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Published in:
Research in Social and Administrative Pharmacy

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
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PII: S1551-7411(21)00134-0
Reference: RSAP 1781

To appear in: Research in Social & Administrative Pharmacy

Received Date: 8 December 2020
Revised Date: 12 April 2021
Accepted Date: 12 April 2021


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A systematic scoping review of interventions to optimise medication prescribing and adherence in older adults with cancer

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Abstract

Background: Older adults with cancer often require multiple medications (polypharmacy) comprising cancer-specific treatments, supportive care medications (e.g. analgesics), and medications for pre-existing health conditions. Increasing numbers of medications may increase risks of potentially inappropriate prescribing and non-adherence.

Objectives: To provide an overview of evaluations of interventions aimed at optimising medication prescribing and/or adherence in older adults with cancer.

Methods: A systematic scoping review was undertaken. Four databases (PubMed, EMBASE, CINAHL, PsycINFO) were searched using relevant search terms (e.g. cancer, older adults). Eligible studies evaluated interventions seeking to improve medication prescribing and/or adherence in older adults (≥65 years) with cancer using a comparative evaluation. All outcomes for studies that met inclusion criteria were included in the review. Extracted data were collated using tables and accompanying narrative descriptive summaries. The review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guidelines.

Results: Nine studies met inclusion criteria comprising five randomised controlled trials (RCTs) and four before-and-after study designs. Studies were primarily conducted in oncology clinics, ranging from single study sites to 109 oncology clinics. Sample sizes ranged between 33-4844 patients. Interventions most commonly involved patient education (n=6) delivered by pharmacists or nurses. Three studies reported on prescribing-related outcomes and seven studies reported on adherence-related outcomes, using different terminology and assessment methods. Prescribing-related outcomes focused on medication appropriateness (using Beers criteria) and drug-related problems including drug interactions. Adherence-related outcomes included assessments of self-reported medication adherence and calculation of patients’ medication possession ratio.
Conclusions: This scoping review highlights a lack of robust evaluations of interventions aimed at optimising medication prescribing and adherence in older adults with cancer. Future research should improve rigour during intervention development, evaluation and reporting in order to generate findings that could inform future practice.

Key words: cancer, oncology, older adults, intervention, prescribing, adherence

Abbreviations
EPOC: Effective Practice and Organisation of Care
PIP: potentially inappropriate prescribing
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RCT: randomised controlled trial
STOPP/START: Screening Tool of Older Person's Prescriptions / Screening Tool to Alert doctors to Right Treatment
Introduction

The global burden of cancer is rapidly increasing and driven to a large extent by advancing population age (1). In 2012, 48% of cancer diagnoses worldwide occurred in older adults (≥65 years), and this is expected to rise to 58% by 2038 (2). Older adults with cancer often have existing health conditions, necessitating the use of multiple medications (3-5). Treatment burden (i.e. the workload of healthcare and its impact on patient functioning and well-being) (6) in this patient cohort can be further potentiated by the addition of cancer-specific treatments and supportive care medications (e.g. analgesics). A sizeable proportion (21%) of admissions to cancer services are related to adverse drug events arising from the use of both cancer-specific and non-cancer treatments (7). Therefore, interventions aimed at optimising medication regimens in older patients with cancer are required.

Medicines optimisation is defined as an approach to care that focuses on ensuring the best clinical outcomes for patients through safe and effective medication use (8). Two key aspects of medicines optimisation involve reducing potentially inappropriate prescribing and enhancing medication adherence (9). Potentially inappropriate prescribing (PIP) encompasses a range of suboptimal prescribing practices, including prescribing medication associated with high risk of adverse drug events, inappropriate doses or treatment durations and errors of omission (under-prescribing) (10). Several criteria have been developed to assess the appropriateness of medication prescribing in the general older population (11-14), and application of these criteria has proven to be effective in reducing PIP (15). However, many of these criteria were not designed specifically for use in older adults with cancer, and therefore, their applicability to this patient cohort is limited. Prescribing for older adults with cancer requires additional considerations such as the risk of drugs becoming inappropriate as a consequence of physiological changes (e.g. weight loss) due to cancer and the associated treatments (16), as well as the increased potential for drug-drug interactions arising from the use of systemic anticancer therapies and supportive treatments (17). Furthermore, existing tools often recommend the avoidance or cessation of certain medications that may be clinically suitable for this patient cohort (e.g. non-steroidal anti-inflammatory drugs for cancer-related pain) (18, 19).

The OncPal deprescribing guideline has been developed which is specific to cancer populations
at the palliative stage of illness (20). However, the extent of its clinical impact has yet to be
determined.

The challenges that polypharmacy (prescribing of ≥5 medicines) (4) present are not limited to
prescribing issues. Previous studies have indicated that polypharmacy and complex medication
regimens negatively impact on medication adherence (21). Adherence can be defined as the
extent to which an individual’s behaviour (e.g. taking medication) corresponds with a
healthcare provider’s agreed recommendations (22). Reported adherence rates in patients with
cancer range from approximately 20–100%, depending on therapy, definition and
measurement of adherence (23, 24). Poor clinical outcomes and increased healthcare costs are
associated with medication non-adherence in patients with cancer (25, 26). Therefore,
optimising medication regimens in patients with cancer is paramount to maximising clinical
outcomes. To date, there is an absence of reviews examining interventions involving medicines
optimisation in older patients with cancer, which limits our understanding of the current
evidence base (27).

The aim of this scoping review was to provide an overview of evaluations of interventions
seeking to optimise medication prescribing and/or adherence in older adults with cancer. The
objectives were to:

1. Characterise the study populations;
2. Identify the types of interventions aimed at optimising medication prescribing and/or
   adherence in older adults with cancer;
3. Characterise key features of the interventions;
4. Examine the evidence base and theories underpinning the interventions;
5. Identify the outcome measures that have been used to evaluate the interventions;
6. Establish key findings of the evaluations relating to the review question.

Methods

The review protocol has previously been published (27) and details of the methods are
summarised briefly below. This review was conducted in accordance with relevant
methodological guidance available from the Joanna Briggs Institute (28, 29) and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guidelines (30).

Search strategy

Four electronic databases (PubMed, EMBASE, CINAHL and PsycInfo) were searched from inception to 29th November 2019 using established search methods for scoping reviews (28). Preliminary searches of each database were undertaken to identify relevant keywords and index terms. Initial key search terms included: “cancer”, “older adults”, “prescribing” and “adherence”. These search terms served to inform a comprehensive search strategy that was developed with the input of a research librarian (Appendix A). Reference lists of all studies meeting inclusion criteria were screened for additional studies.

Inclusion criteria

Types of participants

The review included interventions targeting older adults (≥65 years) with an active cancer diagnosis. Eligible studies were not limited by type of cancer, healthcare setting or number/types of medication prescribed. In order to meet inclusion criteria, studies had to include individuals aged ≥65 years or a study population with a mean/median age of ≥65 years.

Types of interventions

The review included any interventions seeking to optimise medication prescribing or adherence in older patients with cancer (or a study population with a mean/median age of ≥65 years). To be included, interventions had to align with key principles of medicines optimisation which were broadly categorised as: interventions to reduce PIP and interventions to improve medication adherence (8). Interventions could target either the level of the healthcare professional or patient.
Types of studies
Studies had to include some form of comparative evaluation (e.g. inclusion of a control group or use of a controlled before/after design). Only studies published in the English language were eligible for inclusion. Published conference abstracts were not included.

Types of outcomes
As there is no existing overview of outcomes of interventions aimed at improving prescribing or adherence in older patients with cancer, all outcomes for studies that met the above inclusion criteria were included in the review. This allowed for an overview to be provided of the range of outcomes that have been evaluated on this topic.

Study selection
Following deduplication, all abstract titles were screened initially by one review author (X) to remove any that were clearly irrelevant. Of the remaining abstracts, a randomly selected 50% sample were double screened by two review authors working independently (Y, Z). If an abstract appeared to meet inclusion criteria or could not be excluded based on the title or abstract alone, the full-text article was retrieved and independently assessed for inclusion by two reviewers. Any disagreements throughout this process were resolved through consensus discussion with other members of the research team.

Charting, collating and summarising the data
Two reviewers (X, Y) independently performed data extraction (often referred to as “charting” in the scoping review literature (28)), using a data extraction form that was developed in accordance with relevant methodological guidance (31). Data were extracted relating to each of the following: authors; year of publication; country of origin; study design and setting; study aims/purpose; study population; sample size; outcome measures; intervention characteristics; key findings. Interventions were categorised according to the Effective Practice and Organisation of Care (EPOC) taxonomy (i.e. ‘Delivery arrangements’, ‘Financial arrangements’, ‘Governance arrangements’, ‘Implementation strategies’) (32).

Formal assessments of methodological quality of included studies were not undertaken, as the aim of a scoping review is to provide a broad overview of the existing literature (28). A narrative
synthesis was completed following established guidance (33) which involved three key steps (detailed further in the published protocol (27)): (i) development of a preliminary synthesis of key findings; (ii) exploration of relationships in the data; (iii) assessment of the robustness of the synthesis.
Results

Search results

The electronic searches yielded 21,136 citations (Figure 1). Following title and abstract screening, 309 full-text articles were reviewed for eligibility. In total, nine studies met inclusion criteria (34-42). The main reasons for exclusion of the remaining articles were: study population was not cancer specific and/or aged ≥65 years; intervention did not aim to optimise prescribing or adherence; study design did not include a comparative evaluation.

Table 1 provides an overview of the key study characteristics. Study designs consisted of five randomised controlled trials (RCTs) (35-37, 39, 41), including one cluster RCT (39) and four before-and-after study designs with historical control groups (34, 38, 40, 42). Three studies were described as pilot studies (34, 37, 42). Included studies were conducted across five countries: USA (34, 35, 37, 41), Germany (36, 39), Japan (40), Canada (42) and Spain (38). Studies were primarily conducted in oncology clinics, ranging from single study sites to 109 oncology centres and clinics (Table 1).

Study populations (Objective 1)

Study sample sizes ranged from 33 to 4844 patients (Table 1). Two studies reported conducting a sample size calculation prior to data collection (36, 39). All studies had a sample population with a mean or median age of ≥65 years. However, the age profile of patients across included studies varied (range: 18 to 93 years). One study provided a breakdown of participants’ age according to specific age categories (51.4% aged ≥65 years) (36) and only two studies focused specifically on older populations (35, 37). Three studies focused on specific cancer types (e.g. breast cancer (36), prostate cancer (42), renal cell carcinoma (40), while the remainder included patients with various types of cancer. One study described patients’ cancer stage (36) and no studies referred to life expectancy. All patients were receiving active cancer treatment and none were reported to be receiving palliative care. Only two studies reported on comorbidities.
and three studies reported on the numbers of concurrent medications (34, 36, 37).

Detailed breakdowns of the types of medications were not reported.

Intervention details (Objectives 2 and 3)

Details of the interventions are summarised in Table 2 and outlined below. Further details of the interventions are provided in Appendix B. All interventions were classified as ‘delivery arrangements’ according to the EPOC taxonomy (32). Across the included studies, seven studies targeted adherence (34-36, 38-40, 42), three studies targeted prescribing (37, 38, 41) and one study targeted both (38). Interventions most commonly involved patient education as either a sole focus or intervention component (34-36, 38, 39, 42). Other interventions or their components involved patient monitoring (34, 40) and reviews of medication prescribing (37), pain management (41) and adverse events (34, 40).

In four studies, the interventions were pharmacist-led (34, 37, 38, 40) whereby pharmacists monitored patients regularly and provided relevant education or information (34, 40), reviewed patients’ medication history (including vaccination administration) (37), evaluated the appropriateness of prescribing (37), assessed medication-related issues including adherence and adverse events (34, 38, 40) and advised prescribers on recommended changes to existing medications (37).

In two studies, interventions were led by oncology nurses (35, 39). Both of these interventions involved patient education and focused on either the management of pain (35) or medication side-effects (39). One of these studies also included family caregivers who were asked to be present during home visits by the nurses delivering the intervention (35). Another patient education-based intervention was delivered by either an oncology nurse or physician who formed part of patients’ oncology team (42). This intervention focused on bone health in males with prostate cancer who were receiving androgen deprivation therapy and included patient counselling, a customised written pamphlet on bone health and a prescription for healthy bone behaviours such as adequate intake of calcium and vitamin D (42). In another patient education-based intervention, patients with breast cancer received written educational material in the post during the first year of anastrozole therapy to promote adherence (36).
Patients also received gift items of low monetary value (e.g. tablet box). The remaining study focused on pain management whereby patients in the intervention arm completed a pain assessment survey, which was available to their oncologists (41). No further information was provided in terms of how the intervention was delivered.

Interventions were most commonly delivered face-to-face (35, 37, 39, 40, 42) or by telephone (34, 40). A number of interventions used written material (e.g. letters, booklets, pamphlets) as either the core intervention (36) or as a supplementary component (35, 38, 42). Five studies included follow-up interventions that occurred at periods ranging from one week to 12 months (34-36, 39, 42). Intervention time requirements were documented in three studies (34, 37, 39) and ranged from an average of 15-20 minutes (34) to 55 minutes per intervention (37). Only one study reported on intervention preparation time, which ranged from 30-45 minutes for each patient visit (37).

[insert Table 2]

Underpinning evidence and theory base (Objective 4)

Five studies provided information in relation to the intervention development process (35, 36, 38, 39, 42). In all cases, the amount of information provided was limited. One study reported that the intervention was based on the review of existing pain management material and input from pain consultants without providing any further elaboration (35). Three studies reported that components of the interventions were developed in collaboration with patients (36) or clinicians (38, 42) but without describing the process. In the remaining study, the intervention was reportedly based on a teaching tool from a cancer care organisation (39). No studies reported the use of any theory underpinning intervention development.

Outcomes measures (Objective 5)

Outcome measures that were used in included studies are reported in Table 2. Three of the studies reported on prescribing-related outcomes (37, 38, 41) and seven of the studies reported on adherence-related outcomes (34-36, 38-40, 42). Prescribing-related outcomes involved
assessments of medication appropriateness using Beers criteria for potentially inappropriate medication use in older adults (37), drug-related problems (e.g. drug-drug interactions, dosing and administration issues) (38), vaccination rates (37) and pain management (41).

Adherence-related outcomes were described and assessed using varying terminology including adherence (38, 40, 42), compliance (35, 36), persistence on therapy (34, 36) and unplanned therapy interruptions (39). One study examined adherence to healthy bone behaviours which included intake of calcium and vitamin D (42). Most adherence-related outcomes were assessed using patient self-report (e.g. log books) (35, 36, 40, 42). Conliffe et al. measured persistence to therapy as the percentage of patients that remained on the antineoplastic medication three months post-intervention (34). Ribed et al. measured adherence using the medication possession ratio (a ratio of doses delivered to doses the patient should have taken within a certain timeframe), which was automatically calculated by the electronic prescription software (38).

Most studies stated the time points at which outcomes were assessed (34, 36-39, 41, 42) with follow-up assessments ranging from two weeks (39) to 12 months post-intervention (36).

Key findings relating to the review question (Objective 6)

Key study findings relating to the review question are summarised in Table 3 and outlined below.

Of the five studies involving RCT designs, two reported on prescribing-related outcomes (37, 41) and three reported on adherence-related outcomes (35, 36, 39). At the four-week follow-up, Nipp et al. (37) reported positive preliminary findings from a pilot RCT in the intervention group compared to the control group in terms of fewer potentially inappropriate medications (3.46 vs. 4.80, p = 0.069), fewer discrepant medications (5.82 vs. 8.07, p = 0.094), and higher vaccination rates for influenza and pneumonia (Table 3). Trowbridge et al. (41) reported higher post-intervention levels of analgesic prescribing in the intervention group compared to the control group (25% vs 5%, p = 0.0162), but no significant difference between the groups in the under-treatment of pain (35% vs. 38%, respectively).
In terms of adherence-related outcomes, Hadji et al. (36) reported no differences between intervention and control groups for compliance or persistence at 12-month follow-up (36). Riese et al. (39) reported that the chances of a patient-initiated unplanned therapy interruption at two-weeks post-intervention were lower in the intervention group compared to the control group (Odds ratio 0.14, 95% confidence interval 0.03 – 0.69, p = 0.01). This was not sustained at the three-month follow-up assessment whereby no significant differences were observed between intervention and control groups. The study by Ferrell et al. (35) targeted adherence but only reported on preliminary results and did not differentiate between intervention and control group data.

Of the four non-randomised studies, only one reported on prescribing-related outcomes (38). Ribed et al. reported a significantly higher number of drug-related problems (DRPs) in the intervention group compared to the control group (p=0.008). The most commonly identified DRPs were drug-drug interactions (57.3%), dosage errors (11.2%) and administration errors (11.2%). Of the identified DRPs, 74% were rated as significant and 24% were rated as life-threatening.

All four of the non-randomised studies reported on adherence-related outcomes using comparisons between intervention groups and historical control groups. One study reported that a higher proportion of intervention group patients were adherent compared to the control group, at six-months post intervention (95% vs 87.7% respectively, p=0.025) (38). Another study reported no difference in therapy persistence between intervention and control groups at the three-month follow-up (73% vs 59% respectively, p=0.7) (34). The other two studies reported no differences in post-intervention adherence to pazopanib (40) or adherence to calcium and vitamin D intake at three-month follow-up (42).

[insert Table 3]
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Study design</th>
<th>Setting</th>
<th>Aim/purpose</th>
<th>Study population</th>
<th>Sample size</th>
<th>Outcome measures and follow-up assessment timepoints</th>
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</thead>
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<tr>
<td>Conliffe 2019 (34)</td>
<td>United States</td>
<td>Pilot study involving before and after design with historical control group</td>
<td>Genitourinary oncology clinic at an academic medical centre</td>
<td>To assess the impact of a pilot pharmacist-led oral antineoplastic monitoring program</td>
<td>Patients (≥18 years) prescribed an oral antineoplastic agent</td>
<td>33 patients Intervention group (n=11) Control (n=22)</td>
<td>Prescribing-related - Not assessed Adherence-related - Persistence on therapy Other - Adherence to pre-defined monitoring standards - Need to seek medical care (i.e. unplanned admissions) - Patient satisfaction - Financial assessment of cost avoidance Assessment timepoints 3 months</td>
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<tr>
<td>Ferrell 1993 (35)</td>
<td>United States</td>
<td>Randomised controlled trial</td>
<td>Unclear - intervention appears to have been delivered in patients’ home</td>
<td>To report on the development and implementation of a pain management educational intervention for older patients with cancer and their family</td>
<td>Older patients (≥60 years) with cancer and their caregivers</td>
<td>40 patients (number in each group not reported) 29 family caregivers</td>
<td>Prescribing-related - Not assessed Adherence-related - Medication compliance Other - Pain - Quality of life</td>
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<td>Study ID</td>
<td>Country</td>
<td>Study design</td>
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| Hadji 2013 (36) | Germany | Randomised controlled trial | 109 certified breast cancer centres/clinics | To investigate whether providing educational materials to breast cancer patients in the first year of adjuvant endocrine therapy leads to improvements in medication compliance and persistence compared to standard treatment alone | Postmenopausal women with early-stage breast cancer | 4844 patients | - Non-drug interventions (including compliance and perceived effectiveness)  
- Caregiver burden  
**Assessment timepoints Unclear**  
- Prescribing-related  
- Not assessed  
- Medication compliance and persistence  
- Time-to-treatment discontinuation  
**Other**  
- Treatment tolerability and toxicity  
- Disease-free survival  
**Assessment timepoints 12 months** |
<table>
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<th>Study ID</th>
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<th>Study design</th>
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<th>Outcome measures and follow-up assessment timepoints</th>
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<tr>
<td>Nipp 2019 (37)</td>
<td>United States</td>
<td>Pilot randomised controlled trial</td>
<td>General hospital</td>
<td>To demonstrate the feasibility and preliminary efficacy of integrating pharmacists into the care of older adults with cancer in enhancing medication management and vaccination administration</td>
<td>Older patients (≥65 years) receiving outpatient first-line intravenous chemotherapy for breast, gastrointestinal or lung cancer (any stage)</td>
<td>60 patients</td>
<td>Prescribing-related</td>
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<td>Intervention group (n=29) Control (n=31)</td>
<td></td>
<td>- Medication appropriateness (assessed using Beers Criteria (43))</td>
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<td>- Number of discrepant medications (difference between patient report and the electronic health record)</td>
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<td></td>
<td>- Study feasibility and intervention acceptability</td>
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<td></td>
<td></td>
<td>Assessment timepoints (4 weeks)</td>
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<tr>
<td>Ribed 2016 (38)</td>
<td>Spain</td>
<td>Before and after design with historical control group</td>
<td>Tertiary hospital</td>
<td>To evaluate a pharmaceutical care program for cancer outpatients receiving oral anti-cancer</td>
<td>Adult patients with an onco-haematologic tumour starting oral</td>
<td>249 patients</td>
<td>Prescribing-related</td>
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<td></td>
<td>Intervention group (n=134) Control</td>
<td></td>
<td>- Drug-related problems (potential medication errors)</td>
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<td></td>
<td>- Capacity for harm</td>
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<td>Study ID</td>
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| Riese 2017 (39) | Germany | Cluster randomised controlled trial | Outpatient oncology practices (n=28) | To evaluate the effectiveness of a standardised patient education program delivered by specially trained oncology nurses on therapy management regarding side-effects and unplanned therapy interruptions in outpatient oncology care | Patients (≥18 years) newly adjusted on an oral anti-cancer therapy | (n=115) | - Drug interactions  
- Adherence-related  
- Adherence  
- Other  
- Pharmacist interventions  
  (number, type, acceptance rate of recommendations)  
- Adverse events  
- Patient satisfaction  
  Assessment timepoints  
  6 months |
| Todo 2019 | Japan | Before and Outpatient | To evaluate the patients receiving | Patients receiving | 50 patients | Prescribing-related  
- Not assessed  
- Adherence-related  
- Frequency of unplanned therapy interruptions  
- Frequency of therapy-related side-effects  
  Assessment timepoints  
  Multiple timepoints up to 12 weeks |
<table>
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<th>Study ID</th>
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<th>Setting</th>
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<th>Study population</th>
<th>Sample size</th>
<th>Outcome measures and follow-up assessment timepoints</th>
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<tr>
<td>(40)</td>
<td></td>
<td>after study design with historical control group</td>
<td>cancer chemotherapy clinic</td>
<td>effects of a comprehensive pharmaceutical care intervention on the incidence of adverse events and the duration of therapy in outpatients who received pazopanib for renal cell carcinoma</td>
<td>pazopanib for renal cell carcinoma from the outpatient clinic</td>
<td>Intervention group (n=37) Control (n=13)</td>
<td>- Not assessed Adherence-related - Adherence Other - Incidence of adverse events - Time to treatment failure Assessment timepoints Unclear</td>
</tr>
<tr>
<td>Trowbridge 1997 (41)</td>
<td>United States</td>
<td>Randomised controlled trial</td>
<td>23 outpatient oncology clinics</td>
<td>To determine the effectiveness of a clinical practice intervention in improving the control of pain in outpatient cancer patients</td>
<td>Outpatients (≥18 years) with a carcinoma or sarcoma and recurrent or metastatic disease who were experiencing cancer-related pain</td>
<td>320 patients</td>
<td>- Prescribing-related - Pain Management Index Adherence-related - Not assessed Other - Self-rated pain assessment Assessment timepoints Unclear</td>
</tr>
<tr>
<td>Tsang 2018 (42)</td>
<td>Canada</td>
<td>Pilot study involving before and after design with historical control group</td>
<td>Urology and radiation oncology genitourinary clinics at a tertiary cancer</td>
<td>To evaluate the feasibility of implementing a multimodal patient education intervention and</td>
<td>Men with prostate cancer receiving androgen deprivation therapy</td>
<td>103 patients</td>
<td>- Prescribing-related Not assessed Adherence-related Adherence to healthy bone behaviours (including vitamin D and</td>
</tr>
<tr>
<td>Study ID</td>
<td>Country</td>
<td>Study design</td>
<td>Setting</td>
<td>Aim/purpose</td>
<td>Study population</td>
<td>Sample size</td>
<td>Outcome measures and follow-up assessment timepoints</td>
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<td></td>
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<td>Centre</td>
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<td>measure its ability to improve adherence to healthy bone behaviours in men with prostate cancer receiving androgen deprivation therapy</td>
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<td></td>
<td>calcium intake) Other - Study feasibility (recruitment rate, patient satisfaction) - Bone mineral density test ordering - Patient knowledge and health beliefs regarding osteoporosis Assessment timepoints 3 months</td>
</tr>
</tbody>
</table>

**Table 2: Summary of intervention characteristics**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention summary and focus</th>
<th>EPOC classification</th>
<th>Underpinning evidence/theory base</th>
<th>Intervention targets</th>
<th>Intervention deliverer and mode of delivery</th>
<th>Intervention duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conliffe 2019 (34)</td>
<td>Pharmacist-led antineoplastic monitoring program with three follow-up visits. The pharmacists reviewed monitoring parameters, assessed medication-related issues and provided</td>
<td>Delivery arrangements</td>
<td>Not documented</td>
<td>Patients prescribed an oral antineoplastic agent in the genitourinary oncology clinic</td>
<td>Intervention delivered by specialist oncology pharmacist, primarily by telephone (unless patients had previously scheduled</td>
<td>Each follow-up call required approx. 15–20 minutes of time (including preparative work and time on the phone)</td>
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<tr>
<td>Study ID</td>
<td>Intervention summary and focus</td>
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<tr>
<td>Ferrell 1993 (35)</td>
<td>Nurse-led pain management education program with two follow-up visits. The nurse provided verbal instruction and supplemented the intervention with written and audio information. Adherence-focused intervention.</td>
<td>Delivery arrangements</td>
<td>Development of the program materials was reportedly based on a review of existing materials and literature with input from pain consultants. No further details provided and no mention of any underpinning theory.</td>
<td>Older cancer patients and their caregivers</td>
<td>The teaching program was delivered face-to-face by an oncology nurse during home visits. Written patient education booklets and audiocassette tapes were also provided.</td>
<td>Not documented</td>
</tr>
<tr>
<td>Hadji 2013 (36)</td>
<td>Patients received educational material in the post, and gifts of low monetary value to promote medication adherence. Adherence-focused intervention.</td>
<td>Delivery arrangements</td>
<td>All educational materials were reportedly developed in collaboration with breast cancer survivors. No further details provided and no mention of any underpinning theory.</td>
<td>Postmenopausal women with early-stage breast cancer</td>
<td>Intervention deliverer not specified. Educational materials were sent to the patient via mail and this was co-ordinated by the research centre.</td>
<td>Not documented</td>
</tr>
<tr>
<td>Study ID</td>
<td>Intervention summary and focus</td>
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<tr>
<td>Nipp 2019 (37)</td>
<td>Pharmacist-led medication management and vaccination administration program, whereby the pharmacists reviewed patients’ medication history and evaluated the appropriateness of prescribing. Prescribing-focused intervention.</td>
<td>Delivery arrangements</td>
<td>Not documented</td>
<td>Older patients (≥65 years) receiving outpatient first line intravenous chemotherapy for breast, gastrointestinal, or lung cancer (any stage)</td>
<td>A clinical pharmacist delivered the intervention face-to-face during a single in-person visit</td>
<td>Pharmacists spent between 30-45 minutes preparing for each study visit. The median length of the pharmacists’ visits was 55 minutes (range 30-75) per patient.</td>
</tr>
<tr>
<td>Ribed 2015 (38)</td>
<td>Pharmacist-led pharmaceutical care program which consisted of patient education and information brochures for each oral anti-neoplastic agent, with additional personalised instructions for symptom management. Pharmacists identified drug-related problems and made recommendations to patients and/or physicians. Adherence and prescribing focused intervention.</td>
<td>Delivery arrangements</td>
<td>The pharmaceutical care program was reportedly developed by a group of clinical pharmacists, oncologists and haematologists and followed recommended standards for oral antineoplastic agents.</td>
<td>Adult patients starting oral antineoplastic agents</td>
<td>A clinical pharmacist with expertise in oncology and haematology, delivered the intervention during three clinical interviews over a six month period in the outpatient pharmacy (beginning of treatment, one month and six months later). The intervention was</td>
<td>Not documented</td>
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<tr>
<td>Study ID</td>
<td>Intervention summary and focus</td>
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<tr>
<td>Riese 2017 (39)</td>
<td>Nurse-led patient education program comprising four sessions that focused on medication management (including side-effects and unplanned therapy interruptions). Adherence-focused intervention.</td>
<td>Delivery arrangements</td>
<td>Intervention development was reportedly based on a teaching tool from the Multinational Association of Supportive Care in Cancer. No further details provided and no mention of any underpinning theory.</td>
<td>Patients newly adjusted on an oral anti-cancer therapy.</td>
<td>Oncology nurses delivered face-to-face education sessions</td>
<td>The first patient education session was not to take more than 45 minutes. Follow-up sessions were not to take more than 30 minutes.</td>
</tr>
<tr>
<td>Todo 2019 (40)</td>
<td>Pharmacist-led intervention that included patient education and management of adverse events. A dedicated hotline was also established to enable direct communication between patients and the pharmacist, and facilitate monitoring of adherence and</td>
<td>Delivery arrangements</td>
<td>Not documented</td>
<td>Outpatients with renal cell carcinoma who received pazopanib at the outpatient cancer chemotherapy clinic</td>
<td>Pharmacists (including an oncology pharmacist) conducted face-to-face consultation with patients. Patients could also speak with the pharmacist when</td>
<td>Not documented</td>
</tr>
<tr>
<td>Study ID</td>
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<tr>
<td>Trowbridge 1997 (41)</td>
<td>Oncologists were instructed to review a summary sheet containing results of a pain assessment survey completed by patients, prior to evaluating patients. Prescribing-focused intervention.</td>
<td>Delivery arrangements</td>
<td>Not documented</td>
<td>Cancer patients with pain and their oncologists</td>
<td>Unclear who delivered the intervention and how it was delivered.</td>
<td>Not documented</td>
</tr>
<tr>
<td>Tsang 2018 (42)</td>
<td>Nurse/oncologist led intervention comprising a “healthy bones” prescription, face-to-face education and a customised written pamphlet. Adherence-focused intervention.</td>
<td>Delivery arrangements</td>
<td>The pamphlet on bone health was reportedly created through a collaborative effort between different clinicians (oncologists, a geriatrician, an endocrinologist), a physiotherapist and the hospital patient education department. No further details provided and no</td>
<td>Male cancer patients receiving androgen deprivation therapy for prostate cancer</td>
<td>The intervention was delivered using a combination of face-to-face education and written material by an oncology nurse or physician who were part of the oncology team.</td>
<td>Not documented</td>
</tr>
<tr>
<td>Study ID</td>
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<td>mention of any underpinning theory</td>
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</table>
Table 3: Overview of key findings from included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Key findings relating to medication prescribing and adherence</th>
</tr>
</thead>
</table>
| Conliffe 2019 (34) | **Adherence-related outcomes**  
|               | **Persistence on therapy:** At three month follow-up, a higher proportion of intervention group patients remained on the prescribed oral antineoplastic medication compared to the control group (73% vs 59% respectively, p=0.7). |
| Ferrell 1993 (35) | **Adherence-related outcomes**  
|               | **Medication compliance:** Preliminary results indicated that many patients were only taking 70% of the medications prescribed. Intervention and control group data were not reported separately. |
| Hadji 2013 (36) | **Adherence-related outcomes**  
|               | **Compliance:** At 12-month follow-up, overall compliance across both groups was 88.6%. There was no difference in compliance between the intervention and control group (88.5% vs 88.8% respectively, p=0.81)  
|               | **Persistence:** At 12-month follow-up, overall persistence across both groups was 41.8%. There was no difference in persistence on therapy between the intervention and the control group (40.5% vs 43% respectively, p=0.18). |
| Nipp 2019 (37)  | **Prescribing-related outcomes**  
|               | **Potentially inappropriate medications:** At four-week follow-up, intervention patients had fewer potentially inappropriate medications than control group patients (3.46 vs. 4.80, p = 0.069), although differences were not statistically significant.  
|               | **Discrepant medication:** At four-week follow-up, intervention patients had fewer discrepant medications than control group patients (5.82 vs. 8.07, p = 0.094), although these differences were not statistically significant.  
|               | **Vaccination rates:** At four-week follow-up, intervention patients had higher rates of obtaining vaccinations for pneumonia (27.6% vs. 0.0%, p = 0.005) and influenza (27.6% vs. 0.0%, p < 0.001) than control group patients. Similarly, at eight-week follow-up, intervention patients had higher rates of obtaining vaccinations than control group patients for pneumonia (37.9% vs. 0.0%, respectively p < 0.001) and influenza (31.0% vs. 0.0%, respectively p < 0.001). |
| Ribed 2015 (38) | **Prescribing-related outcomes**  
|               | **Drug-related problems:** Over the six-month follow-up period, a significantly higher number of drug-related problems were detected in the intervention group (n=169) compared to the control group (n=106, p=0.008). Drug-related problems primarily consisted of drug-drug interactions (57.4%), incorrect administration or time of use (11.2%), and... |
### Key findings relating to medication prescribing and adherence

**Excessive drug dosing (8%).**

**Capacity for harm:** Of the drug-related problem identified 74% were rated as significant and 24% were rated as life-threatening. Differences in the capacity for harm between the intervention and control group were not reported.

**Drug interactions:** During the six-month follow-up, 80 interactions were identified in the control group compared to 93 interactions in the intervention group. The only statistically significant between group differences were for type X interactions i.e. involving contraindications or drug combinations that are to be avoided (6.7% in the intervention group vs. 26.3% in the control group; $p = 0.001$).

**Adherence-related outcomes**

**Adherence:** At six-months follow-up, a higher proportion of intervention group patients were adherent compared to control group patients (95% vs 87.7% respectively, $p=0.025$).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Adherence-related outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riese 2017 (39)</td>
<td><strong>Unplanned therapy interruption:</strong> The intervention group had a lower chance of experiencing a patient-initiated unplanned therapy interruption two weeks’ post-intervention (Odds ratio; 0.14, 95% confidence interval; 0.03, 0.69; $p=0.01$). This was not sustained at three follow-up assessments over a three-month period whereby no significant differences were observed between intervention and control groups ($p &gt;0.05$).</td>
</tr>
<tr>
<td>Todo 2019 (40)</td>
<td><strong>Adherence:</strong> There was no reported post-intervention change in adherence in the intervention group, whereas non-adherence occurred in five out of 13 patients (38%) in the control group.</td>
</tr>
</tbody>
</table>
| Trowbridge 1997 (41) | **Prescribing-related outcomes**

**Prescribing patterns of analgesics:** There was a significant post-intervention difference in analgesic prescribing ($p=0.0162$) with changes in prescriptions observed in 25% of intervention group patients (reduction in prescribing in 5% and an increase in prescribing in 20%) compared to 14% of control group patients (all involved increases in prescribing).

**Under-treatment of pain:** No significant post-intervention difference in the under-treatment of pain between intervention and control group (35% vs. 38% respectively) |
| Tsang 2018 (42) | **Adherence-related outcomes**

**Self-reported adherence to vitamin D intake ≥ 1000 IU/day:** At three-month follow-up, the intervention had no
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Key findings relating to medication prescribing and adherence</th>
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<tbody>
<tr>
<td></td>
<td>statistically significant effect on the odds of receiving vitamin D &gt; 1000 IU per day compared to the control group (adjusted odds ratio [OR] 1.8, 95% confidence interval [CI] 0.74–4.5, p = 0.19)</td>
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<td></td>
<td><strong>Self-reported adherence to calcium intake 1000–1500 mg/day:</strong> At three-month follow-up, the intervention had no statistically significant effect on the odds of receiving the recommended amount of daily calcium (1000–1500 mg/day) compared to the control group (adjusted OR 1.5, 95% CI 0.63–3.4, p = 0.37).</td>
</tr>
</tbody>
</table>
Discussion

This scoping review provides an overview of interventions evaluated to date that have targeted medication prescribing and/or adherence in older adults with cancer. Given the growing burden of cancer among the older population (44), interventions targeting medicines optimisation within this patient population are of considerable importance in terms of ensuring appropriate prescribing and use of medicines, and maximising their clinical benefits for patients. Despite the recognised need for optimising medication prescribing and adherence in older adults with cancer (45-47), this review has identified a paucity of rigorous evaluations of interventions specific to these issues using robust study designs. The review also highlights sources of heterogeneity across included studies in terms of study populations, interventions and outcome measures, which would limit the potential for pooling outcome data in any future systematic review.

In this review, study populations comprised patients with active cancer diagnoses and a mean or median age of ≥65 years. However, the age of individual participants varied considerably within and between studies (range 18 to 93 years) and only two studies focused specifically on older adults (35, 37). Differing age profiles among patients with cancer may present different clinical challenges, particularly in terms of the prevalence of multimorbidity (two or more chronic conditions) which increases with age (48). Furthermore, a cancer diagnosis frequently results in the prescription of multiple additional medications, contributing to increased risk of drug-drug interactions (49, 50). Other important considerations in patients with cancer include stage of disease, remaining life expectancy, and time to treatment benefit. For patients with life-limiting illnesses such as cancer, preventative medications for existing health conditions are often continued in cases where they may no longer be clinically beneficial (51, 52). None of the included studies referred to life expectancy or stated that patients were receiving palliative care. There is a need for optimisation of medications throughout the disease trajectory, as medication appropriateness can change with cancer stage, depending on various factors including weight, organ function and side-effects of systemic anticancer therapies (53).
Across included studies, interventions more commonly targeted adherence (seven studies) than prescribing (three studies), with only one of the included studies targeting both (38). Intervention components included patient education and medication reviews and were primarily delivered by pharmacists and nurses. However, in many cases, detailed descriptions of intervention were lacking. It has yet to be determined which healthcare professionals would be best suited to delivering interventions to this group of patients and how frequently interventions should be delivered. Based on previous research conducted among the general older population (i.e. non-cancer specific), it has been suggested that multifaceted interventions comprising several intervention components may be more likely to improve prescribing and adherence than single component interventions (10, 54). In order to enhance adherence to oral cancer therapy in older adults, the International Society of Geriatric Oncology has recommended that self-management interventions (e.g. patient education, self-monitoring for toxicity) be combined with adherence interventions led by healthcare professionals (55). It also recommended that technologies such as text messaging, electronic mail and other automated alert systems be used to promote adherence within this population. The interventions identified in this review were most commonly delivered either face-to-face or by telephone and none of them reported including a technological component. A recent review examining the use of information technology in the monitoring of older patients with cancer concluded that technology could be beneficial in this patient cohort, but any technology employed needs to be tailored to the unique needs of this population (e.g. text should be of appropriately large font size, audio prompts with adjustable volume) (56).

One particular challenge that arose in synthesising information across included studies related to differences in terminology. For example, in terms of medication adherence, different parameters were examined across studies including compliance (now superseded by adherence), persistence and time-to-treatment discontinuation. Medication compliance and persistence are two different constructs (57) whereby compliance refers to ‘the extent to which patients act in accordance with the prescribed dosing regimen instructions’, and persistence refers to ‘the act of continuing the prescribed treatment for the intended duration’ (57). In addition to this, most studies relied on self-reported data, with only one study using an
objective measure of adherence in the form of the medication possession ratio (38). Although there is no gold standard assessment for adherence, it is recommended that a combination of measures is used to overcome the limitations of any single assessment tool (58).

Variation also existed in the focus of prescribing-related outcomes and the tools that were used across included studies. For example, one study examined drug-related problems, including drug interactions (38), while another study examined prescribing of analgesics as part of a pain management intervention (41). The only study that assessed the appropriateness of medication prescribing (37) used the Beers criteria (18). The Beers criteria are a well-established and widely used form of explicit prescribing criteria for older adults. However, they were not specifically designed or intended to assess prescribing for older adults with cancer and do not target prescribing omissions (under-prescribing). The FORTA (Fit fOR The Aged) List classifies medication into four categories (indispensable, beneficial, questionable, avoid) according their safety, efficacy and overall appropriateness in older adults and includes classifications of medications for specific types of cancer, as well as a limited number of supportive therapies (59). Other tools such as the OncPal deprescribing guideline, have been developed specifically with the aim of identifying PIP among patients with cancer (20). Similar to the Beers criteria, they focus on the deprescribing of potentially inappropriate medications. The application of OncPal as part of a clinical intervention targeting older adults with cancer has yet to be assessed (20). Further research is also required to assess potential prescribing omissions (under-prescribing) among older patients with cancer and whether patients are receiving appropriate medications for common symptoms, such as pain.

To enhance future research in this field, more robust processes should be undertaken at all stages of intervention development, evaluation and reporting. The UK Medical Research Council's framework on the development and evaluation of complex interventions advocates that intervention development should be underpinned by evidence and theory with input from relevant stakeholders (60). The intervention development process precedes preliminary evaluations of the interventions in the form of pilot and feasibility studies which can be undertaken in preparation for a definitive trial evaluation to determine whether the intervention is effective and should be implemented on a wider scale. Five studies referred to
intervention development, albeit with limited detail, and none of the included studies referred to the use of any underpinning theory. This limits our ability to understand how the interventions were intended to exert their effects (61). Future research could benefit from the application of behaviour change theory by framing the clinical issue to be addressed as a behaviour and identifying relevant barriers and facilitators that need to be modified using evidence-based behaviour change techniques. This type of robust methodology has been previously operationalised in the development and evaluation of interventions targeting appropriate prescribing and medication adherence for older adults in primary care (62-65). It remains to be seen whether interventions targeting the general older population can be applied to older adults with cancer.

The main strength of this scoping review is that it provides a broad overview of literature in this area. The review followed established methods as set out in the published protocol (28). The issues highlighted in terms of study design, intervention development and outcome assessment may help to inform future related research. The review’s methods and search strategies may serve to inform the development of a protocol for a future systematic review on this topic. Notable limitations of this review were that it was limited to studies published in the English language and grey literature was not searched. The limited number of RCT designs and the inclusion of studies that employed historical control groups, coupled with the fact that methodological quality of individual studies was not formally assessed, preclude any definitive conclusions being made regarding intervention effectiveness. Of the five studies involving RCT designs, one study reported on preliminary data (35) for which no follow-up paper was identified and another involved a pilot design which was not powered to assess effectiveness (37). The other three RCTs had mixed results in terms of the outcomes of interest in this review.

**Conclusion**

The scoping review provides a broad overview of the existing literature on interventions aimed at optimising medication prescribing and adherence in older adults with cancer. The review findings highlight a paucity of robust study designs and a lack of specific focus on older adults with cancer. Heterogeneity was also apparent across included studies in terms of study
populations, interventions and outcome assessments, thereby limiting our ability to draw firm conclusions. Future research should exercise greater rigour during the stages of intervention development, evaluation and reporting in order to generate findings that could contribute to a cumulative evidence base and serve to inform future practice.
Acknowledgements

The authors are grateful to X, for her assistance in reviewing the search strategy.

Conflicts of interest

None

Funding

A is supported by B.

C is jointly supported by the D and E [grant number: X].

F is supported by G [grant number: Y].
References


49. 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...


Records identified through database searching (n = 26,688)

Additional records identified through other sources (n = 18)

Records after duplicates removed (n = 21,136)

Records screened (n = 21,136)

Records excluded (n = 20,827)

Articles assessed for eligibility (n = 309)

Articles excluded (n = 300)

Studies included in qualitative synthesis (n = 9)

Figure 1: PRISMA flow diagram