Rationalising medications at the end of life

Jo Thompson
Lead Nurse – Supportive & Palliative Care
Royal Surrey County Hospital
Objective

- Review the rationale / evidence of safety of discontinuing long standing medication at the end of life
Overview of the session

- Discuss why we should rationalise medications, and why we don’t

- Provide an overview of the tools available to support the process

- Look at the evidence for specific drugs
Polypharmacy
Polypharmacy
Patients at the end of life
Polypharmacy

• Describes a patient’s use of several drugs

• The term is sometimes used more generally to describe unnecessary drug prescriptions
Polypharmacy and end of life care

- 20% of palliative cancer patients were taking a potentially inappropriate medication (PIM) (Lindsay et al 2014)
Polypharmacy and end of life care

- Secondary analysis of data from a prospective trial of adults with an estimated prognosis of less than 1 year
- Medications were recorded at least monthly from study enrolment through to death
- 244 patients (47.5% had cancer) took an average of 11.5 medications at the time of enrolment and 10.7 at death or study termination
Medication burden

Fig. 1.
Medications per patient at baseline.
Medications in the last year of life

Fig. 2.
Percentage of patients taking the most common medication classes.
Studies on polypharmacy in patients with cancer  

(LeBlanc et al 2015)

<table>
<thead>
<tr>
<th>Country</th>
<th>Setting</th>
<th>n</th>
<th>Age</th>
<th>Number of prescribed drugs</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cashman et al, 2010</td>
<td>UK</td>
<td>100 patients with metastatic cancer</td>
<td>Median 7</td>
<td>Median 7 (IQR 1-27)</td>
<td>82% of patients were on drugs for a previously diagnosed comorbidity. Anti-hypertensive drugs were most common.</td>
</tr>
<tr>
<td>Fede et al, 2011</td>
<td>Brazil</td>
<td>87 ambulatory patients with advanced cancer</td>
<td>Median 61 years (IQR 27-87)</td>
<td>Median 4 (IQR 1-13)</td>
<td>24% of patients with advanced cancer were taking unnecessary drugs (including statins, anti-hypertensives, gastric protective drugs, and diabetes treatments).</td>
</tr>
<tr>
<td>Jorgensen et al, 2012</td>
<td>Denmark</td>
<td>24 808 patients with cancer and 99 229 control participants without cancer</td>
<td>Median 68 years (IQR 58-77)</td>
<td>Median 3 (IQR 1-6)</td>
<td>35% of patients aged 70 years or older used five or more drugs daily. In the 6 months before a cancer diagnosis, the total number of medications increased.</td>
</tr>
<tr>
<td>Kotlinska-Lemiesz et al, 2014</td>
<td>Europe</td>
<td>2282 patients with cancer and pain receiving a step III opioid</td>
<td>Mean 62-3 years (SD 12.3)</td>
<td>Mean 7-8 (SD 3.2)</td>
<td>More than 25% of patients were prescribed ten or more drugs. The most commonly prescribed drugs were proton-pump inhibitors, laxatives, corticosteroids, paracetamol, and non-steroidal anti-inflammatory drugs.</td>
</tr>
<tr>
<td>Maggiore et al, 2014</td>
<td>USA</td>
<td>500 patients (307 [61%] patients with stage IV disease)</td>
<td>270 [54%] were aged 72 years or older</td>
<td>Median 5 (SD 4-0)</td>
<td>Polypharmacy was not statistically associated with chemotherapy-related toxic effects or hospital admission.</td>
</tr>
<tr>
<td>Puts et al, 2009</td>
<td>Canada</td>
<td>112 patients aged 65 years or older with newly diagnosed cancer</td>
<td>Mean 74-2 years (SD 6.0)</td>
<td>Median 5 (IQR 3-9)</td>
<td>The most common drugs included lipid-lowering drugs, anticoagulants, diuretics, bisphosphonates, and gastrointestinal drugs. 47-6% were at risk for potential drug-drug interactions.</td>
</tr>
<tr>
<td>Baijmakers et al, 2013</td>
<td>Italy</td>
<td>121 patients with cancer at the end of life</td>
<td>Mean age in hospital 76 years (SD 12); mean age in hospice 72 years (4-14)</td>
<td>Mean in hospital 5-3 (SD 2-4); mean in hospice 4-7 (1-8)</td>
<td>Drug use varied by setting. Patients in hospital were less likely to receive opioids, midazolam, and haloperidol than were those in the hospice. They were also more likely to receive additional drugs, such as supplements, replacement hormones, and anti-hypertensives, than were patients in the hospice.</td>
</tr>
<tr>
<td>Scollo et al, 2007</td>
<td>USA</td>
<td>100 patients aged 70 years or older with cancer</td>
<td>Mean 78 years (range 70-90)</td>
<td>Mean 8-1 (SD not reported)</td>
<td>The most common drugs prescribed for chronic disorders were cardiovascular and gastrointestinal drugs. Slightly less than 50% of patients reported use of complementary or alternative medicines.</td>
</tr>
<tr>
<td>Todd et al, 2013</td>
<td>England</td>
<td>20 patients with advanced lung cancer who were taking erlotinib</td>
<td>Not reported</td>
<td>Mean 8 (range 1-16; SD not reported)</td>
<td>The most common drugs prescribed were cardiovascular, gastrointestinal, and respiratory drugs. 19 (95%) patients were taking a drug that was deemed inappropriate in conjunction with erlotinib.</td>
</tr>
<tr>
<td>Turner et al, 2014</td>
<td>Australia</td>
<td>385 patients with cancer aged 60-80 years or older</td>
<td>Mean 76-7 (SD 4-8)</td>
<td>Mean 5-7 (SD 3-7)</td>
<td>When adjusted for age, sex, and the Charlson comorbidity index, polypharmacy was significantly associated with frailty or a pre-frail state. Patients defined as pre-frail or frail according to the Fried's frailty phenotype were more likely to be taking ten or more drugs than those defined as robust.</td>
</tr>
</tbody>
</table>

Table 1: Studies on polypharmacy in patients with cancer
Studies on polypharmacy at end of life in patients with cancer

<table>
<thead>
<tr>
<th>Country</th>
<th>Setting</th>
<th>n</th>
<th>Age</th>
<th>Number of prescribed drugs</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumow et al., 2007 - Australia</td>
<td>Specialised palliative care services funded by the state government provide consultative specialist nursing, medical, and allied health support for family doctors and community nurses who are the primary point of care</td>
<td>260 (87% of whom had diagnosis of cancer)</td>
<td>Mean 71 years (SD 12)</td>
<td>Mean 4-9 (SD 2-8) at baseline, mean increase of 1-49 medications overall at death</td>
<td>Because of introduction of symptom management drugs, total number of drugs increases as a patient approaches death</td>
</tr>
<tr>
<td>Sera et al., 2014 - USA</td>
<td>Hospices in 11 states</td>
<td>4252 (35% of whom had diagnosis of cancer)</td>
<td>Mean 77.5 (SD 14-3)</td>
<td>Mean 15 (range 3-100)</td>
<td>362 patients were prescribed 30 drugs or more. A mean of 7-9 “as needed” drugs were prescribed, and 8-3 were regularly scheduled. The most common drugs were paracetamol, morphine, haloperidol, lorazepam, prochlorperazine, and atropine (all of which are part of the symptom management kit that every patient received upon admission)</td>
</tr>
<tr>
<td>Lundy et al., 2013 - Ireland</td>
<td>Five inpatient hospices</td>
<td>138 (91% of whom had diagnosis of cancer)</td>
<td>Median 68 (IQR 20-93)</td>
<td>Mean 8 (range 0-17) at admission and 2 (0-15) at death</td>
<td>Polypharmacy is prevalent in hospice care. The mean number of medications increased to ten at time of discharge from inpatient hospice to another setting (eg, their home)</td>
</tr>
<tr>
<td>McLean et al., 2013 - Ireland</td>
<td>A palliative care service in a rural region (an integrated service, comprising an acute hospital and community team)</td>
<td>52 (79% of whom had advanced cancer)</td>
<td>Median 74.5 (IQR 36-0-91-0)</td>
<td>Mean 4-6 drugs for comorbidities in patients older than 65 years; an overall mean ten drugs were prescribed at 1 week before death</td>
<td>Total drug burden increases as a patient approaches death because they continue to take drugs for comorbidities and symptom management</td>
</tr>
<tr>
<td>Nauck et al., 2004 - Germany, Switzerland, Austria</td>
<td>57 palliative care units and hospices</td>
<td>1304 (more than 95% of whom had primary diagnosis of cancer)</td>
<td>Mean 65.2 (SD 12-8)</td>
<td>Mean 3-2 (SD 2-4) at admission and 4-8 (2-3) during inpatient treatment</td>
<td>Overall medication burden increases during inpatient treatment. The most common medications included dipyrone, morphine, fentanyl, dexmetomidine, and metoclopramide. The top 15 drugs prescribed accounted for 54% of all drug prescriptions</td>
</tr>
<tr>
<td>Russell et al., 2014 - Australia</td>
<td>Specialised palliative care services funded by the state government provide consultative specialist nursing, medical, and allied health support for family doctors and community nurses who are the primary point of care</td>
<td>203 (58% of whom had cancer)</td>
<td>Mean 72.9 (SD 12-6)</td>
<td>Mean 7-2 (SD 3-7) regularly prescribed</td>
<td>Most drugs were prescribed for comorbidities (mean 5-3 [SD 3-5] drugs for comorbidities). 21-7% of patients were prescribed a statin, of whom 40-5% were taking the drug for primary prevention</td>
</tr>
</tbody>
</table>

Table 2: Studies on polypharmacy at end of life in patients with cancer
Why is polypharmacy a problem?

- Evidence to suggest negative outcomes for patients, even those taking as few as four drugs (LeBlanc et al 2015)

- Increased risk of ADEs
  - 13% with 2 medications
  - 58% with 5 medications
  - 82% with 7 or more medications (Patterson et al 2014)

- Increased pill burden

- Poor concordance
Why aren’t medications routinely rationalised?

• Fear that patients may feel HCPs are ‘giving up hope’

• Continued uncertainty on the part of clinicians about the benefits afforded in continuing the treatment

• HCPs potentially overestimate patients’ discomfort with stopping medications (study in family practice 2001)

• The complexity of more patients receiving cancer directed therapies and palliative or symptom management therapies simultaneously

• Multiple prescribers and patients being seen by different specialties
Why aren’t medications routinely rationalised?

- Majority of drug research is designed to explore how to start drug treatment – almost no effort is geared towards discontinuing
- Limited time
- Difficulty in predicting the timing of the shift
- Fear of adverse drug withdrawal effects, despite the fact these occur much less frequently than ADEs
Why aren’t medications routinely rationalised?

- Uncertainty.....

The future is completely uncertain...

...I am completely certain of this.
Tools to support rationalising medications

- Majority of the tools are those used in elderly care:
  - Beers criteria
  - MAI (medications appropriateness index)
  - STOPP (Screening Tool of Older People’s potentially inappropriate Prescriptions)
Interventions to improve the appropriate use of polypharmacy for older people (Review)

Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, Hughes C

Authors' conclusions

It is unclear whether interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in clinically significant improvement; however, they appear beneficial in terms of reducing inappropriate prescribing.
Can we apply these tools to end of life care?
Tools to support rationalising medications at the end of life

- Although useful, these tools cannot be easily translated for use in patients at the end of life

- Some drugs considered inappropriate according to these tools are those used regularly in supportive, palliative and end of life care
Tools

- ‘OncPal deprescribing guideline’ (Lindsay et al 2015)
  
  - Tool to assist the identification of medications suitable for discontinuation in palliative cancer patients

  - Literature relating to different medication classes was systematically reviewed (according to the European Pharmaceutical Market Research Association anatomical classification list)

  - Medication classes not listed in the tool have either demonstrated benefits in this population or the literature is lacking to guide decision making
‘OncPal deprescribing guideline’

• Development of the tool used a single phase consensus model, the draft guideline sent to 3 palliative care consultants, 3 oncology consultants and 3 senior pharmacists

• Validated in study with 61 patients
  • Each patient’s medications were reviewed by an expert panel; radiation oncologist, medical oncologist and palliative medicine consultant
  • In parallel each patient’s medications were reviewed by a pharmacist using the OncPal guideline
‘OncPal deprescribing guideline’

• Proportion of medications assessed correctly using OncPal compared to the expert panel was 94% (concordance was Kappa 0.83 – agreement considered to be outstanding)

  • 70% patients were taking at least one PIM

  • 21.4% of total medications found to be PIM
Specific drugs
Specific drugs

• What’s the evidence?
Statins

- Evidence from one study that 62% of patients with cancer and a poor prognosis continued to receive statins, often for primary prevention

- A further study showed 31% of patients with cancer requested a repeat px for statins within 30 days of death

- Unclear as to what the barriers are to stopping these medications
Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness
A Randomized Clinical Trial

Jean S. Kutner, MD, MSPH; Patrick J. Blatchford, PhD; Don H. Taylor, PhD; Christine S. Ritchie, MD; Janet H. Bull, MD; Diane L. Fairclough, DrPH; Laura C. Hanson, MD; Thomas W. LeBlanc, MD; Greg P. Samsa, PhD; Steven Wolf, MS; Noreen M. Aziz, MD, PhD; David C. Currow, BMEd; Betty Ferrell, PhD; Nina Wagner-Johnston, MD; S. Yousuf Zafar, MD; James F. Cleary, MD; Sandesh Dev, MD; Patricia S. Goode, MD; Arif H. Kamal, MD; Cordt Kassner, PhD; Elizabeth A. Kvale, MD; Janelle G. McCallum, RN, MSN; Adebayo B. Ogundehin, MD; Steven Z. Pantilat, MD; Russell K. Portenoy, MD; Maryjo Prince-Paul, PhD; Jeff A. Sloan, PhD; Keith M. Swetz, MD; Charles F. Von Gunten, MD, PhD; Amy P. Abernethy, MD, PhD
Statins

• Adults with a life expectancy of 1 month to 1 year who had been taking statins for 3 months or more and no active cardiovascular disease that required ongoing therapy

• 381 patients enrolled
  • 189 randomised to discontinue
  • 192 randomised to continue

• Primary outcome  - death within 60 days
  • Survival, CV events, PS, QoL, symptoms, no. of non-statin meds and cost savings
Statins - Results

- Proportion of patients who died within 60 days was not significantly different between groups
- Few patients experienced CV events
- Overall QoL was better in the non-statin group

- Stopping statin medication is safe and may be associated with benefits including improved QoL, use of fewer non-statin medications and reduction in costs
Evidence for other drugs

"Is there a pill I can take to feel better about all the pills I take?"
## Other drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin for primary prevention</td>
<td>Little short or medium risk of stopping</td>
</tr>
</tbody>
</table>

### Antihypertensives

If sole use is to reduce mild to moderate hypertension, for secondary prevention of cardiovascular events or as management of stable coronary artery disease

*Some short term benefits need consideration – recommended to monitor BP after discontinuation. Some agents should be continued for symptom management eg. Heart failure or irregular hear rhythm
## Other drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis medication (unless if used to treat hypercalcaemia or pain from bone metastases)</td>
<td>Little short or medium term risk of stopping</td>
</tr>
<tr>
<td>PPIs &amp; H2 antagonists (unless history of GI bleed, peptic ulcer, gastritis, GORD or use with NSAIDs &amp; steroids)</td>
<td>Ongoing therapy unnecessary in shortened life expectancy</td>
</tr>
<tr>
<td>Oral hypoglycaemics if sole use is to reduce mild hyperglycaemia, for secondary prevention of diabetic associated events</td>
<td></td>
</tr>
</tbody>
</table>
Medications in the terminal phase - insulin

C.- Yellow “Continuing Care” Deteriorating Weeks prognosis – box 5

Patients may present at this stage, in which case all of the suggested changes above should be considered but keeping in mind that there may be little time to get used to a new insulin regimen. Intensive support can be needed for dose adjustments as well-being, activity and appetite can change day to day. Managing diabetes can be an added stress at an emotional time for patients and carers. Relaxing targets for control may seem like ‘giving up” for some while others may view managing diabetes in addition to their terminal illness as “pointless”

D-Red “Days” Final days / Terminal Care Days prognosis-box 6

Ideally by this stage diabetes treatment has been minimised so that few changes are needed in the last days of life. If the stage is reached where the patient is bedbound, semi-comatose, no longer able to take tablets, no longer able to eat and only able to take sips of fluid, use of the Liverpool Care Pathway (LCP) or a local alternative such as Deciding Right should be considered.

At this stage, the Flowchart for Diabetes at End of Life describes how to manage diabetes in the dying patient and complements the LCP. It can be reassuring for relatives and carers to know that this additional pathway of care is being followed and that the diabetes is being managed differently rather than being “ignored”.

The flowchart has been devised to minimise symptoms of diabetes and keep invasive testing to the minimum needed to achieve that aim.
Medications in the terminal phase - insulin

End of Life Diabetes Management - Care Pathway
For use in conjunction with Liverpool Care Pathway or local equivalent

Discuss changing the approach to diabetes management with patient and/or family if not already explored. If the patient remains on insulin ensure the Diabetes Specialist nurses are involved and agree monitoring strategy.

- Type 2 diabetes
  - Diet controlled or Metformin treated
  - Stop monitoring blood sugars
- Type 2 diabetes on other tablets and/or Insulin / GLP1 Agonist
  - Stop tablets and GLP1 injections
  - Consider stopping insulin depending on dose
- Type 1 diabetes always on insulin
  - Continue once daily morning dose of insulin Glargine (Lantus*) with reduction in dose

If insulin stopped:
- Urinalysis for glucose daily - If over 2+ check capillary blood glucose
- If blood glucose over 20 mmol/l give 6 units rapid acting insulin *
- Recheck capillary blood glucose after 2 hours

If insulin to continue:
- Prescribe once daily morning dose of isophane insulin* or long acting insulin Glargine (Lantus*) based on 25% less than total previous daily insulin dose

Check blood glucose once a day at teatime:
- If below 8 mmol/l reduce insulin by 10-20%
- If above 20 mmol/l increase insulin by 10-20% to reduce risk of symptoms or ketosis

If patient requires rapid acting insulin* more than twice consider daily isophane insulin* or G largine (Lantus*)
In summary

"Well... the Glaxo pill protects my heart from the side effects of the Pfizer pill that prevents potential liver failure due to the Merck pill that minimizes the risk of stroke posed by the Novartis pill that reduces blood clots caused by the Glaxo pill.

"The devil of it is I can't remember the illness that started all this..."