusion criteria. None of the tools identified in included studies specifically addressed under-prescribing of medications for symptomatic relief in palliative care.

To supplement the scoping review, a literature search was undertaken to identify reviews examining the effectiveness of drug treatments used for managing symptoms included in the European Association for Palliative Care dataset for describing a palliative care cancer population [27]. Diarrhoea and delirium were added to this list of symptoms by the Project Steering Group based on clinical experience. The searches were conducted in April 2019 and focused initially on the Cochrane Library and were subsequently expanded to PubMed on account of an absence of up-to-date Cochrane systematic reviews on many of the symptoms. Search terms included 'palliative care', 'end of life' and relevant terms and synonyms for each of the symptoms (e.g. breathlessness, dyspnoea). All types of reviews were eligible for inclusion provided that they focused on populations with cancer and/or receiving palliative or end-of-life care. The findings and recommendations from systematic reviews were prioritised over non-systematic reviews. Forty review articles were reviewed in developing the draft criteria (Appendix 1).

Draft criteria for prescribing of medication for the management of each of these symptoms were then developed by the research team based on a distilled summary of the literature review findings. A criterion relating to therapeutic duplication was also included. The Palliative Care Formulary [28] was used as a reference resource, where necessary, to provide additional clinical information (e.g. clinical indications, dosing). The criteria were developed with the intention of providing a tool for clinicians and researchers to facilitate review of the appropriateness of prescribing in older adults with cancer who are receiving palliative care and have an estimated life expectancy of <1 year, after attempts have been made to address any underlying causes of the symptoms and non-pharmacological measures have been trialled where appropriate. The draft list of criteria was reviewed and refined by the Project Steering Group before the main consensus exercise.

### 2.2. Selection of the Delphi panel

There is no universally agreed sample size for Delphi exercises. In line with previous related studies [23,24], 30 individuals with relevant expertise in palliative care, oncology and/or geriatric medicine across Ireland and the United Kingdom were invited to participate in the study. Panellists were, firstly, identified from studies retrieved as part of the scoping review. Members of the Project Steering Group then proposed additional panellists to achieve the required sample size. Two additional clinicians who heard about the study through colleagues made contact with the research team and asked to take part. A total of eighteen clinicians consented to take part comprising fourteen experts from the Republic of Ireland (nine consultants, three pharmacists, one specialist registrar, one research physician) and four from the United Kingdom (two consultants, one pharmacist, one medical director of a hospice).

### 2.3. Data collection and analysis

The Delphi exercise consisted of two rounds of web-based questionnaires. The initial questionnaire was piloted using a convenience sample ($n = 4$) of academics and researchers based at the Schools of Pharmacy in RCSI and Queen's University Belfast to check face validity and usability of the online questionnaire software (SurveyGizmo®). These responses were not included in the final analysis.

The first round of the Delphi exercise took place between September and October 2019 and the second round took place between December 2019 and January 2020. For each round, participants were emailed a web-link to the online questionnaire and instructions on how to complete it. Reminder emails were sent to panellists to maximise the response rate. Criteria were grouped according to symptom class (e.g. constipation, diarrhoea) and each criterion was presented in the same format (i.e. the drug or drug class deemed a potentially inappropriate prescription or prescribing omission). The underlying rationale for each criterion was also provided together with a link to the relevant evidence resources where available (Appendix 1).

Participants were asked to rate their level of agreement with each statement using a 5-point Likert scale (where 1 indicated strongly disagree and 5 indicated strongly agree) that was based on previous Delphi studies [23,24]. For each criterion, the median response and interquartile range was calculated. A priori decision rules were used to determine which criteria were accepted, rejected or included in the second round of the Delphi exercise. A lower quartile ≥4 indicated general agreement with the criterion amongst panel members and the criterion was accepted. An upper quartile ≤2 indicated general disagreement with the criterion amongst panel members and the criterion was rejected. An interquartile range that included 3 indicated a lack of agreement amongst panel members and a need for further review of the particular criterion. In such cases, the criteria were reviewed by the Project Steering Group and either revised and included in the second round or rejected based on the additional comments received from panel members.

In Round 1, participants had the opportunity to add free-text comments to each of the criteria and to suggest additional criteria for inclusion in the study. In Round 2, participants were provided with a summary of Round 1 scores which included information on how they individually rated each criterion and group feedback showing the average score for each criterion. Participants also had the option of adding free-text comments to each of the criteria. The same analysis of responses and application of decision rules was undertaken as per Round 1.

## 3. Results

Twenty-eight criteria were developed and presented in the first round of the Delphi exercise. All eighteen panellists who agreed to participate in the study completed the first round Delphi questionnaire. Group consensus was achieved for fifteen criteria which were accepted and included in the final set of criteria (Table 1). No criteria were rejected outright by the panel in Round 1. However, following a review of the panel's ratings and additional comments for the remaining thirteen criteria not achieving consensus in Round 1, the Project Steering Group removed four of these criteria from Round 2 (Table 2). No additional criteria were added following Round 1.

The second round questionnaire was completed by seventeen of eighteen panel members from Round 1. No reason for non-participation in the second round was provided. Group consensus was achieved for all nine criteria included in Round 2 resulting in the inclusion of 24 criteria in the final set of criteria. The final criteria for identifying potentially inappropriate prescribing in older adults with cancer receiving palliative care (PIP-CPC) are presented in Table 3 and comprised 24 criteria relating to: anorexia-cachexia ($n = 1$); anxiety ($n = 2$); constipation ($n = 5$); delirium (n = 1); depression ($n = 3$); diarrhoea (n = 1); dyspnoea/breathlessness (n = 1); fatigue (n = 2); insomnia (n = 2); nausea and vomiting (n = 2); pain (n = 3); duplicate drug classes (n = 1). Appendix 2 provides a complete summary of the progression of the criteria through the Delphi exercise.

## 4. Discussion

This study used a Delphi consensus exercise to develop criteria for identifying potentially inappropriate prescribing of medications for symptomatic relief in older adults (≥65 years) with cancer who are receiving palliative care and have an estimated life expectancy of less than one year. The PIP-CPC criteria consist of 24 criteria for the treatment of symptoms listed in the European Association for Palliative Care's dataset for describing a palliative care cancer population [27]. Previous research has highlighted increases in the severity of symptoms such as pain, fatigue and appetite loss amongst patients with cancer towards end of life [29]. Identifying better ways of managing symptoms in palliative care populations is a priority research area [30]. The purpose of the PIP-CPC criteria is to act as a tool to facilitate review of existing prescribing practices in palliative cancer populations towards end of life by both clinicians and researchers. These criteria are intended to be applied where attempts have been made to address any underlying causes of the symptoms and non-pharmacological measures have been trialled where appropriate.

This study advances the existing literature as previous research examining the appropriateness of prescribing for patients with life-limiting illnesses, such as cancer, has largely focused on preventative medications [31,32]. The preceding scoping review highlighted that none of the included studies applied tools that specifically focused on the prescribing of medication for symptomatic relief [25]. Rather, most of the tools applied in included studies focussed on deprescribing of unnecessary or futile medications. A list of essential medicines for treating commonly encountered symptoms in palliative care has previously been developed by the International Association of Hospice and Palliative Care [33]. However, this list is not intended for assessing the

**Table 1**
Overview of the number of criteria accepted, rejected and revised following each round of the Delphi exercise.

| Section | Round 1 – Panel ratings | | | | Criteria removed by Steering group following Round 1 | Round 2 – Panel ratings | | | | Final set of criteria |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total criteria | Accept | Revise | Reject | | Total criteria | Accept | Revise | Reject | |
| Anorexia-cachexia | 2 | 0 | 2 | 0 | 1 | 1 | 1 | 0 | 0 | 1 |
| Anxiety | 2 | 0 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 |
| Constipation | 5 | 4 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 5 |
| Delirium | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| Depression | 3 | 3 | 0 | 0 | 0 | – | – | – | – | 3 |
| Diarrhoea | 1 | 1 | 0 | 0 | 0 | – | – | – | – | 1 |
| Dyspnoea/ Breathlessness | 1 | 1 | 0 | 0 | 0 | – | – | – | – | 1 |
| Fatigue | 2 | 0 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 |
| Insomnia | 2 | 0 | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 |
| Nausea and vomiting | 4 | 2 | 2 | 0 | 2 | – | – | – | – | 2 |
| Pain | 4 | 3 | 1 | 0 | 1 | – | – | – | – | 3 |
| Duplicate drug classes | 1 | 1 | 0 | 0 | 0 | – | – | – | – | 1 |
| Total | 28 | 15 | 13 | 0 | 4 | 9 | 9 | 0 | 0 | 24 |

**Table 2**
Statements removed by the Project Steering Committee after Round 1.

| Section | Statement | Round 1 ratings (median, IQR) | Panel member comments |
|---|---|---|---|
| Anorexia-cachexia | Megestrol acetate should be used if longer term treatment (>4 weeks) is required for anorexia-cachexia. | 2 (2–3) | "Risk of thrombotic events in older cancer patients; less accessible & (anecdotally) less well tolerated than steroids."<br>"I never use this due to the likelihood of risks outweighing any potential benefit. I would be reverting to non-pharmacological approaches if no response to steroids." |
| Nausea and vomiting | The use of metoclopramide for the treatment of nausea and vomiting should be limited to short periods (≤5 days). | 2 (1–3) | "Risk benefit balance generally in favour of treatment & I would continue it if effective for nausea and vomiting"<br>"More prolonged treatment is reasonable if there is a good therapeutic response." |
| Nausea and vomiting | The use of domperidone for the treatment of nausea and vomiting should be limited to short-periods (≤7 days). | 2 (1–4) | "The literature is applicable to the general population not older palliative care patients"<br>"Patient selection and review is important but would tend to continue for longer periods if working well" |
| Pain | Celecoxib (selective COX-2 inhibitor) should be used as first-line treatment for patients requiring non-steroidal anti-inflammatory drugs (NSAIDs). | 3 (2–4) | "I use diclofenac / ibuprofen. Am conscious of the risk of GI & renal side effects & would always co-prescribe PPI & check renal function in advance"<br>"This is not a medication that we would use routinely in palliative in my area"<br>"I use ibuprofen first line, diclofenac has many attractions too." |

appropriateness of the individual medications in specific populations (e.g. older adults with cancer) but rather to guide decisions regarding medication availability for palliative care within healthcare systems.

A number of previous studies [9,34] have applied prescribing tools, such as Beers criteria [35–37], that were not specifically designed or intended to be applied to patient populations requiring palliative care. The use of such tools in palliative care could potentially result in the misclassification of medications as inappropriate when in fact they have important roles to play in managing patients' symptoms. For example, due to the risk of gastrointestinal bleeding, Beers criteria recommend avoiding non-steroidal anti-inflammatory drugs in older adults. These drugs can, however, be of particular benefit in treating various forms of cancer pain (e.g. metastatic bone pain) [38]. Existing prescribing tools, such as the OncPal deprescribing guideline [19], that have been specifically developed for cancer populations receiving palliative care are primarily focussed on deprescribing of unnecessary medications for pre-existing conditions. While these types of tools can help to identify potentially inappropriate medications and opportunities for deprescribing, they do not assess symptomatic medications and the potential for prescribing omissions. The criteria developed as part of this study seek to address this gap and could ultimately help to address the underprescribing of analgesics and other symptom-specific medications that has been documented in palliative care populations [15,39–42]. The criteria may also assist practitioners to deprescribe medications prescribed for symptom management which are not appropriate or where the burden exceeds benefit (e.g. tablet burden).

Two key challenges were encountered in developing the PIP-CPC criteria. The first challenge related to the limited evidence base for many pharmacotherapies in palliative care. In line with the methods employed by several other Delphi studies that have developed established prescribing criteria for different patient groups [23,24,43,44], GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology [45] was not used to formally rate the quality of evidence identified as part of this study. However, it is evident from the findings of the literature review that there is a paucity of high quality evidence examining the effectiveness of medications used to control many of the symptoms included in the current criteria (e.g. anxiety [46], constipation [47,48], delirium [49], depression [50], diarrhoea [51], dyspnoea/breathlessness [52,53], fatigue [54], insomnia [55,56], nausea and vomiting [57–60]). This is a well-recognised issue and reflects the challenges of conducting robust experimental studies in palliative care populations [61,62]. Therefore, a Delphi exercise was an appropriate choice of research method as it enabled the collective opinions and experiences of a group of expert stakeholders working in palliative care to be captured through a consensus-building exercise. The second challenge was that, for symptoms such as nausea and vomiting [63], there are several different treatment options available. In such cases, it was not feasible to develop explicit statements that would cover the full scope of available treatment options as each of these cases would have required the development of a separate guideline which was beyond the scope of this study. Rather, we focused on developing statements that referred to existing local protocols and guidelines within the particular clinical setting in which clinicians are practising. Therefore, the PIP-CPC criteria need to be used in conjunction with local protocol/guidelines and are not intended to replace clinical judgement.

In terms of study strengths, the PIP-CPC criteria were developed using a robust methodology used in developing other prescribing criteria [[23,24] with input from a diverse panel of expert stakeholders from Ireland and the United Kingdom. There was also very little attrition between Delphi rounds. The main limitation of the Delphi study design is the potential lack of reproducibility, whereby results may be dependent on the chosen panellists [23]. In order to reduce this potential bias, a diverse group of expert stakeholders was invited to participate in the study. Furthermore, the rationale for each criterion was provided in each Delphi round, together with a link to relevant evidence resources.

Further research is needed to test the applicability of the PIP-CPC criteria. A future study will assess the application and validity of these criteria using clinical records for older patients with cancer who were receiving palliative care during the last year of life. As with other prescribing criteria, some modifications may be required to individual statements to account for country-specific clinical practices, prescribing guidelines and drug formularies [23]. There may be scope to use these criteria in conjunction with other prescribing tools that focus on deprescribing of unnecessary preventative medicines (e.g. OncPal [19]) to provide a more detailed and comprehensive assessment of the appropriateness of prescribing for older adults with cancer who are receiving palliative care and have limited life expectancy.

## 5. Conclusion

A consensus agreed set of prescribing criteria has been developed using a Delphi exercise involving an expert panel of palliative care clinicians. The PIP-CPC criteria consist of 24 criteria for identifying potentially inappropriate prescribing of medications for symptomatic relief

**Table 3**
The PIP-CPC criteria.

| Section | | Statement and rationale |
|---|---|---|
| Anorexia-cachexia | 1.1 | Corticosteroids should be limited to short-term use (≤4 weeks total treatment including weaning period; with administration of a maintenance dose as low as possible if the patients' symptoms deteriorate during weaning) for the treatment of anorexia-cachexia, unless there is a marked decrease in appetite following discontinuation.<br>*Rationale*: The appetite stimulating effects of corticosteroids tend to decrease after four weeks of treatment. |
| Anxiety | 2.1 | Benzodiazepines should be limited to short-term use (≤4 weeks) where possible for the treatment of anxiety, and the benefits associated with the ongoing prescription of benzodiazepines should be regularly balanced against potential risks (e.g. falls, delirium).<br>*Rationale*: There is a lack of evidence to support long-term use of benzodiazepines as anxiolytics and they are associated with numerous adverse events (e.g. falls, cognitive impairments), particularly if used for extended periods. |
| | 2.2 | Selective serotonin reuptake inhibitors (SSRIs) should be considered as first-line treatment for anxiety if longer term treatment (>4 weeks) is required.<br>*Rationale:* Despite a lack of high quality evidence to support the use of any specific drug for the treatment of anxiety in patients with cancer receiving palliative care, SSRIs are commonly recommended as first-line pharmacological treatment for anxiety in patients with cancer. |
| Constipation | 3.1 | Ensure that patients requiring pharmacological treatment for constipation are prescribed laxative treatment in accordance with current clinical guidelines and/or treatment protocols<br>*Rationale*: There is a lack of available evidence to inform optimal laxative management for constipation in patients receiving palliative care and, therefore, relevant clinical guidelines or treatment protocols should be followed. |
| | 3.2 | Avoid combinations of different classes of laxatives as routine first-line treatment for constipation.<br>*Rationale*: There is a lack of evidence to support routine use of combinations of different classes of laxatives in patients receiving palliative care. |
| | 3.3 | Avoid the use of oral liquid paraffin as a laxative.<br>*Rationale*: There is potential for aspiration and other adverse effects (e.g. anal discharge and irritation, granulomatous reaction). Safer alternatives are available. |
| | 3.4 | Patients who are prescribed opioid analgesics should also be prescribed laxative treatment in accordance with current clinical guidelines and/or treatment protocols.<br>*Rationale*: Most patients with palliative care needs who are receiving treatment with opioids require a regular laxative. |
| | 3.5 | Reserve the use of μ-opioid receptor antagonists (e.g. methylnaltrexone, naloxegol) for patients experiencing opioid-induced constipation who fail to respond to laxative therapy.<br>*Rationale*: It is recommended that μ-opioid receptor antagonists should only be considered in patients experiencing opioid-induced constipation who fail to respond to laxative therapy. |
| Delirium | 4.1 | Antipsychotics should be considered as first-line pharmacological treatment for the management of delirium involving distressing symptoms, and following a comprehensive review of reversible causes and use of non-pharmacological approaches.<br>*Rationale*: Despite a lack of high quality evidence to support the use of any specific drug for the treatment of delirium in patients with cancer receiving palliative care, antipsychotics are commonly recommended as first-line pharmacological treatment. |
| Depression | 5.1 | Ensure that patients requiring pharmacological treatment for depression are prescribed antidepressant treatment in accordance with current clinical guidelines and/or treatment protocols.<br>*Rationale*: There is a lack of available evidence to inform optimal pharmacological management of depression in palliative care and, therefore, relevant clinical guidelines or treatment protocols should be followed. |
| | 5.2 | Avoid the use of tricyclic antidepressants (e.g. amitriptyline, nortriptyline) as first-line treatment for depression.<br>*Rationale*: Safer alternatives are available. |
| | 5.3 | Avoid the use of monoamine oxidase inhibitors (e.g. moclobemide, tranylcypromine).<br>*Rationale*: These drugs can interact with drugs and dietary substances causing serious, and potentially fatal, adverse events (e.g. hypertensive crises). Safer alternatives are available. |
| Diarrhoea | 6.1 | Loperamide should be considered as first-line treatment for mild (≤4 loose motions per day) to moderate uncomplicated diarrhoea (4–6 loose motions per day) except in cases where there is a clearly identifiable cause that requires an alternative treatment approach (e.g. infectious diarrhoea, overflow, drug-induced diarrhoea).<br>*Rationale*: Despite a limited number of robust and large-scale evaluations of loperamide for the treatment of diarrhoea in patients receiving palliative care, it is commonly recommended as first-line treatment. Loperamide lacks CNS effects at therapeutic doses and also has more potent anti-diarrhoeal effects and a longer duration of action than other drugs, such as diphenoxylate and codeine. |
| Dyspnoea/Breathlessness | 7.1 | Low dose opioids (up to a maximum of 30 mg oral morphine equivalent/day) should be considered as first-line pharmacological treatment for dyspnoea/breathlessness where the management of the underlying cause(s) of dyspnoea has been optimised.<br>*Rationale*: Low dose opioids may help to relieve breathlessness in adults with advanced disease and terminal illness. |
| Fatigue | 8.1 | The use of corticosteroids for the treatment of fatigue should only be considered on a short-term trial basis and should be discontinued if no evidence of treatment benefit within 3–5 days.<br>*Rationale*: There is a lack of available evidence to support the use of any specific drug for the treatment of fatigue in patients with cancer receiving palliative care. However, based on clinical experience, a short trial of corticosteroids may be beneficial. |
| | 8.2 | The use of psychostimulants (e.g. methylphenidate) for the treatment of fatigue should only be considered on a short-term trial basis initially (≤3 days treatment after titration to the appropriate dose) and discontinued if no evidence of treatment benefit. |

*(continued on next page)*

**Table 3** (*continued*)

| Section | | Statement and rationale |
|---|---|---|
| | | *Rationale*: There is a lack of available evidence to support the use of any specific drug for the treatment of fatigue in patients with cancer receiving palliative care. However, based on clinical experience, a short trial of psychostimulants may be beneficial if contraindications do not exist. |
| Insomnia | 9.1 | Benzodiazepines should be limited to short-term use (≤4 weeks) for the treatment of insomnia, unless there is a marked increase in symptoms following discontinuation, and where the underlying cause of insomnia e.g. pain, depression, has been addressed.<br>*Rationale*: There is a lack of evidence to support long-term use of benzodiazepines for insomnia and they are associated with numerous adverse events (e.g. falls, cognitive impairments), particularly if used for extended periods. |
| | 9.2 | *Z*-drugs (e.g. zopiclone, zolpidem) should be limited to short-term use (≤4 weeks) for the treatment of insomnia, unless there is a marked increase in symptoms following discontinuation and where the underlying cause of insomnia e.g. pain, depression, has been addressed.<br>*Rationale*: There is a lack of evidence to support long-term use of *Z*-drugs for insomnia and they are associated with numerous adverse events (e.g. falls, cognitive impairments), particularly if used for extended periods. |
| Nausea and vomiting | 10.1 | Ensure that patients requiring pharmacological treatment for nausea and vomiting are prescribed anti-emetic treatment in accordance with current clinical guidelines and/or treatment protocols, taking into account the underlying cause of the nausea and vomiting and tailoring the treatment appropriately.<br>*Rationale*: There are multiple different underlying causes of nausea and vomiting in older patients with cancer with palliative care needs which has implications in terms of treatment strategies and, therefore, relevant clinical guidelines or treatment protocols should be followed. |
| | 10.2 | Avoid the use of hyoscine hydrobromide as first-line treatment for nausea and vomiting.<br>*Rationale*: Hyoscine is highly anticholinergic and can cause a range of side-effects such as dry mouth and constipation. |
| Pain | 11.1 | Ensure that patients requiring pharmacological treatment for pain are prescribed analgesic treatment in accordance with current clinical guidelines and/or treatment protocols.<br>*Rationale*: There are multiple different underlying causes of pain in older patients with cancer with palliative care needs which has implications in terms of treatment strategies and, therefore, relevant clinical guidelines or treatment protocols should be followed. |
| | 11.2 | Patients who are prescribed a long-acting opioid preparation (e.g. modified or sustained release formulation) should also be prescribed a short-acting opioid for break-through pain.<br>*Rationale*: Breakthrough pain is common in patients with cancer and can negative impact on their quality of life. Therefore, patients should be prescribed a short-acting opioid for break-through pain to be taken if required. |
| | 11.3 | Avoid the concurrent use of NSAIDs and corticosteroids without prophylactic treatment with a gastroprotective drug (e.g. proton pump inhibitor).<br>Rationale: Concurrent use of NSAIDs and corticosteroids increases the risk of gastric bleeding and, therefore, it should be avoided or else a gastroprotective drugs should also be administered. |
| Duplicate drug classes | 12.1 | Avoid using two or more drugs from the same pharmacological class where possible, except if prescribing is in line with current clinical guidelines (e.g. short-acting and long-acting opioids)<br>*Rationale*: Unnecessary therapeutic duplication and potential to increase risk of adverse events. |

in older adults with cancer who are receiving palliative care and have an estimated life expectancy of less than one year. Future studies should look to test the application and validity of these criteria using clinical records for older adults with cancer who are receiving palliative care.

## Author contributions

Conception and Design: Cathal Cadogan, Melanie Murphy, Sarah McLean, Kathleen Bennett, Carmel Hughes.
Data Collection: Cathal Cadogan.
Analysis and Interpretation of Data: Cathal Cadogan, Melanie Murphy, Sarah McLean, Kathleen Bennett, Carmel Hughes.
Manuscript Writing: Cathal Cadogan, Melanie Murphy.
Approval of Final Article: Cathal Cadogan, Melanie Murphy, Sarah McLean, Kathleen Bennett, Carmel Hughes.
All authors have reviewed and approved the final version of the manuscript.

## Funding

Cathal Cadogan was jointly supported by the Irish Cancer Society and All Ireland Institute of Hospice and Palliative Care [grant number: PAL17CAD].
Melanie Murphy was supported by a Clement Archer Scholarship from the School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland.
Kathleen Bennett was supported by a Health Research Board award [grant number: RL-15-1579].

## Declaration of Competing Interest

The authors declare that there is no conflict of interest.

## Acknowledgements

The authors are grateful to all of the panellists who took part in the Delphi study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2021.06.003.

## References

[1] Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: a population-based study. Int J Cancer. 2019;144(1):49–58.
[2] Mahumud RA, Alam K, Dunn J, Gow J. The burden of chronic diseases among Australian cancer patients: evidence from a longitudinal exploration, 2007-2017. PLoS One. 2020;15(2):e0228744.
[3] Loeppenthin K, Dalton SO, Johansen C, Andersen E, Christensen MB, Pappot H, et al. Total burden of disease in cancer patients at diagnosis—a Danish nationwide study of multimorbidity and redeemed medication. Br J Cancer. 2020;123(6):1033–40.

[4] Deliens C, Deliens G, Filleul O, Pepersack T, Awada A, Piccart M, et al. Drugs prescribed for patients hospitalized in a geriatric oncology unit: potentially inappropriate medications and impact of a clinical pharmacist. J Geriatr Onc. 2016;7(6):463–70.
[5] Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.
[6] Chen LJ, Trares K, Laetsch DC, TNM Nguyen, Brenner H, Schottker B. Systematic review and meta-analysis on the associations of polypharmacy and potentially inappropriate medication with adverse outcomes in older cancer patients. J Gerontol A Biol Sci Med Sci. 2021;76(6):1044–52.
[7] Mohamed MR, Ramsdale E, Loh KP, Arastu A, Xu H, Obrecht S, et al. Associations of polypharmacy and inappropriate medications with adverse outcomes in older adults with cancer: a systematic review and meta-analysis. Oncologist. 2020;25(1):e94-108.
[8] McLean S, Sheehy-Skeffington B, O'Leary N, O'Gorman A. Pharmacological management of co-morbid conditions at the end of life: is less more? Ir J Med Sci. 2013;182(1):107–12.
[9] Currow DC, Stevenson JP, Abernethy AP, Plummer J, Shelby-James TM. Prescribing in palliative care as death approaches. J Am Geriatr Soc. 2007;55(4):590–5.
[10] Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. Drug Saf. 2016;39(2):109–16.
[11] Turner JP, Shakib S, Bell JS. Is my older cancer patient on too many medications? J Geriatr Oncol. 2017;8(2):77–81.
[12] Morin L, Vetrano DL, Rizzuto D, Calderon-Larranaga A, Fastbom J, Johnell K. Choosing wisely? Measuring the burden of medications in older adults near the end of life: Nationwide, longitudinal cohort study. Am J Med. 2017;130(8):927–36 [e9].
[13] Oliveira L, Ferreira MO, Rola A, Magalhaes M, Ferraz Goncalves J. Deprescription in advanced cancer patients referred to palliative care. J Pain Palliat Care Pharmacother. 2016;30(3):201–5.
[14] Frechen S, Zoeller A, Ruberg K, Voltz R, Gaertner J. Drug interactions in dying patients: a retrospective analysis of hospice inpatients in Germany. Drug Saf. 2012;35(9):745–58.
[15] Rodriguez KL, Hanlon JT, Perera S, Jaffe EJ, Sevick MA. A cross-sectional analysis of the prevalence of undertreatment of nonpain symptoms and factors associated with undertreatment in older nursing home hospice/palliative care patients. Am J Geriatr Pharmacother. 2010;8(3):225–32.
[16] Tan T, Cheang F. A single-center retrospective analysis of interventions provided to geriatric inpatients receiving end-of-life care. Prog Palliat Care. 2016;24(6):332–8.
[17] LeBlanc TW, McNeil MJ, Kamal AH, Currow DC, Abernethy AP. Polypharmacy in patients with advanced cancer and the role of medication discontinuation. Lancet Oncol. 2015;16(7):e333–41.
[18] Fede A, Miranda M, Antonangelo D, Trevizan L, Schaffhausser H, Hamermesz B, et al. Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. Support Care Cancer. 2011;19(9):1313–8.
[19] Lindsay J, Dooley M, Martin J, Fay M, Kearney A, Khatun M, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer. 2015;23(1):71–8.
[20] Hsu C, Sandford S. The Delphi technique: making sense of consensus. Pract Assess Res Eval. 2007;12(10):1–8.
[21] Jansen K, Haugen DF, Pont L, Ruths S. Safety and effectiveness of palliative drug treatment in the last days of life-a systematic literature review. J Pain Symptom Manag. 2018;55(2):508–21 [e3].
[22] Junger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on conducting and REporting DElphi studies (CREDES) in palliative care: recommendations based on a methodological systematic review. Palliat Med. 2017;31(8):684–706.
[23] Cooper JA, Ryan C, Smith SM, Wallace E, Bennett K, Cahir C, et al. The development of the PROMPT (PRescribing optimally in middle-aged People's treatments) criteria. BMC Health Serv Res. 2014;14:484.
[24] Barry E, O'Brien K, Moriarty F, Cooper J, Redmond P, Hughes CM, et al. Pipc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. BMJ Open. 2016;6(9):e012079.
[25] Cadogan C, Murphy M, Boland M, Bennett K, McLean S, Hughes C. Prescribing practices, patterns, and adverse outcomes in patients receiving palliative care: a systematic scoping review. Palliat Med. 2020;34(1S):172.
[26] Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015;13(3):141–6.
[27] Sigurdardottir KR, Kaasa S, Rosland JH, Bausewein C, Radbruch L, Haugen DF. Prisma. The European Association for Palliative Care basic dataset to describe a palliative care cancer population: results from an international Delphi process. Palliat Med. 2014;28(6):463–73.
[28] Twycross R, Wilcock A. P. H. Palliative Care Formulary. 6th ed.. Pharmaceutical Press (London); 2018.
[29] Verkissen MN, Hjermstad MJ, Van Belle S, Kaasa S, Deliens L, Pardon K. Quality of life and symptom intensity over time in people with cancer receiving palliative care: results from the international European palliative care Cancer symptom study. PLoS One. 2019;14(10):e0222988.
[30] Hasson F, Nicholson E, Muldrew D, Bamidele O, Payne S, McIlfatrick S. International palliative care research priorities: a systematic review. BMC Palliat Care. 2020;19(1):16.
[31] Todd A, Husband A, Andrew I, Pearson SA, Lindsey L, Holmes H. Inappropriate prescribing of preventative medication in patients with life-limiting illness: a systematic review. BMJ Support Palliat Care. 2017;7(2):113–21.
[32] Poudel A, Yates P, Rowett D, Nissen LM. Use of preventive medication in patients with limited life expectancy: a systematic review. J Pain Symptom Manag. 2017;53(6):1097–110 [e1].
[33] De Lima L. Key concepts in palliative care: the IAHPC list of essential medicines in palliative care. Eur J Hosp Pharm. 2012;19:34–7.
[34] Russell BJ, Rowett D, Currow DC. Pro re nata prescribing in a population receiving palliative care: a prospective consecutive case note review. J Am Geriatr Soc. 2014;62(9):1736–40.
[35] Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716–24.
[36] By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2019 updated AGS beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–94.
[37] American Geriatrics Society Beers Criteria Update Expert P. American geriatrics society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–31.
[38] Whitman AM, DeGregory KA, Morris AL, Ramsdale EE. A comprehensive look at polypharmacy and medication screening tools for the older cancer patient. Oncologist. 2016;21(6):723–30.
[39] Borgsteede SD, Deliens L, Zuurmond WW, Schellevis FG, Willems DL, Van der Wal G, et al. Prescribing of pain medication in palliative care. A survey in general practice. Pharmacoepidemiol Drug Saf. 2009;18(1):16–23.
[40] Lau DT, Dwyer LL, Shega JW. Concomitant opioid and laxative use in older adults in hospice care in the United States: 2007. J Am Geriatr Soc. 2016;64(11) e160-e5.
[41] Skollerud LM, Fredheim OM, Svendsen K, Skurtveit S, Borchgrevink PC. Laxative prescriptions to cancer outpatients receiving opioids: a study from the Norwegian prescription database. Support Care Cancer. 2013;21(1):67–73.
[42] Romem A, Tom SE, Beauchene M, Babington L, Scharf SM, Romem A. Pain management at the end of life: a comparative study of cancer, dementia, and chronic obstructive pulmonary disease patients. Palliat Med. 2015;29(5):464–9.
[43] Lavan AH, Gallagher P, Parsons C, O'Mahony D. StoppFrail (screening tool of older persons prescriptions in frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600–7.
[44] O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
[45] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
[46] Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated with anxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017;5:CD004596.
[47] Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Cochrane Database Syst Rev. 2015;5:CD003448.
[48] Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Database Syst Rev. 2018;6:CD006332.
[49] Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M. Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev. 2012;11:CD004770.
[50] Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev. 2018;4:CD011006.
[51] Pastrana T, Meissner W. Treatment of diarrhea with loperamide in palliative medicine. A systematic review. Schmerz. 2013;27(2):182–9.
[52] Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev. 2016;10:CD007354.
[53] Haywood A, Duc J, Good P, Khan S, Rickett K, Vayne-Bossert P, et al. Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults. Cochrane Database Syst Rev. 2019;2:CD012704.
[54] Mucke M, Mochamat Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2015;5:CD006788.
[55] Hirst A, Sloan R. Benzodiazepines and related drugs for insomnia in palliative care [withdrawn from cochrane library]. Cochrane Database Syst Rev. 2002;4:CD003346.
[56] Howell D, Oliver TK, Keller-Olaman S, Davidson JR, Garland S, Samuels C, et al. Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice. Ann Oncol. 2014;25(4):791–800.
[57] Cox L, Darvill E, Dorman S. Levomepromazine for nausea and vomiting in palliative care. Cochrane Database Syst Rev. 2015;11:CD009420.
[58] Storrar J, Hitchens M, Platt T, Dorman S. Droperidol for treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2014;11:CD006938.
[59] Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2015;11:CD006271.
[60] Vayne-Bossert P, Haywood A, Good P, Khan S, Rickett K, Hardy JR. Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). Cochrane Database Syst Rev. 2017;7:CD012002.
[61] Aoun SM, Nekolaichuk C. Improving the evidence base in palliative care to inform practice and policy: thinking outside the box. J Pain Symptom Manag. 2014;48(6):1222–35.
[62] Visser C, Hadley G, Wee B. Reality of evidence-based practice in palliative care. Cancer Biol Med. 2015;12(3):193–200.
[63] Collis E, Mather H. Nausea and vomiting in palliative care. BMJ. 2015;351:h6249.