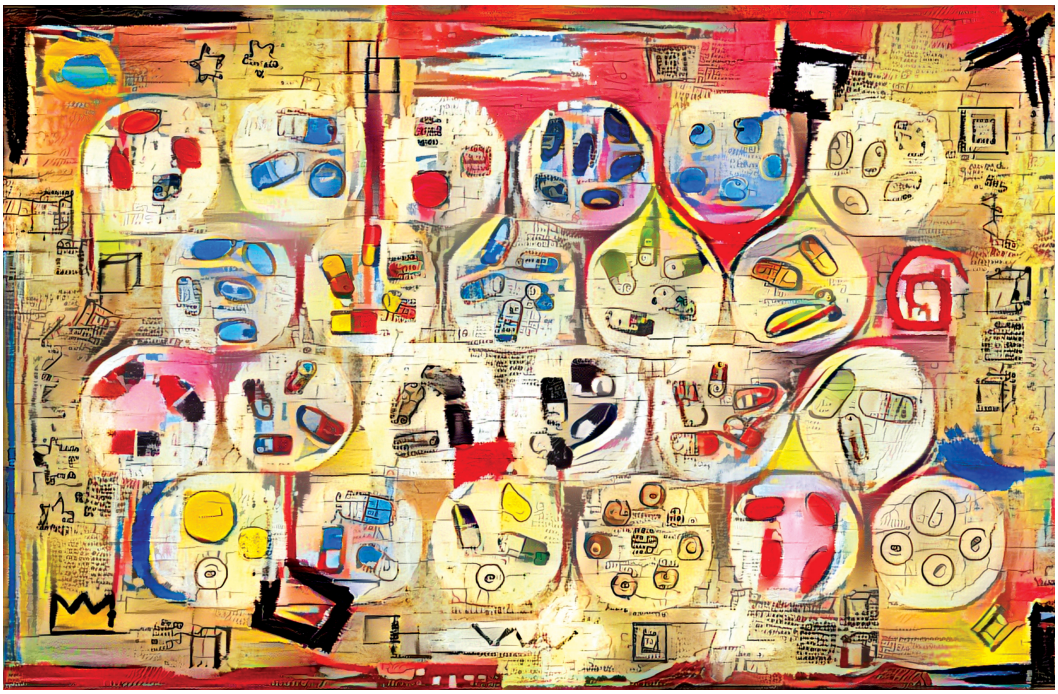
Thesis for doctoral degree (Ph.D.)
2019

Too much, too late? Drug prescribing for older people near the end of life



Lucas Morin

Karolinska Institutet

From the Aging Research Center (ARC)
Department of Neurobiology, Care Sciences and Society

Karolinska Institutet, Stockholm, Sweden

TOO MUCH, TOO LATE?
DRUG PRESCRIBING FOR OLDER PEOPLE NEAR THE END OF LIFE

Lucas Morin

Karolinska Institutet

Stockholm (2019)

All previously published papers were reproduced with permission from the publishers.
Cover illustration: Lucas Morin
Published by Karolinska Institutet.
Printed by E-Print AB, 2019

ISBN 978-91-7831-516-1

TOO MUCH, TOO LATE? DRUG PRESCRIBING FOR OLDER PEOPLE NEAR THE END OF LIFE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

Thesis defended on Friday 20 September 2019 at 9:30 am
at Gustaf Retzius auditorium, Karolinska Institutet, Berzelius väg 3, Solna

By

Lucas Morin

Principal Supervisor:

Professor Kristina Johnell
Karolinska Institutet
Department of Medical Epidemiology
and Biostatistics

Co-supervisor(s):

Professor Johan Fastbom
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Professor Marie-Laure Laroche
INSERM 1248, Faculté de Médecine,
Université de Limoges, France

Opponent:

Professor Cynthia Boyd
Johns Hopkins University
Department of Medicine
Division of Geriatric Medicine and Gerontology

Examination Board:

Associate Professor Björn Wettermark
Karolinska Institutet
Department of Medicine

Associate Professor Hugo Lövheim
Umeå Universitet
Department of Community Medicine and
Rehabilitation

Associate Professor Karin Modig
Karolinska Institutet
Institute of Environmental Medicine

To Irène

ABSTRACT

Background. The burden of drugs prescribed to older persons at the end of life has recently drawn increasing scrutiny. Growing evidence suggests that patients with life-limiting diseases and poor prognosis are prescribed drugs that may do more harm than good or treatments that have little chance of achieving their benefit during the patients' short remaining lifespan. The overall aim of this thesis was to evaluate the quality of drug prescribing in older adults near the end of life. Except for Study III, all studies are based on routinely collected administrative and healthcare data with national coverage in Sweden.

Study I. We found that, throughout their last year of life, older adults (n=511 843) used an increasing number of prescription drugs. The proportion of older adults exposed to ≥10 drugs increased from 30.3% one year before death to 47.2% during the last month of life. Polypharmacy was fuelled not only by the initiation of symptomatic drugs to ensure comfort but also by the frequent continuation of long-term preventive treatments and medicines prescribed for the management of chronic diseases that may otherwise lead to short-term complications.

Study II. Older adults who died with solid cancer (n=151 201) often continued to receive preventive drugs until the very end of life. Over the course of the last 12 months of life, there was little change in the receipt of antihypertensive agents (absolute change -0.3%, 95% CI -0.6 to 0.0), vitamin K antagonists (+1.5%, 95% CI 1.1 to 1.9), antiplatelet agents (-1.5%, 95% CI -1.8 to -1.2), statins (-4.7%, 95% CI -5.0 to -4.4), bisphosphonates (-0.3%, 95% CI -0.4 to -0.2), or vitamins (+1.0, 95% CI 0.8 to 1.2). During the last year before death, median drug costs amounted to $1482 (interquartile range [IQR], $700-$2896]) per person, including $213 (IQR, $77-$490) for preventive therapies. We found important differences between cancer types with regard to the use and costs of preventive drugs, which can be explained only in part by age and chronic multimorbidity.

Study III. Forty European experts in geriatrics, clinical pharmacology, and palliative medicine from 10 different countries participated in a Delphi consensus panel to identify drugs deemed "often adequate", "questionable", or "often inadequate" for use in older patients aged ≥75 years with an estimated life expectancy of 3 months or less. Drug classes rated as "often adequate" are predominantly indicated for symptom management and comfort care. Among the drugs and drug classes considered "questionable" for use near the end of life, a vast majority are prescribed for the long-term management of non-life-threatening chronic conditions or for the secondary prevention of chronic diseases that may otherwise quickly lead to serious clinical complications. Finally, drugs defined as "often inadequate" encompasses mostly drugs and supplements prescribed for primary prevention or as part of a long-term strategy of secondary or tertiary prevention.

Study IV. By applying the list mentioned above to a cohort of 58 415 older persons who died from conditions potentially amenable to palliative care in 2015, we found that 32% *continued* and 14% *initiated* at least one drug considered "often inadequate" during their last three months of life. Excluding older adults who died from acute and potentially unpredictable fatal events had little if any influence on the results.

Conclusion. Older people are prescribed an increasing number of drugs as they approach the end of life. A sizeable fraction of these drugs is not directed towards the relief of distressing symptoms but instead aims at prolonging survival and managing chronic comorbidities. We have developed a consensus-based set of explicit criteria for delineating drugs that are "often adequate" from those deemed "questionable" or "often inadequate" for use in older persons at the end of life. In the absence of high-quality data from randomised clinical trials and sufficiently robust observational studies, these criteria can be used not only to provide guidance at the bedside but also to generate comparable epidemiological evidence across patient groups, care settings, regions, and countries.

Keywords. Aging; Deprescribing; Drug Prescribing; End-of-Life Care; Geriatrics; Inappropriate Prescribing; Older People; Polypharmacy; Quality of Care; Palliative care

SAMMANFATTNING

Bakgrund. Läkemedelsbehandlingen hos äldre personer i livets slutskede har tilldragit sig ett ökande intresse under senare tid. Allt fler forskningsresultat tyder på att äldre patienter med dålig prognos förskrivs läkemedel som kan vara till mer skada än nytta, eller som med stor sannolikhet inte hinner vara till nytta under den korta tid patienten har kvar att leva. Det övergripande syftet med denna avhandling var därför att utvärdera kvaliteten på förskrivningen av läkemedel till äldre nära livets slut. Med undantag för Studie III är alla studierna baserade på rutinmässigt insamlade administrativa och hälsodata med nationell täckning i Sverige.

Studie I. Vi fann att äldre personer (n = 511 843) använde ett ökande antal receptbelagda läkemedel under sitt sista levnadsår. Andelen äldre exponerade för ≥10 läkemedel ökade från 30,3% ett år före döden till 47,2% under den sista månaden i livet. Polyfarmaci drivs inte bara av nyförskrivning av symtomlindrande läkemedel vid livets slut, utan också av en fortsatt läkemedelsbehandling—med långsiktigt förebyggande läkemedel och för kroniska sjukdomar som annars kortsiktigt kan leda till komplikationer.

Studie II. Äldre personer som dog av cancer (n = 151 201) fick ofta fortsatt behandling med förebyggande läkemedel ända fram till livets slut. Under de sista 12 månaderna av livet förekom endast små förändringar i medicineringen av antihypertensiva medel (absolut förändring -0,3%, 95% Cl -0,6 till 0,0), vitamin K-antagonister (+ 1,5%, 95% Cl 1,1 till 1,9), trombocytaggregationshämmare (-1,5%, 95% Cl -1,8 till -1,2), statiner (-4,7%, 95% Cl -5,0 till -4,4), bisfosfonater (-0,3%, 95% Cl -0,4 till -0,2) eller vitaminer (+1,0, 95% Cl 0,8 till 1,2). Under det sista levnadsåret uppgick mediankostnaden för läkemedel till $ 1482 (interkvartilt intervall [IQR], $ 700-$ 2896]) per person, inklusive $ 213 (IQR, $ 77- $ 490) för förebyggande läkemedelsbehandlingar. Vi fann viktiga skillnader mellan olika cancertyper med avseende på användning och kostnad för förebyggande läkemedel, som endast delvis kan förklaras av ålder och kronisk multisjuklighet.

Studie III. Fyrtio europeiska experter inom geriatrik, klinisk farmakologi och palliativ medicin från tio olika länder deltog i en Delphi-konsensuspanel för att identifiera läkemedel som bedömdes som ”ofta adekvata”, ”tveksamma” eller ”ofta inadekvata” för behandling av äldre patienter ≥75 år med en beräknad livslängd om högst tre månader. Läkemedelsklasser som bedömdes som ”ofta adekvata” är till övervägande del indicerade för symtombehandling och för att minska lidande nära livets slut. Bland de läkemedel och läkemedelsklasser som ansågs vara ”tveksamma” för användning i livets slutskede ingick huvudsakligen läkemedel för långtidsbehandling av icke livshotande kroniska tillstånd eller för sekundärprevention av kroniska sjukdomar som annars snabbt kan leda till allvarliga kliniska komplikationer. Slutligen omfattade kategorin ”ofta inadekvata” främst läkemedel och tillskott som förskrivs för primärprevention eller som del i en långsiktig strategi för sekundär- eller tertiärpreventiv behandling.

Studie IV. Den ovannämnda listan från Studie III tillämpades på en kohort av 58 415 äldre personer som under 2015 avled av tillstånd som ofta innebär palliativ vård. Vi fann att 32% fortsatte med, och 14% fick en ny förskrivning av, minst ett läkemedel som betraktades som "ofta inadekvat", under de sista 3 månaderna i livet. Exkludering av äldre som dog av akuta och potentiellt oförutsägbara dödliga tillstånd hade liten eller ingen inverkan på studieresultaten.

Slutsatser. Äldre personer förskrivs ett ökande antal läkemedel när de närmar sig slutet av livet. En stor del av dessa läkemedel är inte inriktade mot lindring av lidande och besvär i livets slutskede, utan syftar snarare till att förlänga överlevnaden och hantera kroniska sjukdomar. Vi har utvecklat en konsensusbaserad uppsättning av kriterier för att åtskilja läkemedel som är "ofta adekvata" från dem som kan anses vara "tveksamma" eller "ofta inadekvata" för behandling av äldre personer i livets slutskede. I avsaknad av högkvalitativa randomiserade kliniska prövningar och tillräckligt robusta observationsstudier, kan dessa kriterier användas, inte bara för att ge vägledning i det kliniska arbetet, utan också för att jämföra epidemiologiska data mellan patientgrupper, vårdinrättningar, regioner och länder.

Nyckelord. Äldre människor; Deprescribing; Geriatrik; Läkemedelsförskrivning; Olämplig förskrivning; Palliativ vård; Polyfarmaci; Vård i livets slutskede; Vårdkvalitet;

LIST OF SCIENTIFIC ARTICLES

The doctoral thesis is based on the following original articles.

I. **Morin L**, Vetrano DL, Rizzuto D, Calderón-Larrañaga A, Fastbom J, Johnell K. Choosing Wisely? Measuring the Burden of Medications in Older Adults near the End of Life: Nationwide, Longitudinal Cohort Study. *The American Journal of Medicine*; 2017;130(8):927–936.e9.

II. **Morin L**, Todd A, Barclay S, Wastesson JW, Fastbom J, Johnell K. Preventive drugs in the last year of life of older adults with cancer: Is there room for deprescribing? *Cancer*. 2019;125(13):2309-2317.

III. **Morin L**, Laroche ML, Vetrano DL, Fastbom J, Johnell K. Criteria for adequate and inadequate drug prescribing in older adults at the end of life: European expert consensus. *European Journal of Clinical Pharmacology*. 2018; 74(10):1333-42

IV. **Morin L**, Wastesson JW, Laroche M-L, Fastbom J, Johnell K. How many older adults receive drugs of questionable clinical benefit near the end of life? A cohort study. *Palliative Medicine*. 2019;33(8):1080-1090.

OTHER SCIENTIFIC ARTICLES

The following articles were published during the doctoral education and are related to the topics of medication use in old age and/or end-of-life care but are not included in this doctoral thesis.

1. **Morin L**, Calderon-Larrañaga A, Welmer AK, Rizzuto D, Wastesson J, Johnell K. Polypharmacy and injurious falls in older adults: a nationwide nested case-control study. *Clinical Epidemiology*. 2019;11:483-493
2. Janah A., Gauthier L, **Morin L**, Bousquet JP, Le Bihan C, Tuppin P, Peretti-Watel P, Bendiane MK. Access to palliative care for cancer patients between diagnosis and death: a national cohort study. *Clinical Epidemiology*. 2019;11:443—455
3. Roux B, **Morin L**, Papon A, Laroche M-L. Prescription and deprescription of medications for older adults receiving palliative care during the last 3 months of life: a single-center retrospective cohort study. *Eur Geriatr Med*. 2019;10(3):463-471.
4. Wastesson J, **Morin L**, Tan E, Johnell K. An update on clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opinion on Drug Safety*. 2018 Dec;17(12):1185-1196
5. Wastesson J, **Morin L**, Laroche ML, Johnell K. How chronic is polypharmacy in old age? A longitudinal nationwide cohort study. *J Am Geriatr Soc.* 2019; 67(3):455-462
6. Laroche M-L, Sirois C, Reeve E, Gnjidic D, **Morin L**. Pharmacoepidemiology in older people: Purposes and future directions. *Therapies*. 2019;74(2):325-332.
7. Goldwasser F, Vinant P, Aubry R, Rochigneux P, Beaussant Y, Huillard O, **Morin L**. Timing of Palliative Care Needs Reporting and Aggressiveness of Care Near the End of Life in Metastatic Lung Cancer: A National Registry-Based Study. *Cancer* 2018;124:3044–51
8. Beaussant Y, Daguindau E, Chauchet A, Rochigneux P, Tournigand, Aubry R, **Morin L**. Hospital end-of-life care in haematological malignancies. *BMJ Supportive & Palliative Care*. 2018;8(3):314–24.
9. **Morin L**, Johnell K, Laroche ML, Fastbom J, Wastesson J. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clinical Epidemiol*. 2018; 10:289-298
10. Harding R, Marchetti S, Onwuteaka-Philipsen BD, et al. Place of death for people with HIV: a population-level comparison of eleven countries across three continents using death certificate data. *BMC Infect Dis*. 2018;18(1):55.
11. Tan E, Sluggett J, Johnell K, Onder G, Elseviers M, **Morin L**, Vetrano DL, Wastesson JW, Fastbom J, Bell SJ. Research priorities for optimizing geriatric pharmacotherapy: an international consensus. *J Am Med Dir Assoc*. 2018; 19(3):193–9.

12. Kelfve S, Wastesson J, Fors S, Johnell K, **Morin L**. Is the level of education associated with transitions between care settings in older adults near the end of life? A nationwide, retrospective cohort study. *Palliat Med*. 2018; 32(2):366–375.

13. Grande G, **Morin L**, Vetrano DL, Fastbom J, Johnell K. Drug Use in Older Adults with Amyotrophic Lateral Sclerosis Near the End of Life. *Drugs Aging*; 2017;34(7):529–533.

14. Kempf E, Tournigand C, Rochigneux P, Aubry R, **Morin L**. Discrepancies in the use of chemotherapy and artificial nutrition near the end of life for hospitalized patients with metastatic gastric or oesophageal cancer. *Eur J Cancer*; 2017;79(1):31–40.

15. Cohen J, Beernaert K, Van den Block L, **Morin L**, et al. Differences in place of death between lung cancer and COPD patients: A 14-country study using death certificate data. *NPJ Primary Care Respiratory Medicine*. 2017; 27(1):1-14

16. **Morin L**, Vetrano DL, Grande G, et al. Use of Medications of Questionable Benefit During the Last Year of Life of Older Adults With Dementia. *J Am Med Dir Assoc*; 2017;18(6):551.e1-551.e7.

17. Rochigneux P, Raoul JL, Beaussant Y, Aubry R, Goldwasser F, Tournigand C, **Morin L**. Use of chemotherapy near the end of life: what factors matter? *Ann Oncol*; 2017;28(4):809–817.

18. **Morin L**, Aubry R, Frova L, et al. Estimating the need for palliative care at the population level: A cross-national study in 12 countries. *Palliat Med*; 2017;31(6):526–536.

19. **Morin L**, Laroche ML, Texier G, Johnell K. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. *J Am Med Dir Assoc*. 2016;17(9):862.e1-862.e9;

20. **Morin L,** Aubry R. Palliative care in hospital-at-home services in France: a nationwide study using administrative data. *Médecine Palliat*. 2017;16:7–20 [article in French]

21. **Morin L**, Laroche ML. Medication use in adults aged 60 years and older in France: a population-level study using national health insurance data. *Rev Gériatrie*; 41(6): 335-49 [article in French]

22. **Morin L**, Beaussant Y, Aubry R, Fastbom J, Johnell K. Aggressiveness of End-of-Life Care for Hospitalized Individuals with Cancer with and without Dementia: A Nationwide Matched-Cohort Study in France. *J Am Geriatr Soc*. 2016

23. Gallais-Sérezal I, Beaussant Y, Rochigneux P, Tournigand C, Aubry R, Lindelöf B, **Morin L**. End-of-life care for hospitalised patients with metastatic melanoma in France: a nationwide, register-based study, *Br J Dermatol*. 2016;175(3):583-592.

24. **Morin L**, Johnell K, Van den Block L, Aubry R, Discussing end-of-life issues in nursing homes: a nationwide study in France. *Age Ageing*. 2016;45(3):395-402

25. Pivodic L, Pardon K, **Morin L**, et al. Place of death in the population dying from diseases indicative of palliative care need: a cross-national population-level study in 14 countries. *J Epidemiol Community Health*. 2016; 70(1):17-24.

26. Håkanson C, Ohlen J, **Morin L**, Cohen J. A population-level study of place of death and associated factors in Sweden. *Scand J Public Health*. 2015; 43(7):744-51

27. Moens K, Houttekier D, Van den Block L, Harding R, **Morin L**, Marchetti S et al. Where do people living with Parkinson's disease die? A population-level study in 11 countries. *BMC Palliat Care*. 2015;14(1):28.

28. **Morin L**, Fastbom J, Laroche M-L, Johnell K. Potentially inappropriate drug use in older people: a nationwide comparison of different explicit criteria for population-based estimates. *Br J Clin Pharmacol*. 2015;80(2):315-324.

29. **Morin L**, Johnell K, Aubry R. Variation in the place of death among nursing home residents in France. *Age Ageing*. 2015;44(3):415-421.

30. Reyniers T, Deliens L, Pasman HR, **Morin L**, et al. International Variation in Place of Death of Older People Who Died From Dementia in 14 European and non-European Countries. *J Am Med Dir Assoc*. 2015;16(2):165–71.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AMD	Adjusted Median Difference
ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DDD	Defined Daily Dose
EAPC	European Association for Palliative Care
GEE	Generalised Estimating Equation model
GLM	Generalised Linear Model
HR	Hazard Ratio
ICD	International Classification of Diseases
LISA	Longitudinal integrated database for health insurance and labour market studies
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OR	Odds Ratio
OTC	Over-the-Counter drugs
PDD	Prescribed Daily Dose
RCT	Randomised Controlled Trial
RR	Risk Ratio
SEK	Swedish Crowns
WHO	World Health Organization

TABLE OF CONTENT

“Elle est morte de quatre médecins et de deux apothicaires”

Molière, *L'Amour médecin* (1665)

1. INTRODUCTION

1.1 DYING IN OLD AGE

Population ageing and increased age at time of death

High-income countries have witnessed substantial gains in life expectancy in old age.[1] While women aged 65 years were expected to live for another 9 years in 1800, their life expectancy was 13 years in 1900 and they can now expect to live for 21 years (**Figure 1**). Recent projections suggest that this trend will continue[2] and that most of the future gains in life expectancy will be due to enhanced longevity in old age.[3,4] After the dramatic compression of mortality among children and young adults during the first half of the 20th century, the last seventy years have been marked by a steep reduction of death rates among older adults (**Figure 2**). As a result, the share of older people in the total population has grown substantially. In Sweden, persons aged ≥75 years accounted for 3% of the population in 1950 (n≈ 242 000), 9% in 2015 (n≈ 850 000), and should represent 14% of the population in 2050 (n≈ 1.6 million).[5] Population ageing is also a challenge for middle- and low-income countries, where the older population is expected to increase by 60% between 2015 and 2030.[6,7]

One of the visible features of population ageing is the concentration of deaths in the upper tail of the age distribution, that is among the oldest old. As illustrated in **Figure 3**, the median age at death increased from 49 to 81 years in the course of a century. In 1900, only 5% of the Swedish population died at age 83 or older. This proportion reached 50% in 2015 and should rise to 75% in 2050. These findings have led scientists to speculate about the biological limits of longevity, fuelling a heated debate between scholars claiming that human lifespan may have reached its natural ceiling[8,9] and those arguing that there is no solid evidence to support this hypothesis[10–13] and that delaying the ageing process is a plausible therapeutic target.[14]

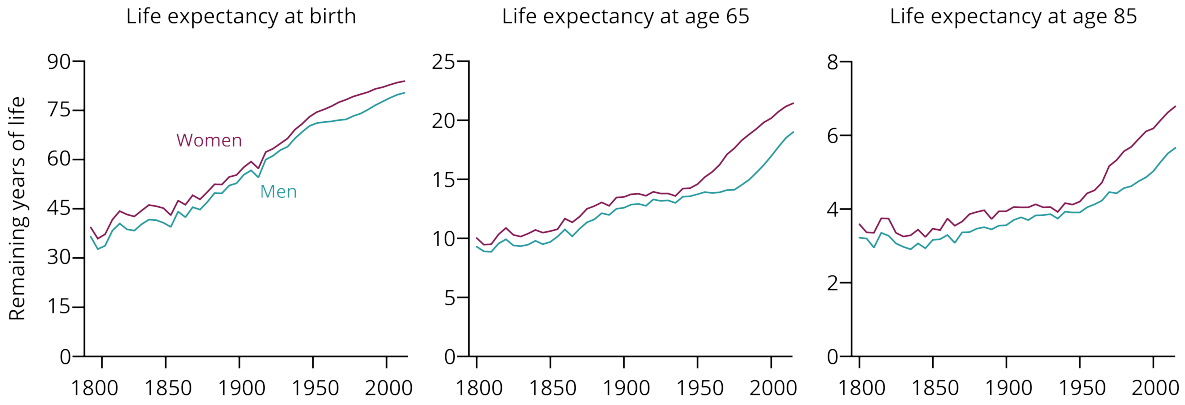


Figure 1. Changes in life expectancy at birth, at age 65 and 85 years in Sweden between 1800 and 2018, and projections for 2019–2050

Source: Human Mortality Database, University of California Berkeley and Max Planck Institute for Demographic Research (available at: https://www.mortality.org/). Projections from 2019 to 2050 are indicated with dotted lines and a derived from official population forecast data provided by Statistics Sweden. Data accessed in July 2019.

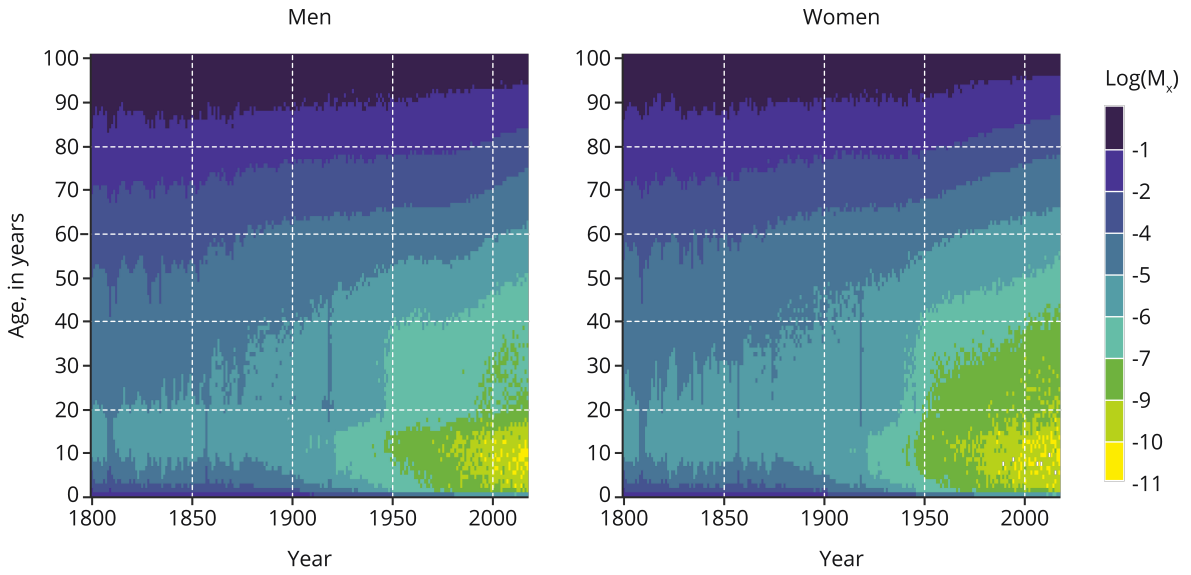


Figure 2. Surface plots of observed mortality rates (logarithmic scale) for females and males in Sweden, for ages 0 to 100 years between 1800 and 2017.

Source: Human Mortality Database, University of California Berkeley and Max Planck Institute for Demographic Research. Data accessed and analysed in June 2019. Log(Mx): natural logarithm of the year-specific mortality rate.

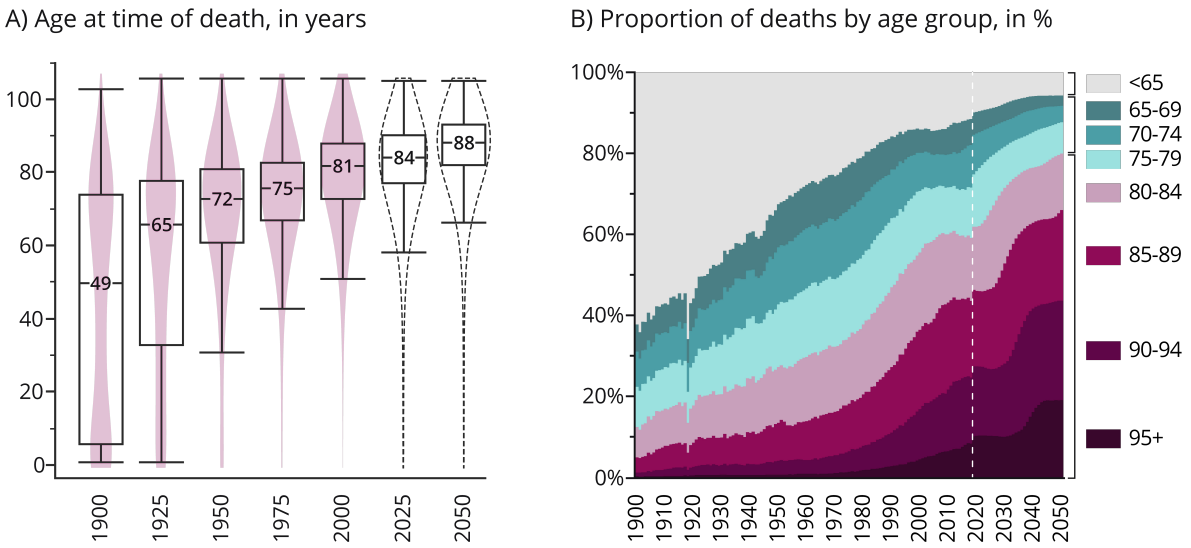


Figure 3. Changes in the age at time of death and in the relative distribution of deaths by age in Sweden between 1900 and 2018, and projections for 2019–2050

Source: Human Mortality Database, University of California Berkeley and Max Planck Institute for Demographic Research; and official population projections, Statistics Sweden. Panel A represents a series of Tukey outlier box plots, where the lower whisker is equal to the 1st quartile – 1.5x interquartile range, and the upper whisker is equal to the 3rd quartile + 1.5 x interquartile range. Values provided in the centre of the box correspond to median age at time of death. Shaded areas correspond to violin plots depicting the distribution of deaths by single age groups. Data about age at time of death are truncated at 105 years to ensure the anonymity of decedents (count <10 persons). Information about the years 2025 and 2050 are provided by Statistics Sweden as part of a larger series of population-level projections.[15] Panel B represents the distribution of deaths according to the attained age at time of death. The denominator is the total number of registered deaths annually. The vertical dashed line indicates the break between observed deaths (1900–2018) and the projected number of deaths (2019–2050). These projections are based on various assumptions about mortality rates, which are detailed elsewhere.[15]

Be this as it may, even if current trends continue the marginal health gains carried by each additional year of life expectancy will—at least in the foreseeable future—most likely diminish.[16] The increasing age at death has not only led to a larger number of people living to very old age but also to a larger number of people living and dying with a high burden of morbidity and disability.[17–19] By comparing two waves of the Cognitive Function and Ageing Study in the United Kingdom, Kingston et al. showed that although older adults aged 65 years in 2011 could expect to live on average about 2 additional years with low dependency (i.e. care less than daily), they were also living 1 more year with high-dependency (24h-care needs) than the generation 20 years before.[20] This new paradigm of mortality is often acknowledged by demographers and epidemiologists.[16,21,22] However, its consequences in terms of care needs are seldom discussed beyond general considerations about the economic sustainability of healthcare systems and the necessity to better address the multifaceted health needs of older adults.[23]

Change in the leading causes of death in older adults

The observed changes in the leading causes of death are a key marker of the epidemiological transition that has occurred during the last century, which is characterised by a shift from infectious and acute diseases to non-communicable and chronic conditions. In 1900, the top three leading causes of death among older Americans (≥65 years) were influenza and pneumonia, tuberculosis, and diarrhoea. One hundred years later, heart diseases, cancer, and stroke had become the leading causes of death, accounting for more than 60% of all deaths in 2000.[24] The World Health Organization (WHO) estimates that cardiovascular diseases account for a little over 50% of deaths among people aged 75 years and older in Europe.[25] Despite some disparities in the proportion of deaths attributable to different causes of death, overall trends appear to be similar in Sweden and in other European countries (**Table 1**). Cancer and dementia are now the second and third most common causes of death, respectively. These changes have important consequences for policymakers and healthcare providers, as mortality patterns have a direct influence on care needs near the end of life.[26]

	Sweden, %		Europe, %		United States, %	
	2000	2016	2000	2016	2000	2016
Cardiovascular diseases	51.8	39.2	59.2	51.0	46.1	34.5
Ischemic heart disease	31.1	20.1	33.9	29.9	30.3	20.3
Stroke	13.2	8.1	18.2	12.9	9.2	6.8
Cancer	17.2	19.7	15.2	16.9	18.0	17.5
Neurological conditions	7.1	15.6	4.7	9.8	7.5	18.2
Alzheimer disease and other dementias	6.3	13.8	3.7	8.2	5.9	15.7
Chronic respiratory diseases	5.2	6.0	6.0	5.8	8.8	10.0
Pneumonia and other respiratory infections	5.3	3.5	3.8	3.0	4.2	2.7

Table 1. Five leading causes of death among people aged ≥75 years (2000–2016)

Source: WHO, Global Health Estimates 2016. Available at http://terrance.who.int/mediacentre/data/ghe (data updated on May 22, 2018). 'Europe' includes all countries in the WHO European region.

Trajectories of functional decline and need for palliative care at the end of life

Depending on their underlying health problems and causes of death, people who near the end of life experience different patterns of decline in physical function. This idea was first introduced in the late 60s' by American sociologists Barney Glaser and Anselm Strauss who suggested the existence of three typical dying trajectories, each characterised by a specific duration and shape: abrupt and unexpected deaths, expected lingering, and *entry-reentry* deaths.[27] These trajectories, almost exclusively based on qualitative research and observations, were progressively enriched to incorporate the emotional, psychological, and social aspects of dying[28] and had much influence on policymakers and stakeholders who sought to improve access to end-of-life care at the turn of the century.[29] However, robust empirical evidence remained scarce to confirm their validity in daily clinical practice.[30,31] This prompted epidemiologists to make use of population-based cohorts and routinely collected data to classify deceased older persons in order to examine differences in healthcare utilisation and costs at the end of life.[32,33] In the Established Populations for Epidemiologic Studies of the Elderly (EPESE) study, a community-based, prospective cohort in the United States, Lunney et al. analysed longitudinal changes in self- and proxy-reported ADL dependency among 4190 decedents who had been interviewed during the year before death.[34] They confirmed that a 4-group categorisation was able to differentiate people who died suddenly, with no or little warning sign and limited contact with healthcare services before death; from those who died (1) after a short period of evident decline marked by the terminal phase of a severe illness (typically cancer); or (2) after a trajectory of intermittent decline, with long-term limitations and frequent acute episodes that characterise, for instance, severe congestive heart failure and COPD; or (3) as the result of a slow and gradual decline in physical and/or cognitive functioning, such as frail older adults with dementia or neurodegenerative diseases (**Figure 4**).

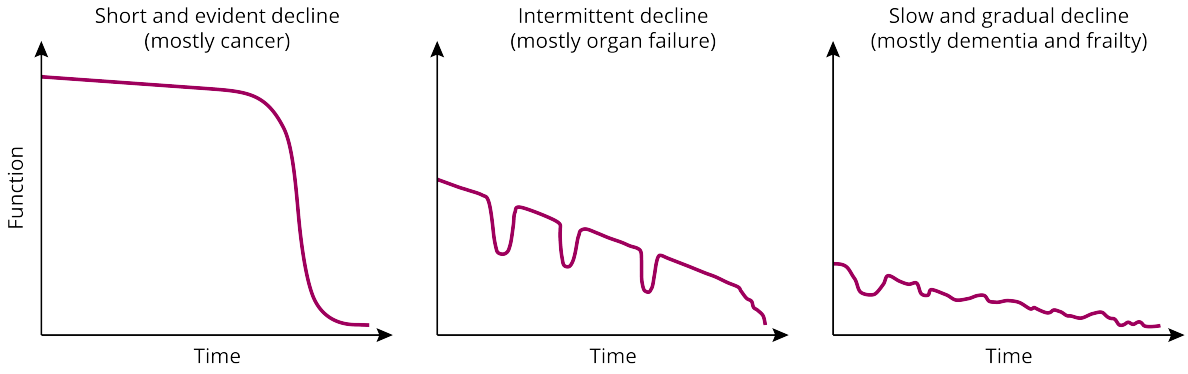


Figure 4. Illness trajectories of older adults with serious illness at the end of life

Adapted from Lynn et al.[35], and reprinted with permission from RAND corporation (Santa Monica, CA). The trajectory of functional decline of older people with cancer often spans 3-5 years, with a clear deterioration during the last 3-6 months of life. Among patients with organ failure, serious acute decompensations and clinical complications can result in repeated non-elective hospitalisations during the last 2-3 years of life. The trajectory of decline of frail older people with dementia and neurodegenerative diseases is typically longer, and punctuated with the gradual worsening of mobility impairments, IADL disability, cognition, communication, and dysphagia.

These three typical illness trajectories were subsequently popularised by Murray et al.,[36] who compared the course of physical decline with trajectories of social, psychological and existential distress.[37,38] **Table 2** shows the distribution of illness trajectories among older decedents in Sweden. More recent investigations have called into question the relevance of these four illness trajectories, driven by the observation that, at the patient level, the condition leading to death is seldom sufficient to predict the pattern of physical decline and disability near the end of life.[39,40] However, other parameters remain strongly correlated with the underlying cause of death (e.g. prognosis, likelihood of clinical complications, burden of symptoms, patterns of co-morbidities, and healthcare utilisation). Illness trajectories thus remain a useful tool to differentiate groups of decedents that share a set of common features and care needs as death approaches.[41] Hence, older people who die as the result of either cancer, progressive organ failure, or dementia and neurodegenerative disease require access to different health services to address different needs at different time points over the course of their disease.[42] Understanding this high variability in dying trajectories is crucial to avoid a one-size-fits-all approach to caring for vulnerable older adults with life-limiting illnesses.

	65-74 years	75-84 years	≥85 years	Total
Sudden death	*8.1%*	*7.0%*	*7.8%*	*7.6%*
Short and evident decline (e.g. cancer)	47.3%	34.4%	18.6%	28.6%
Intermittent decline (e.g. organ failure)	35.4%	38.9%	39.6%	38.7%
Slow and gradual decline (e.g. dementia)	9.3%	19.7%	34.0%	25.1%

Table 2. Illness trajectories among older adults who died in Sweden (2007-2015)

Source: National Cause of Death Register, Swedish Board of Health and Welfare. Illness trajectories were constructed using all the diagnoses mentioned on the death certificates. Detailed methods about the operationalisation of these trajectories are described elsewhere.[43] We applied a previously described hierarchy to obtain a single trajectory for each decedent (i.e. cancer > dementia > organ failure > sudden death).[39,44]

What these people have in common, however, is the need for adequate *palliative care*, including the management of distressing symptoms (both physical and psychological) and the appropriate support of family caregivers. The WHO defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with a life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[45] While the core components of palliative care can be provided by healthcare professionals from any discipline in any care setting ('generalist palliative care'), patients with complex needs are usually referred to specialised multidisciplinary teams with extensive training in this field ('specialist palliative care').[46–48] Palliative care was initially developed to address the needs of patients with terminal cancer at the end of life and was, for the most part, delivered in hospitals and hospice facilities.[49] However, the past two decades have seen a substantial shift towards the broadening of the target population, the development of community-based services, and the earlier integration of a palliative approach in standard care.[50,51] Palliative care is thus no longer focused solely on people with advanced cancer; it is also

beneficial for patients with serious and life-limiting chronic conditions such as congestive heart failure, chronic obstructive pulmonary disease, kidney disease, diabetes, and dementia.[52–54] Palliative, contrary to popular belief, is not limited to patients whose death is imminent and is not synonymous with *hospice care*, which is primarily directed towards patients with a terminal illness and a short prognosis.[55,56] On the contrary, recent initiatives have underscored the notion that palliative care should be available from the time of diagnosis until death, bolstered by the mounting body of evidence showing the benefits of integrating a palliative approach earlier in the course of the disease, alongside disease-oriented treatments.[57–59]

Oncologists have been particularly receptive to this new model of palliative care, especially since Temel et al. demonstrated in a landmark randomised controlled trial that, among patients with metastatic non-small-cell lung cancer, early palliative care could improve both well-being and survival.[60] A myriad of trials have since consistently reported positive effects on quality of life, comfort, satisfaction with care, physician-patient communication, decreased aggressiveness of care at the end of life, and healthcare expenditures.[61–64] These studies served as a springboard to promote broader and earlier access to palliative care integrated with standard oncologic care.[65–69] In the United States, the 2019 clinical practice guidelines developed by the National Coalition for Hospice and Palliative Care insists on the fact that palliative care is "appropriate at any stage in a serious illness, and it is beneficial when provided along with treatments of curative or life-prolonging intent."[70] The integration of palliative care in other medical specialities remains largely suboptimal, despite recent efforts to implement and evaluate tailored interventions targeting patients with heart failure, COPD, end-stage renal disease, multiple sclerosis, or dementia.[71–76] The situation is especially disquieting in nursing homes, where access to palliative care lacks for 30% of the residents without cancer, and seldom occurs before the last two weeks of life when it is available.[77]

In a cross-sectional study using death certificate data from 12 high-income countries, we found that about 64% of all deaths were directly attributable to advanced diseases that indicate a need for palliative care;[43] a proportion similar to previously reported estimates.[78–81] The number of older people dying from conditions amenable to palliative care is expected to grow markedly in the future.[26] Sleeman et al. anticipate that the need for palliative care will increase by 87% worldwide between 2016 and 2060 (from 26 to 48 million people annually), with a remarkably steep increase among older adults and people with dementia and respiratory diseases.[82] This epidemiological reality is both the consequence and the cause of the escalating medicalisation of the final stage of life. "Medicine found ways to cut the mortality of heart attacks, respiratory illnesses, stroke, and numerous other conditions that threaten adult life", Atul Gawande writes.[83] "Eventually, of course, we all die of something. But even then, medicine has pushed the fatal moment of many diseases further outward. [...] Instead of just delaying the moment of the downward drop, treatments can stretch the descent out until it ends up looking less like a cliff and more like a hilly road down the mountain."

1.2 THE MEDICALISATION OF DEATH AND DYING: A BRIEF HISTORY

Over the past 70 years, medical progress has brought about dramatic changes in the circumstances surrounding the end of life and the moment of death. The following sections provide a brief overview of the main events and scientific advances that have contributed to the intense medicalisation of the dying process. Understanding these contextual factors is important to make sense of current interrogations about the appropriateness of drug treatments for older people near the end of life, which are at the core of the present thesis.

Bringing the dead back to life

After decades of experimental research on rats, monkeys, chickens, and dogs, the successful use of an electric defibrillator on a quivering open human heart by Claude Beck in 1947 paved the way to modern resuscitation.[84] This technique was soon surpassed by the advent of external defibrillators, after a team of Harvard cardiologists led by Paul Zoll showed that ventricular fibrillation could effectively (and safely) be reverted with electrodes placed on the surface of the patients' closed chest.[85] Concurrently, a group of electrical engineers and thoracic surgeons at Johns Hopkins University developed the prototype of a portable defibrillator mounted on a wheeled cart, which they unveiled in 1957.[86] Three years later, building upon recent discoveries by anaesthesiologists James Elam and Peter Safar at Baltimore City Hospitals on mouth-to-mouth ventilation[87–89] and intrigued by earlier experiments suggesting that adequate blood circulation could be maintained by applying regular compression on the sternum, William Kouwenhoven, James Jude, and Guy Knickerbocker developed one of the most iconic procedures of modern medicine: cardiopulmonary resuscitation (CPR).[90,91] The importance of CPR was quickly realised, and medical societies around the World began organising training programmes for clinicians and laypersons. Moreover, this breakthrough came at the same time as major advances in respiratory care.

From artificial ventilation to intensive care

In the wake of the first large-scale poliomyelitis epidemics in the United States (in 1916 alone, nearly 30 000 people were diagnosed and 6000 died[92]), physicians were desperately trying to find a way to treat the many children and young adults who had been left paralyzed and often incapable of breathing on their own.[93,94] Harvard researcher Philip Drinker devised a vacuum pump-powered machine that could provide artificial respiratory support over an extended time.[95,96] This so-called 'iron lung', together with the improved version designed by John Emerson and the cuirass shell patented by Rudolf Eisenmenger, were widely used in the United States until the mid-1950s' and saved or prolonged the life of tens of thousands of young patients.[97–99] In England, the 1938 epidemic prompted the mass-production of a simpler and cheaper version of Drinker's iron lung, which was manufactured and subsidised by Lord Nuffield—a bicycle and car

tycoon turned philanthropist who also donated £2 million to help establish the Oxford Medical School and the Nuffield Department of Anaesthetics, the first of its kind in Europe. A total of 1750 ventilators were donated to hospitals across Britain and the Commonwealth. However, iron lungs had notable drawbacks, including the fact that patients had to synchronise swallowing with the machine and had to be able to maintain their airway open. They also remained too large, cumbersome, and expensive to accommodate the needs of a growing number of polio patients. In the United States, the epidemic took tidal-wave proportions in the early 1950s, with 65 000 new paralytic cases between 1951 and 1954.[100] Other countries were also affected, not least in Scandinavia.

A large international polio conference was held at the University of Copenhagen in September 1951. The next summer the metropolitan area of Copenhagen was hit by a sudden and catastrophic outbreak, most likely initiated by silent carriers among the experts who had attended the conference. About 2800 patients (including 860 with paralysis) were admitted to the Blegdam Hospital in less than five months. "During the week August 28 to September 3, our hospital admitted 335 patients with polio, or nearly 50 cases daily. About one-tenth of these patients were suffocating or drowning in their own secretions", Henry Lassen, the hospital's chief physician, reported. "I do not want to dramatize the state of affairs existing in the middle of August 1952, but it certainly was desperate. Nearly all our patients with bulbar poliomyelitis had died!"[101] Indeed, an unusually large fraction of these patients presented with both bulbar and spinal paralysis, a group in which intermittent negative pressure ventilation was mostly ineffective and mortality reached 95%. Only one iron lung and six cuirass shell respirators were available. "The great number of severely ill patients pouring in made therapeutic improvisations necessary. During these months, we have in fact been in a state of war, and we were not nearly adequately equipped to meet an emergency of such vast proportions."[102]

Bjørn Ibsen, a Danish anaesthesiologist who had returned to Copenhagen after spending a year at the Massachusetts General Hospital in Boston, was called in for a consultation in late August. This proved to be a watershed moment. Recognising the signs of severe respiratory acidosis, Ibsen quickly realised that polio patients were dying not from a devastating viral infection in the brain but from respiratory failure.[103] He suggested that patients receive manual intermittent positive pressure ventilation, administered through a cuffed tracheostomy tube connected to a rubber bag filled with oxygen. In just a few days, mortality among paralytic polio patients plummeted, from about 87% down to 40%. However, the manual ventilation of up to 70 patients simultaneously required a considerable workforce (during the peak of the epidemic, 250 medical and dental students were enlisted to work in 6-hour shifts alongside 40 experienced physicians). It also became evident that a better understanding of acid-base physiology in critically ill patients was crucial, and that new laboratory techniques of blood gas analysis—such as the ones ushered by chemist Poul Astrup—were needed.[104] Convinced that trained staff and specialised medical equipment should be concentrated in a single multidisciplinary unit, Ibsen established the World's first intensive care unit (ICU) in December 1953 at the

Municipal Hospital of Copenhagen.[105–107] In Sweden, a similar unit was created a few months later in Borås[108] and Carl-Gunnar Engström, a physician and epidemiologist trained as Karolinska Institutet, introduced one of the first modern mechanical ventilators for long-term use.[109] In the United States, Walter Dandy opened a three-bed post-operative nursing unit for neurosurgical patients at Johns Hopkins in 1923, and a dedicated burn unit was created at Massachusetts General Hospital in the aftermath of the disastrous *Cocoanut Grove* nightclub fire in 1942.[110,111] However, the first hospital ward with round-the-clock staff entirely devoted to critically ill patients was inaugurated at Dartmouth Medical College in 1955, at the instigation of William Mosenthal.[112,113] Before long, leading institutions in the countries were following suit; both the 'Shock Ward' of the University of Southern California and the 'Intensive Care Unit' at Johns Hopkins opened in 1958.[114,115] With the development of resuscitation, medical imaging, and respiratory monitoring, and hemodynamic support, "the modern ICU was ready for prime time."[116]

When the brain dies but the heart keeps beating

Few anticipated that the brazen successes of medicine would, in just a few years, entirely redefine death and dying. The rapid development of intensive care in Northern America and Europe resulted in a growing number of patients who could be kept alive with artificial ventilation despite irremediable neurological impairments. In 1959, Pierre Mollaret and Maurice Goulon provided a detailed account of a series of 23 unconscious patients who had previously been admitted in a critical care unit in Paris, France. All of these patients presented a complete and persistent abolition of consciousness, no reaction to elicitable reflexes, no spontaneous respiration, and flat electro-encephalography (EEG) denoting the absence of electrical activity in the brain.[117] The authors coined this state 'coma dépassé', i.e. *beyond coma*. They reflected that "such a coma is both a *revelation* and a *ransom* of the progress made in cardiorespiratory resuscitation. A *revelation*, because the survival of these patients was only made possible by the technical advances [in artificial ventilation and critical care]. A *ransom*, because survival in the context of irreversible coma requires increasingly demanding efforts from the ICU staff and prolongs a spectacle that is more and more painful for the families."[118]

Earlier that year, a group of neurosurgeons from Lyon, France, had proposed a set of diagnostic criteria for what they described as the 'death of the nervous system' in the presence of cardiac activity, and recommended that, in the future, artificial ventilation should be discontinued if the absence of EEG activity was confirmed.[119] This approach was similar to that of American neurologist Robert Schwab, who suggested in 1963 that EEG investigation should be one of the core components of the legal determination of death.[120] At the Massachusetts General Hospital in Boston, he had already taken responsibility for pronouncing the death of 15 unconscious patients based on EEG findings.[121] This was not an isolated practice. The proliferation of patients in irreversible coma raised thorny ethical questions regarding the termination of life-sustaining treatments, igniting a heated debate in the medical community and beyond. Even

religious authorities were involved. Asked by an anaesthesiologist from Innsbruck, Austria, whether it was morally acceptable to withdraw mechanical ventilation before cardiac arrest, Pope Pius XII answered in the affirmative. His position was that "when the soul may already have left the body [...], one is held to use only ordinary means, that is to say means that do not involve any grave burden for oneself or another."[122,123] In France, Pierre Wertheimer published several accounts of unconscious patients who died as the result of life-support termination.[124,125] In Sweden, a neurosurgeon named Kjell Frykholm proposed that—unless they were suitable donors for organ transplants—patients with no brain activity should be declared dead and disconnected from the ventilator.[126]

Drawing the line between life and death

The ability to artificially maintain cardiorespiratory functions (thereby preserving organ perfusion and oxygenation) among patients with no measurable brain activity created a unique opportunity for the nascent field of organ transplantation. "By artificial means, different organ systems can be kept in a fairly good functioning state for a considerable time. It is such dead individuals with partly living organs who form one of the largest groups which are the best to select as organ donors", Clarence Crafoord, a surgeon at Karolinska University Hospital, argued.[127] Between 1960 and 1962, after a handful of successful kidney transplants between homozygotic and dizygotic twins, Boston surgeons Joseph Murray and John Merrill transplanted thirteen patients, including five with organs from 'cadaveric donors' who had been declared dead after cardiac arrest following the elective withdrawal of artificial ventilation.[128] They later reported that, by March 1965, at least 241 kidney transplants from deceased donors had been performed internationally.[129] In 1963, Thomas Starzl and James Hardy demonstrated the feasibility of, respectively, transplanting livers and lungs from deceased donors.[130,131] French surgeon Jean Hamburger carried out the first renal transplant from a patient in *coma dépassé*. Yet, in all these cases organs were harvested after the donors' death had been established by cardiopulmonary standards, that is after the ventilator was turned off.[132]

However, it became apparent that some transplant surgeons were removing kidneys from coma patients who were still on life support. In Belgium, Guy Alexandre, a surgeon at the Catholic University of Louvain who had previously completed a research fellowship under Joseph Murray's supervision, developed a set of criteria to ascertain death among potential donors with severe cerebral injuries whose heart had not stopped. These criteria overlapped substantially with those proposed by French physicians Mollaret and Goulon in 1959.[118] Between June 1963 and March 1966, Alexandre performed nine kidney transplants from "heart-beating, brain-dead donors."[133,134] The case of a kidney donor with brain injury who died only after the respirator was disconnected following the nephrectomy was also reported in Newcastle, England, in 1963.[135] In Sweden, the chief of the urology clinic at Karolinska Hospital, Gustav Giertz, recounted the 1964 case of a 40-year-old dying women whose kidney had been removed and who remained artificially ventilated for 48 hours afterwards.[136,137]

Invited to participate in a close-door symposium in London to discuss the ethical and legal implications of medical progress (**Box 1**), the key figures of modern organ transplantation underlined the dilemmas posed by the lack of a clear and consensual characterisation of death for patients with irreversible brain damage.[138,139] "Since we find that transplantation of a kidney from a living person without his permission is not acceptable, but that the law [...] permits the use of organs from the dead", Giertz argued, "it is then a question of drawing the line between life and death."[136] Legal scholars had, for the most part, already made up their minds. Carl Wasmuth—who would later serve both as the president of the American College of Legal Medicine and as the president of the American Society of Anesthesiologists—reiterated his contention that legislative changes were warranted to facilitate the decision-making process prior to organ procurement from dying patients.[140] At the annual meeting of the American College of Legal Medicine in June 1965, he had already affirmed in no unambiguous terms that the progress of medical science and transplantation had rendered the definition of death obsolete, and that it was thus bound to evolve: "It becomes evident that death is no longer determined by the lack of respiration or the lack of a heartbeat or the lack of circulation [since these two functions may be carried on by artificial means]."[137] The first successful heart transplant by South African surgeon Christiaan Barnard in December 1967[141,142] prompted questions about the vital status of the donors at the time of the organ procurement and made the cardiorespiratory definition of death all the more untenable.[143,144]

On March 9-11, 1966, the Ciba Foundation (a non-profit organisation created in 1949 and funded by the Swiss pharmaceutical company *CIBA*, now *Novartis*) organised a multidisciplinary symposium on the ethical and legal issues raised by recent progress in organ transplantation.[139] The symposium was instigated by Sir Michael Woodruff, an English surgeon at the University of Edinburgh who had performed the first kidney transplant in the UK[145], because of "the growing realization that progress in medicine brings in its train ethical problems which are the concern not only of practising doctors but of the whole community." Attendees included the World leaders in transplantation: Roy Calne (who initiated the transplantation programme at Cambridge University and later performed the first liver transplant in Europe), Jean Hamburger, Joseph Murray, John Merrill, Thomas Starzl, and Keith Reemtsma (who had performed the first xenotransplantation in 1964 and assembled the team that would, 12 years later, implant the first total artificial heart). It also included Guy Alexandre, Gustav Giertz, George Pickering, Robert Platt, Carl Wasmuth, and George Schreiner. Reactions to Alexandre's proposed criteria for defining death were mixed. While Murray and Hamburger were positive ("this new approach [...] has a serious pathological basis"), others were sceptical (Roy Calne: "I feel that if a patient has a heartbeat he cannot be regarded as a cadaver"; Pickering: "The public [...] would require a lot of evidence to persuade them that it was justified to take a kidney from a person who still had a heart beat and a circulation, and who, according to the ordinary standards, was still alive"; Reemtsma: "at present it would not be acceptable in many countries to remove vital organs from living persons prior to what we now accept as death"). However, Alexandre made his premise clear: "there has never been [...] any question of taking organs from a dying person. The question is of taking organs from a dead person, and the point is that I do not accept the cessation of heart beats as the indication of death. [...] I think irreversible damage to the central nervous system is an indication of physiological death that permits us to take an organ from a body that is already a cadaver." Concluding the exchange, Michael Woodruff noted: "We really need a conference of a slightly different composition to consider this business of what is death." This would occur just two years later, in 1968, with the installation of the Harvard Committee.

Box 1. Questioning the ethical implications of medical progress at the Ciba symposium (1966)
A detailed account of this symposium can be found in Ross et al., 2016 and Machado et al., 2005 [133,138]

Redefining death

Christopher Pallis, a prominent British neurologist, commented that "modern technology, in its desperate attempts to save human life, has produced an entity known as brain death. It has also generated a conceptual crisis: that of knowing—at the simplest, bedside level—whether a patient is alive or dead."[146] This ethical problem was not lost on Henri Beecher, an anaesthesiologist at Massachusetts General Hospital who had recently made his mark as a sharp critic of unethical clinical research with a landmark article published in 1966 in the *New England Journal of Medicine.*[147] In October 1967, concerned with the ethical difficulties generated by the growing number of 'hopelessly unconscious patients',[148,149] he convinced the dean of Harvard Medical School to assemble an *ad hoc* committee to "come to some subtle conclusion as to a new definition of death."[150] Their first meeting was held in March 1968, two years to the day after the Ciba symposium.

This committee was composed of thirteen members, including Boston surgeons Joseph Murray and John Merrill and neurologists Raymond Adams and Robert Schwab. The latter played a central role in drafting the report.[150] A pioneer of electroencephalography, Schwab had founded the Brain Wave Laboratory (now *Laboratory for NeuroImaging of Coma and Consciousness*) at the Massachusetts General Hospital, the first hospital-based clinical EEG laboratory in the United States.[151] Confronted to an increasing number of comatose patients in his critical care unit, he had developed a set of basic criteria to identify patients for whom "the prolongation of cardiac circulation serves no purpose."[120] In a series of 90 cases examined between 1962 and 1968, he had established that unconscious patients with no elicitable reflexes, no spontaneous respiration, and a flat ('isoelectric') EEG had a very short survival and presented markedly necrosed brain tissues at autopsy. He came to the conclusion that the absence of EEG activity was not the mere indication of a dysfunction of the central nervous system; it was the sign that the brain was irremediably and permanently damaged and that despite a beating heart the patients were, in fact, *dead*.[152] The other members of the Harvard Committee largely approved of Schwab's approach.[150] Technical precisions were added to operationalise the triad criteria, including considerations about the clinical ascertainment of un-responsiveness (no response to external stimuli), the lack of spontaneous breathing for at least 3 minutes, the abolition of reflexes (e.g. fixed pupils, no ocular movement or blinking, absence of postural activity), and the duration of isoelectric EEG (at least 10 minutes of recording, repeated 24 hours later). The first draft was ready by the end of June, and the final report was published in the *Journal of the American Medical Associations* on 5 August 1968.[153] This new definition based on neurological criteria was met with mostly positive reactions and proved to be a turning point in the conceptualisation of death. It was, for instance, instrumental in the evolution of the legal definition of death in France (1968)[154,155] and in the development of the Swedish guidelines for the diagnosis of irreversible loss of brain functions (1973).[156–158] Nevertheless, three reasons prevented these criteria from prevailing entirely during the next decades.

First, the lack of clear equivalence between brain death and death became the subject of a long-lasting debate among scholars. Many were puzzled by the fact that 'irreversible coma' was presented as a criterion for pronouncing death but not as death itself, and by the vagueness of the proposed definition: "an organ, brain or other, that no longer functions [...] is *for all practical* purposes dead." This ambiguity reflected the hesitations of Beecher and Schwab (in a letter to Beecher, the latter suggested to avoid redefining death and, instead, to "concentrate on [...] what constitutes irreversible coma"[159]). Wary of the confusion that this could cause, Joseph Murray protested in an earlier draft that "the term 'brain death' should be eliminated. Death is what we are talking about, and adding the adjective 'brain' implies [...] an incomplete type of death."[150] In contrast with the cautionary approach of the Harvard Ad Hoc Committee, the British Conference of Medical Royal Colleges was unequivocal when, in 1976, it stated that "brain death represents the stage at which a patient becomes truly dead, because by then all functions of the brain have permanently and irreversibly ceased. [...] The identification of brain death means that the patient is dead, whether or not the function of some organs, such as a heartbeat, is still maintained by artificial means."[160]

A second limitation was the inclusion of non-brainstem (i.e. cortical) reflexes and the mention of the "great confirmatory value" of an isoelectric EEG. Although subsequent studies corroborated the importance and reliability of EEG measurements in brain dead patients,[161,162] it opened Pandora's box. Before long, questions arose regarding the adequate time between sequential EEGs, the interpretation of cortical brain activity in otherwise unresponsive patients, the accuracy of brain death diagnosis based on clinical examination of brainstem reflexes alone, and the necessity to perform a confirmatory angiogram to determine the absence of cerebral blood flow.[163–167] "The determination of brain death is still seen by many as a problem", Peter Black laconically summarised in a review for *The New England Journal of Medicine* in 1978.[168,169] This was especially problematic given the lack of standardisation in the criteria being used to determine death across U.S. jurisdictions.[170] Moreover, in 1976 the United Kingdom adopted diagnostic criteria for brain death centred around the absence of brainstem reflexes, stating that "it is now widely accepted that electroencephalography is not necessary for diagnosing brain death."[171] This meant that unconscious patients with abolished brainstem function but preserved cortical activity (which EEG measures) would be considered alive in the United States but dead in the United Kingdom. Incidentally, this transatlantic divide in the definition of brain death led to the broadcasting of an episode of the BBC television programme *Panorama* entitled 'Transplants: Are the Donors Really Dead?', which sparked outrage in the British medical community.[172–174] To clarify the situation, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research was established in the fall of 1978. Its main goal was to propose a uniform, well-defined, conceptually coherent, and socially acceptable notion of death in order to propose "the same basic rule about who is dead, and who is not, everywhere in the United States."[175] Their report, published in 1981, was largely

influenced by the contribution of Alexander Capron and Leon Kass[176,177] and by the landmark paper from James Bernat.[178] The whole-brain definition of death eventually prevailed: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the *entire brain*, including the brain stem, is dead."[179] This definition became the Uniform Determination of Death Act (UDDA), a statute which was progressively adopted by most U.S. states. The American Academy of Neurology guidelines were published in 1995, which largely contributed to standardising the neurological criteria used for the determination of brain death.[180] Of note, the use of confirmatory EEG or cerebral blood flow test is now generally deemed superfluous, although it remains legally mandatory in some countries.[181]

The third limitation is of contextual and historical nature. Because preoccupations about the determination of brain death and concerns regarding the availability of organs for transplantation arose in parallel, the criteria proposed by the Harvard Committee have cast doubt about the ulterior motives of its members.[144,182] The framing and writing of the final report left the impression that the redefinition of death was mainly designed to facilitate organ procurement, and external factors largely reinforced this impression. During the Summer of 1968, in the aftermath of the two successful heart transplants performed by Christiaan Barnard a few months earlier, three international events addressed the issue of brain death with a clear focus on the ethical problems of organ procurement from deceased donors.[183] The main event was *Declaration of Sydney on Human Death* issued by the 22nd World Medical Assembly, which made an explicit reference to "the use of cadaver organs such as heart or kidneys for transplantation."[184,185] Fortuitously, the Declaration of Sydney was published on 5 August, the same day as the article from the Harvard Committee. An even stronger connection between brain death and transplantation was made by the *JAMA* itself, who published the 'Ethical guidelines for organ transplantation' of the Judicial Council of the American Medical Association back-to-back with Beecher's report.[186] Moreover, the report was released less than one week after the adoption of the Uniform Anatomical Gift Act by the U.S. Senate, on 30 July 1968.[187] In France, the decision to codify the new definition of death just three days before Christian Cabrol performed the first heart transplantation in Europe also bolstered the suspicion that transplant surgeons influenced the legislator to bolster their agenda.[188,189] However, historians have demonstrated with sound evidence[150,190,191] that "although [organ transplantation] clearly benefited from a new definition of death, it was not a principal driving force in its creation."[166]

The tortuous and lingering process that led to the redefinition of death on neurological and neurophysiological grounds illustrates the ambivalence—and, for many, the uneasiness—of physicians regarding the most appropriate care for unconscious patients with no hope of recovery. This process was not primarily motivated by ontological concerns (*what is death?*) or by opportunistic motivations (*when can organs be harvested?*); it stemmed from the burgeoning ethical malaise towards the reckless use of invasive treatments in an attempt to salvage patients whose condition was precisely the by-

product of medical progress. “Do not attempt to redefine death. Concentrate on the agreement as to what constitutes ‘irreversible coma’”, Schwab suggested in a memo to Beecher during the Harvard Committee. He explained: “If we establish the concept of irreversible coma with the cessation of function at all levels of the [central nervous system], it will not be difficult for those in charge [...] to withhold or discontinue mechanical, electrical, or pharmacological aids.”[159]

In a context where the ever-changing limits of what is medically possible blurred the boundaries between life and death, the ability to pronounce death despite the presence of a heartbeat was less a legal necessity than a mean to act on the ethical obligation to discontinue sophisticated yet futile machinery and to withhold senseless ‘heroic measures’. Concerns about the futility of pursuing invasive treatments in dying patients had already been overtly brought up during the 1966 Ciba symposium in London.[139] For George Schreiner (a nephrologist who would later be instrumental in obtaining federal funding for the End-Stage Renal Disease Medicare Program), the necessity of redefining death was first and foremost dictated by the gruesome reality of modern clinical practice: “We have seen people with a virtual transection of the brain kept alive for days and days simply because there was an intact cardiovascular system and a respirator. The clinician has to decide, from a set of criteria, at which point he will stop employing extraordinary means for the prolongation of life. Some research on the criteria is essential [...] to decide how many ribs to break with cardiac massage, or how many old people should unnecessarily be subjected to thousands of dollars’ worth of resuscitation, or whether it is ever possible to die without a series of cardiac arrests.” Paradoxically, the unprecedented advanced of medicine had created a situation where the physicians’ ability to cure, save, replace and repair became more worrisome than their failure to do so. Karolinska Hospital urologist Gustav Giertz commented that “the thought that we should be obliged to keep a patient alive with a respirator when there is no possibility of recovery, solely to try to prolong his life by perhaps 24 hours, is a terrifying one.”[136]

Care for the dying: questioning futile treatments

Throughout the 1950s, the number of unconscious patients supported with artificial ventilators increased rapidly. Among them, a small but growing fraction survived without regaining consciousness, sometime with no other sign of life but a beating pulse. Physicians tending to these patients found themselves facing unprecedented dilemmas. Should life-sustaining treatments be continued in patients who might essentially be dead? Should ‘extraordinary measures’ be attempted to resuscitate a patient with a trivial chance of recovery? Is it ethically acceptable to withdraw or withhold treatments designed to save lives? Robert Schwab, at Massachusetts General Hospital, reported what is probably the first documented case where artificial ventilation was purposefully discontinued in 1954 (for a detailed account, see Belkin, 2003[191]). A few years later, in 1959, French neurologists Michel Jouvet and Pierre Wertheimer published a series of four clinical cases of comatose patients whose central nervous system functions are

irreversibly abolished, including a 53-year-old female patient for whom the respirator was turned off. "We believe that the prolongation of artificial ventilation is only conceivable if there is still a chance of central nervous system activity recovery", they argued.[125,192] Their contribution generated animated discussions. Mollaret and Goulon, who coined the expression 'coma dépassé', were for instance explicitly opposed to the withdrawal of artificial ventilation. During a lecture in Paris, the former explained: "In the face of these unfortunate people, when the heart continues to beat day after day without the slightest awakening of a function, despair vies with pity and the temptation of the liberating click becomes throbbing. May I be forgiven, but I have not yet been able nor willing to consent to the *pollice verso*."[118]

In the United States, these issues were first brought to light in January 1957 with the publication of an editorial in *The Atlantic Monthly* entitled "A Way of Dying", in which a widow recounted the medicalised agony of her husband in a large metropolitan hospital.[193] The editors from *The New England Journal of Medicine* praised the article, describing it as "required reading for physicians", and harshly criticised the "immaculate, modern aseptic skills that can keep a diseased, half-dead, cancerous body alive, by intravenous nourishment and with the magic of penicillin and round-the-clock special nursing [with little regard for dignity]".[194] Before long, similar opinions appeared in the *Journal of the American Medical Association*. "When death is imminent and inevitable, it is neither scientific nor humane to use artificial life-sustainers to protract the life of a patient", Franck Ayd advocated in 1962, adding that "physicians must recognize man's right to live and die peacefully. Otherwise life-preserving treatments may become a scientific weapon for the prolongation of agony."[195] Hamlin held essentially the same position in his article on the role of EEG in the determination of brain death two years later, by concluding that "withholding fruitless efforts at resuscitation [...] would grant solace to relatives who under current hospital practices often have to await the grim and foregone verdict until the final beat of the dying heart has been recorded."[121] In Sweden, the decision of a physician to withdraw artificial hydration in an older patient who had experienced a massive haemorrhagic stroke came before the Royal Medical Board in 1961. The physician was later prosecuted but finally acquitted on the grounds that "[although] treatment undertaken to maintain life shall not be withdrawn, it is conceivable that it may be justified by certain circumstances [...], in which it would be pointless to continue the treatment."[136,196]

Concerns about the potential futility of treatments at the end of life were not limited to intensive care. Oncologists were also starting to question the aggressiveness of anticancer treatments in the terminal stage of the disease.[197,198] In 1959, Edward Rynearson caused a fierce controversy with an essay published in the American Cancer Society's journal *CA*, where he observed that "by means of tubes inserted into their stomachs, or into their veins, or into their bladders, or into their rectums, [...] we can keep people suffering for an indeterminate number of months."[199] Six months later, the journal released a total of 39 letters to the editor responding to Rynearson's article—mostly

concurring with his views.[200] Nevertheless, in spite of a growing awareness among oncologists that 'radical surgeries' and evermore aggressive chemotherapy could be of limited benefit for some patients, the vast majority believed that, ultimately, medical decisions had to be made by medical professionals. This paternalistic approach was also evident in the lack of patient-physician communication regarding the disclosure of cancer diagnosis. In 1953, it was reported that 70% of physicians in Philadelphia never or seldom told their patients that they had cancer.[201]In a much-discussed article published in 1961, Donal Oken revealed that 90% of physicians preferred not to disclose the diagnosis to their patients, most of the time based on emotion-laden personal judgments.[202]

Decisions regarding the continuation or discontinuations of life-prolonging treatments were often made unilaterally, with no or little discussion with patients and their caregivers. Some terminally ill patients were being resuscitated and put on life support notwithstanding their explicit wish to forgo treatments.[203–205] On the other hand, for fear of setting off legal disputes and conflicts with family members, decisions to withdraw or withhold therapy were often made without their assent. These decisions were motivated not only by of the perceived futility of treatments for individual patients but also out of growing concern for the scarcity of available medical resources. Hence, in September 1967, the British audience discovered in the popular BBC television programme *Tomorrow's World* that, nearly 18 months before, the medical director of Neasden Hospital had issued a memo to all the staff regarding the criteria to select patients for resuscitation in the event of cardiac arrest ("the following patients are *not* to be resuscitated: very elderly, over 65 years; malignant disease; chronic chest disease; chronic renal disease"), causing a public outcry.[206–208]

Twenty years later, a special grand jury investigation discovered that La Guardia Hospital in Queens, New York, had instituted a process of designating patients who should not be resuscitated by sticking small purple dot decals on their nursing records, which were then discarded when the patients were discharged or died. This so-called 'no-code status' was never mentioned to patients and family members and, in order to avoid legal exposure, was kept separate from the medical charts so that the decision could not be traced back to a specific physician.[209–212] The investigation also revealed that hospital staffs commonly used delaying tactics to make sure that resuscitation efforts would fail while still being able to tell the bereaved family member that everything possible had been done. As the limited efficacy of cardiopulmonary resuscitation became increasingly clear—Bedell reported in 1984 that only 14% of patients who underwent CPR survived until discharge,[213] a finding well within the range of contemporaneous studies[214–217]—physicians and nurses began to perform less-than-full resuscitation efforts when they believed that the patient's prognosis was too poor. This practice (nicknamed 'slow code', 'Hollywood code', 'light-blue code', or 'coffee code') was mostly used for patients with terminal cancer, advanced dementia, or in a vegetative state. It was seldom discussed openly, and most often "performed without the consent and without the knowledge of the patient or the patient's family."[218]

Towards the primacy of patient autonomy

Between the late 1970s and the mid 1990s, the notion of patient autonomy—the right for a competent person to decide which medical interventions he or she wants to accept or refuse—gained considerable influence in Western countries, Northern America and Europe alike. Considerations for autonomy first arose from the Nuremberg Code and the Declaration of Helsinki, focused on the issue of informed consent of participants in human clinical research.[219–221] It came under intense scrutiny throughout the 1960s and 1970s amid a series of research scandals, including the abuses revealed by Henri Beecher in 1966 and the fallout of the Tuskegee syphilis trial in 1972 that eventually led to the systematisation of institutional review boards (note: for a comprehensive and gripping historical account, see Capron 2018[222]). The recognition of the respect for autonomy as one of the basic tenets of clinical practice occurred much later, through a succession of high-profile legal cases and under the pressure of civil societies. While the right of competent patients to refuse treatments—even life-saving ones—was progressively guaranteed, the possibility to withdraw treatments and to turn off life-supporting measures in unconscious (and thus incompetent) patients remained problematic.[223]

In the United States, the case of Karen Quinlan, a 21-year-old woman in a persistent vegetative state following a drug overdose, was a turning point.[224] In 1976, after a much publicised and commented trial, the New Jersey Supreme Court decided that Karen Quinlan's father, acting as her legal guardian, had the right to withdraw artificial ventilation provided that her physician could determine the irreversibility of her condition and that the hospital's ethics committee give its approval.[225] A few months later, two major hospitals in Boston (Beth Israel and Massachusetts General Hospital) paved the way for more transparent institutional policies regarding the termination of life support by publishing their own internal guidelines in *The New England Journal of Medicine*.[226,227] This initiative was considered as an important milestone ("the hospitals are coming out of the closet!", Fried celebrated in an accompanying editorial[228]). It should nevertheless be noted that national CPR standards published in 1974 already explicitly recommended against resuscitation attempts in patients with very poor prognosis, and advised that do-not-resuscitate (DNR) orders should be documented in the patient's medical records.[229] The notions that mechanical ventilation could be withdrawn without fear of criminal charges or legal liability and that surrogates could make decisions on incompetent a patient's behalf were subsequently recognised[230] and gradually gained consensus in the medical community.[231–234] The right to forgo life-supporting treatments was then progressively extended to other measures such as artificial nutrition and hydration.[235–239] Moreover, the necessity to place patients at the centre the decision-making process has become an essential precept in clinical practice.[234,240–242] This change of ethical paradigm has been described as "a shift from the primacy of beneficence to the primacy of autonomy".[243,244] To enforce the preferences of patients with advanced illness regarding the continuation or discontinuation of treatments at the end of life and to enable healthcare professionals to provide goal-concordant care, a special task force at the

Center for Ethics in Health Care at Oregon Health and Science University developed the Physician Orders for Life-Sustaining Treatment (POLST) Programme. It was implemented throughout Oregon in 1995 and extended to other states in 2004.[245] The POLST programme is part of a wider effort to promote advance care planning as a way for patients to preserve their decisional autonomy, should they become incapable of self-determination later.[246–248]

In Sweden, although the delegation for medical ethics of the Swedish Society of Medicine (Swedish: *Läkaresällskapets*) already recognised in 1978 that life support could be withdrawn when death was imminent,[249] official guidelines from the National Board of Health and Welfare were not published before 1992[250] (these guidelines have been updated and reinforced in 2011[251,252]). In England, the British Medical Association released its first position statement in 1999, after a long consultation process.[253–255] In France the *Leonetti* law was passed in April 2005, in the wake of the public debate prompted by the tragic death of Vincent Humbert.[256,257] This legislation, which was updated in 2016, grants the right for patients with advanced disease to obtain the withholding or withdrawal of any treatment that was deemed "useless, disproportionate or having no other purpose than the artificial preservation of life." It also enables patients to write advanced directives and to appoint a surrogate decision maker.

Tragic choices: medical decisions before death

Under the combined influence of progress in acute medical care, legal and judicial recognition of decisions to forgo treatments, and increasing appreciation of the right for patients and their surrogate to decline or stop life-prolonging therapy, the number of deaths preceded by a medical decision increased considerably in the late 1980s and throughout the 1990s. "Now that medical technology has teased apart the dying process, we have had to select a time of death when many signs of life do, in fact, remain", Stuart Youngner noted.[258] The first large-scale investigation, conducted from July 1987 to June 1988 in two intensive care units affiliated to the University of California San Francisco, revealed that out of 224 deceased patients 114 (51%) died after support was withheld or withdrawn. In this landmark study, Nicholas Smedira et al. also showed that only a minority of these critically ill patients for whom a medical decision was made at the end of life were capable of participating in the decision themselves.[259] Five years later, the proportion of deaths following a medical decision in the same two ICUs reached 90%.[260,261] Other observational studies have reported rates of end-of-life decisions in intensive care units ranging from 40% to 70%.[262–264]

In Europe, findings from the EURELD study shed light on the frequency of end-of-life decisions in the general population in six different countries. In 2003, Van der Heide et al. reported that, out of 20 480 deceased individuals included in the analysis, death was anticipated in two-third of cases and was preceded by a medical decision in 23% of cases in Italy, 36% in Sweden, up to 51% in Switzerland.[265] Decisions to alleviate pain or other

distressing symptoms while accounting for the possible hastening of death as a secondary, unintended consequence ('double effect') were the most common. Decisions to withhold or withdraw life-sustaining or potentially life-prolonging treatments were found in 33% of decedents in Sweden and affected primarily medications, artificial hydration or nutrition, and artificial ventilation.[266] In addition, a do-not-resuscitate decision was enacted in over 70% of all non-sudden deaths.[267] These decisions occurred not only in intensive care units or in acute care hospital wards, but also in the community and, increasingly, in nursing homes (where the proportion of older adults with severe cognitive impairment and limited decisional capacity is high). In Belgium, Chambaere et al. recently examined end-of-life decisions among older adults with dementia. They found that 28% of deaths followed treatment withholding or withdrawal, and 37% were preceded by a decision to intensify analgesics or sedatives.[268] It has also been recently shown that the frequency of treatment withdrawal decisions among persons with dementia has increased substantially between 1998 and 2013 (from 20 to 35%).[269] In sum, a large proportion of people now die as the direct or indirect result of a medical decision regarding treatments, whether this decision is to withhold a potentially life-saving therapy, to discontinue a drug that was prescribed to prevent adverse clinical events, or to withdraw an apparatus without which vital functions cannot be maintained. These decisions are, for the most part, the unforeseen consequence of the provision of high-intensity care for patients with advanced illness near the end of life.

The rising intensity of care at the end of life

Countless studies have investigated the provision of care during the final months of life, most often to emphasise the intensity of disease-oriented treatments.[59,270,271] Briefly, three main themes emerge from the current literature. First, ICU admissions close to death seem increasingly frequent.[272,273] In the United States, the proportion of Medicare fee-for-service decedents admitted to ICUs during their last month of life rose from 24% in 2000 to nearly 30% in 2015.[274] This is far more than any other countries. In an international study comparing seven developed nations, Bekelman et al. showed that among older patients with cancer, the proportion admitted in intensive care during their final month of life varied from 7–11% (Belgium, Canada, The Netherlands) to 27% in the United States.[275] This comes with a sizeable number of individuals with tracheostomy and invasive mechanical ventilation initiated near the end of life. One explanation for this high ICU admission rate is the substantial number of older adults with limited life expectancy who, in the U.S., undergo inpatient surgery within three months before death.[272,276]

Second, studies conducted in Northern America and Europe have found that approximately 20% of patients with advanced cancer receive chemotherapy, targeted therapy, or immunotherapy during the last month before death.[277–282] There are, however, wide cross-national differences in chemotherapy use at the end of life. The above-mentioned international study led by Bekelman et al. reported that the proportion of lung cancer patients who used chemotherapy during their last 30 days of life varied

from 17% in Germany to 12.1% in the United States, down to 6% in Canada.[283] In Sweden, Näppa et al. showed that among cancer patients who died in 2008, 23% had been treated with chemotherapy during the last month before death.[281] In Belgium, 17% of all people who died from cancer in 2012 received chemotherapy during their last month of life, 3.3% had disease-oriented surgery, and 2.6% were admitted to an ICU.[284] In France, a series of large retrospective cohort studies revealed that out of 110 631 hospitalised older adults (≥75 years) who died from metastatic cancer in 2010-2013, 10% received chemotherapy during their last month of life.[279] Moreover, the rate of chemotherapy use was only marginally associated with the assumed chemosensitivity of the tumours; hospitalised patients with metastatic pancreatic cancer, melanoma, mesothelioma, soft-tissue sarcoma or biliary tract tumours—all known for their poor response rate to IV chemotherapy—had surprisingly high rates of chemotherapy close to death.[285]

Third, the use of feeding tubes and artificial nutrition for critically ill patients or in older adults with terminal cancer or advanced dementia has come under scrutiny. Among critically ill patients in the United States, the incidence of gastrostomy tube placement has increased from 12 to 29 per 100 000 person-years between 1994 and 2014, with a parallel increase in the proportion of patients discharged to long-term care facilities.[286] Kempf et al. described that patients with metastatic oesophageal or stomach cancer had decreasing rates of chemotherapy but increasing rates of artificial nutrition near the end of life, despite clinical guidelines that unambiguously recommend limiting the use of artificial nutrition in the context of advanced cancer and limited life expectancy.[287] The European Society for Clinical Nutrition and Metabolism (ESPEN) states that, near the end of life, "treatment needs to focus on symptomatic support including alleviating hunger and thirst, while all additional nutritional support may do more harm than good."[288] The ESPEN also explicitly recommends that "older persons with low nutritional intake in the terminal phase of illness shall be offered comfort feeding instead of enteral nutrition."[238] In the context of advanced dementia, Mitchell et al. found that, in 1999, 34% of U.S. nursing home residents with severe cognitive impairment had feeding tubes.[289] Although there has been a notable decrease in the incidence of percutaneous endoscopic gastrostomy in this population since 2000,[290,291] artificial nutrition with feeding tubes remains frequent despite explicit clinical guidelines advising against it.[238,292–294]

Transitions between care setting and final place of death

Late hospitalisations and in-hospital deaths are one of the most visible consequences (or, some would argue, one of its latent causes) of the medicalisation of the dying process. Both elective and non-elective hospital admissions are frequent during the months before death. In the United States, Teno et al. calculated that among the 251 229 Medicare fee-for-service older adults who died in 2015, 54% had been hospitalised during the last 30 days of life, 7% had been hospitalised at least three times during the last 90 days, and 11% had transitioned from one place of care to another.[274] Older adults with advanced illness and multimorbidity often follow a complex sequence of care transitions

during their last year of life.[295] Important disparities across countries have been noted. Among older cancer patients, the proportion of individuals hospitalised during their last month of life varies from 45% in the Netherlands and Germany, to 50% in the United States, up to 60% in Canada and Norway.[283] It has also been demonstrated that a substantial share of nursing home residents are hospitalised near the end of life, oftentimes prompted by the onset of potentially avoidable condition.[296] In Sweden, we recently reported that 22% of older adults had at least one elective hospitalisation during their last month of life and that 51% had at least one non-elective hospitalisation, with substantial socioeconomic differences.[297]The proportion of individuals hospitalised during any given day increases at a faster pace during the last three months before death than during the preceding months, especially among older adults with cancer (**Figure 5**). These findings fit well with the state of knowledge published in other countries.[298–303]

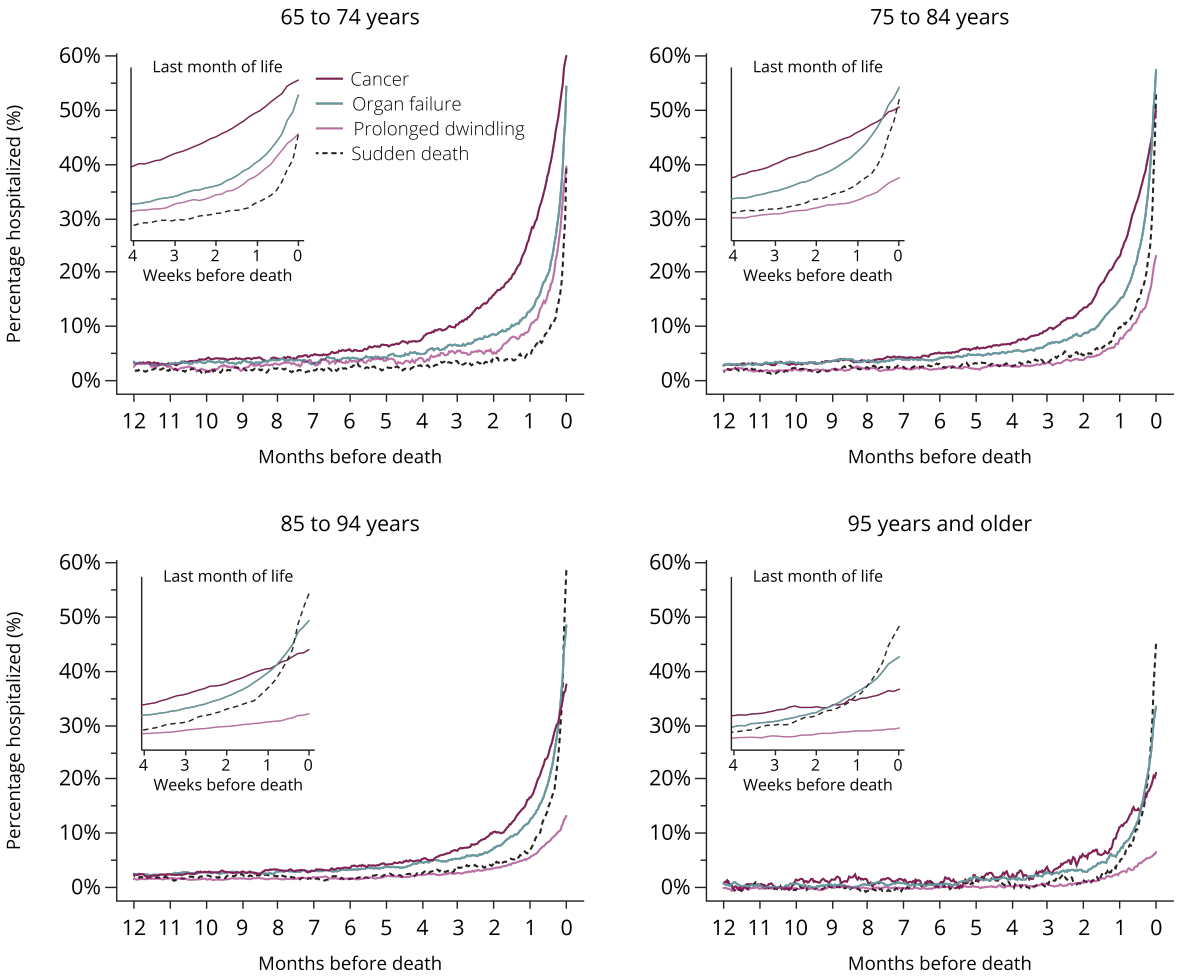


Figure 5. Percentage of individuals hospitalised throughout the last year of life, by age and illness trajectory (Sweden, 2015)

Source: National Cause of Death Register and National Patient Register, Swedish Board of Health and Welfare. A total of 78 226 older adults (≥65 years) who died in Sweden between 1 January and 31 December 2015 were included. Trajectories of functional decline were derived from multiple cause of death data, using a methodology described elsewhere.[43] The percentage of individuals who were hospitalised throughout the last year of life (28 630 716 person-days) was calculated from data from the National Patient Register, by using the dates of admission and discharge of every inpatient hospitalisation.

As a consequence, a large number of older persons die in hospitals or long-term care facilities rather than in the community. In practical terms, Haider Warraich writes, "the vast majority of people die in places where inert tones provide the palette, disinfectant the aroma, alarm bells the soundtrack, and open-back johnnies the wardrobe."[116] In Sweden, among decedents aged 65 years and over, 41% died in hospitals, 42% in nursing homes, and 16% at home. The proportion of death occurring in nursing homes increases dramatically with age, from 18% among decedents aged 65–74 years to 67% among those aged 95 years and older (**Table 3**). Moreover, hospitals are the most common place of death for people who died with cancer, organ failure, or sudden causes, while nursing homes are by far most common among decedents with dementia. These proportions are consistent with findings from other European and North American countries.

The percentage of in-hospital deaths among people who die from conditions amenable to palliative care has been found to vary from 38% in the United States, to 45-50% in Italy and England, up to 60-65% in France, Spain, and Canada.[304] These proportions are typically higher among cancer patients[305], and lower among persons with dementia.[306,307] In the United States, Teno et al. have reported a substantial reduction of in-hospital deaths between 2000 and 2015 (from 33% to 20%), and a clear increase in home and hospice deaths. The proportion of older adults dying in nursing homes, on the other hand, remained stable at 25% of all deaths.[274,308] Similar patterns have been found in the United Kingdom, which has led public health researchers to conclude that, if current trends remain stable, the number of people who will need adequate end-of-life care in the community and in nursing homes will increase considerably during the next two decades.[309] Therefore, new models of palliative care delivery are warranted to ensure appropriate support across care settings.

	Home	Hospital	Nursing home	Other
All decedents	16.2%	40.6%	42.1%	1.1%
Sex				
Men	18.8%	45.2%	34.5%	1.5%
Women	13.9%	36.6%	48.8%	0.7%
Age at time of death				
65–74 years	27.1%	52.7%	17.8%	2.4%
75–84 years	17.6%	46.6%	34.5%	1.3%
85–94 years	11.6%	34.8%	53.1%	0.5%
95 years and older	10.5%	22.1%	67.2%	0.2%
Illness trajectory				
Short and evident decline (e.g. cancer)	20.3%	45.8%	32.5%	1.4%
Intermittent decline (e.g. organ failure)	18.7%	50.8%	29.6%	0.9%
Slow and gradual decline (e.g. dementia)	7.3%	16.5%	76.1%	0.1%
Sudden death (e.g. injury, sepsis)	20.2%	54.1%	22.2%	3.4%

Table 3. Places of death among older people in Sweden (2015)

Source: National Cause of Death Register, Swedish Board of Health and Welfare. Out of 79 473 older adults aged 65 years and over who died in 2015, the place of death was not reported for 1817 (2.3%) individuals. These percentages are thus calculated for a total of 77 656 decedents.

1.3 THE COMPLEX BURDEN OF MORBIDITY NEAR THE END OF LIFE

Multimorbidity in old age

Multimorbidity is defined as the co-occurrence of multiple chronic diseases in the same person.[310,311] This notion differs from that of *comorbidity*, which is defined in reference to an index disease.[312] A systematic review conducted in 2011 identified 39 different multimorbidity indices, 18 of which were weighted indices designed specifically to predict adverse health outcomes.[313] The authors found considerable heterogeneity in the definition and selection of chronic diseases, and the data source used to capture these diseases, leading to large variability in prevalence estimates (from 55 to 98% among older adults).[314–319] To overcome this predicament and improve the comparability of future epidemiological studies, Calderón-Larrañaga et al. developed a clinically-driven consensus classification of chronic diseases.[320] This methodology enable us to detect a comprehensive set of chronic diseases that either have a long-lasting impact on older adults' autonomy and quality of life, or that require enduring contacts with healthcare services. It can be implemented with both population-based survey data and routinely collected administrative data. Among older adults included in the *Swedish National study of Aging and Care in Kungsholmen* (SNAC-K), 89% had at least 2 chronic diseases and 56% were living with at least 4 co-existing chronic diseases.[320]

Few studies have investigated the prevalence of multiple chronic diseases among older adults near the end of life. Rosella et al. have described the increasing burden of chronic conditions and multimorbidity among adult decedents in Ontario, Canada, between 1994 and 2013.[321] To our knowledge, this is to date the only large-scale published study on this topic. However, it well established that chronic multimorbidity is closely associated with mortality in old age.[322] In a pooled analysis of more than 698 000 individuals enrolled in 91 distinct prospective cohort studies, researchers found that the combination of three diseases (diabetes mellitus, stroke, myocardial infarction) was associated with a 15-year reduction of life expectancy at age 60.[323] Recently, it has been shown that multimorbidity is the single most important factor of shortened survival among older persons, accounting for 7.5 years of life lost.[324] Using routinely collected data for a random sample of 100 000 individuals drawn from the total Swedish older population aged 75 years and older, **Figure 6** demonstrates the strong correlation between the number of co-existing chronic diseases, the risk of death within an year, and the remaining life expectancy. For instance, while older men with a single chronic disease can expect to live for another 16.1 years, those with 5 concomitant conditions have a life expectancy of 13.1 years.

Several published studies have also modelled the life expectancy of older adults with multiple chronic diseases. In Germany, Tetzlaff et al.[325] recently reported the results of a study based on administrative claims data investigating the proportion of life expectancy spent with chronic multimorbidity defined as the presence of ≥6 chronic diseases and ≥5 chronic medications.[326] Years of life with multimorbidity account for one third of the total

life expectancy at age 60 (e.g. 7.9 out of 24.7 years for women). At age 70 and 80, this proportion rises to 40% and 45%, respectively. Using a 5% sample of Medicare beneficiaries without a history of cancer (n= 407 749), Cho et al.[327] found that the life expectancy of American men at age 75 varied from 13 years among those without chronic diseases to 7 years among those with a high burden of chronic diseases (compared with 10 years in the average U.S. population). Correlatively, their results demonstrate that the survival probability of women with high morbidity at age 75 is similar to that of women aged 81 years in the total U.S. population. DuGoff et al.[328] reached similar conclusions based on a large dataset combining the 5% Medicare sample with data from the *Chronic Condition Warehouse* developed by the Centers for Medicare and Medicaid Services.[329] At age 75, older adults with 5 chronic diseases can expect to live 5 years less than those with no chronic disease. These findings have two important clinical consequences. First, they suggest that there is a substantial burden of chronic diseases during the final years of life, which may come with an equally important number of medications. Second, it implies that chronological age is of limited value to estimate the remaining life expectancy of older persons with multiple chronic diseases, and thus to determine whether treatments are likely to achieve their benefit in a timeframe that is meaningful for patients.

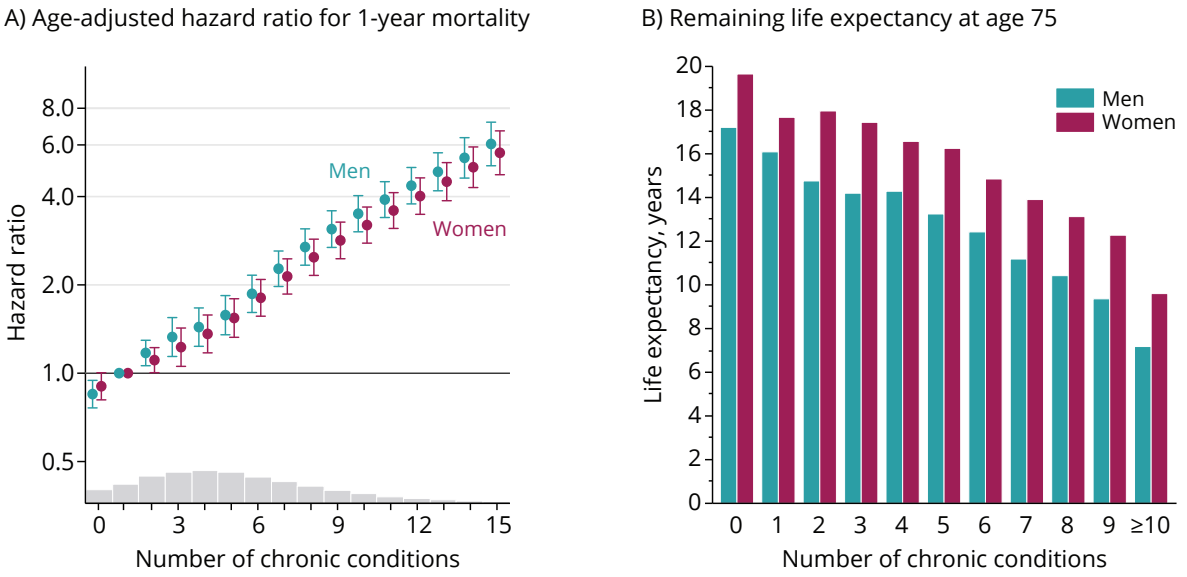


Figure 6. Multimorbidity, mortality risk and remaining life expectancy in old age

Source: National Patient Register and National Prescribed Drugs Register, Swedish Board of Health and Welfare. A random sample of 100 000 older adults (≥75 years) living in the community on 1 June 2013 was drawn from the total population. These individuals were followed-up until 31 May 2014. Chronic diseases were captured by using the list proposed by Calderón-Larrañaga et al.[320], based on ICD-10 codes reported for all inpatient and specialised outpatient care admissions, ATC codes for prescribed drugs, and free-text drug indications reported during a 5-year period before baseline. Panel A shows the estimated hazard ratio for 1-year mortality as a function of the number of co-existing chronic conditions (reference: 1). These estimates were calculated with Cox proportional hazard regression analysis after adjustment for age, by using restricted cubic splines with 5 knots placed at 1, 3, 5, 7 and 11 chronic conditions. The histogram at the bottom of panel A represents the distribution of individuals according to the number of co-existing chronic conditions (median: 5, interquartile range: 3–7). Panel B illustrates the remaining life expectancy of men and women aged 75 years according to their number of co-existing chronic conditions. To estimate the number of years of remaining life expectancy, period life tables were constructed based on the observed mortality rates at each subsequent attained age. The overall life expectancy of community-dwellers at age 75 was 15 years for women and 12 years for men.

Physical frailty and vulnerability

In combination with chronic multimorbidity and disability, frailty contributes to the complexity of older persons' clinical profile near the end of life.[59,308] Frailty can be broadly defined as a state of high vulnerability in which relatively minor stressors can cause disproportionate adverse health outcomes. The inability to return to homeostasis is the consequence of a progressive decline in multiple organ systems and of impaired physiological reserve.[330] Numerous definitions of frailty have been proposed, based either on the notion of accumulated deficits[331,332] or on a specific phenotype.[333] This second approach laid the foundation to build a large consensus about the notion of physical frailty, "a medical syndrome [...] characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency or death."[334] The prevalence of physical frailty in the general older population is estimated to be 10-20% among community-dwellers[335,336] and above 50% among nursing home residents,[337] with great heterogeneity across studies. Although frailty is a transitional, non-absorbing state, trajectories of worsening disabilities are more common than trajectories of durable improvement.[338] Hence, at age 75 women can expect to live 5.5 years with physical frailty out of 14 years of total life expectancy.[339] Therefore, the burden of morbidity directly attributable to frailty is substantial near the end of life.[340] In a prospective study of community-dwelling older adults in Connecticut, Gill et al. found that frailty was the most common condition leading to death, accounting for 28% of all deaths (n=107/383).[39] A large retrospective cohort study based on a sample of 57 753 deceased patients enrolled in the Veteran Affairs health system recently showed that 18% of older adults had a primary diagnosis of frailty.[341] Similar estimates were calculated in the Health and Retirement Study (15%, n= 7204 decedents).[342] In Catalonia, advanced frailty was found to be the most common underlying condition of older adults in need of palliative care (31%), before dementia (23%) or cancer (13%).[343]

The transition from fit to pre-frail or from pre-frail to frail is often prompted by the progression of an underlying disease.[344–346] However, findings from multiple studies suggest the existence of iatrogenic transitions, namely incident impairments attributable to the utilisation of healthcare services (e.g. excessive bed rest during hospital stays, overuse of diapers and urinary catheterization, inappropriate drug prescribing, use of physical restraints).[347–349] Repeated hospital admissions near the end of life have also been found to play an important role in the worsening of functional decline in frail individuals.[350] Among older patients with cancer, systemic treatments and invasive interventions (e.g. surgery, chemotherapy, radiation therapy) can also challenge physiological reserve and trigger a spiral of decline.[351] After summarizing the evidence from 20 observational studies that included 2916 older patients with solid or haematological malignancies, Handforth et al. reported a median prevalence of frailty of 42%, and found that frailty was associated with a 4-fold increased risk of chemotherapy intolerance and severe postoperative complications within 1 month.[352]

Frailty often overlaps with disability and multimorbidity.[353,354] However, geriatricians have called for a shift in the understanding of frailty in old age, suggesting to move past the predominantly disease-centric approach of geriatric care[355] and to tailor health interventions for older adults with impaired physical functioning but no disability.[356–358] This is particularly relevant in the context of end-of-life care, since the natural course of frailty with no underlying advanced disease is often hardly predictable.[359,360] For instance, Gill et al. could not find any obvious pattern in the disability trajectories during the last year of life of frail older persons.[39] Likewise, although earlier reports suggested a more homogeneous clinical course of disability in frail older people near the end of life, no study could identify clear and consistent trajectories of functional decline combining multimorbidity, disability and physical frailty in a foreseeable manner.[361,362] However, public health researchers at the University of Newcastle have recently demonstrated that older adults at highest risk of dying had a distinct trajectory of frailty during their last year of life. They suggested that routinely collected data at the population level can be leveraged to facilitate the identification of individuals at high risk of frailty near the end of life.[363] They also argued that while frail older patients are often more inclined to express a preference for minimally invasive medical treatments at the end of life, these preferences are susceptible to shift during critical phases of care.[364] Clinicians caring for frail older adults thus face important challenges, including the timely recognition of the palliative phase, the management of symptoms associated with frailty (e.g. weight loss, weakness, fatigue, musculoskeletal pain), and the coordination of multiple professional caregivers scattered across different care settings.[365,366] All these factors can make the prescribing process even more difficult at the end of life.

Prevalence of distressing symptoms near the end of life

Many older adults experience distressing symptoms during the final months before death, which adds to the existing burden of morbidity due to multimorbidity, disability, and frailty. Several systematic reviews and meta-analyses have been published over the past decade, documenting the high prevalence of physical and psychological symptoms at the end of life (**Table 4**). Overall, the most common symptoms are pain, fatigue, dyspnoea, dry mouth, cough, nausea, constipation, anorexia, depressed mood, anxiety, delirium and insomnia. In a systematic review and meta-analysis focused on the prevalence of symptoms in older cancer patients receiving palliative care, Van Lancker et al.[367] found that fatigue (78%), urinary incontinence (71%), asthenia (66%), pain (66%), and constipation (52%) were frequent at the end of life. However, it is a misconception that only cancer patients experience distressing symptoms at the end of life. Older persons who die from end-stage heart failure, renal failure, COPD, Parkinson's disease, or dementia also express significant discomfort.[368] Stow et al. recently reported the results from a systematic review showing that older adults with frailty often experience pain, nausea, shortness of breath, fatigue, and drowsiness. These findings highlight the considerable burden that physical and psychological symptoms exert on older people's well-being near the end of life, regardless of their cause of death.

Author, year	Inclusion criteria and target population	No. studies	No. persons	Summary of main findings
Janssen, 2008[369]	Quantitative studies reporting the prevalence of symptoms in patients with end-stage chronic organ failure (CHF, COPD, ESRD) at the end of life	39	NR	Daily symptom burden was high in end-stage chronic organ failure, irrespective of the underlying disease. Burdensome symptoms included fatigue, dyspnea, insomnia, pain, dry mouth, cough, anorexia, depression, anxiety, constipation, nausea, and delirium.
Mitchell, 2011[370]	Quantitative, interview-based studies reporting the prevalence of depression in adult patients with cancer in palliative care settings	24[a]	4007	Pooled prevalence of depression was 16.5% (95% CI, 13.1–20.3) according to DSM or ICD criteria. Prevalence of major depression was 14%. Prevalence of all types of depression combined was of 24·6% (95% CI 17.5–32.4).
Moens, 2014[368]	Quantitative studies reporting the prevalence of symptoms among patients with advanced cancer, AIDS, chronic heart failure, COPD, ESRD, MS, PD, and dementia	143	78 469	Largest number of published studies for advanced cancer (n=57) and end-stage renal disease (n=47). Four symptoms (pain, fatigue, anorexia, and dyspnea) had a prevalence rate ≥50% for all studied diagnostic groups. Other common symptoms included nausea, insomnia, constipation, depression and anxiety.
Murtagh, 2007[371]	Quantitative studies reporting the prevalence of symptoms among adult patients with end-stage renal disease	61[b]	NR	Commonly reported symptoms included fatigue (71%), pruritus (55%), constipation (53%), anorexia (49%), pain (47%), sleep disturbance (44%), anxiety (38%), dyspnea (35%), nausea (33%), and depression (27%)
Solano, 2006[372]	Quantitative studies reporting the prevalence of symptoms among patients with advanced or terminal cancer, AIDS, heart disease, COPD, or renal failure.	64	NR	Prevalence of 11 symptoms was reported, with important heterogeneity across studies and across diseases. Three symptoms (pain, breathlessness, and fatigue) had a prevalence rate ≥50% for all five diseases. Dyspnea was also common (10–95%).
Teunissen, 2007[373]	Quantitative studies reporting the prevalence of symptoms among adult patients with incurable cancer.	44[c]	25 074[c]	The authors report the prevalence of 37 symptoms assessed in at least five studies. Five symptoms (fatigue, pain, weakness, and appetite loss) had a prevalence ≥50%
Van den Beuken, 2016[374]	Quantitative studies reporting the prevalence of pain in patients with advanced cancer[e]	24[d]	9653	Pooled prevalence rate of pain in patients with advanced, metastatic, or terminal cancer was 66% (95% CI, 58–75).
Van Lancker, 2014[367]	Quantitative studies reporting the prevalence of symptoms in older adults (≥ 65 years) with cancer receiving palliative care	17	652[e]	A total of 32 symptoms were identified, of which 16 were included in the meta-analysis. Symptoms reported by >1 study included fatigue (pooled prevalence 78%), incontinence (71%), weakness (67%), pain (66%), constipation (52%), nausea (35%), anorexia (41%), dyspnea (33%).

Table 4. Prevalence of symptoms near the end of life: overview of published systematic reviews and meta-analyses (2000-2019)

Abbreviations: AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; PD, Parkinson's disease; MS, multiple sclerosis; NR, not reported. Note: this overview does not include the systematic review by Lokker et al.[375], which included only quantitative studies (n=29) reporting the prevalence of death rattle in the dying phase of adults (n=8280). [a]Mitchell et al. also report the prevalence of depression and related mood disorders in 70 additional studies with 10 071 individuals in oncological and haematological settings. [b]These 61 studies were reported in 64 different articles c Including 6 studies (n= 2219 patients) about symptom prevalence during the last 1-2 weeks of life. [d]Out of a total of 122 studies included in the review. [e]Maximum number of participants included in the pooled prevalence rates.

1.4 DRUG UTILISATION IN OLD AGE AND NEAR THE END OF LIFE

One more pill for every ill

With the advent of evidence-based medicine in the mid-1990s—the term was first coined by Gordon Guyatt in 1991[376,377]—clinical practice guidelines have progressively become one of the cornerstone of modern medicine. Clinical practice guidelines are defined by the Institute of Medicine as "recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[378] They are used by physicians and patients to make decisions about the use of diagnostic, preventive, and therapeutic interventions. The tools and criteria used to assess the quality of the evidence upon which clinical guidelines are built (e.g. Grading of Recommendations, Assessment, Development and Evaluations [GRADE] rating framework[379]) give considerably more weight to randomised controlled trials and meta-analyses than observational studies, owing to the risk of confounding bias and—among other issues—immortal time bias, performance bias, and detection bias that often plague the latter. Randomised clinical trials are, in their vast majority, designed to measure the effect of a single intervention on a single health problem; for instance, the efficacy and safety of a specific drug treatment for the management of a specific disease. Moreover, trial participants are typically sampled from a population of individuals who only have the disease of interest, with no or few comorbidities.[380–383]

As a result, because the available evidence only allows for drawing inference about one treatment-disease pair at a time, recommendations embedded into clinical practice guidelines address single diseases. For certain chronic diseases such as hypertension, heart failure or diabetes, a carefully vetted combination of several therapies is sometimes recommended to maximise benefits and minimise adverse outcomes. Energetic implementation policies from medical specialty societies and pay-for-performance programmes or similar value-based models initiated by healthcare authorities aim at increasing physicians' adherence to guideline-recommended treatments. In many cases, this disease-specific approach can lead to remarkable improvements in the management of isolated conditions. One pitfall of this silo-based model, however, is the situation of multimorbid patients, who account for a substantial fraction of the older population. For these patients, the application of single-disease clinical practice guidelines can lead to an exponential number of prescribed drugs and increasingly complex regimens.[384–386] Boyd et al. estimated that, if all applicable recommendations were followed, a hypothetical 79-year-old woman with five concomitant chronic conditions (hypertension, diabetes, osteoporosis, osteoarthritis, and COPD) would be treated with 12 different prescription drugs, requiring 19 doses per day taken during 5 distinct dosing times.[387] Okeowo et al. recently reiterated this simulation exercise, with similar results.[388] In sum, multimorbidity leads to an accumulation of treatments recommended for the compartmentalised management of a specific health problem, which may have conflicting pharmacological targets, cause harmful interactions, and set off hazardous prescribing cascades.

Polypharmacy and inappropriate drug use in the general older population

Polypharmacy is the concurrent utilisation of several medications by a single individual. There is currently no consensual operationalisation of polypharmacy. However, previous studies have frequently relied on a cut-off point of ≥5 medications to measure its prevalence in the older population.[389–391] Estimates from the National Health and Nutrition Examination Survey in the United States suggest that 39% of community-dwellers aged ≥65 years are exposed to polypharmacy.[392,393] In Sweden, recent findings indicate that the prevalence of polypharmacy in the community rises up to 42% and that the incidence rate is 20 per 100 person-years.[394] Among older adults living in nursing homes, a cross-national study conducted in Europe showed that polypharmacy affected about 75% of residents.[395] A review of the literature showed that the proportion of older adults with polypharmacy is increasing worldwide.[396] As discussed previously, the high prevalence of polypharmacy mirrors the prevalence of multimorbidity in old age, which partly explains the observed association with age (**Figure 7**).

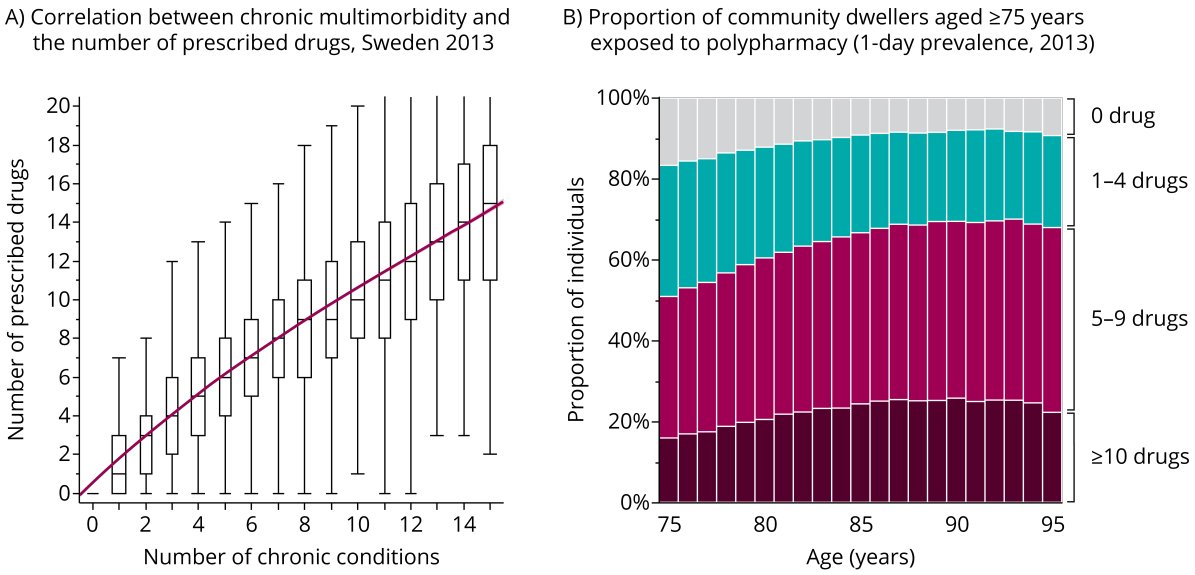


Figure 7. Polypharmacy in relation to multimorbidity and age among older adults in Sweden

Source: Cross-sectional data from the Swedish Prescribed Drugs Register, linked at the individual level with the Total Population Register and the National Patient Register. Random sample of 100 000 older adults living in the community (i.e. not institutionalised) on 1 June 2013. In panel A, chronic diseases were captured by using the list proposed by Calderón-Larrañaga et al.[320] The curve corresponds to the polynomial (degree 3) fit of the number of prescribed drugs according to the number of chronic diseases. In panel B, the stacked bars represent – for each given age – the distribution of the population according to the number of prescribed drugs.

The prescribing of many different drugs may often be justified by the necessity to properly manage multiple chronic diseases and symptoms.[397–399] In other words, polypharmacy is not necessarily inappropriate.[400] However, it poses important clinical challenges as it comes with increased risk of negative health outcomes.[401–406] Polypharmacy has, for instance, been found to be associated with a substantial rise in potentially harmful drug-drug interactions[407,408] and serious adverse drug reactions.[409–417]

Furthermore, recent studies have suggested that the mere number of drugs may increase the risk of injurious falls, beyond the effect of specific pharmacological classes known to induce imbalance, sleepiness, reduced vigilance, or mobility difficulties.[418–420] Older adults with polypharmacy are also less likely to maintain adequate adherence to chronic treatments.[421,422] Finally, the number of medications used concomitantly by a person is the single most important predictor of potentially inappropriate drug use[423–426], which further amplifies the risk of serious drug-related adverse events.[427]

The ageing process is characterised by important changes in body composition and organ functions.[428–431] These modifications not only alter the absorption, distribution, metabolism and excretion of drugs (pharmacokinetics) but also enhance the sensitivity of older adults to specific drugs (pharmacodynamics), which in turn increases the risk of adverse drug reactions.[409,413,431–433] Therefore, some drugs with a favourable benefit–risk ratio in the general population are contraindicated for older adults. In the geriatric pharmacology literature, drugs are considered *potentially inappropriate* when the risk of harmful effects outweighs their expected benefit, or when there exist a safer, better tolerated or more effective alternative.[434] Inter-individual variation in the risk of adverse drug-related event makes the selection of appropriate and inappropriate medications challenging. To guide clinicians in their prescription, multiple instruments have been developed over the past 25 years (**Table 5**). Although some of these assessment tools are based on the implicit judgment of prescribers,[435–438] most have been constructed around explicit criteria defined through literature reviews and expert consensus methods.[439–441] Existing criteria present major differences in their content and methodology.[442]

In a nationwide, cross-sectional study of 1.3 million older adults aged ≥65 years in Sweden, we found that the prevalence of potentially inappropriate drug use varied from 16% to 24% depending on the assessment tool we used.[424] Despite this variability, the rate of potentially inappropriate drug use in the community (15-22%) was very similar to the pooled estimates previously reported in two distinct systematic review of the literature (20-23%).[443,444] Among nursing home residents, we found that between 36% and 51% of the individuals living in institutions received potentially inappropriate drugs. We later confirmed this finding through a meta-analysis of 43 published studies (weighted average prevalence: 43.2%).[445] Across different criteria, the most commonly reported inappropriate drug classes are long-acting benzodiazepines (e.g. diazepam), tricyclic antidepressants (e.g. amitriptyline) and other medications with anticholinergic properties (e.g. hydroxyzine, oxybutynin), nonsteroidal anti-inflammatory drugs, digoxin, and long-term use of proton-pump inhibitors.

A considerable body of literature has investigated the role of potentially inappropriate drug use in the occurrence of negative health outcomes. In a meta-analysis of three observational studies accounting for a total of 1.8 million older people in the United States,[446–448] researchers recently showed that incident use of inappropriate drugs was associated with a 60% relative increase of 1-year mortality.[470]

Criteria, year	Country	Target population	Content
Beers, 2019[449]	United States	Older adults (≥ 65 years), excl. palliative care	114 single drugs or drug classes to avoid; 71 drugs or drug classes to avoid in older adults with specific diseases or syndromes; 16 medications to be used with caution; 13 clinically important DDIs; 20 drugs to avoid or to adapt according to the renal function.
EU(7)-PIM[450]	Europe	Older adults (≥ 65 years)	282 drugs considered potentially inappropriate (including 72 identified as "most frequent")
EURO-FORTA, 2018[451]	Europe	Older adults (≥ 65 years)	264 items organised into 26 main indication groups, and graded from "A (Absolutely) : indispensable drug" to "D (Don't): avoid in older people."
Laroche, 2007[452]	France	Older adults (≥ 75 years)	34 criteria, including 29 single drugs or drug classes to avoid and 5 drugs or drug classes to avoid in older adults with specific diseases or syndromes.
Maio, 2010[453]	Italy	Older adults (≥ 65 years)	23 criteria, including 17 drugs that should always be avoided, 3 drugs that are rarely appropriate, and 3 drugs that may have an indication but are often misused.
McLeod, 1997[454]	Canada	Older adults (≥ 65 years)	38 criteria, including 18 drugs generally contraindicated for elderly people, 16 drug–disease interactions and 4 drug–drug interactions.
NORGEP, 2009[455]	Norway	Older adults (≥ 70 years) in general practice	36 criteria, including 21 single drugs and 15 drug combinations considered potentially inappropriate for older adults.
NORGEP-NH, 2015[456]	Norway	Older adults (> 70 years) in nursing homes	34 criteria, including 11 single drugs and 14 drug combinations that should be avoided, as well as 8 drug classes that should be re-assessed and possibly deprescribed
PRISCUS, 2010[457]	Germany	Older adults (≥ 65 years)	83 single drugs considered potentially inappropriate.
STOPP/START, 2014 [458]	United Kingdom	Older adults (≥ 65 years)	114 criteria, including 80 drugs and drug-disease combination considered potentially inappropriate (STOPP) and 34 drugs considered appropriate and indicated for older adults (START).
STOPPFrail, 2017[459]	United Kingdom	Frail older adults (≥ 65 years) with limited life expectancy	27 criteria, including 2 implicit criteria suggesting to deprescribe any medication without a proper indication or with too poor compliance, and 25 drugs or drugs classes that are considered potentially inappropriate
Swedish Board of Health and Welfare, 2017 [460]	Sweden	Older adults (≥ 65 years)	34 criteria, including 8 drug classes and drug combinations that should be avoided in older adults.

Table 5. Selected list of explicit criteria for inappropriate drug use in older adults

Note: The first version of the Beers criteria was published in 1991[461] and aimed to identify potentially inappropriate medication use among nursing home residents. It was first revised in 1997[462] and made applicable also for community-dwelling older people. The list was thereafter revised in 2003[463], 2012[464], 2015[465], and more recently in 2019[449]. The EURO-FORTA list is an extension of the FORTA (*Fit fOr The Aged*) initiative which was initially released in 2013[466], validated with an expert consensus in 2014[467], and updated in 2015[468]. The Laroche list (2007) is currently being updated in France. The first version of the STOPP/START criteria was published in 2008[469], and updated in 2014[458]. The Swedish criteria were first introduced in 2004, and were updated in 2010 and 2017[460].

Others studies reported a substantial rise in the risk of non-elective hospitalisation[471–475] and hip fracture,[476] with particularly deleterious effects among older adults with dementia.[477,478] However, previously developed criteria (e.g. Beers, STOPP–START, NORGEP) are of limited clinical value to evaluate the quality of drug prescribing in the context of end-of-life care. Drug classes considered potentially inappropriate because of their side effects (e.g. opioids, benzodiazepines, scopolamine) may for instance be indicated for the management of distressing symptoms during the final weeks of life. On the contrary, drugs deemed appropriate for older adults in general may have no substantial benefit and present a higher risk of harmful effects during the final months of life. As noted by Spinewine et al., "much of the published work has condensed the notion of appropriateness to simply pharmacological appropriateness, i.e. whether a drug is seen as safe and effective, or sometimes cost-effective."[434] A number of studies have emphasised the need to look beyond pharmacology and to adopt a broader view of the quality of prescribing in older adults.[479–482] There is a need to reconsider what constitutes 'potentially inappropriate prescribing' in older adults at the end of life.[483–487]

Overtreatment and low-value care

The challenge of drug prescribing for older persons during the final months before death is not only to avoid serious adverse events and to ensure optimal symptom management, it is also to avoid *overtreatment*, namely providing medical resources that present a trivial or no benefit during a patient's lifetime.[488,489] Some authors favour the expressions *non-beneficial treatments* or *low-value care* to express the disproportion between the intensity and the potential harms of treatments on the one hand, and the expected benefit in terms of health improvement, survival, or quality of life on the other hand.[270]

As mentioned earlier, considerations about the use of potentially futile treatments near the end of life have first surfaced in the field of intensive care in the late 1980's and early 1990's. Debates were fuelled by growing concerns that life-sustaining interventions for critically ill persons (e.g. use of mechanical ventilation or cardiopulmonary resuscitation for patients in a persistent vegetative state) may have no clinical benefit and only serve to prolong the dying process with substantial discomfort.[490,491] The appropriateness of treatments in the context of limited life expectancy has also been questioned in medical oncology.[492–497] Over the past three decades, ground-breaking progress of anticancer therapy has indeed been accompanied by the increased aggressiveness of disease-targeted treatments during the final months and weeks of life of terminally ill patients.[277,282,498,499] This has raised serious questions for the quality of end-of-life cancer care due to the lack of benefit of chemotherapy close to death, its potentially disastrous toxicity, and its negative impact on quality of life.[500,501] As a result, the American Society of Clinical Oncology (ASCO) has included the use of chemotherapy for patients with advanced cancer and low performance status in its top-five list of "tests, procedures and treatments whose common use and clinical value are not supported by available evidence."[502]

The issue of overtreatment extends far beyond end-of-life care and patients with serious illness. It is a widely acknowledged challenge for modern healthcare systems[503–505] and has received considerable attention from the medical profession and the lay public.[506–509] Overtreatment is often the consequence of *overdiagnosis*, that is the diagnosis of a condition or physiological abnormality that, if unrecognised, would not have caused symptoms or harms in the first place.[510–512] Overdiagnosis includes, for example, routine electrocardiograms in patients with no history of cardiovascular disease,[513] screening for abdominal aortic aneurysm,[514] or screening for breast cancer in women aged 75 years or older with less than 10 years of remaining life expectancy.[515–518] The overuse of diagnostic, preventive, and therapeutic interventions can have unintended negative consequences and trigger a cascade of downstream services.[519,520] Korenstein et al. recently proposed a conceptual map that classifies the harms of overdiagnosis and overtreatment in six different domains: physical (e.g. pain, injuries, disability, infections, adverse drug reaction), psychological (e.g. anxiety, stress, depression), social (e.g. disruption of familial, intimate, and social life), financial (direct and indirect economic costs), treatment burden (e.g. pill burden, INR testing), and dissatisfaction with care.[521]

The provision of low-value medical services is well documented[504] and has become commonplace. In the United States, Schwartz et al. estimated that in 2009 between 25% and 42% of patients covered by Medicare (≥65 years) received at least one of 26 examined low-value care procedures. Low-value care amounted to $1.9–$8.5 billion in healthcare expenditures nationally.[522] In Canada, about 30% of older adults aged 75 years and over had received at least one of 10 low-value services.[523]

These findings are problematic for three main reasons. First, because overtreatment exposes patients to unwarranted harm, either as a direct result of healthcare encounters and treatment uptake or indirectly through the use of downstream health services. In a recently published systematic review and meta-analysis of the literature (n=70 studies), Panagioti et al. calculated that 6% of patients were affected by preventable medical harm, most often involving drugs (25%) and other treatments (24%).[524] Older persons are particularly vulnerable to adverse drug reactions; drugs that are usually well tolerated can cause serious harms that outweigh the benefit of the pre-existing treatment regimen. Second, because the overuse of non-beneficial treatments can paradoxically lead prescribers to omitting necessary treatments whose clinical value is well established, thus creating situations of undertreatment.[421,525–530] Third, because overtreatment is the cause of considerable healthcare expenditures, generated not only by the treatments themselves but also by the resources needed to manage their iatrogenic effects. These healthcare costs could instead be dedicated to other patients who may need the treatments in question (economic transfer between patient groups to advance social justice) or to effective healthcare interventions that currently not readily available (economic transfer across medical services to optimize cost-effectiveness). The overuse of medical treatments has come under particularly close scrutiny in the context of advanced illness, limited life expectancy, and palliative goals of care.

Rationalising drug prescribing at the end of life

Initially focused on medical interventions considered particularly invasive, concerns about the lack of meaningful clinical benefit and the potential for harm among patients at the end of life have since been extended to a broader range of treatments, including prescription drugs.[531,532] In a 2004 article published in the *British Medical Journal*, Stevenson et al. examined the issues surrounding the decision to continue or discontinue medications prescribed for the management of chronic comorbidities in patients with life-limiting illness.[481] "As prognosis worsens", they wrote, "the challenge is to balance the diminishing benefits with the increasing side effects." The difficulty is also to predict the appropriate time for gradually shifting the therapeutic objectives from predominantly preventive and curative treatments to predominantly palliative and symptomatic care.[533]

Non-symptomatic drugs prescribed to older people with limited life expectancy are sometimes deemed 'inadequate' or 'unnecessary' based on their insufficient effectiveness and the high risk of undesirable effects that they can cause.[534–537] This approach is characterised by a *probabilistic* view of what constitute adequate treatments near the end of life: medications are evaluated based on the likelihood that they will provide a significant benefit in terms of symptom control or survival *vs*. the likelihood that they will have side effects. A second model relies on a modified version of the Medication Appropriateness Index, a set of implicit criteria focused on the quality of the *prescribing process* (namely the existence of a clear indication for the drug, the appropriateness of the dosage, the absence of duplicates, and the risk of drug-drug interactions).[436,538,539]

A third approach has been developed by Holmes et al.,[540,541] that builds on the pillars of the two above-mentioned prescribing models but incorporates two additional elements. First, clinicians should carefully compare the time needed for the treatment to achieve its benefit ('time to benefit'[542,543]) and the patient's remaining life expectancy. Long-term preventive drugs that typically yield a measurable absolute risk reduction only after a few months or a few years may for instance be of little value for an 85-year-old patient with metastatic non-small cell lung cancer and five chronic comorbidities, whose life expectancy does not extend beyond 6 months and who will most likely die before the benefit of the drugs can accrue. Second, Holmes argues, the therapeutic outcome that the treatment is expected to achieve should remain aligned with the goals of care established with the patient. In other words, drug treatments should be prioritised according to their ability to obtain a health outcome that the patient values as important.

This patient-centric approach to drug prescribing provides a useful roadmap to re-examine the notion of *benefit* when discussing the appropriateness of drugs near the end of life. The proposed framework is also well in keeping with the American Geriatrics Society's guiding principles on the care of older adults with multimorbidity,[544] and is closely aligned with recent initiatives aiming at reducing wasteful clinical practices such as the *Choosing Wisely* campaigns in the United States and 19 other countries.[545–549]

Lack of evidence to estimate the burden of inadequate drugs at the end of life

Despite mounting interest in geriatric medicine and in the palliative care community, only a handful of studies investigating drug prescribing patterns among older adults at the end of life were published before this thesis started in June 2015. A review of the literature (**Appendix Table**) suggests that a large proportion of persons at the end of life is exposed to polypharmacy[539,550–565] and that the number of drugs often increases as death approaches.[551,558,566] Furthermore, previous studies have suggested that the continuation of preventive medications is commonplace during the final months and weeks before death.[534–536,538,567–578] Some authors also reported that drug-drug interactions were highly prevalent.[539,552,556] One study indicates that the anticholinergic load rises near the end of life, partly because of the increasing use of medications for symptom management (e.g. oxycodone, morphine, fentanyl, scopolamine).[579]

However, the available evidence stemmed mostly from studies conducted in selected populations, which were defined either based on an index disease (e.g. cancer, dementia) or on a specific care setting (e.g. nursing home). The generalisability of these findings was therefore limited, and large-scale epidemiological studies were warranted to examine the patterns of drug prescribing near the end of life at the population level.

In addition, high-quality evidence from randomised clinical trials or well-designed, prospective observational studies about the effectiveness and safety of drug treatments in older persons with advanced illness and limited life expectancy is lacking. As a result, clinical guidance regarding the initiation, continuation, and discontinuation of drugs is limited. The development of consensus-based criteria to identify drugs that are most likely *adequate*, *questionable*, or *inadequate* for older adults at the end of life could thus represent an important step towards providing clinicians with tools to help them rationalise drug prescribing in this context.[580] Such criteria would also enable researchers to generate comparable epidemiological evidence across patient groups, care settings, regions, and countries.

2. AIMS AND RESEARCH QUESTIONS

2.1 OVERALL AIM

The overarching aim of this doctoral thesis was to evaluate the quality of drug prescribing in older adults near the end of life. We set out to examine drug utilisation patterns during the last year of life of older adults, to propose consensus criteria for evaluating the adequateness of drug treatments for older adults at the end of life, and to investigate the prevalence, determinants, and cost of potentially inadequate drugs in this setting.

2.2 RESEARCH QUESTIONS

The overall aim was examined in four individual studies, which addressed specific research questions.

Study I: How does the burden of prescription drugs among older adults develop throughout their last year of life?

In the first study we aimed to measure longitudinal changes in the number of prescribed drug treatments and in the prevalence of polypharmacy, and to identify the most commonly used drugs and drug classes during the last months before death in a cohort of older adults who died from any cause.

Study II: Do older adults who died with solid cancer continue to receive preventive drugs near the end of life? What are the costs of these preventive drugs?

In the second study, we focused our attention on older adults who died with solid malignancies. Our objective was to evaluate the uptake of preventive drug therapy between the 12th month before death and the final month of life, and to estimate the direct costs of these treatments across different cancer types.

Study III: What drugs and drug classes are most often of limited clinical benefit for older adults at the end of life?

The purpose of the third study was to develop consensus criteria for identifying drugs of limited clinical benefit for older people at end of life, through a Delphi survey involving European experts in palliative care, geriatrics, general practice, and pharmacology.

Study IV: Are drugs of limited clinical benefit often continued or initiated near the end of life?

In the fourth and last study, we aimed to measure the proportion of older adults with life-limiting illness who either continued or initiated potentially inadequate drugs during their last months of life, according to the criteria developed in Study III.

3. MATERIALS AND METHODS

3.1 DATA SOURCES

All studies included in the present thesis (except Study III) are based on routinely collected administrative and healthcare data, that is data collected as part of a standard administrative or care process independently of specific *a priori* research purposes.[581,582]

Total Population Register

The Total Population Register (Swedish: *registret över totalbefolkningen*) was established in 1968 by *Statistics Sweden*, based on computerised records from the local population registers. Individuals are assigned a unique personal identity number, which was first introduced in 1947. The register is maintained continuously and updated 5 times per week with data from the Swedish Tax Agency. It covers all persons registered as Swedish residents, including immigrants. A detailed account of the Total Population Register and its use in medical research is available elsewhere.[583]

National Cause of Death Register

The Swedish National Cause of Death Register (Swedish: *dödsorsaksregistret*) is administered and curated by the National Board of Health and Welfare. It is deemed complete since 1952, although detailed data about causes of death are available at the national level since 1911.[584] Sweden has a long and well established tradition of collecting high-quality mortality data, with nationwide statistics dating back to 1751.[585,586]

Death certification follows a 2-step procedure. First, the physician who pronounces death must notify the Swedish Tax Agency without delay. After this first notification, the medical death certificate is sent to the National Board of Health and Welfare within 3 weeks by the family physician or by the physician who last saw the patient either on paper (**Figure 8**) or electronically. Causes of death are coded with the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). For each decedent, up to 48 distinct causes of death can be recorded. In keeping with the ICD-10 rules for mortality coding, the underlying cause of death is defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury."[587] Electronic classification systems have been used since 1987 to facilitate the selection and coding of the underlying cause of death (ACME software from the U.S. NCHS). With the adoption of the Iris system in 2012 and the switch to Iris v5 in 2017, the selection of the underlying cause of death is now based on the *Multicausal and Unicausal Selection Engine* (MUSE). About 1% of all deaths have no reported underlying cause of death. Out of ~90 000 deaths annually, 5000 undergo a specific forensic investigation (i.e. 7% of deceased women and 15% of deceased men). Swedish residents who die abroad are accounted for.

Socialstyrelsen

DEATH CERTIFICATE

☐ Replaces previously issued certificate

Personal information about the decedent

Personal ID number (12 digits)	Date of birth (YYYY-MM-DD) and sex if the personal ID number is missing ☐ Woman ☐ Man ☐ Cannot be determined	
Last Name	First Name	
Home address	Zip code	City
Country (if the person is not a permanent resident)	Ascertainment of the decedent's identity	

Date of death

YYYY-MM-DD (Fill in with zeros if exact details are missing) ☐ Certain ☐ Uncertain	If uncertain, date when the body was found (YYYY-MM-DD)

Place of death

Municipality (if unkown, municipality where the body was found)	☐ Hospital ☐ Nursing Home ☐ Home ☐ Other / Unkown

Children who died no later than 28 days after birth

☐ Stillbirth ☐ Deceased within 28 days

Cause of death

Disease or injury that led to the final cause of death		Approximate onset (YYYY-MM-DD)	Acute	Chronic	Unknown
A	The final cause of death was:		☐	☐	☐
B	which was a consequence of:		☐	☐	☐
C	which was a consequence of:		☐	☐	☐
D	which was a consequence of:		☐	☐	☐

Other diseases or injuries contributing to death (*up to 48)		Acute	Chronic	Unknown
		☐	☐	☐
		☐	☐	☐
		☐	☐	☐

Surgical operation within 4 weeks before death

☐ No ☐ No information about surgery		
☐ Yes	Date of surgery (YYYY-MM-DD)	Condition that motivated the procedure

Injury / Poisoning

☐ Accident ☐ Suicide ☐ Assault / homicide ☐ Event of undetermined intent	Date of injury / poisoning (YYYY-MM-DD)
Brief description of how the injury / poisoning occurred	

The cause of death is based on:

☐ Examination before death ☐ External examination after death ☐ Clinical autopsy
☐ Forensic autopsy ☐ Forensic medical examination

Signature of the certifying physician

Place Date (YYYY-MM-DD)	Signature	
Last name and first name of the physician		Position
Workplace		
Mailing address	Zip code	City
Phone number	Email	

Figure 8. Standard death certificate in Sweden (unofficial English translation)

Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (Swedish: *läkemedelsregistret*) was implemented in July 2005.[588,589] Data about all prescription drugs dispensed at pharmacies in Sweden are transferred on a monthly basis to the National Board of Health and Welfare. Approximately 85% of all dispensed defined daily doses (DDDs) are covered by the register. Over-the-counter medications (12% of DDDs), drugs administered in hospitals (3% of DDDs) are not included. Vaccines and drugs dispensed in nursing homes with a drug storeroom are only partially covered. Between 2005 to 2015 the Swedish Prescribed Drug Register collected data about 660.7 million prescriptions drugs dispensed to 2.8 million persons aged 65 years and older.

National Patient Register

The National Patient Register (Swedish: *patientregistret*) was started in 1964 and has full national coverage for inpatient care since 1987. It includes all inpatient admissions in Sweden from both public and private providers, with >99% completeness for somatic and psychiatric hospital discharges. Clinical diagnoses are coded according to the ICD classification (ICD-10 since 1997). The validity of these diagnoses has been found to be very high, with a positive predictive value greater than 95% for acute and severe conditions.[590] It also collects data about specialised outpatient care since 2001, including day surgery and psychiatric care. The coverage of outpatient diagnoses is typically lower than for inpatient data but remains above 80% overall. The National Patient Register does not contain information about primary care.

Social Services Register

In Sweden, elderly care is primarily funded by local taxes and government grants to municipalities (>95%). While medical care is organised by county councils, the responsibility for social and long term care lies with the 290 municipalities, which have a legal obligation to provide adequate care and housing for older people and people with disabilities.[591] Social care is a universal right provided based on needs assessment and largely subsidised.[592] The Social Services Register (Swedish: *registret över socialtjänstinsatser till äldre*) collects individual-level data about the provision of care services to older persons and persons with functional impairments. It was first launched in 2007 and has been implemented in routine since 2013. The register contains data about persons who live in nursing homes and residential care homes, persons who have been granted home care help or assistance for their activities of daily living in the community, and persons who are admitted into short-term nursing facilities. The status of each individual is reported on the last day of each month (e.g. 31 October). The overall quality of the data is good, but some municipalities have lower-than-average reporting rates. On average, about 5% of persons aged ≥65 years (n= 82 000) live permanently in nursing homes.

Swedish Register of Education

The Swedish Register of Education (Swedish: *utbildningsregistret*) was first established in 1985. It contains data from the 1970 and 1990 population and housing censuses, as well as annual updates from Statistics Sweden from 2000 to 2014. Data are reported directly by educational institutions, thereby increasing the validity of the register. Educational attainments are coded with the SUN2000 nomenclature, which is adapted to the International Standard Classification of Education (ISCED-97).[593]

Longitudinal integration database for health insurance and labour market studies (LISA)

The LISA database was established in 1990 (and expanded considerably in 2004) to track workers' health in relation with their professional occupation.[594] It includes all individuals aged ≥16 years registered in Sweden on 31 December of each year. In this thesis, disposable income was defined as the total income received during the year prior to the year of death minus taxes. Disposable income includes earning (e.g. salaries), business income, sickness allowances, disability pensions, unemployment benefits, retirement and old-age pensions (National Retirement Pension Scheme), and general social support provisions. The disposable income of each individual was equivalised by dividing the total household disposable income by the number of consumption units in the household, in keeping with the OECD modified scale (first adult = 1.0, second adult = 0.51).[595,596]

Database	Population covered	Information available
Total Population Register (RTB)	All persons aged ≥65 years registered in Sweden	Sex, date of birth, country of birth, municipality of residence, living arrangement, civil status, year of first and last immigration, year of last emigration
Swedish Education Register	All persons aged ≥65 years registered in Sweden	Highest educational attainment
LISA	All persons aged ≥65 years registered in Sweden	Disposable income, source of income
National Cause of Death Register	All decedents aged ≥65 years at time of death	Sex, date of birth, underlying and contributing causes of death (ICD-10), place of death, civil status
National Patient Register (inpatient and specialised outpatient care)	All persons aged ≥65 years in Sweden	Sex, age, date of admission and discharge, planned/unplanned admission, main diagnosis, secondary diagnoses, injuries, medical or surgical procedures, department of admission, provenance, destination.
Social Services Register	All persons aged ≥65 years eligible under the Social Service Act	Sex, age, provision of home care help (with type of ADL-help and number of hours per month), housing in a nursing home, date of enforcement
Swedish Prescribed Drugs Register	All persons aged ≥65 years in Sweden with at least 1 drug prescription	Sex, age, date of prescription, date of dispensing, type of dispensing (e.g. multi-dose), total dose, prescribed daily dose (free text), number of DDDs dispensed, ATC code, generic name, costs, characteristics of prescribers

Table 6. Summary of data sources used in Study I, Study II, and Study IV

3.2 STUDY DESIGNS AND POPULATIONS

All studies but Study III were register-based, nationwide retrospective cohort studies, where older adults were selected at time of death from the National Cause of Death Register and followed-back over 1 year to reconstruct their healthcare utilisation history near the end of life. **Table 7** presents an overview of the four studies.

The first study included all older adults who died at age ≥66 years between 1 January 2007 and 31 December 2013 in Sweden, notwithstanding those who had no reported cause of death, and/or no prescription drug history during their last 3 months of life. Out of 545 212 older persons who died during the study period, 511 843 decedents (93.9%) met the inclusion criteria. Among them, 39 610 (7.7%) died from sudden causes of death.

In the second study, we focused our attention on older people who died with solid tumours, a set of conditions often associated with a rapid functional decline marked by a short and clear terminal phase. We included older people aged ≥65 years who died between 1 January 2007 and 31 December 2013 in Sweden and who had a diagnosis of solid cancer (ICD-10 codes C00–C76 and C80) reported in the National Patient Register during the last 2 years of life or in the National Cause of Death Register as either the underlying or one of the contributing causes of death. Decedents were excluded from the study population if they were diagnosed with a concomitant haematological malignancy near the end of life, if they had no reported cause of death; if they had no prescription drug history during the last 6 months before death; or if they remained hospitalised continuously during the last 3 months before death. Of the 545 212 decedents identified during the study period, 151 201 were eligible.

The third study was based on a consensus panel of European experts, who participated in a web-based Delphi survey. This methodology is often used by researchers to elicit opinions from a group of experts about a subject for which there is insufficiently robust factual evidence to generate consensus. More details about this approach are provided hereafter (see *3.7 Delphi consensus*). Among the 58 geriatricians, palliative care physicians,

Study	Population	Design	Outcomes
Study I	Older adults (≥65 years) who died in 2007–2013	Retrospective cohort of decedents	Polypharmacy, most commonly prescribed drugs
Study II	Older adults (≥65 years) who died with solid cancer in 2007–2013	Retrospective cohort of decedents	Use and costs of preventive drugs
Study III	Panel of European experts	Delphi consensus survey	Adequate, questionable and inadequate drugs at the end of life
Study IV	Older adults (≥75 years) who died in 2015 from conditions amenable to palliative care	Retrospective cohort of decedents	Continuation and initiation of potentially inadequate drugs

Table 7. Overview of the four studies included in the thesis

general practitioners, pharmacists, pharmacologists and psychiatrists who were invited to contribute, 40 (69%) agreed to participate and were thus included.

In the fourth study (follow-back cohort of decedents), we included all older adults aged ≥75 years who died between 1 January and 31 December 2015. Only those individuals who died from non-sudden conditions potentially amenable to palliative care were eligible for inclusion, and decedents were further stratified according to their most likely trajectory of functional decline at the end of life based on the clinical conditions leading to death (**Table 8**). We excluded individuals with no exact date of death or no reported cause of death, as well as those who had no prescription drug history during the last 6 months before death. Out of 64 715 older adults aged 75 years and over who died in 2015, a total of 58 415 (90.3%) met our eligibility criteria.

Illness trajectory, conditions	ICD-10 codes
Trajectory 1. Short decline with evident terminal phase	
Solid tumours and haematological malignancies	C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D09, D32, D33, D37-D48
Trajectory 2. Long-term limitations with intermittent acute episodes	
Diabetes	E10-E14, G590, G632, H360, M142, N083
Other endocrinal diseases	E70-E72, E75-E77, E84-E85
Infectious and parasitic diseases	A520-A523, A527, A810, A812, B15-B19, B20-B24
Diseases of the blood	D60, D61, D69, D70, D752, D758, D86
Diseases of the cardiovascular system (incl. cerebrovascular diseases)	I231-I233, I238, I25, I50, I60-I67, I680-I682, I688, I69, G46, I27, I42, I43, I51, I520, I70, I73, I74, I792, I970, I971, I978, I980, I981, I988
COPD and other respiratory diseases	J40-J44, J47, J60-J62, J66, J701, J80, J841, J951-J953, J96, J980-J984, R060, R062-R065, R068
Liver failure and other digestive diseases	K44, K50, K51, K55, K56, K70-K77, K85, K86, K87, K90
Diseases of the skin	L305, L40-L42, L44, L93, L945
Diseases of the musculoskeletal system	M360, M361, M05, M06, M13, M15, M21, M30-M35, M40-M43, M45-M51, M53, M54, M638, M80, M81, M820, M821, M843, M844, M86-M88, M907, M961
Renal failure and genitourinary diseases	N02-N05, N11, N12, N136, N160, N18, N19, N25, N312, N318, N319, N82
Other (incl. congenital conditions)	Q01-Q06, Q078, Q079, Q20-Q28, Q31, Q33, Q40-Q45, Q60-Q68, Q714, Q75-Q79, Q850, Q86-87, Q89-Q93, Q95-Q97, Q99
Trajectory 3. Prolonged dwindling with progressive loss of physical and cognitive capacities	
Alzheimer's disease	G30-G32
Dementia and mental disorders	F00, F01, F02, F03, F05, F06, R54
Parkinson's disease	G20-G23
Multiple sclerosis	G35-G37
Other diseases of the nervous system	G10, G12, G70-G73, G03-G05, G07, G478, G518, G551, G608, G80-G83, G90-G99
Trajectory 4. Sudden death, conditions not amenable to palliative care	
None of the conditions above	N.A.

Table 8. List of conditions potentially amenable to palliative care and categorisation into illness trajectories at the end of life

3.3 ASSESSMENT OF DRUG EXPOSURE

In drug utilisation research and pharmacoepidemiologic studies, the accurate estimation of drug exposure is crucial. In Sweden, drugs are dispensed for up to 90 days. The date of dispensing is thus not sufficient to estimate whether an individual was exposed to specific drugs during a given day or a given period of time (e.g. week, month). Since the number of days covered (number of days' supply) when a prescription is filled is seldom reported in routinely collected data, the duration of drug exposure must often be calculated or predicted by using proxies.[597–600]

To construct drug exposure periods in Studies I and II, we used information from the Swedish Prescribed Drug Register, which collected data about all prescription drugs dispensed at pharmacies in Sweden. Drugs are defined by their product name, a 7-digit Anatomical Therapeutic Chemical Classification (ATC) code, and a national drug code (Swedish: *varunummer*). The national drug code allows for identifying the manufacturer, the specific strength, pharmaceutical formulation and dosage form (e.g. tablet, capsules, liquid solutions, inhaler, suppository) of each drug, as well as the number of units and the number of defined daily doses per package. From July 2005 to December 2015, there were a total of 48 588 distinct pharmaceutical products authorised on the Swedish market, corresponding to 2520 chemical substances (5th level of the ATC classification).

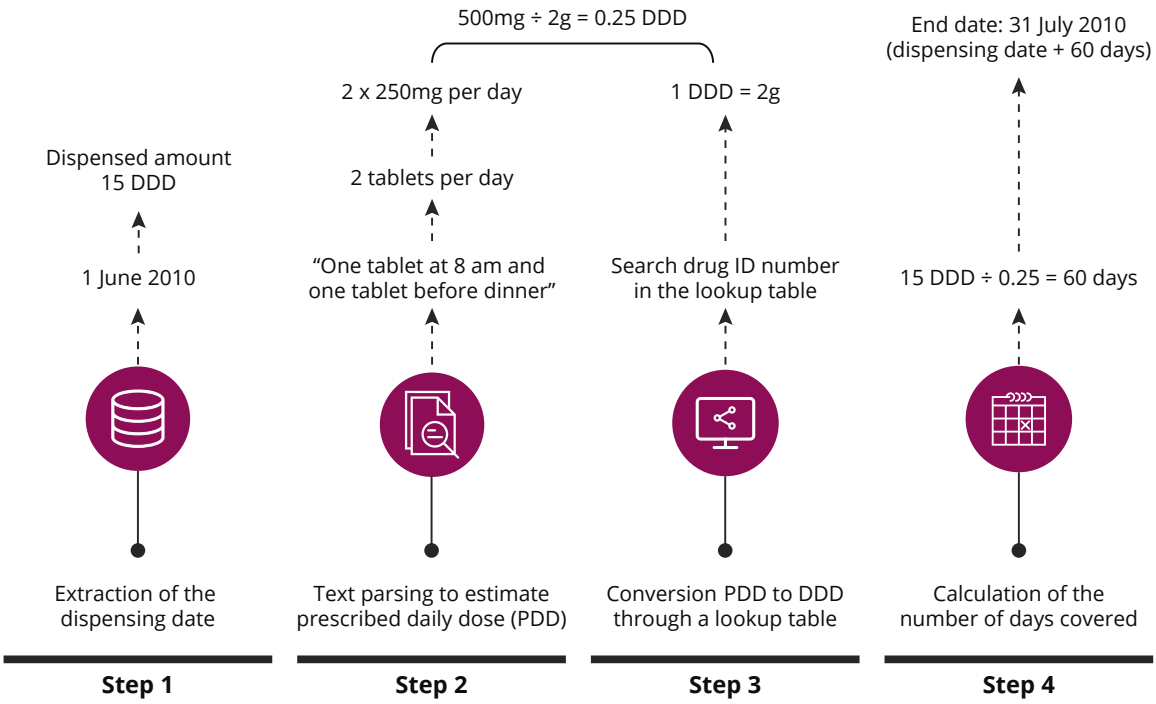


Figure 9. Estimation of prescribed daily doses and calculation of numbers of days covered

In this example, an individual filled a prescription on 1 June 2010 and received 1 drug package containing the equivalent of 15 defined daily doses (DDD). Based on the dosage written by the prescriber, the algorithm determines that the prescribed daily dose is equal to 2 tablets of 250mg (i.e. 500mg). According to the national drug database, this dosage corresponds to 25% of the defined daily dose for this specific drug. Thus, the individual was covered for 15 ÷ 0.25 = 60 days, assuming that he or she used the drug as prescribed.

For every dispensed drug, we calculated the duration of exposure by applying the procedure shown in **Figure 9**. First, we extracted the dispensing date and the total dispensed amount expressed as a number of defined daily doses. Second, a rule-based text parsing algorithm was used to transform the dosage reported by the prescriber in free text (e.g. "One tablet at 8am and one tablet before dinner") into a numerical estimate of the prescribed daily dose (e.g. 2 x 250mg = 500mg). Third, this prescribed daily dose was converted to defined daily doses with a lookup table (e.g. 500mg = 0.25 DDD). In the fourth and final step of the process, assuming that patients took their drugs at the prescribed dosage, the total number of defined daily doses filled by the patient was divided by the prescribed daily dose to obtain an estimation of the number of days covered (e.g. 15 DDDs ÷ 0.25 = 60 days). Drugs dispensed in multidose disposable strip pouches were assumed to be prescribed for a duration of 14 days.[601]

When no information was available regarding the actual dosage (**Box 2**), we imputed the prescribed daily dose by using the year-specific average in the population. Drugs prescribed as needed were assumed to have a dosage equal to 50% of the average daily dose in the population. Finally, we used the defined daily doses as a proxy for the prescribed daily dose of dermatological drugs and eye preparations.[602] Once the number of days covered was estimated for each dispensing episode, periods of drug exposure were constructed with regards to the date of death of study participants. This enable for investigating changes over time in drug exposure, or to calculate the prevalence of a polypharmacy during a given period (**Figure 10**). In the first and second studies, we split the last year of life into twelve consecutive 30-day periods. In our fourth study, we considered 3-month time periods in order to calculate the proportion of older adults who continued/initiated drugs of limited benefit.

To evaluate the completeness of dosage information in the Swedish Prescribed Drug Register, we extracted a random sample of 100 000 persons aged ≥65 years on 1 January 2013 from the total Swedish population. Among these individuals, 90 586 were dispensed at least one drug in 2012. They filled a total of 3.1 million drugs during that period, scattered across 9375 unique pharmaceutical products (national drug codes) and 1123 chemical substance groups (ATC codes). Of these, 1.22 million drugs (39.3%) were dispensed in multidose strip pouches covering 14 days at a time. Among the remaining 1.88 million drugs dispensed through community pharmacies, 2.9% were non-therapeutic products, 4.5% were eye preparations, 3.3% were dermatological drugs, 1.7% were Vitamin K antagonists (dosage is adjusted according to the target international normalized ratio [INR]), 1.6% were insulins and analogues (dosage is adjusted according to the targeted haemoglobin A1c and blood glucose levels), and 13.6% of drugs were prescribed "as needed" thus resulting in less precise estimates of the number of days covered. While only 0.9% drugs were dispensed with no information whatsoever about the prescribed daily dose, 2.1% did not have sufficient documentation to enable the text-parsing algorithm to extract a numerical estimate of the prescribed daily dose. In addition, ~1% of dispensed drugs were documented with complex dosage information that the text-parsing algorithm could not interpret (e.g. "4 tablets in 1 day for the first two weeks, thereafter 6 tablets per week for rheumatoid arthritis"). For the remaining drugs, the estimated number of days covered seems highly accurate: we obtained a 96% agreement when comparing our automated algorithm with manual calculations in a random sample of 1000 filled prescriptions.

Box 2. Completeness of dosage information in the Swedish Prescribed Drug Register

Drug	Amount dispensed	Prescribed daily dose	No. days covered	Month -3	Month -2	Month -1		
Drug A	18 DDDs	1g = 0.2 DDDs	90					
Drug B	36 DDDs	250ml = 0.6 DDDs	60					
Drug C	15 DDDs	2mg = 0.5 DDDs	30					
Drug D	20 DDDs	2 drops = 1 DDD	20					
Drug E	12 DDDs	1.5g = 0.25 DDDs	48					
Drug F	15 DDDs	2ml = 0.17 DDDs	90					
Number of drugs **dispensed** during each period				3	1	2	0	0
Number of drugs potentially **taken** during each period				3	4	5	0	0

Figure 10. Construction of drug exposure periods

In this example, monthly periods of exposure are constructed for 6 different drugs. The thick vertical back represents the date of death. For each drug, the cap represents the date of dispensing, and the arrow the number of days covered. Hence, during the final month before death, this individual filled only 2 prescription drugs but potentially took 3 other drugs that he/she had filled before (total: 5 drugs).

3.4 ESTIMATION OF DRUG COSTS

In our second study, we investigated not only the *use* but also the *costs* of preventive drugs throughout the last year of life. Preventive drugs were defined on the basis of a recent systematic review by Todd et al.[603], and included drugs for diabetes (ATC codes A10A, A10B), vitamins (A11), mineral supplements (A12), antithrombotic agents (B01A), antihypertensives (C02, C03A, C03B, C07, C08 excl. C08D, and C09), statins (C10AA), bisphosphonates (M05B), and medications for chronic anaemia (B03A). Drug costs were defined as the combined amount paid by the county council under the pharmaceutical benefits scheme and by the patient as out-of-pocket costs. The latter represents ~20% of the total costs of prescription drugs during the final year of life. To avoid artificially concentrating costs around the dispensing date, we distributed costs over time by following a 2-step approach depicted in **Figure 11**.

Drug	Purchase cost (USD)	Daily cost	No. days covered	Month -3	Month -2	Month -1		
Drug A	$135	$1.50	15 + 30 + 30					
Drug B	$30	$0.50	10 + 30 + 20					
Drug C	$90	$3.00	0 + 0 + 10					
Drug D	$200	$10.0	0 + 0 + 20					
Drug E	$96	$0.50	30 + 18 + 0					
Drug F	$360	$4.00	0 + 15 + 30					
Costs of drugs **dispensed** during each period				$261	$360	$290	$0	$0
Costs of drugs **potentially taken** during each period				$42.5	$129	$405	$0	$0

Figure 11. Estimation of drug expenditures across exposure periods

The costs of drugs dispensed during a given month are calculated as the sum of the total market price of each prescription drug filled during that month (e.g. 135 + 30 + 96 = $261 for Month-3). In contrast, the costs of drugs potentially taken during a given month are equivalised according to the number of days covered by each drug during that month (daily cost x number of days covered). Depending on the metric used, estimated drug expenditures vary substantially. Abbreviation: USD, US dollars.

First, we divided the total cost of each dispensed drug by the estimated number of days covered in order to obtain its daily cost – based on the assumption that patients used each drug at a constant dosage until the next purchase. Second, we multiplied the daily cost by the number of days covered during each of the 12 months before death to equivalise drugs expenditures according to the estimated duration of exposure. After summing up the estimated monthly costs of the drugs of interest, we standardised the obtained values by using the harmonised index of consumer prices (HICP) in order to correct for inflation between 2007 and 2013.[604,605] Costs were then converted from Swedish Kronor (SEK) into US dollars (USD) based on Sweden's Central Bank annual average exchange rate from 1 January to 31 December 2013 to facilitate international comparisons (1 SEK = 0.1535 USD).

3.5 INDIVIDUAL CHARACTERISTICS

Sociodemographic characteristics

In Studies I, II, and IV, the sex and date of birth of decedents were extracted from the National Cause of Death Register and were cross-validated for quality control with data from the Total Population Register. To protect data anonymity and prevent the re-identification of individual patients, the date of birth was truncated by removing the day of death and replacing it with the mid-month value (i.e. 15 or 16). The age at time of death was thus calculated as the difference between the pseudo birthday and the date of death.

The level of education of decedents was assessed through deterministic record linkage with the Swedish Register of Education. We categorised their lifetime highest educational attainment according to the SUN2000 and ISCED-97 classification systems as primary, secondary or tertiary education.[593,606] This categorisation is detailed in Table 9**.** Since primary schooling was made compulsory in Sweden in 1842 (with an extension from 6 to 7 years in 1936-37)[607] and since our cohort of older adults who died between 2007 and 2015 was born between 1899 and 1950, we have no record of persons with no formal education. However, 25 838 out of 703 863 decedents (3.7%) had missing information about their level of education, ranging from 6.8% in 2007 to 2.2% in 2015.

Level of education	Categories	ISCED97	SUN2000
Primary education	Primary education or first stage of basic education	1	100
Secondary education	Lower secondary education	2A	200-206
	Upper secondary education ≤ 2 years	3C	310-327
	Upper secondary education ≥3 years	3A	330–337
	Post-secondary, non-tertiary education <2 years	4C, 4A	410–417
Tertiary education	Tertiary education for practical/ technical occupations	5B	520–527
	Tertiary or academic education giving access to professions with high skills requirements	5A	530–557
	Post-graduate education (licentiate/doctorate)	6	600–640

Table 9. Categorisation of educational levels in the present thesis

Chronic diseases and multimorbidity

Studies I, II and IV made use of the methodological approach proposed by Calderón-Larrañaga et al. to identify chronic conditions and to appraise the burden of multimorbidity among older adults.[320] Briefly, it consists of a clinically-driven list of 60 chronic conditions selected by a multidisciplinary team of epidemiologists, geriatricians, and general practitioners, who defined as 'chronic' any long-lasting disease or conditions that leads to (1) residual disability or impaired quality of life or (2) a prolonged period of care, treatment or rehabilitation. This tool was primarily developed for the purpose of measuring multimorbidity in population-based cohort studies, where self-reported and clinician-reported clinical diagnoses, medical journals, and biological parameters are typically available. It has for instance been used with data from the SNAC-K cohort (~3000 older adults ≥60 years followed since 2001) to identify clusters of chronic diseases or to investigate the potential role of various life experiences in the speed at which chronic diseases accumulate in old age.[608,609] However, it can also be implemented in routinely collected administrative and healthcare data.[610]

In Study I, we considered the full list of 60 chronic diseases, which we identified by using three distinct sources of information: the ICD-10 codes from the National Cause of Death (underlying and contributing causes of death), the ICD-10 codes reported in the National Patient Register for all inpatient admissions and specialised outpatient visits during the last 2 years before death, and ATC codes extracted from the Swedish Prescribed Drug Register for specific medications dispensed during the last 2 years before death. In Study II, we made two minor adjustments to this methodology: we first removed solid tumours and haematological malignancies from the list of chronic conditions (since the former was the main eligibility criteria and the latter was one of the exclusion criteria), and we then extended the lookback period to 3 years for capturing ICD-10 codes in the National Patient Register and in the Swedish Prescribed Drug Register.

In Study IV, we further refined this approach to improve its sensitivity and increase the detection of chronic conditions. For this purpose, we extended the lookback period to 5 years before death while excluding the last 3 months of life (since this was the time window used for assessing the outcomes). In addition, we discarded 5 conditions that we believe are more likely to be the symptoms of an underlying disease rather than distinct nosological entities (anaemia, asthma, chronic ulcer of the skin, colitis and diarrhoea, and sleep disorders) as well as 4 conditions that, in our experience, tend to be poorly reported in routinely collected data (allergies, dorsopathies, dyslipidaemia, and obesity). Finally, we supplemented ICD-10 and ATC codes with semi-structured information from the Swedish Prescribed Drug Register. A rule-based text parsing algorithm was developed to extract relevant clinical indications from the prescribed dosages mentioned by the prescribers in free text. This novel methodology has the advantage of capturing chronic diseases of mild-to-moderate severity that are likely to be underreported in hospital records (e.g. hypertension, COPD, atrial fibrillation, osteoporosis, depression).

Hospital Frailty Risk Score

In Study IV, we computed the Hospital Frailty Risk Score of each individual based on inpatient and specialised outpatient care diagnoses reported during a period ranging from 5 years to 3 months before death. The Hospital Frailty Score was recently proposed by Gilbert et al. (United Kingdom) in an attempt to automatize the identification of older adults at high risk of adverse outcomes due to frailty syndromes, based solely on clinical diagnoses reported in inpatient electronic records.[611] Briefly, this tool was developed in 3 consecutive steps: (1) a data-driven cluster analysis was carried out to confirm that a 'frail' group of older patients could be delineated based on their ICD-10 codes, length of hospitalisation, and hospital costs; (2) a risk score was calculated by using ICD-10 codes that were substantially over-represented in the 'frail' group and by weighting each of these codes proportionally to how strongly they predicted cluster membership based on logistic regression coefficients; (3) this weighted score was applied in two distinct validation datasets. First, the association between the Hospital Frailty Risk Score and various outcomes (e.g. 30-day mortality) was assessed based on Hospital Episode Statistics (HES) data in a national cohort of older adults aged ≥75 years who experienced a non-elective admission in 2014–2015. Second, the authors used a local database linked to HES data to test whether older adults identified as frail according to the Hospital Frailty Risk Score overlapped with those captured when using a validated, clinician-administered frailty scale (either the Fried phenotype[333] or the Rockwood Frailty Index[332]). Although in this study the Hospital Frailty Risk Score itself showed only moderate performance to predict 30-day mortality and a fair degree of correspondence with other frailty assessment tools, its implementation from ICD-10 codes rather than primary care Read codes (used to calculate the electronic frailty index[363,612]) is a key advantage. Moreover, some of our recent work suggests that this score can be useful to stratify older adults according to their risk of adverse event or nursing home admission (**Table 10**).

Hospital Frailty Risk Score	Incidence rate (95% CI)	Crude HR	Adjusted HR (sex, age)
All-cause mortality			
Low risk (<5)	40 (39–41)	1	1
Moderate risk (5–15)	109 (104–114)	2.74 (2.58–2.91)	2.32 (2.19–2.46)
High risk (>15)	201 (182–222)	5.07 (4.56–5.64)	3.96 (3.56–4.41)
Non-elective hospitalisation			
Low risk (<5)	230 (226–233)	1	1
Moderate risk (5–15)	530 (517–542)	2.29 (2.22–2.35)	2.09 (2.03–2.15)
High risk (>15)	926 (875–980)	3.96 (3.73–4.20)	3.46 (3.26–3.67)
Nursing home admission			
Low risk (<5)	29 (28–30)	1	1
Moderate risk (5–15)	109 (104–114)	3.75 (3.52–4.00)	2.99 (2.80–3.18)
High risk (>15)	257 (234–282)	8.82 (7.97–9.76)	6.49 (5.85–7.18)

Table 10. Association between baseline Hospital Frailty Risk Score and selected outcomes

Cohort of 100 000 community dwellers selected randomly from the total Swedish population alive on 1 June 2013 and followed-up for 1 year or until the occurrence of a censoring event. Hazard Ratios (HR) were calculated with Cox proportional hazard regression models and are reported with 95% confidence intervals (CI).

Living arrangement

The living arrangement of individuals during their last year of life was defined as community-dwelling or nursing home, based on data from the Social Services Register. It is notoriously challenging to establish whether various institutional care facilities for older adults can be labelled as 'nursing homes' as there is much ambiguity around this term in the international literature.[613,614] In Sweden, municipalities are primarily responsible for organising social care services and elderly care. This leads to much heterogeneity in what 'special housing facilities' (Swedish: *särskilt boende*) actually refer to depending on their geographical location.[615,616] However, all of these facilities meet the basic criteria proposed in 2015 by Sanford et al.[617]: (1) they provides 24-hour functional support for older adults who require assistance with activities of daily living and have complex health needs and/or moderate-to-severe cognitive impairment; (2) they are staffed with trained health care professionals; (3) they provide long-term care as part of hospital avoidance or to facilitate early hospital discharges; (4) they are not hospital-based and do not function as hospital wards; (5) they provide palliative care at the end of life.[618]

In the first and second studies, we categorised as nursing home residents any decedent who had been admitted into a nursing home either before the final year of life or during one of the last 12 months of life, excluding older persons who died shortly after their admission (<15 days). In the fourth study, the living arrangement of decedents was defined by using a lookback period ranging from 12 to 3 months before death. This was done not only because the quality of the Social Services Register was substantially improved in 2015 compared with 2007–2013 (there was, therefore, no need to extend the lookback period beyond 12 months), but also because the last 3 months of life were used to assess the outcomes of interest.

Place of death

On Swedish death certificates, the place of death is defined as either 'Home', 'Hospital', 'Nursing Home', or 'Other'. This variable was however missing for 7.7% of all decedents aged ≥65 years (2007–2015), declining from 10.3% in 2007 to 5.0% in 2015. By cross-referencing data from the National Cause of Death Register with information from the National Patient Register and from the Social Services Register, we reduced missing values to 5.3% overall (2.0% in 2015). In Study II, for clarity, we grouped the places of death into 'Usual place of living' (i.e. home or nursing home) and 'Hospital facility'.

Marital status

The marital status of decedents was only available to us for the fourth and final study. It was ascertained with data from the National Cause of Death linked to the Total Population Register. Individuals were categorised as 'Married', 'Single or divorced' or 'Widowed'. Missing values (< 0.01%) were completed through record linkage by using the spouses' unique identifier to capture recent, unreported cases of spousal loss.

3.6 STATISTICAL ANALYSES

Overall

In all four studies, the participants' characteristics were reported by using absolute numbers and percentages, or means and standard deviations (SD), when appropriate. Statistical analyses were performed with SAS JMP® versions 12.1, 13.0, and 14.1 (SAS Institute, Cary, NC) and Stata® version 14.1 (StataCorp, College Station, TX) software.

Polypharmacy and number of drugs throughout the last year of life

We calculated the monthly prevalence of polypharmacy as the proportion of individuals who were exposed to ≥10 different drugs during each of the last 12 months before death. In addition, we computed the average number of prescription drugs over the course of the last year of life. Descriptive results comparing community-dwellers and nursing home residents were standardised for both sex and age, based on the structure of the total study population (direct standardisation approach). The prevalence of the 20 most commonly prescribed drugs and drug classes was calculated for the 12^{th} month, the 6^{th} month, and the last month before death.

To examine trends in polypharmacy throughout the last year of life, we first calculated the relative change in the prevalence of polypharmacy between the 12^{th} month and the final month before death. Second, logistic regression models were fit to estimate the odds of being exposed to ≥10 drugs during the final month before death compared with 12 months before, with time as the sole independent variable. We used robust standard errors to account for correlation of observations within individuals.

We identified the factors associated with the magnitude of change in the number of prescription drugs throughout the last year of life by fitting generalised estimating equation (GEE) models with a factor $\times$ time interaction term. These models produce population-averaged effect estimates for panel data, where the β coefficient for the interaction term can be interpreted as the rate of change over time conditional on a given set of parameters (e.g. the rate of change among women compared with that of men, while adjusting for age and end-of-life illness trajectory). GEE models were specified with a Gaussian distribution, an *identity* link function, and unstructured within-group correlation. Results are presented as adjusted β coefficients with their 95% confidence intervals (CIs). In sensitivity analyses, the same models were computed by removing analgesics from the total number of drugs.

Preventive drugs among older adults with cancer at the end of life

Variation in the use of preventive drugs over the course of the last year of life of older adults with solid cancer was first assessed by calculating, for each drug class separately, the absolute change in the prevalence rate between the 12^{th} month and the final month

before death. Absolute change was reported in percentage points with 95% CIs. We also examined the continuation and initiation of preventive drugs during the last year of life. Continuation rate was calculated as the percentage of older adults who were exposed to a given drug class of during the last month before death among those already exposed 1 year before. The initiation rate was calculated as the percentage of decedents who were dispensed a given drug class during the last year of life (namely, between the 11th and the final month before death) among those not exposed during the 12th month before death.

The overall costs of prescription drugs and the costs of preventive drugs per capita were calculated according to the procedure detailed earlier (see page 62) and stratified by cancer type. Because healthcare cost data tend to be highly skewed to the right (i.e. gamma-shaped distribution, where most data points fall to the left of the mean)[619,620], we reported the median and interquartile range of drug costs rather than their mean for descriptive purposes. In addition, the proportion of the total drug costs dedicated to preventive drugs was calculated for the entire last year of life, the 12th month and the final month before death.

We used quantile regression models to analyse drug costs across cancer types while adjusting on sex, age, number of chronic comorbidities, living arrangement and level of education. While linear regression allows for modelling the mean of an outcome of interest, quantile regression is used to model it quantiles (e.g. median).[621,622] The β coefficients obtained from quantile regressions can be interpreted as the adjusted median difference (AMD) in costs compared with the reference group. To ensure that the average median effects were concordant – in both direction and magnitude – with the average mean effects, we compared our results with estimates calculated by fitting Generalised Linear Models (GLM) with a log link function and a gamma distribution. GML models have the advantage of being more flexible than ordinary least square regressions, they do not require a log transformation of the outcome (which, by nature, makes it impossible to account for observations with zero costs and thus leads to biased estimates), and they correct for heteroscedastic errors.[623,624] The β coefficients were reported together with their 95% CIs. Two sets of sensitivity analyses were performed to mitigate the risk of bias due to the potentially unpredictable time of death of older adults with cancer, which would explain why preventive drugs were continued until the very end of life. First, we excluded patients whose underlying cause of death suggested an acute and potentially unpredictable fatal event (e.g. stroke with no prior history of ischemic heart disease). Second, we stratified our analyses according to the lag between cancer diagnosis and death, thereby differentiating older adults who were diagnosed >12 months before death from those who died within 6 months after their diagnosis. Individuals with missing data regarding the time between diagnosis and death (n= 7863 patients; 5.2%) were excluded from this sensitivity analysis. We tested for the difference in the median cost of preventive drugs according to the timing of diagnosis by using non-parametric Wilcoxon rank sum test.

Use of drugs of questionable clinical benefit at the end of life

In the fourth and final study of the present thesis, drugs of questionable clinical benefit near the end of life were defined according to the set of consensus-based criteria developed in Study III (see section 3.7 below). Although this list also encompasses drugs deemed 'questionable' for use among older adults with a remaining life expectancy of <3 months, we restricted our study to drugs considered 'often inadequate' and—out of caution—referred to them as drugs of questionable clinical benefit.

The main outcomes were the *continuation* and the *initiation* of drugs of questionable clinical benefit during the last 3 months of life. Continuation was defined as the dispensing of at one such drug during the 91-day period before death, among older persons who had initiated the treatment before. Initiation was defined as the dispensing of at least one drug of questionable clinical benefit during the 91-day period before death among individuals who had not been treated with the same drug during the 9-month period prior (i.e. between 365 and 92 days before death). Individuals who were potentially exposed to drugs of questionable clinical benefit during the last 3 months of life but did not refill their prescription were considered as having discontinued their treatment.

To identify factors independently associated with the *continuation* or the *initiation* of drugs of questionable clinical benefit near the end of life, we fitted log-binomial regression models (i.e. GLM models with log link function and binomial distribution). Log-binomial models have the advantage of estimating risk ratios (RR) rather than odds ratios (OR), and thus to avoid overestimating the effect estimates in cohort studies when the outcome of interest is common.[625] RRs and 95% CIs were adjusted for sex, age at time of death, illness trajectory, number of chronic diseases, Hospital Frailty Risk Score, living arrangement, marital status, and level of education. Decedents with missing data about their level of education (2.2%) were excluded from multivariable analyses.

We carried out a series of sensitivity and subgroup analyses. First, much like in Study II, we removed older adults whose underlying cause of death suggested an acute and potentially unpredictable fatal event from the study population. This was done to examine whether the observed patterns of drug utilisation near the end of life were substantially different among older adults whose death may not have been anticipated despite the presence of a life-limiting disease (e.g. pneumonia, accident, suicide). In subgroup analyses, we examined patterns of continuation and initiation of drugs of clinical benefit at the end of life across illness trajectories and living arrangements.

3.7 DELPHI CONSENSUS

Objectives of the Delphi consensus survey

The third study of the present thesis (Study III), we aimed to develop consensus-based criteria to identify prescription drugs most likely 'adequate', 'questionable' or 'inadequate' for older persons aged ≥75 years with an estimated life expectancy of 3 months or less. More specifically, we set two specifications for these criteria: (1) they should provide guidance for prescribers caring for older patients nearing the end of life; and (2) they should be easily applicable in routinely collected healthcare and administrative data.

The Delphi methodology

The Delphi method is an approach developed in the late 50s and early 60s by the U.S. non-profit think tank RAND as a structured, systematic, interactive, and iterative method for eliciting and refining expert opinion in order to provide long-range forecasting and to improve decision-making process on topics for which empirical evidence is either lacking or inconsistent.[626,627] Olaf Helmer-Hirschberg, one of its architects, defined it as "a systematic procedure for obtaining the opinions of experts on a particular subject."[628]

In practical terms, the Delphi procedure relies on a panel of experts who have extensive knowledge of the area of interest (in this case, drug prescribing for older adults near the end of life) and who are asked to formulate a judgment about a set of questions or items over two or more rounds. The procedure has three key features: (1) anonymity, not only to reduce the influence that the authority, reputation or personality of some participants may have on the opinion that other participants express, but also to allow respondents to deviate from dominant theories, beliefs or views; (2) controlled feedback, namely providing participants with a summary of the results after each round in order to give them the opportunity to revise their own opinion iteratively; (3) the statistical group response is defined *a priori*, which reduces the pressure for conformity and ensures that the judgment of every panel participant is accounted for.[627] Contrary to nominal group discussion techniques and consensus development conferences, the Delphi method does not require face-to-face meetings. This methodology has been used previously to develop consensus-based lists of potentially inappropriate drugs for older adults, including earlier versions of the Beers criteria, the STOPP/START tool, or more recently the EURO-FORTA list (see Table 5, page 48).[629–632] More generally, the Delphi technique is a commonly used for developing and selecting healthcare quality indicators.[633]

Selection of tentative criteria

To identify drugs and drug classes deemed potentially adequate or inadequate for use among older adults in the context of palliative and end-of-life care, we first conducted a scoping review of the literature to update the findings from Todd et al. (which were first published on 5 January 2016).[603] This review included original, quantitative studies

published between January 1990 and March 2016. We later updated the search to include studies published until June 2017. Methodological details are presented in **Table 11**. Overall, our review included 47 articles, 9 of which were published after March 2016 (see **Appendix Table**). Based on this material, a preliminary list of 49 drug classes was prepared by our multidisciplinary research team, consisting of two clinical pharmacologists, one pharmacist, one geriatrician, and one pharmaco-epidemiologist. We included pharmacological subgroups (e.g. drugs for peptic ulcer and gastro-oesophageal reflux) rather than individual drugs (e.g. omeprazole). Since this study was focused on prescription drugs, other types of medical treatments such as herbal products, mechanical ventilation, or tube feeding were not included.

Aims	To investigate the use of medications among adult patients with life-limiting conditions near the end of life, and to identify potentially *adequate* and *inadequate* drugs in this context.
Inclusion criteria	Original, quantitative studies published between January 1, 1990 and March 30, 2016, describing the use of drug treatments among adult patients at the advanced stage of a serious and incurable disease with limited life expectancy.
Exclusion criteria	Narrative studies, reviews or original studies published before 1990. Publications in another language than English were not considered.
Search strategy	MEDLINE/PubMed search, combining MeSH terms with specific keywords. This online database search was completed by a manual screening of previous systematic reviews (Maddison, 2011[634]; Todd, 2017[603]; Leblanc, 2015[635])

Table 11. Summary protocol of the scoping review undertaken prior to the Delphi survey

Selection of panellists

The Delphi panel consisted of European clinicians and researchers with a high degree of expertise about drug prescribing for older adults with limited life expectancy. Only healthcare professionals with clinical experience in either palliative medicine, geriatrics, family medicine, or pharmacology were eligible for inclusion. Potential participants were identified through a literature review, selecting principal investigators and corresponding authors of recent original studies on the same topic. To broaden the panel of experts and avoid 'academic homogamy', we also asked key informants to provide the name and contact information of potentially eligible clinicians. Overall, 58 experts from 10 different European countries were invited to participate. Age, gender, occupational, and geographical balance were ensured during the panel selection. Eligible panellists were sent an email invitation, which presented the aims of the study and the main features of the Delphi procedure. Those who agreed to participate were required to sign an electronic consent form and were informed that they could withdraw from the Delphi survey at any time. Their anonymity was ensured throughout the procedure, and panellists could choose whether they want to be acknowledged for their participation or not. No financial incentive was provided.

Delphi survey

The tentative list of drug classes established based on the literature was submitted to the panellists through a web-based interactive survey, hosted on a secure platform (Artologik *Survey&Report*® software, version 4.3). Panellists were asked to consider the situation of older adults aged ≥75 years with an estimated life expectancy of 3 months or less, regardless of their underlying condition and regardless of the clinical indication of the drug. They were explicitly instructed to take into account the need to ensure impeccable symptom management, the obligation to minimise the risk of adverse drug-related event, and the potential futility of drug treatments in the context of very limited life expectancy.

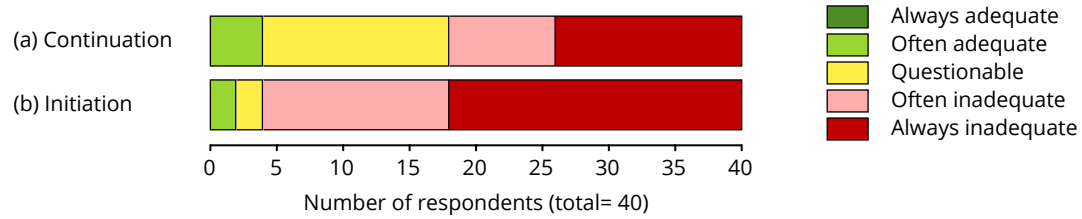
For each drug class, we distinguished two scenarios: (1) the continuation of a drug class that was previously prescribed, and (2) the initiation of a new drug. Panellists were asked the following question: "In your opinion, in older adults (≥75 years) with an estimated life expectancy of 3 months or less, how adequate or inadequate are the *continuation* and *initiation* of the following drugs or drug classes?". They provided their answer by using a 5-point, non-numerical Likert scale ('Always inadequate', 'Often inadequate', 'Questionable', 'Often adequate', or 'Always adequate'). They also had the opportunity to suggest breaking down large drug classes into specific drugs or adding drugs or drug classes that were not included in the preliminary list, and to leave comment in free text.

The first round took place between 1 June and 31 August 2016. Participants were informed that consensus would be achieved if at least 75% (30 out of 40) panellists rated a given drug class as either 'Always/often inadequate' or 'Always/often adequate'. Drugs for which consensus was reached at this stage were not reviewed again during the subsequent rounds. The second round took place between 1 November and 31 December 2016. The panellists were provided with controlled feedback consisting of aggregated results for each drug class evaluated during the first round as well as comments and suggestions from the other participants. Based on this feedback, they were asked to re-evaluate the drug classes for which consensus had not been achieved, and to provide their expert opinion about the drugs or drug classes suggested by the participants. They were also invited to leave any comment or suggestion about the different items (**Figure 12**).

We analysed the results from the second round by calculating the degree of agreement for each criterion. Drugs and drug classes that were rated as 'Always' or 'often adequate" by ≥75% of the respondents were included in the list and labelled as 'Often adequate'. Likewise, drugs rates as 'Always' or 'often inadequate" by ≥75% of the respondents were included in the list and labelled as 'Often inadequate'. The remaining drugs and drug classes were defined as 'Questionable' if they were rated either 'questionable', 'often', or 'always inadequate' by ≥75% of respondents. Drugs with a moderate (65–74%) or low (<65%) level of agreement were not included in the final list. This study adheres to the CREDES guidelines on conducting and reporting Delphi studies in palliative care.[636]

Anti-dementia drugs
(ATC codes N06DA, N06DX01)

Results from the first Delphi round:



Conclusions from the first round:
(a) Regarding the continuation of this drug class: no consensus yet
(b) Regarding the initiation of this drug class: consensus (initiating anti-dementia drugs is often inadequate)

Suggestions from the respondents:
Consider anticholinesterases (e.g. donepezil, rivastigmine, galantamine) and memantine separately

Second Delphi round:

In your opinion, in older adults (≥75 years) with an estimated life expectancy of 3 months or less, how adequate or inadequate is the **initiation** of the following drugs or drug classes?

	Initiating this drug (or drug class) is...				
	Always inadequate	Often inadequate	Questionable	Often adequate	Always adequate
Anticholinesterases (N06DA)	◯	◯	◯	◯	◯
Memantine (N06DX01)	◯	◯	◯	◯	◯

You can write your comments, remarks, and suggestions here:

**Please note that clicking on any ATC code gives you a direct access to the ATC classification (WHOCC website).*

Figure 12. Example of controlled feedback and second round of Delphi procedure

In this example, panellists were asked to rate the adequateness or inadequateness of anti-dementia drugs. In the upper part of the questionnaire, the drug or drug class of interest is described with its ATC code in order to prevent any ambiguity. In the second part, a stacked-bar graph shows the aggregated results of the first round of the Delphi survey. It appears that while the panellists' opinion was heterogenous regarding the *continuation* of anti-dementia drugs near the end of life, there was a high degree of agreement to consider *initiation* either 'often' or 'always' inadequate (36 / 40 = 90%). Therefore, only the *continuation* of anti-dementia drugs was submitted for review during the second round. The panellists also suggested to break down the drug class 'anti-dementia drugs' into more precise items: acetylcholinesterase (AChE) inhibitors on the one hand, and memantine (a NMDA receptor antagonist) on the other hand. During the second round, the respondents were therefore presented with the possibility of rating both drug classes separately. They could also provide free-text comments and suggestions.

3.8 ETHICAL CONSIDERATIONS

The four studies that compose the present thesis were all approved by Stockholm's Regional Ethical Review Board (**Table 12**). Studies I, II, and IV are based on de-identified, routinely collected administrative and healthcare data. The use of such data for academic research purposes raises two important ethical issues: the lack of informed consent from the persons included in the studies, and the need to protect health and personal privacy.

Informed consent is a tenet of medical research. It is of paramount importance in clinical trials and other interventional studies, since the participants must be able to make their own assessment of the risks associated with the experiment.[637,638] In other words, the obligation to obtain informed consent from research participants matches the bioethical principle of respect for personal autonomy.[639,640] However, since routinely collected administrative and healthcare data require, by definition, no *ad hoc* intervention or data collection, study participants are not exposed to the potential harms of physically or psychologically invasive procedures that usually come with biomedical research. This argument alone could potentially justify waiving the obligation of informed consent, provided that adequate mechanisms are in place to allow individuals to opt-out if desired.[641,642] In addition, requiring written informed consent from each person whose personal data were collected in a national register would often prove unfeasible or prohibitively expensive. This is particularly true for retrospective cohort studies of decedents, which is the case of Study I, Study II, and Study IV.

In fact, it could be argued that collecting data specifically for research purposes (i.e. prospective or retrospective study by questionnaire or face-to-face interviews) would prove more invasive for the study participants or their relatives, less reliable in terms of data quality, and more prone to selective participation. By conducting research after the death of the individuals with routinely collected data, epidemiologists make sure that their investigation does not have any direct or indirect incidence on the persons, namely that it doesn't interfere with the provision of care and the psychological wellbeing of the patient and his/her relatives). A recent qualitative study in the United Kingdom suggests that there is a strong support from patients and family members regarding the secondary use of de-identified electronic health records in research, provided that data were not shared with for-profit organisations and were handled in a secure manner.[643] These findings resonate with the increasing scrutiny of stakeholders[644,645] and with the pressing societal demand for transparency and trust in the use of big data.[646–648]

Health and personal privacy are of particular concern when dealing with sensitive data.[649] The personal integrity of individuals included in a registry could for instance be compromised if their anonymity was not ensured.[650] This risk was mitigated by the register holders (*Socialstyrelsen* and *Statistics Sweden*), who de-identified the records. The pseudo-identifiers used by our research team did not allow for tracing back the information to a given individual. In addition, some individual data have been aggregated

into categories to prevent any attempt of backward-identification: detailed zip codes were for instance not available, and the exact birthday was replaced by a dummy value (YYYY-MM-15).

In Study III, study participants were physicians and pharmacists who agreed to take part in a Delphi consensus panel. Before the survey was conducted, all participants signed an electronic consent form that explicitly mentioned the aims of the study, the procedure, the possibility to withdraw at any time, the means and methods used to analyse and safely store all data material, the confidential nature of their personal data, and the opportunity to be acknowledged in the ensuing publication if desired. No financial incentive was offered.

All studies included in the present thesis comply with the Ethical Principles for Medical Research Involving Human Subjects stated in the World Medical Association Declaration of Helsinki, and with the "Good research practice" guidelines of the Swedish Research Council (Swedish: *Vetenskapsrådet*).

Study	Title of the application	Date application	Date decision	DNR reference
Studies I & II	Drug use as risk, protective or predictive factor for care utilisation, dementia and mortality: a register-based project	2013-11-05	2013-12-04	2013/1941-31/3
Studies I & II	Amendment to DNR 2013/1941-31/3	2015-08-03	2015-08-19	2015/1319-32
Study III	Läkemedelsbehandling i livets slutskede	2015-08-03	2015-09-02	2015/1341-31/1
Study IV	Frisk till livets slut? Hälsa, funktionsförmåga, vård och läkemedelsbehandling hos äldre	2016-05-09	2016-06-08	2016/1001-31/4

Table 12. Overview of ethical permits

4. MAIN FINDINGS

4.1 GENERAL CHARACTERISTICS OF THE STUDY POPULATION

Between 1 January 2007 and 31 December 2015, a total of 703 863 persons aged ≥65 years died in Sweden. Of them, 671 754 (95.5%) met our general eligibility criteria. Women accounted for 53.9% of the decedents and the mean age at death was 84.1 (SD 8.2) years. The most commonly reported underlying causes of death were ischaemic heart diseases (17%), dementias (9%), cerebrovascular diseases (9%), digestive cancers (7%), and heart failure (5%). Over time, there was a subtle yet evident increase in the proportion of older adults who died from cancer or neurodegenerative diseases, as well as a noticeable decrease in the proportion of those who died from organ failure (**Table 13**). The proportion of decedents who had only attended compulsory primary school declined substantially, from 58.5% in 2007 to 46.5% in 2015. The proportion of hospital deaths remained stable (~41%).

A striking characteristic was the substantial burden of chronic multimorbidity at the end of life. On average, older adults who died in 2015 had 6.6 (SD 3.2) co-existing chronic conditions, and nearly 18% had 10 or more chronic diseases diagnosed at time of death. This multimorbidity was primarily fuelled by the high prevalence of cardiovascular diseases, solid tumours, depression, diabetes, and dementia (**Figure 13**)

As mentioned earlier (see *3.2 Study designs and populations*), specific eligibility criteria were applied in each study. The first study included 511 843 older persons who died between 2007 and 2013 of any cause. The second study included 151 201 older persons diagnosed with solid cancer who died during the same period. The fourth study included 58 415 individuals aged ≥75 years who died from conditions potentially amenable to palliative care. Their characteristics are reported in the corresponding articles.

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Women, %	54.6%	54.3%	54.0%	53.9%	53.9%	54.0%	53.9%	53.4%	53.3%
Age in years, median	84.9	85.0	85.1	85.2	85.3	85.4	85.2	85.2	85.3
Level of education, %									
Primary	58.5%	57.2%	55.8%	54.4%	53.1%	51.6%	49.7%	48.1%	46.4%
Secondary	32.9%	33.9%	34.8%	35.7%	36.8%	37.7%	38.9%	39.9%	41.4%
Tertiary	8.6%	8.9%	9.3%	9.9%	10.1%	10.7%	11.4%	12.0%	12.2%
Illness trajectory, %									
Cancer	27.8%	27.9%	28.3%	28.6%	29.0%	28.8%	29.3%	30.1%	29.9%
Organ failure	40.8%	40.5%	39.8%	38.8%	38.0%	37.6%	37.2%	36.7%	36.4%
Prolonged dwindling	23.5%	23.7%	24.2%	25.2%	25.7%	26.3%	26.1%	26.0%	26.3%
Sudden death	7.9%	8.0%	7.7%	7.4%	7.3%	7.3%	7.4%	7.2%	7.4%
Hospital deaths, %	41.6%	42.0%	41.8%	41.4%	41.0%	41.2%	41.8%	41.9%	41.1%

Table 13. Main characteristics of older adults (≥65 years) who died in Sweden in 2007–2015

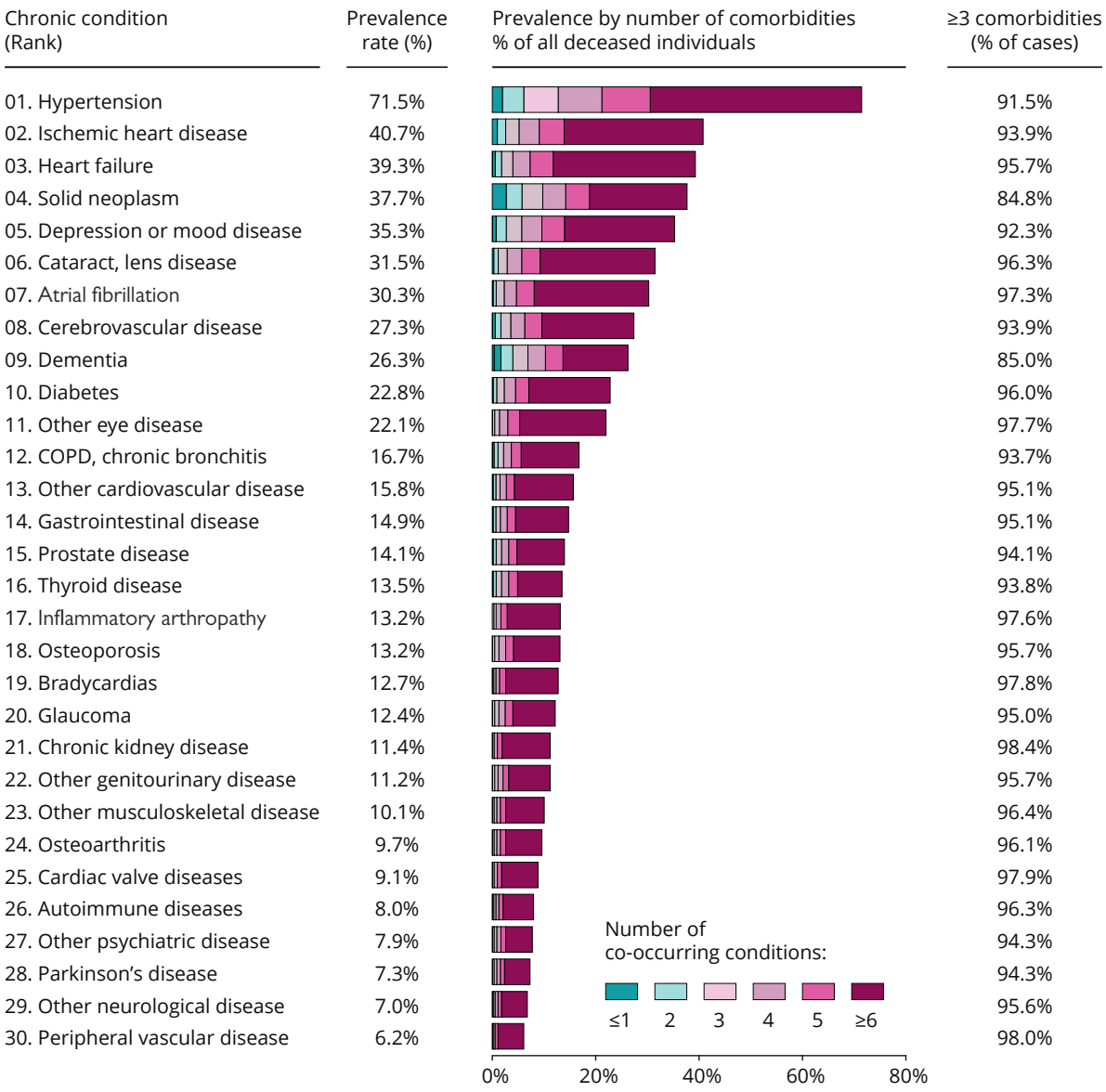


Figure 13. Prevalence of the 30 most common chronic diseases among older adults (≥65 years) who died in 2015, by number of co-existing conditions

Source: National Cause of Death Register, National Patient Register and National Prescribed Drugs Register (Swedish Board of Health and Welfare). N= 78 226 older adults aged 65 years and over who died in 2015. A total of 51 chronic diseases were identified during the 5-year period preceding death (see methods page 64).

4.2 POLYPHARMACY OVER THE COURSE OF THE LAST YEAR OF LIFE

In Study I, we first found that, throughout their last year of life, older adults (n=511 843) used an increasing number of prescription drugs. The average number of drugs rose from 7.6 (SD 4.4) during the 12th month before death to 9.6 (SD 4.7) during the final month (**Figure 14**). During the same period, the proportion of older adults exposed to ≥10 drugs increased by 55.9%, from 30.3% to 47.2%. This upward trend in the burden of drugs was especially pronounced among individuals aged 66–74 years, among community dwellers, and among those who died with only 1 or 2 chronic conditions. The likelihood of being exposed to polypharmacy during the final month of life compared with 12 months before

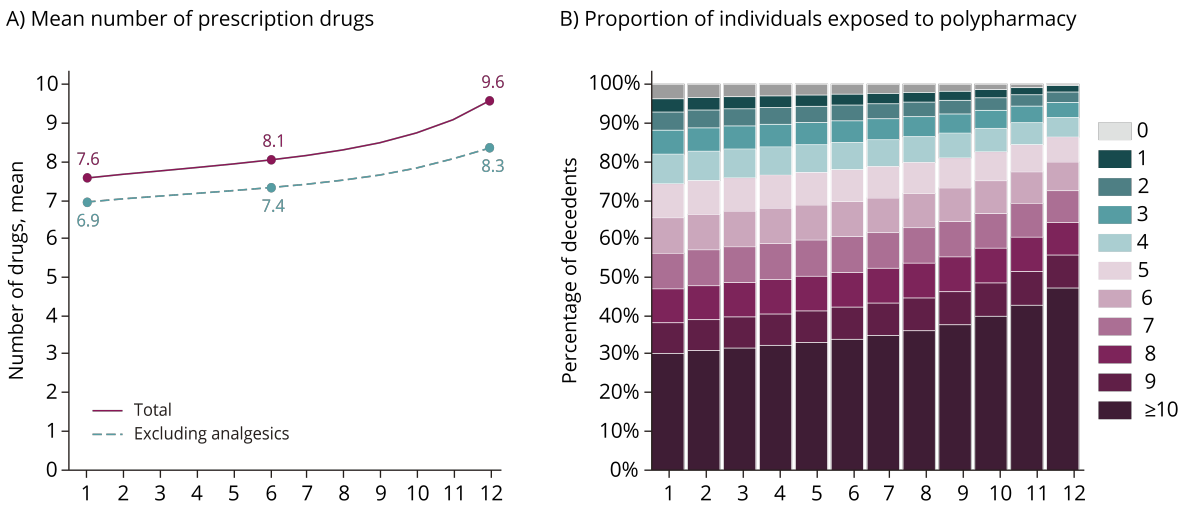


Figure 14. Change in the number of prescription drugs and polypharmacy

Study population: 511 843 older adults (≥66 years) who died from any cause in 2007–2013 in Sweden.

was also substantially higher among cancer decedents (OR 3.34, 95% CI 3.29 to 3.39) than among older adults who died from organ failure (OR 1.73, 95% CI 1.71 to 1.76) or dementia and other neurodegenerative disorders (OR 1.74, 95% CI 1.71 to 1.77). While adjusting for sex, age, multimorbidity, level of education, and illness trajectory, we found that the number of drugs increased at a slower rate among nursing home residents than among community dwellers (β coefficient -0.90, 95% CI -0.92 to -0.87). Cancer decedents had the steepest escalation in the number of prescribed medicines, even after analgesics were excluded from the analysis. Of note, a higher level of education was independently associated with a greater increase in the burden of drugs near the end of life (β 0.09, 95% CI 0.05 to 0.12).

4.3 MOST COMMONLY PRESCRIBED DRUGS AT THE END OF LIFE

In addition, Study I showed that the growing proportion of older adults exposed to polypharmacy near the end of life was fuelled not only by symptomatic drugs but also by the sustained prevalence of long-term preventive treatments and medicines prescribed for the management of chronic diseases that may otherwise lead to short-term complications (e.g. insulin and oral blood glucose-lowering agents).

The use of opioid analgesics and paracetamol increased substantially (38.5% and 49.2% during the last month of life, respectively), as did the prescribing of drugs for constipation, anxiolytics, hypnotics and sedatives, antidepressants (**Table 14**). However, cardiovascular drug treatments remained impressively stable over time: there was no or only a minimal decrease in the use of vitamin K antagonists, antiplatelet drugs, diuretics, beta-blockers, ACE inhibitors, ARBs, statins, and calcium channel blockers. During their last month of life, patients aged ≥85 years received on average 2.4 different cardiovascular drugs, including 9.2% treated with statins, 28% with ACE inhibitors or ARBs, 40% with beta blockers, 47% with low-dose aspirin, and 16% with calcium channel blockers.

	12th month	9th month	6th month	3rd month	Last month
Antithrombotic agents	52.5	53.2	53.5	53.9	53.8
Vitamin K antagonists	7.9	7.9	7.7	7.4	6.7
Heparin group	1.6	1.9	2.5	3.6	5.2
Platelet aggregation inhibitors	44.3	44.8	44.9	45.1	44.9
Diuretics	47.1	48.2	49.2	50.8	53.1
Low-ceiling diuretics	6.0	5.9	5.7	5.5	5.2
High-ceiling diuretics	37.2	38.6	40.1	42.5	45.6
Potassium-sparing agents	13.2	13.5	13.6	14.0	14.8
Analgesics	40.2	42.6	45.9	51.9	60.8
Opioids	17.5	19.0	21.4	26.9	38.5
Other analgesics	35.0	36.9	39.6	44.2	49.2
Psycholeptics	39.5	41.0	42.8	45.9	51.2
Antipsychotics	7.8	8.3	8.9	9.9	11.5
Anxiolytics	16.7	17.6	18.8	21.1	26.6
Hypnotics and sedatives	28.1	28.8	29.9	31.8	34.5
Beta blockers	39.4	40.0	40.3	40.8	41.1
Renin-angiotensin agents	31.8	32.0	31.9	31.5	30.6
ACE inhibitors	21.6	21.8	21.9	21.8	21.4
Angiotensin II receptor blockers	10.9	10.8	10.7	10.4	9.8
Anti-anaemic preparations	30.6	31.8	32.9	34.1	34.6
Iron preparations	7.8	8.3	8.9	9.8	10.4
Vitamin B12 and folic acid	25.9	26.8	27.5	28.2	28.2
Psychoanaleptics	27.4	28.4	29.5	31.1	32.6
Antidepressants	24.5	25.5	26.6	28.3	30.1
Anti-dementia drugs	5.4	5.5	5.4	5.3	5.0
Drugs for acid related disorders	23.8	25.3	27.4	31.1	35.1
Cardiac therapy	22.2	22.7	23.0	23.6	24.3
Cardiac glycosides	7.9	8.0	8.0	8.1	8.3
Vasodilators	15.5	15.9	16.2	16.7	17.4
Emollients	22.1	23.7	25.3	27.1	28.7
Lipid modifying agents (incl. statins)	18.7	18.5	18.1	17.4	16.3
Calcium channel blockers	17.8	17.5	17.1	16.4	15.4
Mineral supplements	17.6	18.1	18.7	19.7	20.5
Calcium	12.6	12.8	13.0	13.2	12.9
Potassium	5.6	5.9	6.3	7.1	8.1
Drugs used in diabetes	15.1	15.2	15.3	15.4	15.4
Insulin and analogues	8.8	9.1	9.4	9.8	10.3
Blood glucose lowering drugs	8.6	8.4	8.2	7.8	7.4
Ophthalmologicals	14.7	15.0	15.2	15.4	15.3
Drugs for COPD and asthma	12.5	12.8	13.3	13.9	14.9
Inhalants	12.0	12.3	12.7	13.3	13.9
Drugs for systemic use	1.3	1.4	1.5	1.6	2.1
Antibiotics for systemic use	11.5	12.1	13.1	15.8	20.0
Tetracyclines	1.1	1.2	1.3	1.6	2.1
Beta-lactam antibiotics	5.1	5.4	5.9	7.5	10.3
Trimethoprim and sulfonamides	1.4	1.5	1.6	1.9	2.3
Quinolones	1.7	1.8	2.1	2.7	3.6
Thyroid therapy	10.5	10.6	10.8	10.9	10.9
Corticosteroids for systemic use	9.4	10.4	11.8	14.7	18.1

Table 14. Twenty most common drug classes throughout the last year of life (%)

Corresponding ATC codes are provided in the article of Study I. Low-ceiling diuretics include both thiazides (e.g. Bendroflumethiazide, hydrochlorothiazide) and sulfonamides (e.g. metolazone). Potassium-sparing agents include combinations with hydrochlorothiazide. Other analgesics consist almost exclusively of paracetamol. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) include combinations with diuretics and calcium channel blockers. Beta-lactam antibiotics include both penicillin and cephalosporins.

4.4 USE AND COSTS OF PREVENTIVE DRUGS DURING THE LAST YEAR OF LIFE OF OLDER ADULTS WITH SOLID CANCER

In Study II, we found that older adults who died with solid cancer (n=151 201) often continued to receive preventive drugs until the very end of life. These drugs account for ~20% of the total drug expenditures, and there exist substantial variations across cancer types that age and multimorbidity can only partly explain.

Between the 12th month before death and the final month, there was little change in the receipt of antihypertensive agents (absolute change -0.3%, 95% CI -0.6 to 0.0), vitamin K antagonists (+1.5%, 95% CI 1.1 to 1.9), antiplatelet agents (-1.5%, 95% CI -1.8 to -1.2), statins (-4.7%, 95% CI -5.0 to -4.4), bisphosphonates (-0.3%, 95% CI -0.4 to -0.2), or vitamins (+1.0, 95% CI 0.8 to 1.2). We found that the proportion of older adults who continued therapy until their last month of life ranged from 47.6% (95% CI 46.7 to 48.5) for vitamin K antagonists to 65.0% (95% CI 64.4 to 65.5) for statins, up to 82.9% (95% CI 82.6 to 83.3) for beta blockers. Inversely, there was an overall low proportion of individuals initiating preventive drugs during the last year before death, with the notable exceptions of antiplatelet agents (13.4% initiators, 95% 13.2 to 13.6) and heparin (14.9%, 95% CI 14.6 to 15.9), beta blockers (13.3%, 95% CI 13.1 to 13.6), and drugs for anaemia (17.6%, 95% CI 17.4 to 17.8). We found substantial variation in the use of preventive drugs near the end of life across cancer types, also after balancing covariates (**Table 15**).

During the last year before death, median drug cost per capita was $1482 (interquartile range [IQR] $700–2896), including $213 (IQR $77–490) for preventive treatments. **Figure 15** shows that the 25th, 50th, and 75th percentiles of costs for preventive drugs were largely a function of age and multimorbidity, with higher costs among younger individuals with multiple chronic comorbidities. This association was especially clear for the upper part of the cost distribution (75th percentile). Disparities between cancer types remained after controlling for age, multimorbidity, and other potential confounders in quantile regression models. Compared with older adults who died with lung cancer, those who died with gynaecological malignancies (adjusted median difference [AMD] $27, 95% CI $18 to $36), breast cancer (AMD $19, 95% CI $11 to $28), and pancreas or prostate cancer (AMD $13, 95% CI $5 to $20) had higher costs for preventive medications. Overall, there was no decrease—and in fact even a slight increase—in the cost of preventive drugs between the 12th month before death and the final month of life (median difference $0.78, 95% CI 0.60 to 0.95).

In sensitivity analyses, excluding cancer patients whose underlying cause of death suggested an acute and potentially unpredictable fatal event from the analysis did not qualitatively alter our findings. The prevalence and costs of preventive drugs were similar to the main analysis. Also, stratifying the study population according to the delay between cancer diagnosis and death (>12 months, 6 to 12 months, and <6 months) had little influence over the results.

	Drugs for diabetes	Vitamins	Mineral supplements	Antithrombotics	Drugs used in the treatment of hypertension	Statins	Bisphosphonates	Anti-anemic preparations
Respiratory organs	11.8%	9.5%	18.6%	48.9%	58.4%	18.1%	4.5%	27.1%
Esophagus and stomach	11.9%	8.1%	15.2%	42.1%	53.7%	14.1%	1.8%	38.8%
Colorectal	14.1%	8.6%	17.7%	44.1%	58.6%	16.2%	2.5%	33.3%
Liver	22.2%	9.5%	17.1%	43.4%	68.3%	15.3%	3.3%	24.4%
Pancreas	28.2%	7.4%	18.9%	50.1%	61.4%	17.3%	2.3%	23.2%
Other digestive organs	14.8%	8.1%	18.3%	44.4%	60.0%	15.6%	2.6%	29.0%
Breast	16.2%	8.7%	19.1%	50.5%	62.8%	15.4%	6.4%	25.1%
Urinary tract	12.9%	9.8%	16.9%	46.3%	60.4%	17.9%	3.1%	31.2%
Male genital organs	12.0%	8.8%	22.2%	48.3%	58.9%	17.4%	6.0%	29.5%
Female genital organs	14.7%	9.6%	16.4%	52.0%	59.1%	17.0%	2.5%	27.4%
Melanoma of skin	15.2%	8.3%	16.9%	49.8%	65.8%	21.0%	3.9%	25.2%
Brain and meninges	18.9%	5.4%	26.4%	44.7%	56.6%	15.9%	6.7%	19.0%
Unknown primary site	16.0%	9.0%	18.8%	51.1%	63.6%	19.2%	4.0%	28.8%
Other primary tumour	12.1%	10.8%	20.7%	50.9%	61.2%	17.8%	4.2%	28.0%
Multiple solid tumours	13.6%	8.2%	18.4%	45.4%	57.6%	16.3%	3.4%	28.8%
Total cohort	14.9%	9.2%	19.2%	48.1%	60.1%	16.8%	3.9%	30.4%

Table 15. Use of preventive drugs during the final month before death, by cancer type

Predicted probabilities across cancer types are presented as percentages and are adjusted on sex, age at time of death, living arrangement, number of chronic comorbidities, year of death, time from diagnosis to death, and level of education. Predicted probabilities were calculated from logistic regression models and estimated by using the *margins* command in Stata 14.1 (StataCorp, College Station, TX). This allows for interpreting the reported proportions as if covariates were balanced across strata. The list of Anatomical Therapeutic Chemical (ATC) codes corresponding to preventive drug classes and the list of International Classification of Diseases, 10th revision (ICD-10) codes corresponding to the cancer types are available in eTable 1 and eTable 2 of the published article.

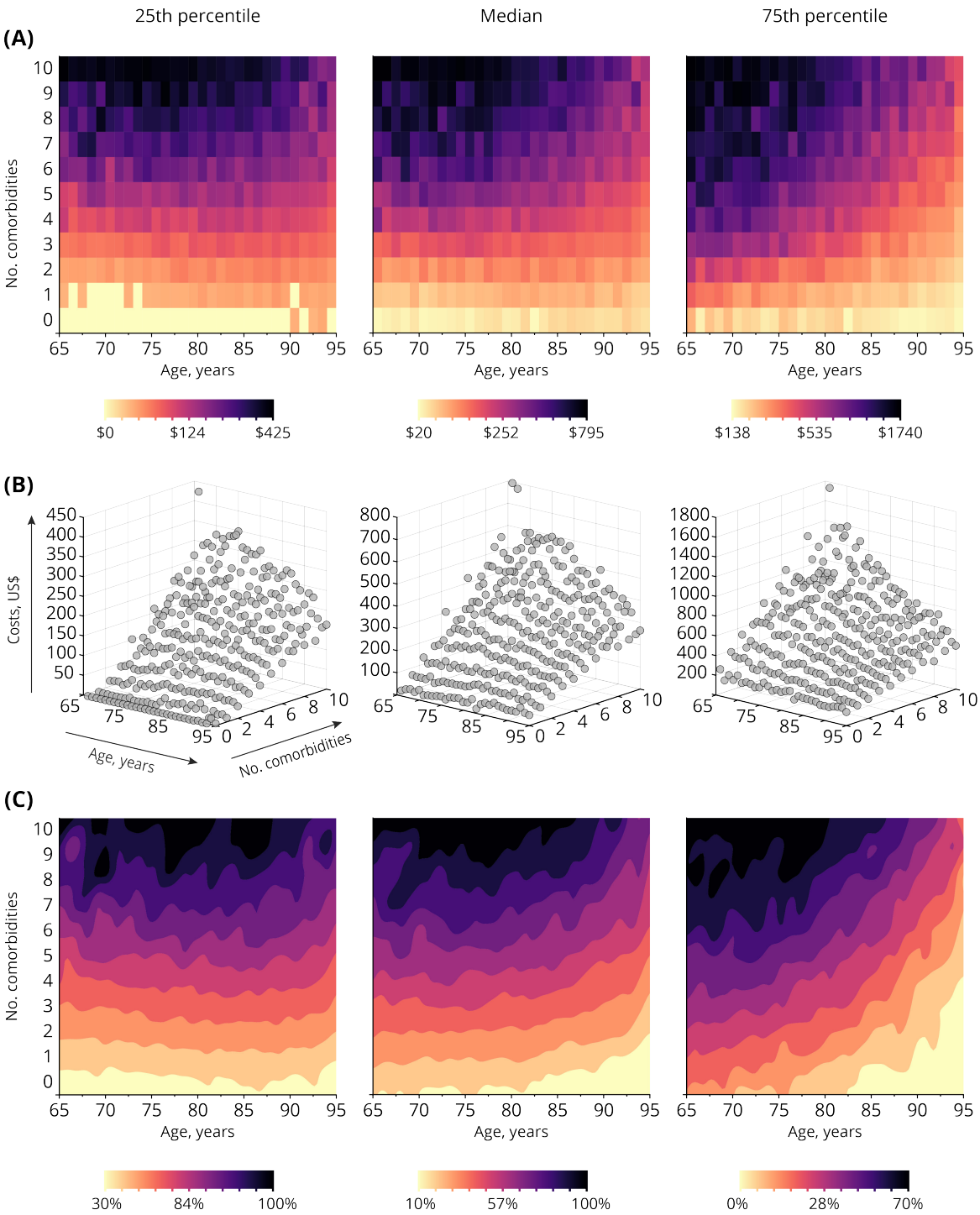


Figure 15. Distribution of costs for preventive drugs during the final year of life of older adults who died with cancer, by age at death and number of chronic comorbidities (2007–2013)

(A) Heatmaps represent the absolute value (in US dollars) of the 25th, 50th, and 75th percentiles of costs for preventive drugs during the last year before death, by age at time of death and number of chronic comorbidities. Cells are coloured according to a scale ranging from the lowest to the highest observed values for the percentile of interest. For instance, the 25th percentile of costs (top-left panel) ranged from $0 to $425. **(B)** 3D scatterplots show the association between age, number of comorbidities, and absolute values for the 25th, 50th, and 75th percentiles of preventive drug costs. **(C)** Contour plots represent the proportion of decedents whose costs for preventive drugs during the last year of life were greater than the population 25th, 50th, and 75th percentiles, respectively. Areas are coloured according to a scale ranging from the lowest to the highest observed proportion and divided into deciles to facilitate interpretation. Costs were standardised by using the harmonised index of consumer prices (see methods page 62), and were converted from Swedish Kronor into US dollars based on Sweden's Central Bank annual average exchange rate in 2013 (1 SEK = 0.1535 USD).

4.5 ADEQUATE, QUESTIONABLE, AND INADEQUATE DRUGS FOR OLDER ADULTS NEAR THE END OF LIFE

Out of 58 European experts invited to participate in Study III, 40 agreed to take part in the panel (including one person who dropped out before the second round). Participants were scattered across 10 different countries. There was a majority of women (n=23), aged 45–54 years (n=12) or ≥55 years (n=11), with more than 10 years of clinical experience (n=34). Most panellists were geriatricians (n=13) or palliative care physicians (n=12), but there were also 7 GPs, 7 pharmacologists and pharmacists, and 1 psychiatrist. After two Delphi rounds consensus was reached on 14 drugs or drug classes deemed 'often adequate', 28 drug classes deemed 'questionable', and 10 drug classes deemed 'often inadequate' for *continuation* among older adults aged ≥75 years with a life expectancy of 3 months or less. Panellists were also in agreement to consider the *initiation* of 10 drug classes 'often adequate', 23 drug classes "questionable", and 23 drug classes 'often inadequate' in this context. To improve clarity and readability, these drug classes were re-combined in a smaller number of homogenous groups in **Table 16**.

Drug classes that were rated as 'often adequate' are predominantly prescribed for symptom management and to ensure comfort care near the end of life. It is for instance the case of opioid and non-opioid analgesics, drugs for constipation, antiemetics and antinauseants (including glucocorticoids such as dexamethasone, e.g. for cancer patients with refractory symptoms), metoclopramide (a prokinetic mainly prescribed to relieve chemotherapy-induced nausea and vomiting, but also for the management of delayed gastric emptying, inoperable GI obstruction without colic, intractable hiccup, drug-induced), anxiolytics, antiepileptics, and butylscopolamine (also known as *hyoscine butylbromide*), which is widely used in palliative care as an antispasmodic and as an antisecretory drug for death rattles. While the continuation of levodopa, thyroid hormones, and inhaled salbutamol was deemed 'often adequate', their initiation wasn't.

Among the drugs and drug classes considered 'questionable' for use near the end of life, a large majority are prescribed for the long-term management of non-life-threatening chronic conditions (e.g. oxybutynin, anti-gout medications, drugs for prostate hypertrophy) or for the secondary prevention of chronic diseases that may otherwise lead to adverse events (e.g. antiplatelet agents, VKA, antihypertensives, blood glucose lowering drugs). Some drugs are also commonly prescribed to prevent the secondary effects of other pharmaceutical treatments (e.g. drugs for acid-related disorders). Drugs that panellists consensually defined as 'often inadequate' encompasses mostly drugs and supplements prescribed for primary prevention or as part of a long-term strategy of secondary or tertiary prevention. For instance, vitamin D, calcium supplements, bisphosphonates, statins, antidementia drugs. This third category of drugs deemed 'often inadequate' for older adults at the end of life was substantially longer when considering the *initiation* of new drugs rather than the *continuation* of treatments prescribed before.

Continuation of drug therapy	Initiation of drug therapy
Often adequate	Often adequate
Butylscopolamine	Butylscopolamine
Antiemetics and antinauseants	Antiemetics and antinauseants
Drugs for constipation	Drugs for constipation
Glucocorticoids for systemic use	Glucocorticoids for systemic use
Thyroid hormones	Metoclopramide
Analgesics (including opioids)	Analgesics (including opioids)
Antiepileptics	Antiepileptics
Anxiolytics: benzodiazepines	Anxiolytics: benzodiazepines
Hypnotics and sedatives: benzodiazepines	
Levodopa	Questionable
Salbutamol, inhalant	Drugs for acid-related disorders, excl. PPIs
Glucocorticoids, inhalants	Intermediate-acting and combined insulin
Ipratropium bromide, inhalant	Blood glucose-lowering drugs
	Unfractionated heparin
Questionable	Low molecular weight heparin
Drugs for acid-related disorders, excluding PPIs	Antiplatelet agents
Blood glucose-lowering drugs, excluding metformin	Blood products
Vitamin K antagonists	Digitalis glycosides
Unfractionated heparin	Low-ceiling diuretics
Antiplatelet agents	High-ceiling diuretics, excluding furosemide and torasemide
Novel oral anticoagulants	Potassium-sparing agents
Other anticoagulants	Beta-blockers
Antianemic preparations	Calcium channel blockers, excluding verapamil
Blood products	Oxybutynin
Digitalis glycosides	Drugs for prostate hypertrophy, excluding finasteride
Other cardiac glycosides	Anti-thyroid drugs and iodine therapy
Alpha-blocker antihypertensives	Anti-gout medications, excluding colchicine
Low-ceiling diuretics	Anti-Parkinson drugs, excluding levodopa
Potassium-sparing agents, excluding spironolactone	Hypnotics and sedatives other than benzodiazepines
Non-selective beta-blockers	Tricyclic antidepressants and monoamine oxidase inhibitors
Calcium channel blockers	Systemic drugs for obstructive airway diseases
Angiotensin-converting-enzyme (ACE) inhibitors	
Angiotensin II receptor blockers (ARBs)	Often inadequate
Finasteride	Vitamin D
Iodine therapy	Calcium supplement
Antineoplastic drugs (including chemotherapy)	Vitamin K antagonists
Endocrine therapies	Novel oral anticoagulants
Immunosuppressants	Other anticoagulants
Anti-gout drugs, excl. allopurinol and colchicine	Iron preparations and erythropoietin
Systemic drugs for obstructive airway diseases	Vitamin B12 and folic acid
	Cardiac glycosides, excluding digoxin
Often inadequate	Other cardiac stimulants
Vitamin D	Antihypertensives
Calcium supplement	Peripheral vasodilators
Cardiac stimulants other than glycosides	Verapamil
Antihypertensives, excluding α-blockers	Angiotensin-converting-enzyme (ACE) inhibitors
Peripheral vasodilators	Angiotensin II receptor blockers (ARBs)
Lipid-modifying agents	Lipid-modifying agents
Immunostimulants	Drugs for incontinence, excl. oxybutynin
Bisphosphonates and other osteoporosis drugs	Finasteride
Antidementia drugs (AChEI and memantine)	Antineoplastic drugs (including chemotherapy)
	Endocrine therapies
	Immunostimulants and immunosuppressants
	Bisphosphonates and other osteoporosis drugs
	Antidementia drugs (AChEI and memantine)

Table 16. Consensus criteria regarding the continuation and the initiation of drug therapy for older adults (≥75 years) with an estimated life expectancy of 3 months or less

Antiepileptics and antidepressants included in this list do not encompass drugs prescribed for the management of neuropathic pain (e.g. gabapentin, pregabalin, amitriptyline, duloxetine, venlafaxine). For clarity, a few pharmacological subgroups have been combined together to form homogenous categories. The detailed list of drugs and drug classes included in each of these categories is available in the published article, together with the corresponding ATC codes.

Consensus remained unachieved regarding the continuation of 53 drugs and drug classes (29 obtained only a moderate level of agreement [65–74%], and 24 had a low [<65%] level of agreement), and regarding the initiation of 40 drugs and drug classes (15 obtained a moderate level of agreement, and 25 had a low level of agreement). Hence, we found that panellists had widely diverging opinions about the *continuation* of proton-pump inhibitors, anti-thyroid drugs, intermediate- and long-acting insulin, muscle relaxants, antipsychotics, olanzapine, or antidepressants (**Table 17**). There was also no consensus about the *initiation* of fast-acting insulin, furosemide, haloperidol, Z-drugs, or selective serotonin reuptake inhibitors (SSRIs). For these drugs, the level of agreement amongst panellists did not improve between the first and the second round.

Continuation of drug therapy	Initiation of drug therapy
Proton-pump inhibitors	Proton-pump inhibitors
Long-acting insulin	Fast-acting insulin
Intermediate-acting insulin	Furosemide
Combined insulin	Mineralocorticoids (e.g. aldosterone)
Torasemide	Acetic acid derivatives (e.g. diclofenac)
Mineralocorticoids	Baclofen
Anti-thyroid drugs	Other muscle relaxants
Acetic acid derivatives (e.g. diclofenac)	Ketamine
Propionic acid derivatives (e.g. ibuprofen)	Haloperidol
Muscle relaxants, excluding baclofen	Levomepromazine
Ketamine	Other antipsychotics
Levomepromazine	Non-benzodiazepine anxiolytics (e.g. hydroxyzine)
Other antipsychotics, excluding haloperidol	Olanzapine
Non-benzodiazepine anxiolytics (e.g. hydroxyzine)	Zopiclone
Olanzapine	Zolpidem
Eszopiclone	Eszopiclone
Tricyclic antidepressants	Selective serotonin reuptake inhibitors
Selective serotonin reuptake inhibitors	Trazodone
Trazodone	Mirtazapine
Mirtazapine	Methadone
Methadone	Inhalants for COPD, excluding salbutamol and ipratropium
Drugs for neuropathic pain:	Drugs for neuropathic pain:
Venlafaxine	Venlafaxine
Lidocaine	Lidocaine
Duloxetine	Duloxetine
Tricyclic antidepressants	Tricyclic antidepressants
	Pregabalin

Table 17. Drugs and drug classes for which consensus was not reached due to a low (<65%) level of agreement among panellists

4.6 CONTINUATION AND INITATION OF DRUGS OF QUESTIONABLE CLINICAL BENEFIT AT THE END OF LIFE

A total of 58 415 older persons who died from conditions potentially amenable to palliative care in 2015 were included in Study IV. Mean age at time of death was 87 (SD 6.3) years, 56% were women, and 42% were living in nursing homes. Based on multiple cause of death records, 28% died from cancer, 40% from organ failure, and 32% followed a trajectory of prolonged dwindling (i.e. dementia and neurodegenerative diseases).

During their last three months of life, 32% of older adults who died from conditions potentially amenable to palliative care *continued* and 14% *initiated* at least one drug of questionable clinical benefit (i.e. drugs deemed "often inadequate", see list page 85). In contrast, 58.6% of decedents neither continued nor initiated such drugs. As shown in **Figure 16**, the proportion of individuals who continued to receive drugs of questionable clinical benefit near the end of life decreased with age and was somewhat higher among women (adjusted RR 1.08, 95% 1.05–1.11). Higher age was also associated with a lower likelihood of initiating drugs of questionable clinical benefit. We found that the proportion of patients who continued drugs of questionable benefit was substantially lower among cancer decedents (26%) than among those who died from organ failure (35%) or dementia (34%). The latter group had the lowest probability of initiating such drugs.

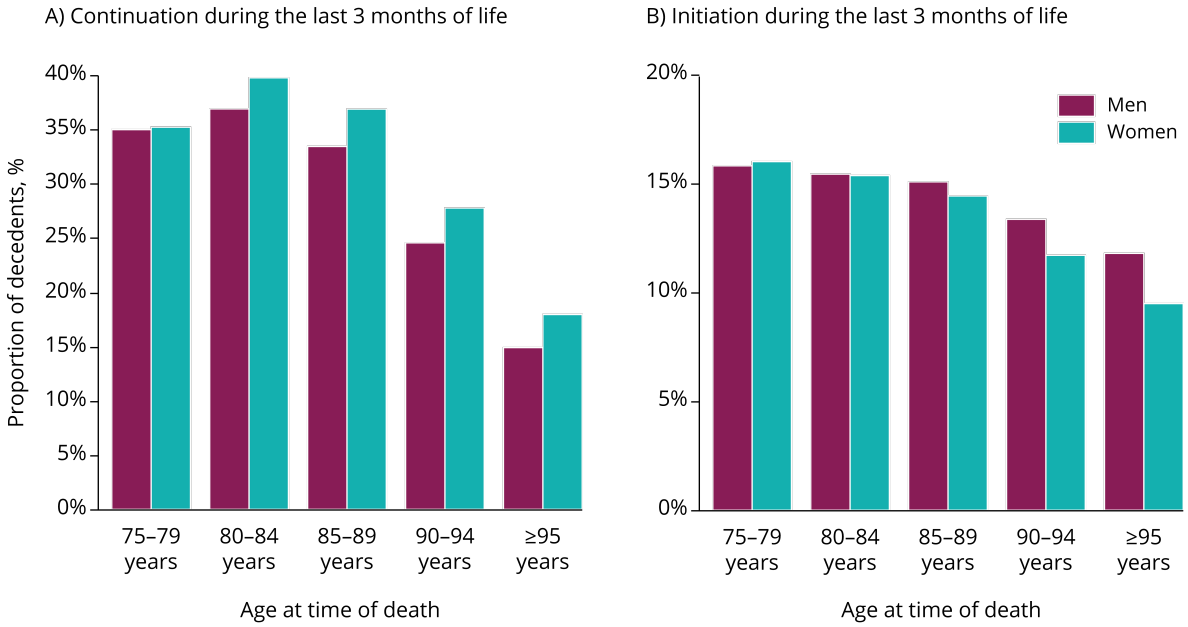


Figure 16. Continuation and initiation of drugs of questionable clinical benefit during the last 3 months of life, by sex and age

The number of co-existing chronic diseases was independently associated with an increase in the probability of both continuing (RR 1.10, 95% CI 1.09–1.11) and initiating (RR 1.05, 1.04–1.06) drugs considered 'often inadequate' near the end of life. Compared with older persons with a low risk of frailty, those with a high risk were more likely to continue questionably beneficial drugs during their last 3 months of life (RR = 1.27, 95% CI = 1.23–1.31). However, they were significantly less likely to initiate these drugs (RR = 0.83, 95% CI = 0.78–0.89). While continuation was equally frequent among community dwellers and nursing home residents (31% and 33%, respectively), initiation was less likely among nursing home residents (RR = 0.56, 95% CI = 0.53–0.59). In sensitivity analyses, we found that excluding older adults who died from acute and potentially unpredictable fatal events (n= 9918 [17%]) led to a qualitatively irrelevant albeit statistically significant reduction in the proportion of individuals exposed to drugs of questionable clinical benefit near the end of life (-1 to -1.5 percentage point difference).

During the last three months of life, statins were the most commonly continued drugs of questionable clinical benefit near the end of life, followed by calcium supplements, antidementia drugs, bisphosphonates and vitamin D (**Table 18**). Drugs for anaemia, ACE inhibitors and angiotensin II receptor blockers, novel oral anticoagulants, statins, and vitamin K antagonists were the most frequently initiated. Overall, both continuation and initiation were more common among older adults who died from organ failure than among those who died from cancer or dementia and neurodegenerative diseases.

	No. / No. at risk	%
Continuation during the last 3 months of life		
At least one drug of questionable clinical benefit	18 681 / 58 415	32.0%
Statins and other lipid-lowering agents	8394 / 12 875	65.2%
Calcium supplements	6855 / 9856	69.6%
Antidementia drugs	4463 / 5459	81.8%
Bisphosphonates and other drugs for osteoporosis	1581 / 2668	59.3%
Vitamin D	1225 / 1905	64.3%
Immunostimulants	32 / 75	42.7%
Peripheral vasodilators	0 / 0	0.0%
Antihypertensives, excluding α-blocker	42 / 62	67.7%
Cardiac stimulants other than glycosides	65 / 185	35.1%
Initiation during the last 3 months of life		
At least one drug of questionable clinical benefit	8180 / 58 415	14.0%
Drugs for anaemia	2090 / 35 959	3.6%
ACE inhibitors or angiotensin II receptor blockers	1333 / 35 858	2.3%
Statins and other lipid-lowering agents	686 / 45 540	1.2%
Vitamin K antagonists	680 / 51 042	1.2%
Novel oral anticoagulants	848 / 56 396	1.5%
Other anticoagulants	5 / 58 414	0.0%
Antineoplastic drugs	259 / 57 613	0.4%
Endocrine therapies	264 / 54 883	0.5%
Immunostimulants	21 / 58 340	0.0%
Immunosuppressants	117 / 57 586	0.2%
Finasteride	0 / 58 415	0.0%
Vitamin D	432 / 56 510	0.8%
Calcium supplement	1002 / 48 559	2.1%
Cardiac glycosides, excluding digoxin	0 / 58 415	0.0%
Other cardiac stimulants	21 / 58 230	0.0%
Antihypertensives	56 / 57 913	0.1%
Peripheral vasodilators	0 / 58 415	0.0%
Verapamil	24 / 57 941	0.0%
Drugs for urinary incontinence, excluding oxybutynin	200 / 57 090	0.4%
Antidementia drugs	359 / 52 956	0.7%
Bisphosphonates and other osteoporosis drugs	286 / 55 747	0.5%

Table 18. Prevalence of the most commonly prescribed drugs of questionable clinical benefit for older adults near the end of life

The proportion of older adults who continued or initiated at least one drug of questionable clinical benefit during the last 3 months before death was calculated as a fraction of the entire study population (n=58 415). For specific drugs and drug classes, the population at risk (denominator) was defined as follow: (a) continuation, individuals already treated with each specific drug class between 12 and 3 months before death; (b) initiation, individuals who were not previously treated and had at least one refill during the last 3 months before death. Drugs for anaemia include iron supplements, vitamin B12, folic acid and erythropoietin. Antidementia drugs include both acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine. The list of Anatomical Therapeutic Chemical (ATC) codes corresponding to the different drugs and drug class is available in Supplementary Table 9 and Supplementary Table 10 of the published article for Study IV.

5. DISCUSSION

5.1 SUMMARY OF THE MAIN FINDINGS

In this doctoral thesis, we investigated changes in the number and type of drugs prescribed throughout the final year of life of older adults in Sweden, we described the use and costs of preventive therapy among older people with cancer at the end of life, we developed a set of explicit criteria for identifying drugs of limited clinical benefit at the end of life, and we examined the continuation and initiation of these drugs in the Swedish population. Our main findings can be summarised as follow:

1. During their last year of life, older adults are prescribed an increasing number of drugs. Half of the decedents were exposed to ≥10 different drugs during the last month before death. Polypharmacy was fuelled not only by the initiation of symptomatic drugs but also by the continuation of drugs for chronic conditions.

2. Among older adults who died with solid cancer, preventive drugs are frequently continued until the very end of life. During the last year before death, the median drug cost per capita was $1482, including $213 for preventive therapies. Disparities between cancer types remained after controlling for age, multimorbidity, and other potential confounders.

3. A Delphi consensus panel allowed to create a set of criteria differentiating drugs and drug classes deemed 'often adequate', 'questionable', and 'often inadequate' for use in older persons aged ≥75 years with a life expectancy of three months or less. However, consensus remained unachieved for a substantial number of drugs commonly prescribed at the end of life (e.g. proton-pump inhibitors, antipsychotics, antidepressants).

4. Upon applying the above-mentioned criteria on a population of older adults who died from conditions potentially amenable to palliative care, we found that 32% *continued* and 14% *initiated* at least one drug considered 'often inadequate'.

The specific findings from each of these four studies have been discussed in the corresponding published articles. However, certain aspects deserve further discussion, as they transcend the individual studies and articles. In our opinion, the necessity to rationalise and improve drug prescribing for older adults near the end of life can be understood from three different yet intertwined perspectives: biological (accounting for the profound alteration of pharmacokinetic parameters at the end of life), clinical (reconsidering the notion of *benefit*), and ethical (minimising the risk of harm). We then discuss the reasons that may, at least partly, explain the prescribing of drugs deemed 'often inadequate' at the end of life. Finally, we review the main methodological limitations of the present thesis, and we reflect on future research perspectives.

5.2 OPTIMIZING DRUG THERAPY IN OLDER PEOPLE AT THE END OF LIFE

The biological perspective: altered pharmacokinetics and pharmacodynamics

Older adults who reach the end of life experience physiological changes that go beyond normal age-related modifications. The pharmacokinetic processes and pharmaco-dynamics of drugs can thus be considerably altered as death approaches. Despite the scarcity of data to shed light on the impact of physiological changes near the end of life, all four pharmacokinetic processes are likely to be affected, thereby increasing the risk of adverse drug reaction.[651–654]

The **absorption** of medications administered *per os* can be influenced by gastrointestinal symptoms. Hence, constipation can either decrease the absorption rate by delaying the dissolution of the drugs (thus affecting the time to peak concentration), or on the contrary increase the overall extent of absorption by prolonging the time of contact with the intestinal mucosa. Additionally, diarrhoea can decrease the bioavailability of drugs by accelerating the bowel transit time, thus affecting the initial peak concentration and total exposure. Optimal absorption is also compromised among patients with gastric or colorectal cancer who undergo surgical resection of their gastrointestinal tract, and among patients with artificial enteral nutrition. Finally, impairments to the gut wall function induced by cachexia or inflammation (frequent among cancer patients) may lead to changes in drug absorption.[655] To our knowledge, it is unknown whether the reduction of first-pass metabolism observed among older adults is accelerated near the end of life.

The volume of **distribution** of drugs can be affected by changes in body composition resulting from the progression of the disease, for instance weight loss, loss of total body water due to dehydration or volume depletion, ascites, oedema, and loss of muscle mass. In advanced cancer and dementia, extreme weight loss and cachexia can occur, which results in subcutaneous and visceral adipose tissue depletion and thus decrease the volume of distribution of lipophilic drugs and—mechanically—increase their peak serum concentration.[655] Decrease in the volume of distribution should mainly be accounted for when prescribing medications with a rapid onset such as analgesics and sedatives, since it affects the initial peak concentration. Alterations of plasma protein binding (typically hypoalbuminemia and increased alpha1-acid glycoprotein[654]) can also influence the volume of distribution, although it is unlikely to be clinically relevant.[410,431] Among older adults with advanced dementia, the enhanced permeability of the blood-brain barrier increases the risk of serious neurological adverse drug reactions.[651]

Metabolism, namely the transformation of drug compounds into metabolites, can be altered by the decline in the ability of the liver to extract drugs from the blood.[656] Two mechanisms are potentially at play: a reduced liver blood flow (frequent among patients with congestive heart failure[657]), and a decreased intrinsic clearance function due, for

instance, to liver metastases, chemotherapy-induced hepatic toxicity (e.g. sinusoidal obstruction syndrome caused by the combination of oxaliplatin with 5-fluorouracil in FOLFOX chemotherapy regimens), or reduced cytochrome P450 3A activity.[658]

The **excretion** of drugs is often compromised, particularly for older adults with renal impairment. Reduced kidney clearance can lead to an accumulation of parent drugs or active metabolites during the final days of life and cause adverse effects (e.g. delirium, myoclonus).[654] Of note, estimating the actual glomerular filtration rate in the population of terminally ill or very frail older adults can be difficult, as the usual methods based on creatinine levels show limited accuracy among patients with low or decreasing muscle mass.[651,659]

As noted by Franken et al., "the pharmacokinetics of drugs in terminally ill patients can be complex [...], and limited evidence exists on guided drug use."[652] Even less is known about the pharmacodynamics of drugs in the context of end-of-life care. While pharmacokinetics refers to the various effects that the organism has on ingested drugs, pharmacodynamics describes how the drugs affect the organism. More specifically, pharmacodynamics corresponds to the set of interactions that occur between the drugs and their receptors in the target organ (signal transduction mechanisms) and the homeostatic regulatory processes that preserve the functional equilibrium of the organism. Although the exaggerated sensitivity to drugs and the higher risk of toxicity are well documented in clinical studies, pharmacodynamics processes are notoriously difficult to predict in individual cases.[660,661] In a review focused on older people with dementia, Reeve et al. emphasised the hazards of central nervous system drugs and anticholinergics but also pointed out the lack of research investigating the effect of frailty on pharmacodynamics.[651] Moreover, because of their low baseline functional status and reduced homeostatic mechanisms (which, one may assume, tend to worsen near the end of life), older adults with advanced illness are more susceptible to develop drug-induced orthostatic hypotension, dehydration, hypokalaemia, or hyponatraemia.[662]

Beyond strictly physiological parameters, the hazard of prescribing drugs to older adults at the end of life is further complicated by the exponentially increasing risk of drug-drug interactions that comes with polypharmacy.[407,663] In a large, multicentre cohort study in 11 European countries, Kotlinska-Lemieszek et al. found that a majority of patients with advanced cancer were exposed to potentially harmful drug-drug interactions.[559] In Australia, Morgan et al. reported that 72% of adult patients referred to specialist palliative care were at risk of drug-drug interaction and stressed the importance of implementing tailored computerised prescribing alerts and developing close collaborations with clinical pharmacists to detect potentially serious drug-drug interactions and adverse drug reactions.[552] In sum, clinicians prescribing for older adults near the end of life must apply utmost caution and carefully consider the risk-benefit ratio of continuing or initiating a new drug and personalise the dose to minimise the burden of side effects.

The clinical standpoint: reconsidering the benefit of medications

Incorporating life expectancy in the assessment of treatment benefits

Assessing the benefits and risks of preventive medicines for older people with advanced illness is challenging since measures typically derived from randomised clinical trials do not account for the amount of time that patients can expect to live. The number needed to treat (NNT) is a commonly used indicator of treatment effectiveness.[664,665] It corresponds to the inverse of the absolute risk reduction (ARR) between patients enrolled in the 'treatment' group and those allocated to the 'control' or 'placebo' group, and it can be interpreted as the number of individuals who need to be treated to avoid one occurrence of the outcome of interest. We illustrate this approach with an example.

In a meta-analysis[666] of 14 clinical trials investigating the effectiveness of statins for the primary prevention of cardiovascular diseases, statins were found to reduce the occurrence of coronary events over 5 years: 820/24 217 (3.4%) in the treatment group versus 1114/23 832 (4.7%) in the 'placebo or usual care' group. Although statistically correct, it would be somewhat misleading for clinicians and patients to describe this finding by saying that statins result in a 27% relative risk reduction (RR=0.73, 95% CI 0.67 to 0.80) of CHD events. Instead, it is preferable to state that statins lead to a 1.3% (95%CI 0.94 to 1.64) absolute risk reduction, or that 78 patients need to be treated for 5 years to prevent one coronary event among persons without a history of cardiovascular disease. Yet, although this would indicate a substantial benefit of statins for the general older population, NNT over 5 years is of limited value for individuals with metastatic cancer or advanced dementia with a predicted life expectancy of less than 6 months.[667–669] As noted by Stevenson et al., "the number needed to treat for a given treatment for a comorbidity will increase as the prognosis decreases."[481] However, since adverse outcomes are seldom distributed evenly over time and since the absolute risk reduction is rarely constant, scaling NNT for different periods of time is rather unhelpful and could lead to overly optimistic estimates.

To tackle this issue and help clinicians prioritise medications offering the best chance of achieving their benefit during the patients' remaining life expectancy, Holmes et al. have promoted the concept of time to benefit.[540] It is defined as "the time until a statistically significant benefit is observed in trials of people taking a therapy compared to a control group not taking the therapy."[542] Since the number of weeks, months or years needed to observe the benefit of a therapy is hardly ever reported as such, several methods have been used to estimate time to benefit from published randomised controlled trials: comparing the absolute risk reduction observed in trials of different durations; using the median or mean follow-up time of individual patients by assuming right-censoring after the outcome of interest; or conducting a visual inspection of cumulative survival or failure curves to identify the earliest time of curve separation.[542,668] However, it should be noted

that these methods present important caveats that make their generalisation challenging. Van de Glind et al. recently proposed a novel approach to overcome these difficulties. Their method relies on *statistical process control* to determine the time point after which the cumulative absolute risk reduction in adverse events become greater than the normal variability observed across treatment groups over time.[670] Another approach has been proposed by Braithwaite et al. to estimate the time until the cumulative benefits of a medical intervention exceed its potential for harms according to the patients' characteristics.[671,672] This *payoff time* model was initially developed to inform policymakers and healthcare stakeholders about the time needed for preventive care guidelines to achieve a net benefit among older adults with multiple chronic diseases (compared with their remaining life expectancy). In a similar perspective, Lee et al. conducted a meta-analysis of 9 population-based, randomised controlled trials comparing the effectiveness of breast and colorectal cancer screening to assess the time until a significant survival benefit is observed.[673] Using annual estimates of the mortality rate among screened and unscreened participants, they calculated the time required to obtain predefined cut-off values of absolute risk reduction. Their results show that it took 11 years (95% CI 4.4–21.6) to prevent one death for every 1000 women who underwent breast cancer screening, and 10 years (95% CI 6.0–16.4) to prevent one death for every 1000 persons who had colorectal cancer screening. These findings have been confirmed by other studies and demonstrate the necessity to account for the remaining life expectancy before recommending the use of preventive health interventions that may yield a significant benefit only years later.[674–679]

Incorporating the time to benefit in the decisions to initiate, continue or discontinue treatments inevitably leads to reconsider what makes a therapy potentially *beneficial* in the context of limited life expectancy: the question is no longer "Is this medication effective?" but rather "Will this medication help the patient during his/her remaining lifespan?." In that sense, the time to benefit is a tool to contextualise measures of benefit. The findings from **Study I** and **Study II** showing that a sizeable proportion of older adults with life-limiting illness continue to receive drugs for the long-term prevention of chronic diseases until their last month of life can, for instance, be interpreted critically in light of the apparent mismatch between the long lag time to benefit of these drugs and the short survival of these patients.

Nonetheless, accounting for life expectancy may not be sufficient to ensure that drug prescribing is adequate. The time to benefit of a specific treatment depends on the outcome selected to judge whether this treatment has reached its intended target. For instance, what if the time to benefit for the primary endpoint (e.g. myocardial infarction) favours the treatment but the time needed to achieve the endpoint that is the most important for the patients (e.g. quality of life) does not? What if the intended benefit accrues at a time when the patient is no longer functional enough to find this benefit meaningful? These questions reveal the importance of aligning the treatment target with the patients' personal preferences and goals of care.[542,680]

Targeting what matters: placing patient preferences at the centre

Older adults often reconsider their preferences regarding the goals of care when the disease progresses, and the perspective of a remission becomes less and less likely. For instance, ensuring symptoms management and maintaining quality of life may become more important for the patient than extending survival.[681] A survey conducted in the United States (n=1006) indicates that for 71% of the population "helping people die without pain, discomfort, and stress" should be the priority of healthcare at the end of life.[682] When asked to rate the importance of different factors in thinking about their own situation, 85% stated that making sure their wishes for medical care were followed was "extremely important" or "very important." Being comfortable and without pain (78%) was more often mentioned as important than living as long as possible (46%). Yet, in a post-death interview study of 1212 family caregivers who lost a relative aged ≥65 years, 13% reported that the care provided during the final month of life was inconsistent with the decedent's stated preferences.[683] This reality had already been described in 2002 by Teno et al., who described that over one-third of seriously ill patients who had expressed a preference for comfort care received treatments that were not concordant with this.[684]

The quality of care can be defined as "the extent to which health services for individuals and populations increase the likelihood of desired health outcomes."[685] In other words, the quality of a medical intervention should be judged according to the capacity of that intervention to achieve a goal valued as important by the person who should benefit from it.[686] Because the priorities of people facing the consequences of a serious and incurable life-limiting illness are likely to be different from those of the general population, what constitutes a desired health outcome also differs.[687] Therefore, treatment benefits should not only be defined according to the mere physiological effect that they produce but according to their ability to address the needs that the patient considers as important and meaningful.[542,688,689] Maintaining a person-centred care plan also means that the benefits and potential harms of treatments should be discussed in the context of the patient's anticipated health trajectory, to ensure that these treatments will remain meaningful throughout the course of the disease and in spite of a likely decline in ADL and mobility functions.[544,690] Since the priorities of seriously ill patients nearing death have been found to vary over time,[691] keeping the therapeutic target aligned with the goals of care requires good communication between the prescriber and the patient.

The ethical point of view: "first, do no harm"

In the previous section, we have demonstrated the necessity for clinicians to ensure that treatments provide a meaningful benefit and are in the patient's best interest as they approach the end of life. It corresponds to the first principle of medical ethics: *beneficence*. A second principle governs decisions to initiate, continue or withdraw medical treatments: *non-maleficence*.[639,640] This relates to the injunction "first do no harm" (*Primum*

non nocere), which dictates that the obligation of beneficence must always be weighed against the obligation not to cause harm. In other words, clinicians should abstain from providing treatments that are likely to do more harm than good.[692–694] While certain drugs are well tolerated and present only a small risk of clinically relevant adverse events, other treatments are particularly prone to cause serious harm. Among older people treated with antidiabetic drugs, for instance, overly intensive glycaemic control often results in hypoglycaemia, which, in turn, increases the risk of injurious falls, physical frailty, and cognitive impairment.[695,696] Insulins and oral blood glucose-lowering drugs have been found to be implicated in nearly 25% of all non-elective hospitalisations of older American.[416] However, despite limited but convincing evidence that deintensification of glycaemic control is feasible, safe, and has the potential of reducing harms,[697,698] less than one-third of patients with very low levels of haemoglobin A1c (HbA1c <6.0%) have their medications revised.[699] Hamada et al. reported that only a small minority discontinue antidiabetics near the end of life,[700] which our own findings confirmed. Another example would be that of anticoagulants for the management of cancer-associated deep-vein thrombosis at the advanced stage of the disease. Low-molecular-weight heparin and direct oral anticoagulants are effective treatments but come with a substantial risk of gastrointestinal and intracranial bleeding.[701–703] In a recently published prospective cohort study of patients with cancer admitted to specialist palliative care units in the United Kingdom, White et al. showed that the prevalence of femoral deep vein thrombosis as assessed with ultrasonography at time of admission was high (34%) but incidence during the next two weeks was very low. "[These findings] suggest that thromboprophylaxis at this stage might be too late", the authors concluded, adding that "the absence of observed association with survival, or symptoms or signs other than leg oedema questions whether thromboprophylaxis offers clinically meaningful benefit."[704]

Potential harms associated with a therapy are often measured through the *number needed to harm* (NNH), a correlate of the number needed to treat (NNT) described earlier. However, just like the NTT, the NNH does not estimate the *time* required for an intervention to cause harm. This means that as prognosis worsens and life expectancy diminishes, clinicians should not only balance the probability that the treatment will benefit against the probability that it causes harm, but also consider the probability that time-to-harm be shorter than time-to-benefit. One can, for instance, imagine a hypothetical trial evaluating the benefits and harms of a cardiovascular treatment intended to reduce the risk of 2-year mortality among older adults who experienced a serious sentinel event. Findings demonstrate a clinically significant decrease in the probability of dying among study participants who were allocated to the treatment arm, with an absolute risk reduction of 2.5% (NNT 40). But the results also show that those who received the treatment were at 2% higher risk of institutionalisation and incident ADL disability (NNH 50). Moreover, detailed analysis reveals that most of the benefit is observed after 1 year while most of the adverse effects are reported during the first months after enrolment. Hence, the authors find that the NNH is greater than the NNT

during the first 6 months, before the ratio gradually inverses and the benefits outweigh the harms. This scenario is not uncommon in published randomised controlled trials and should give pause in the context of limited life expectancy. While the abovementioned trade-off may seem acceptable for the general population of older adults (considering the favourable risk-benefit balance in the long term), it is questionable when considering the case of patients who are unlikely to survive longer than 1 year. These persons would indeed live long enough to experience the harms caused by the treatment, but not long enough to gain any substantial benefit. This example was recently embodied by a large observational study investigating the benefits and harms of beta-blocking agents among frail older adults after acute myocardial infarction.[705,706] In a propensity-matched cohort of 10 992 older adults aged 84 years on average, Steinman et al. found that β-blockers were associated with a significant reduction of mortality (HR 0.74, 95% CI 0.67–0.83) but also with an increased risk of functional decline during the 3-month period after hospital discharge (OR 1.14, 95% CI 1.02–1.28). Furthermore, researchers reported that nursing home residents with moderate to severe cognitive impairment or severe ADL limitations at baseline were the most likely to experience further functional decline. In an accompanying editorial, Tjia et al. commented that these results "confirm that the practice of avoiding prescription of β-blockers in frail and highly vulnerable elders with functional impairment is reasonable. […] As clinicians, we must remember that the spectrum of good prescribing practices spans initiation to discontinuation of therapy. Initiation of therapy, in many ways, is the easy part of the prescribing spectrum. The more challenging part is considering the discontinuation of therapy."[707]

Physicians should consider withdrawing drugs when the potential for harm outweighs the benefits that patients can reasonably expect during their remaining lifespan, or when the treatment target is no longer aligned with the preferred goals of care. As life expectancy diminishes, the spectrum of drugs considered adequate should be gradually reduced (**Figure 17**). The process of *deprescribing* has gained traction in the field of geriatric medicine,[708–711] and is considered as a potentially powerful instrument to reduce inappropriate drug utilisation, lower the prevalence of polypharmacy, and improve health outcomes in multimorbid older adults.[712–717] In the context of end-of-life care, withdrawal of preventive drugs has recently come under the spotlight with the publication of a landmark randomised controlled trial by Kutner et al. evaluating the safety of discontinuing statin medications for patients in the palliative care setting.[718] In this study, a total of 381 individuals (mean age 74 years) with advanced illness and ≤ 12 months life expectancy were randomly assigned to either 'continuing' or 'stopping' statins. There was no clinically relevant difference in the risk of death or in the time to first cardiovascular event. Moreover, patients who discontinued statins reported a higher satisfaction with care and a better quality of life. Whether this conclusion is applicable to other drugs remains uncertain and warrant further research (see *5.6 Future perspectives*).[719–722]

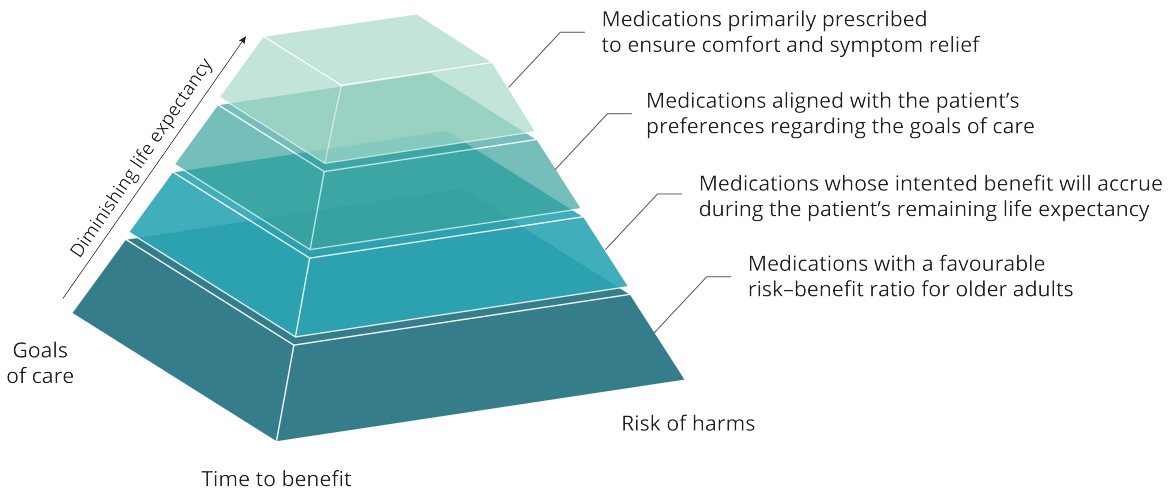


Figure 17. (De)prescribing model for older adults approaching the end of life

Adapted from Holmes HM, et al. (2006).

The clinical and ethical dilemma that results from the obligation of non-maleficence can be extended one step further. Prescribers should indeed balance the lack of benefit of a given drug with the potentially harmful effects of its withdrawal. For instance, the discontinuation of antidementia drugs raises important and unsolved questions. Despite their widely acknowledged ineffectiveness in the treatment of advanced dementia, discontinuation may lead to accelerated cognitive and functional decline and has been linked to a 2-fold increased risk of institutionalisation.[723–725] Decisions about drug discontinuation near the end of life are also made more difficult by three factors: the prognostic uncertainty, the challenge of timely patient-physician communication, and the existence of cognitive biases that may distort the decision-making process.

5.3 THE CHALLENGE OF DEPRESCRIBING AS DEATH APPROACHES

Predicting the unpredictable

Despite a considerable number of studies conducted over the past two decades, predictions about the remaining life expectancy of individual patients remain highly inaccurate. Kimbell et al. recently observed that "predicting how long an individual will live remains an inexact science in all diseases and is nigh on impossible when people have multiple advanced conditions."[726] Predictions made by physicians in routine clinical practice are often far more optimistic than the actual survival time of patients with life-limiting diseases.[727–730] A meta-analysis of 8 studies (n= 1563) published by Glare et al. in 2003 showed that clinical predictions of survival in terminally ill cancer patients were accurate (less than 1-week difference) in 25% of the cases, but overestimated actual survival by at least 4 weeks in 27% of cases.[731] Anecdotally, the predictions of 3-month survival for patients with advanced cancer have been found to be as (in)accurate as 5-day meteorological forecasting.[732] Studies conducted in other patient groups (e.g. heart failure, COPD) showed equally unreliable physician[733] and patient[734] predictions.

Moss et al. developed the 'surprise question' to identify patients who might benefit from palliative care.[735,736] This approach requires clinicians to assess whether they would be surprised if an individual patient died in the next 12 months. It should be noted that the initial aim of the surprise question is not to produce an accurate survival prediction, but rather to serve as a screening tool to emphasise the need for careful re-examination of the patient's goals of care in light of the most likely limited life expectancy.[737] Yet, several studies have investigated the predictive performance of the surprise question to estimate the probability of death within 6 to 18 months. Two recent systematic reviews and meta-analyses show that this tool is insufficiently accurate to predict mortality (area under the curve 0.75–0.81), especially for patients with non-malignant diseases.[738,739]

Efforts have also been made in various medical disciplines to develop more sophisticated predictive algorithms designed to estimate the remaining life expectancy of individual patients based on a broad range of demographic, clinical, and biological information. Yet, until now these instruments have hardly proven to be helpful at the bedside. Out of a total of 16 validated prognostic indices for older adults included in the systematic review published by Yourman et al. in 2012,[740] the area under the curve ranged from 0.64 to 0.83 – which mean that the outcome would be erroneously predicted in 1 out of 3 to 6 patients. Similarly, although several authors reported promising sensitivity/specificity values for various prognostic scores,[741–744] the degree of inaccuracy remains too high to use them as standalone prognostic tools to support decision-making in routine clinical practice. This is particularly true for older adults at the advanced stage of dementia, a disease characterised by its frequently unpredictable clinical course.[745–749] Hence, Mitchell et al. found that the Advanced Dementia Prognostic Tool (ADEPT)[750] performed poorly at predicting 6-month mortality in a prospective cohort of 606 nursing home residents with advanced dementia, which led them to conclude that "care provided to these residents should be guided by their goals of care rather than estimated life expectancy."[751]

This raises challenging questions. How should older adults re-evaluate their goals of care if the information that they receive from their treating physician about their life expectancy is most likely inaccurate? What should guide the decision to initiate, continue, or discontinue a specific treatment if the comparison between the time-to-benefit and the remaining life expectancy is based on unreliable estimates? On the one hand, some anticipate that progress in statistical processing and a better utilisation of available information (e.g. machine-learning, medical imaging, biological markers) will eventually result in optimal prognostic algorithms with nearly perfect predictive performance. Others argue that instead of trying to purge the decision-making process of any form of uncertainty, decisions regarding the course of treatments should include a degree of ambivalence, and use it to help patients express their worries, fears, and priorities.[726,752,753] For older people who live with an advanced, incurable, and progressive illness, uncertainty can be an opportunity to start discussing end-of-life issues; including

how different drug treatments can help them achieve the goals that are important for them and how the most bothersome side effects of drugs can be addressed.[754–756]

End-of-life discussions and shared decision-making

Aligning drug therapy with evolving goals of care near the end of life requires timely discussions between patients, physicians, and relatives.[757–759] Good communication is ranked amongst the most important components of end-of-life care by patients and their informal caregivers.[760] Although some people prefer to be kept at a distance from the decision-making process, a large majority of older adults want to be informed about the course of their illness, to discuss their options in terms of disease and symptom management, and to participate in decisions regarding the initiation, continuation or withdrawal of treatments.[761–763] In a 2016 survey of the US population,[682] 92% of respondents stated that they would be "comfortable talking about their own end-of-life medical wishes with a healthcare provider", and 87% considered that the wishes of patients and relatives should prevail in decisions about the continuation of medical treatments near the end of their lives. Interestingly, despite important cultural differences across countries the proportion of individuals who declare that physicians should be "completely honest even if there is little chance of recovery" with seriously ill patients is similar in Japan (80%), Italy (79%), the United States (88%), and Brazil (80%).[764] Patients themselves often expect their treating physician to cultivate open and honest discussions about their prognosis.[765–768]

Contrary to popular belief, conversations about end-of-life issues do not seem to increase patient emotional distress, anxiety, depressive symptoms, or hopelessness.[759,769,770] In a prospective study of 988 patients with ≤6 months life expectancy who underwent an initial interview about death, dying, and bereavement, 89% of patients and 90% of their relatives reported little or no stress afterwards.[771] On the contrary, Fallowfield et al. noted that "the desire to shield patients from the reality of their situation usually creates even greater difficulties."[766] Consensus about the clinical benefit and the ethical obligation to discuss end-of-life issues has grown stronger in the medical community over the last two decades, which is in line with the earlier-mentioned shift from paternalism to patient autonomy.[772] Yet, many clinicians are still hesitant (and even reluctant) to discuss this topic openly with patients and their caregivers.[773–776]

A substantial share of patients with life-limiting conditions are not given the opportunity to discuss end-of-life issues with a physician.[777–783] For instance, a prospective study of 2155 patients with stage IV lung or colorectal cancer found that 27% of patients had no reported end-of-life care discussion.[784] Among older adults with terminal heart failure, end-of-life issues are rarely (if ever) broached, conversations are mostly focused on disease-modifying therapy.[785] In nursing homes, a growing number of observational studies report that residents are often not informed of their situation and are seldom involved in decisions regarding the continuation or discontinuation of treatments near

the end of life. In France, we showed that out of 674 older adults who died in nursing homes in 2013–2014, no discussion about end-of-life-related topics was reported with the resident or with the relatives in 32% of cases.[786] In Norway, Gjerberg et al. reported similar findings, remarking that "most [residents] stated that they had not had an opportunity to discuss their values and preferences for treatment and care related to end-of-life with the nursing home staff."[787]

This lack of communication has important consequences for the quality of end-of-life care. Failure to disclose the prognosis and to discuss the progression of the disease can lead to unrealistic expectations on the part of the patients and their relatives towards the benefits of treatments. Among 1193 patients receiving chemotherapy for newly diagnosed metastatic lung or colorectal cancer, Weeks et al. found that between 69% (lung) and 81% (colon-rectum) of participants did not understand that chemotherapy was "not at all likely" to cure their cancer.[788] Similarly, a meta-analysis of 34 studies showed that less than half of patients with advanced or terminal cancer had an accurate understanding of their prognosis, reflecting the poor quality of patient-physician communication in these difficult times.[789] On the contrary, seriously ill patients who have the possibility to discuss end-of-life care issues with a physician have a better understanding of their remaining life expectancy and are more likely to receive care and treatments that are aligned with their preferences near the end of life.[784,790–799]

Discussions about end-of-life related issues should not only cover prognosis and life expectancy, but also touch upon broader issues related to the fears and concerns of patients and relatives, the goals of care in the event of a sudden decompensation, the patient's wishes for family involvement, and personal or religious preferences regarding value-laden medical decisions (e.g. continuous sedation, withdrawal of life-sustaining treatments).[759,775,800] Timely discussion about the possibilities in terms of symptom management and palliative care offered by local hospitals, nursing homes, and community-based hospice programs is also essential to avoid the sense of abandonment that patients and relatives may experience while life-prolonging treatments are gradually discontinued. Patients should be reassured that transitioning to palliative goals of care does not amount to 'giving up'.[801–804]

Having these conversations can be exceedingly difficult for clinicians, who find it stressful and emotionally burdensome.[773,805–807] Physicians often mention lack of time and patients' and family members' difficulty understanding the limitations of life-prolonging therapies as important obstacles to end-of-life discussions.[808–811] Recent policy changes have been implemented in the United States to tackle this problem. For instance, the Medicare fee-for-service program now allows for the reimbursement of voluntary counselling sessions designed to promote end-of-life discussions and advance care planning.[59,812–814] Another substantial barrier is the abovementioned difficulty in estimating time to death, and thus in determining when end-of-life discussions should be

started.[815–818] Although this concern is related to clinicians' desire to balance hope with realistic information,[818–824] it often leads to delaying end-of-life conversations until very late in the course of the disease trajectory, at a time when it may be difficult to realign treatments with the patient's preferred goals of care.[66,825,826]

Some argue that shared decision-making is illusory, plagued by ever-changing preferences regarding treatments and by a profound aspiration from the patients and their relatives to avoid difficult decisions about future care plans.[827] It is true that denial of the ineluctably fatal progression of the disease is common and that patients can sometimes feel overwhelmed by difficult decisions. However, these emotional reactions tend to be stronger when discussions about the end of life occur late, in a context of crisis (e.g. unplanned hospitalisation), or when they focus exclusively on treatment options and don't include other non-medical issues.[828] Maskrey et al. recently emphasised that "at its simplest, shared understanding may involve a one-off binary choice (e.g. take an antibiotic or have a surgical procedure), but often it involves a dialogue that must be maintained through the complexities of chronic or comorbid illnesses."[829] In other words, patient-physician dialogue should start early during the course of the disease, and broach the issue of end-of-life care progressively.

Optimal communication and shared decision-making with seriously ill persons require skills for which physicians are rarely trained.[830–832] Clinicians should be encouraged to use checklists, communication-priming leaflets, conversation guides, and video decision aids to ensure that important issues are discussed with patients when prognosis worsens and the continuation of disease-oriented treatments becomes questionable.[833,834] The purpose of these tools is not only to support patient-centred approach to end-of-life care, but also to reduce cognitive biases that may alter the decision-making process.

The therapeutic illusion

In the context of reduced life expectancy, when physicians have reached the limits of modern therapeutic resources, medical decisions are often fuelled not by evidence-based guidelines but rather by intuition, clinical experience, and emotions.[807,823] This paves the way for various cognitive biases, which may distort the assessment of benefits and harms of treatments and thus encourage overtreatment. Both physicians and patients tend to overestimate the control that they can have on the course of the disease, exaggerating the effects of their own actions and underestimating the influence of factors that are outside their control.[835] This illustrates a phenomenon recently described by palliative care physician David Casarett as a *therapeutic illusion*,[836] also known by behavioural psychologists as the *illusion of control*.[837–839] In Australia, Scott et al. have proposed a comprehensive overview of the cognitive biases that "steer clinicians towards continuing to believe in, and deliver, care that robust evidence has shown to be of low value."[840] In particular, the following cognitive biases may play an important role in the decision to prescribe preventive medications to older adults at the end of life.

The *impact bias* leads to overestimating the probability that an intervention will provide a benefit while underestimating the probability that it will cause harm.[841,842] It relates to the *extrapolation bias*, i.e. expecting that the favourable impact of an intervention observed in a specific group of patients will be equally favourable in another population. The *confirmation bias* leads to choosing and remembering the facts that support one's initial assumption while undermining or ignoring facts that contradict that assumption.[843] The *commission bias* refers to the tendency of physicians to act out of a stronger desire to avoid the negative consequences that may result from the omission of an intervention (e.g. treatment, diagnostic test) than to avoid the harms that may result from providing that intervention.[844,845] Believing in the effectiveness of an intervention based on a few, highly selected cases where favourable outcomes were previously obtained reflects an *attribution bias*. In medical oncology, rare situations of rapid and unexpected improvement after salvage chemotherapy are known as the 'Lazarus effect', and may accentuate the propensity of oncologists to suggest a new line of anticancer treatments against all odds.[846,847] The *framing bias* is defined as the inclination of prescribers to present ('frame') the potential benefits associated with an intervention in a more appealing manner than the evidence suggests. For instance, a recent qualitative study revealed that oncologists often used implicit persuasive behaviours to convince patients to accept the therapeutic option that they believe is best.[848] Finally, the *endowment bias* is characterised as the natural tendency to give a greater value to something (e.g. a treatment) that is expected to be discontinued or removed. Behavioural economists have found that people tend to attach a greater value to *keep* an object than they would to *obtain* it if they didn't already own it.[849] In healthcare decision-making, the endowment bias is mirrored by a common preference for *status quo*, i.e. continuing potentially unnecessary and harmful treatments to avoid the feeling of loss that would arise from discontinuation.

To counter these commonly observed cognitive biases and reduce inappropriate drug utilisation in older adults with multimorbidity and limited life expectancy, deprescribing strategies should attempt to rationalise the evaluation of benefits and harms of treatments, and promote shared decision-making.[533,714,850,851] More high-quality empirical evidence is also needed to curtail the use of ineffective drug treatments near the end of life. For instance, haloperidol is currently recommended as first-line treatment for delirium in palliative care,[852] but a recent randomised controlled trial revealed that it has no proven benefit compared to placebo.[853] It is likely that, in **Study III** of the present thesis, the lack of consensus about very commonly prescribed drugs at the end of life (including haloperidol) can be explained not only by the lack of robust empirical evidence but also by some of the cognitive biases described above.

Deprescribing in real-world clinical practice: easier said than done?

Results from **Study IV** clearly demonstrate that a substantial fraction of older people continues to be prescribed drugs considered 'often inadequate' until the very end of life. Besides the difficulties discussed earlier, other challenges rooted in the daily clinical practice may explain the suboptimal rates of deprescribing at the end of life. A series of recent systematic reviews have been conducted on this topic, providing a detailed account of the barriers that hinder deprescribing efforts.[850,854–856] In our view, three of these barriers deserve particular consideration.

First, deprescribing in the context of end-of-life care is seldom about discontinuing a single drug in patients with a single disease. Most older adults with advanced illness live with multiple comorbidities that co-exist with a myriad of symptoms and geriatric syndromes. These health problems and their treatments form a complex nexus, which—in some cases—may be in a state of equilibrium. The withdrawal or tapering of one drug because of insufficient short-term benefit can potentially affect the fragile equipoise that prevailed until then and thus prove unrewarding because of unintended collateral consequences. This line of thinking is behind the 'Never change a winning team' principle endorsed by Onder et al. in a recent editorial.[857] This approach, they argue, differs from therapeutic inertia in the sense that is does not stem from a failure to act in the presence of side effects of goal-discordant care, but instead is the result of a clinical decision guided by a personalised assessment of the benefits and harms of continuing vs. stopping an otherwise well-tolerated treatment.

Second, discontinuing drugs in seriously ill, multimorbid, symptomatic older patients requires what—in most care settings—are the two of the most sought-after resources: time and expertise. Deprescribing necessitates the presence of trained clinicians at the bedside and close collaboration with clinical pharmacist and pharmacologists, with careful monitoring of patients during the following days and weeks to ensure that no adverse effect is developing. Some treatments should also be tapered progressively to avoid withdrawal syndromes and rebound effect, which requires multiple encounters with the prescriber, sometimes over several weeks. This is the case, for instance, of benzodiazepines and zolpidem, antidementia drugs, antidepressants, beta-blockers, and other antihypertensives. Therefore, staff shortages and the lack of on-site pharmacological expertise may impede deprescribing in routine clinical practice.

Third, because they can only afford to spend a limited amount of time with each patient, physicians have to make trade-off decisions between attempting to deprescribe drugs of limited clinical benefit on the one hand and managing the increasingly complex care needs of older people as they approach the end of life. This is especially an issue for GPs, whose average consultation time varies from 10 minutes in England and in the Netherlands, to 15 minutes in Belgium and France, up to 20 minutes in the United States.[858] The same applies in nursing homes, where trained geriatricians are scant.[859,860]

5.4 METHODOLOGICAL CONSIDERATIONS

Study design

Three of the four studies included in the present thesis rely on a retrospective cohort design, where older adults were selected at time of death and followed-back in time to reconstruct their drug utilisation history near the end of life. This design has been criticised by Bach et al., who argued that studies "resurrecting the treatment histories of dead patients" yield different results than studies based on a prospective cohort design where individuals are selected at the time when their prognosis worsens and followed-up until death.[861] Two mechanisms can indeed introduce bias.

First, patients who die during a given period are not entirely similar to patients who had the same profile (e.g. sex, age, primary life-limiting condition, number of chronic co-morbidities, level of ADL disability) but remained alive. In other words, studies examining decedents may leave out part of the population of interest. This selection effect has serious implications when it comes to discussing the potential benefits and harms of treatments: by design, people who did benefit from the treatments and did not suffer substantial harms are excluded from mortality follow-back studies. Also, considering the "last months of life" of patients who died leads to underestimating the prognosis uncertainty that these patients, their family caregivers, and healthcare professionals experienced at the time. We have tried to mitigate this risk of bias by stratifying older decedents according to their illness trajectory (**Study I**), by selecting patients whose death should have been anticipated at least a few months ahead (**Study II**), by selecting only people who died from conditions amenable to palliative care (**Study IV**), and by removing patients who died from an acute and potential unpredictable cause (**Studies II and IV**).

Second, while prospective studies will only count as contributing time the period ranging from the diagnosis of a serious illness until death, retrospective cohorts of decedents will almost inevitably consider a fixed period before death irrespective of the timing of diagnosis. By pooling together months spent with and without a serious illness, the retrospective design may introduce *immortal time bias*. This is particularly true for older adults, who can expect to live fewer months after a diagnosis of serious illness and also experience a higher risk of death in the absence of a serious condition. However, in our view, immortal time bias would only arise if the outcome is dependent on the diagnosis (e.g. prescribing of chemotherapy for patients with metastatic cancer) or if the outcome of interest is cumulative over time (e.g. accumulated healthcare expenditures over the last year of life). In **Study II**, we found that stratifying the results according to the time from cancer diagnosis and death made little difference. In a study comparing deceased patients identified retrospectively with patients prospectively identified at high probability of dying at the time of hospital admission, Barnato et al. reported similar estimates for a range of healthcare utilisation indicators.[862]

Misclassification of drug exposure

In pharmacoepidemiologic and drug utilisation studies, the exposure to drugs must be ascertained in a rigorous, reproducible, and accurate manner. Most databases contain the date of prescription, the date of dispensing, or both. Researchers typically use this information to define the beginning of a new exposure period or to determine the prolongation of an antecedent period. However, the number of days covered is seldom available in routinely collected data (Medicaid and Medicare Part D claims data being notable exceptions[597,863]). In the absence of explicit information about the number of days' supply, the duration of drug exposure is often estimated by using proxies. Although many studies rely on defined daily doses to estimate windows of drug exposure, this can result in serious misclassification bias and is thus not a recommended approach.[597] Others have suggested using the distribution of the interval between prescription refills to predict the duration of a new exposure period, for instance by considering specific percentiles of the waiting time distribution for a given drug class in order to calculate the typical number of day until the next purchase.[864–867] However, this method relies on the assumption that drugs prescribed for different clinical indications are used at the same rate and that refill patterns are constant over time, i.e. that there is no within-person change in the prescribed daily dose. The limitations of both methods have been demonstrated by Tanskanen et al.,[599] who recently proposed a novel data-driven approach for estimating drug exposure periods.[868]

In this thesis, we have used yet another methodology, based on the interpretation of written instructions for the prescribed daily dose (see *3.3 Assessment of drug exposure*). We have established that the number of days' supply estimated by using our algorithm is very close to that of a manual, line-by-line screening by a human operator. Moreover, the Swedish Prescribed Drug Register reports data about dispensed rather than prescribed drugs, which means that our results are not affected by primary non-adherence (i.e. treatments that are prescribed but not redeemed at pharmacies[869,870]). However, several shortcomings may have led to a misclassification of drug exposure for a fraction of individuals. First, this register only collects data on prescription drugs dispensed at community pharmacies. Over-the-counter (OTC) drugs, drugs administered in hospitals or in nursing homes with a drug storeroom are thus not included, leading to some degree of underestimation. To minimise the risk of bias that could arise from these 'blind spots', we excluded older adults who had no history of drug utilisation during the 3–6 months before death (~5% of decedents). Second, the estimated prevalence of polypharmacy, preventive drugs, and drugs of questionable benefit relies on the assumption that older adults used their treatments in keeping with the prescribed dosage, namely at the dose and frequency indicated by the physician at the time when the drug prescription was initiated or renewed. Our results may thus be affected by secondary non-adherence (drugs were dispensed but not ingested), dose tapering (the prescribed daily dose was reduced in the midst of an exposure period), and drug discontinuation (the drug regimen was stopped before the 'end date' calculated based on the number of days' supply). These

three scenarios—to which the algorithm that we devised is blind—are most likely common near the end of life and could lead to overestimating the actual use of chronic drugs during the months before death. Further methodological developments are thus warranted to assess and improve the accuracy of routinely collected drug data in the context of advanced illness and end-of-life care. However, it is unlikely that our approach for estimating the duration of drug exposure leads to differential misclassification.

Measurement errors and information bias

Using routinely collected administrative and healthcare data for research purposes raises a number of methodological issues, not least the presence of upcoding errors, opportunistic coding practices, inconsistencies across geographical areas or care settings, and changes in coding strategies over time.[871] For instance, the validity of dementia diagnoses in electronic health records, hospital discharge reports, and death certificates should be examined critically in light of recent studies demonstrating high specificity but overall low sensitivity.[872,873] In Sweden, Rizzuto et al. showed that, in the general older population, only half of dementia cases were ever captured by the National Patient Register or the National Cause of Death Register; detected cases were recorded on average 5.5 years after the first diagnosis of dementia.[874] In the studies included in the present study, we made all efforts to optimise the detection of chronic conditions by extending the lookback period up to 5 years, by considering not only ICD-10 diagnoses but also specific ATC codes for prescribed drugs, and by using an advanced text-mining algorithm to interpret clinical indications for drug treatments. It should be noted that while some chronic conditions are most likely underreported in national registers (e.g. hypertension, asthma, depression, gynaecological diseases) the more severe illnesses have been found to be very accurately coded (e.g. cancer, stroke, history of AMI, Parkinson's disease). We also have reasons to believe that, prior to 2013, the monthly assessment of nursing home residence in the Social Services Register was suboptimal, which could have led to a misclassification of living arrangement for a fraction of decedents in **Study I** and **Study II**. We minimised the risk of bias by cross-referencing data from the Social Services Register with the place of death recorded in the National Cause of Death Register and with hospital discharge data from the National Patient Register (which contains information about the patients' destination after discharge).

Illness trajectories and patterns of functional decline at the end of life

It has recently been demonstrated that, contrary to earlier assumptions, the condition leading to death (which we used to construct *illness trajectories* in the present thesis) was only weakly correlated with the actual course of disability near the end of life. In other words, people dying from a certain set of diseases may not experience a homogenous and predictable pattern of functional decline that would differentiate them from those who died from another set of diseases.[39] By using prospective data from the Health, Aging

and Body Composition (Health ABC) study, Lunney et al. made it clear that there exists little overlap between illness trajectories and mobility or ADL disability[41], and that longitudinal, within-person changes in health status or disability did not differ substantially according to the underlying disease.[875] While physical functioning seems to oscillate to a greater extent among patients with congestive heart failure or COPD, which is reflected in their higher rate of non-elective hospitalisations at the end of life, there is no evidence a single trajectory of disability that would accurately describe a majority of decedents.[876] In a large cohort study based on data collected prospectively by 115 specialist palliative care services participating in the Palliative Care Outcomes Collaboration in Australia,[877] Morgan et al. found that patients who died from cancer, solid organ failure, and cardiovascular diseases shared a similar profile of 'precipitous deterioration of functional decline' during their last 4 months of life, while patients with dementia and neurological conditions — including stroke — followed a largely common path of slow and prolonged decline.[40] The authors interpret their findings as the logical consequence of effective medical interventions for life-limiting diseases (e.g. cancer immunotherapy, thrombolysis for acute ischemic stroke) and better management of chronic co-morbidities, which further extend the lifespan of seriously ill patients and tend to exacerbate the final drop in physical functioning shortly before death. Recent improvements in cancer treatments are currently transforming the landscape of supportive care in oncology, with a substantial proportion of older patients now surviving conditions that would have been lethal in the short term less than 10 years ago (e.g. metastatic melanoma, advanced lung cancer).[878–880] Be that as it may, stratifying older adults according to the clinical conditions leading to death remains a useful approach to understand the heterogeneity in healthcare utilisation and palliative care needs near the end of life. In **Study I** and **Study IV**, we showed that drug prescribing patterns among people who die from cancer, organ failure, or dementia and neurodegenerative conditions are markedly different, and that decedents in each group shared distinct sociodemographic features. Moreover, operationalising these illness trajectories based not only on the underlying cause of death but also on contributing causes allows for a more nuanced assessment of the most likely course of disease at the end of life.

Illness trajectory	Cancer	Organ failure	Dementia
Short and evident decline (e.g. cancer)	100%	39.70%	11.40%
Intermittent decline (e.g. organ failure)	18.60%	100%	26.90%
Slow and gradual decline (e.g. dementia)	11.50%	58.10%	100%

Table 19. Overlap between illness trajectories at the end of life

Percentages represent the proportion of decedents (≥65 years) whose multiple causes of death suggested overlapping illness trajectories. For instance, out of the 23 289 older adults who died with cancer, 39.7% also had a cause of death categorised as 'organ failure' and 11.4% had a cause of death categorised as 'dementia'. To assign decedents to a single trajectory, we applied the hierarchy proposed by Gill et al.[39] and Chaudry et al.[44]: cancer > dementia > organ failure > sudden death.

Generalisability and transportability

An aspect of the validity of a study is the ability to extrapolate its results beyond the group of individuals that were empirically observed in order to draw inference about the target population. Generalisability—which is also referred to as *external validity*—can be affected by selective inclusion into the study, selective attrition during follow-up, selective assignment of the exposure, and non-random missing data about either the exposure, the outcome, or potential confounders.[881] While modern epidemiology is mostly concerned with threats to externally valid causal effect estimates (e.g. ensuring that the average treatment effect observed in the study population is an unbiased estimator of the *true* average treatment effect in the population of interest[882,883]), in the three epidemiological studies included in this thesis we were mainly interested in providing descriptive and predictive results that would pertain to the entire population of older adults nearing the end of life. This issue can be approached from two different angles.

First, are the findings observed in the sample population of each study *unbiased approximations* of what we would have found if we had been able to measure them in the whole target population under perfect conditions? The use of high-quality, routinely collected administrative and healthcare data with national coverage is key to avoid selection bias and attrition due to loss to follow-up that are often encountered in surveys and population-based studies. Our cohorts were constructed based on the Total Population Register and the National Cause of Death Register, which both cover the full Swedish population with virtually 100% completeness. This removes concerns about random (i.e. sampling) error. However, because we excluded older adults who died from unknown or unreported cause and date of death, those who had no history of drug dispensing during the months before death, and those who remained hospitalised continuously during their last 3 months of life, about 5% of decedents were not included. Doing so created a statistically perceptible but qualitatively trivial distortion between the sociodemographic characteristics of the entire cohort of decedents over the study period and those of the subjects included in the different studies (e.g. slight underrepresentation of younger-old decedents). We found no evidence that the study populations in **Study I**, **Study II**, and **Study IV** differed in meaningful ways from their hypothetical target populations with respect to sex, living arrangement, level of education, marital status, and final place of death. Moreover, the proportion of individuals with missing data for their educational attainment who were thus excluded from multivariable regression analyses ranged between 4.7% in Study I and 2.3% in **Study IV**. Although these data were clearly not missing at random (concentration around people aged 95 years and over), it is unlikely that the relative risks and adjusted median differences estimated in each study would have been noticeably different had these people been included in the analysis.

Second, are these findings *transportable* to a broader population that does not entirely overlap with (and may even substantially differ from) the study population at hand? For

instance, can we make inference about the patterns of drug prescribing for older people at the end of life in other countries? In regions that share a social, economic, cultural, and healthcare environment similar to Sweden and (e.g. Nordic European countries, Germany, United Kingdom, France, Canada), one could expect to observe comparable rates of polypharmacy and potentially inadequate drugs during the last months of life. This assumption is supported by recent studies conducted in Ireland[884], France[885], Beligum[886], New-Zealand[887], and Australia[888–890]. However, our findings may not be entirely applicable to countries with vastly different healthcare systems. Cross-national studies have hitherto been limited, thus precluding reliable international comparisons. Some evidence suggests that the use of medications of questionable clinical benefit near the end of life may be more frequent among older adults with dementia in the United States[570] than in Sweden[568], Canada, or Taiwan[573]. A head-to-head comparison between two hospitals in the U.S. and in England also showed a greater burden of preventive drugs among American lung cancer patients than among their British counterparts.[891] Nevertheless, Zueger et al. found that older Medicare Part D-enrolled beneficiaries who died between 2008 and 2013 following hospice admission continued to receive preventive medications to the same extent as in Sweden.[892,893]

Residual confounding

Confounding refers to the bias resulting from the existence of common causes of both the exposure and the outcome. When "the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for the actual effect of the exposure [on the outcome]", Rothman writes, then the association between exposure and outcome is *confounded* and cannot be interpreted as a strictly causal relationship.[881] In other words, confounding arises if the direct path between the exposure X and the outcome Y ($X \rightarrow Y$) is seconded by an indirect path running through a common cause L ($X \leftarrow L \rightarrow Y$). In this case, association cannot be interpreted as causation because there is a lack of exchangeability between individuals exposed ($X = 1$) and unexposed ($X = 0$).

This can be expressed in counterfactual terms by comparing the difference in the *observed outcome* between the exposed ($\Pr[Y = 1 \mid X = 1]$ and unexposed ($\Pr[Y = 1 \mid X = 0$) with the difference in the *potential outcome* had everyone been exposed ($\Pr[Y^{x=1} = 1]$) in contrast with a situation where nobody had been exposed ($\Pr[Y^{x=0} = 1]$). If there is no confounding, then $\Pr[Y^{x=1} = 1] - \Pr[Y^{x=0} = 1] = \Pr[Y = 1 \mid X = 1] - \Pr[Y = 1 \mid X = 0]$.[894] This would be the expected setting in a well-designed randomised clinical trial, where individual participants have the exact same probability of receiving the treatment and are assigned to a treatment group by the flip of a coin. The randomisation procedure normally ensures the marginal exchangeability of study participants since there exists no common cause of X and Y. In observational research, however, exposures are seldom determined by chance and are usually driven by many factors L that can also influence the likelihood of experiencing the outcome of interest. To enable causal inference for the effect of X on Y, all indirect paths ('backdoors') must be blocked by conditioning on the covariates that

represent a common cause—in this case, either *L* itself or a proxy for *L*. These measured *confounders* can be accounted for by adjusting the analysis with either stratification-based methods (e.g. stratification, restriction, matching, regression, propensity scores) or G-methods (e.g. G-formula, inverse probability weighting, G-estimation).[895]

In the studies included in this thesis, our aim was not to establish causal relationships, but rather to identify independent determinants of specific patterns of drug prescribing at the end of life. We handled the issue of confounding by conducting various regression analyses adjusted for relevant covariates identified *a priori* based on expert-matter knowledge and information available in routinely collected data. We interpreted results from these regression models not as average causal effect estimates but as average predicted risk differences.[896] In **Study II**, for instance, the β coefficients derived from quantile regression can be thought of as the estimated median difference in costs among older people who died from cancer *A* compared with those who died from cancer *B* if decedents in both groups had, on average, had the same sex, age, number of chronic diseases, living arrangement, and level of education. Nonetheless, whether they are used for *prediction* purposes or to make causal inferences, adjustment methods rely on the untestable assumption that the available covariates represent a set of confounders that is sufficient to block all indirect paths between exposure and outcome and that there is no *unmeasured confounding*. Although we have made every effort to control for sociodemographic characteristics, illness trajectory, chronic multimorbidity and (in Study IV) risk of physical frailty, we cannot rule out the presence of residual confounding.

The granularity and the diagnostic accuracy of the data used in our studies are most likely insufficient to guarantee that the magnitude of the association observed between potential predictors and drug utilisation at the end of life is unbiased. For instance, the lack of information about the stage, the clinical characterisation, and the physiopathology of the underlying disease and about the severity of chronic comorbidities is a clear threat to the validity of our estimates. The Hospital Frailty Risk Score developed by Gilbert et al.[611] is, by any standard, an imperfect surrogate for the actual level of frailty of older adults. Because ICD-10 codes are used to evaluate the case-mix of healthcare services and to construct Diagnosis-Related Groups (both of which are the cornerstone of current reimbursement procedures in the U.S. and in most European countries), they are notoriously affect by opportunistic coding practices. Some have argued that frailty-related ICD-10 codes are not as well documented as the organ-related acute medical issues that typically trigger hospital admissions in old age, owing to the fact that the latter result in higher reimbursement and are thus economically more rewarding for healthcare providers.[897] Yet, contrary to the United Kingdom where hospital data can be linked in routine to high-quality primary care medical records,[898,899] such data are not available for the full Swedish population. This prevented us from computing a more sensitive and reliable frailty instrument, such as the newly developed electronic Frailty Index (eFI),[612] which has shown great potential for palliative and end-of-life care research.[363]

5.5 CONCLUSIONS

By examining drug utilisation patterns during the last year of life of older adults, we found that the number of drugs increased significantly, fuelled not only by the initiation of symptomatic drugs to ensure comfort but also by the frequent continuation of preventive and disease-oriented treatments. The use of high-quality mortality and drug dispensing data with full population coverage, the categorisation of decedents into four illness trajectories, and the development of robust and scalable methods for estimating drug exposure periods in large cohorts represent important methodological contributions to the published literature on this topic.

We demonstrated that older adults with unpredictable end-of-life trajectories were not driving the observed increase in polypharmacy and in the continuation of preventive drugs. Among individuals who died with solid cancer—a set of diseases most often characterised by a poor prognosis and a clinically discernible terminal phase—drugs prescribed for the long-term management of chronic comorbidities were frequently continued until the last month of life. Moreover, we estimated that preventive drugs account for ~20% of the total drug expenditures. In our opinion, even though preventive drugs are not necessarily clinically inappropriate at the end of life, the large proportion of older cancer patients who continue to receive statins, antihypertensives, low-dose aspirin, and vitamins until the very end of life does indicate that routine-based prescribing practices contribute to low-value albeit costly treatments.

We also provided a clinically-driven, consensus-based list of drugs considered 'often adequate', 'questionable', and 'often inadequate' for use in older persons aged ≥75 years with a life expectancy of three months or less. In the absence of robust evidence from randomised controlled trials and well-designed observational studies, these criteria represent an important step in the on-going international effort to rationalise drug therapy among older people near the end of life. They also offer a standardised methodology to examine the prevalence and adverse outcomes associated with the use of drugs of limited clinical benefit at the end of life.

Finally, by applying these criteria on a population of older adults who died from conditions potentially amenable to palliative care, we found that one out of three patients *continued* and one out of seven patients *initiated* at least one drug considered 'often inadequate' during their last three months of life.

In sum, the findings from this thesis indicate that many older people are probably overtreated at the end of life, which exposes them to unnecessary risks. Deprescribing in the context of end-of-life care is not about denying older people access to treatments that would be beneficial. It is about avoiding harm, maintaining the best possible quality of life, and minimising the disruptive impact of medicine on the patients' everyday life.

5.6 FUTURE PERSPECTIVES

The epidemiological studies that compose the present thesis provide a bird's eye view of drug treatments among older adults at the end of life. Furthermore, the proposed set of consensus-based criteria can provide guidance to clinicians and facilitate comparisons across patient populations, care settings, and countries. However, future research efforts are required to improve prescribing practices and reduce the burden of unnecessary and potentially harmful drugs near the end of life. In our opinion, future studies would be particularly helpful in four research areas.

First, the available data were insufficient to shed light on the prevalence of undertreatment among seriously ill older adults at the end of life, both in terms of disease management and in terms of symptom relief. Investigating the underuse of necessary drug treatments is made difficult by the fact that it requires an impeccable assessment of the care needs at the patient level and precise information about the indication of the prescribed drugs. In specific cases, underuse is easily detected in electronic medical records (e.g. absence of antithrombotic therapy among patients at high risk of stroke). However, in the context of end-of-life care—at a time when the non-initiation of otherwise recommended drugs can be justified by patient preferences and poor prognosis—measuring underuse with routinely collected administrative and healthcare data proves to be prohibitively difficult. Cross-sectional (e.g. single-day prevalence surveys) and prospective cohort studies with specific data collection procedures, fine-grained clinical appraisal of care needs, and patient-reported outcome measures would be better suited for this purpose.

Second, we believe that qualitative evidence is warranted to gain a better understanding of the underlying mechanisms that drive the provision of preventive drugs at the end of life, especially to disentangle prescribing practices guided by clinically justified reasons from low-value care driven by cognitive biases and irrational decision-making. In addition, carefully designed longitudinal studies with repeated in-depth qualitative interviews could shed light on the experience of seriously ill older adults regarding the impact of disease-oriented drug treatments on their quality of life and wellbeing. Ideally, such studies would enrol patient-caregiver dyads rather than patients or caregivers alone, in order to allow for triangulating similarities and divergences between them. Conducting this type of research comes with important challenges, including the recruitment of participants and the substantial attrition rate during follow-up. However, researchers in The Netherlands have recently demonstrated that longitudinal qualitative studies among advanced cancer patients are practically feasible and provide invaluable.[822,900]

Third, there is a need for leveraging the potential of pharmacoepidemiological methods to evaluate the harms of inadequate drug prescribing among older adults with life-limiting disease and poor prognosis. The validity of comparative effectiveness and safety studies using observational data is typically compromised by the lack of conditional

exchangeability between the *treated* and the *untreated* patients due to the residual, unmeasured confounding that stems from the prognostic imbalance between these two groups (confounding-by-indication bias).[901,902] In other words, even if all measured covariates are perfectly balanced at baseline, the main reason why some patients received the treatments while others did not is most likely related to the prognosis established by the prescribers. If cancer patients who continue statins seem to live longer than those who discontinue their treatment, it is less because statins prolong their lives than because the high risk of death was precisely the reason that prompted the decision to forgo treatment in the first place.[903] Without random treatment assignment, removing confounding-by-indication bias is a daunting task in observational parallel-group study designs. However, two methodological approaches could potentially help overcome this conundrum: (1) *prior event rate ratio* analysis,[904–907] which relies on the assumption that the difference in the likelihood of having experienced the outcome of interest before treatment initiation reflects the influence of confounders independently from the effect of the treatment; and (2) case-time-control design,[908–910] a variation of the case-crossover design in which the change in treatment exposure between T_0 and T_1 among cases (i.e. individuals who develop the adverse outcome of interest during the T_1 time window) is compared to the change in treatment exposure among controls (i.e. individuals who do not develop the outcome during T_1). The main limitation of both methods is their intrinsic inability to examine non-repeatable events and, thus, to study mortality as the outcome of interest. Moreover, implementing these designs will require high-quality data to assess the exposure of study subjects during different observation windows and to ascertain the occurrence of the clinical outcomes under observation with sufficient accuracy.

Finally, pragmatic randomised clinical trials should be designed and implemented to assess the efficacy, safety, and cost-effectiveness of different deprescribing approaches among older adults with life-limiting disease and poor prognosis. To date, only one such RCT has been conducted, which showed that statins could be safely withdrawn among patients with a predicted life expectancy inferior or equal to 12 months and that discontinuation was associated with modest improvements in quality of life.[718] Other clinical trials have also proven the feasibility and safety of deprescribing cardiovascular drugs in the more general context of ageing and frailty, such as the DANTE trial (antihypertensives in older adults with mild cognitive impairment[911]) and the ECSTATIC study (lipid-lowering medications and antihyper-tensives among adult patients at low risk of cardiovascular event[912]). However, these trials failed to unequivocally demonstrate the *benefit* of discontinuing unnecessary drugs in terms of symptom management, quality of life, adverse events, and survival. The purpose of deprescribing is not merely to discontinue unnecessary drugs; it is to discontinue unnecessary drugs to avoid harms and improve health outcomes. In future trials, a potentially fruitful approach could be to focus on high-risk medications (e.g. anticoagulants, low-dose aspirin, antipsychotics) among patients at high risk of drug-related harm (e.g. frailty, multimorbidity) in high-risk situations (e.g. cardiovascular polypharmacy, surgery, transition between care settings).

ACKNOWLEDGEMENTS

Throughout my doctoral education, I have worked with many excellent researchers, colleagues and friends.

First, I would like to express my gratitude to Professor **Kristina Johnell**, my main supervisor. You gave me a chance when I knocked at your door five years ago, and you gave me the freedom and independence I needed while remaining supportive and attentive to details. We have always worked together in an atmosphere of mutual respect, transparency and simplicity. Your kindness and support have helped me grow as a researcher. For this and for everything else, I am deeply thankful.

My co-supervisor Professor **Johan Fastbom**, without whom the data behind most of this thesis would still be locked in a gargantuan and inaccessible database. Thank you for making your expertise and skills available to me, and for showing me support all the way through. This thesis also owes a lot to the input of my co-supervisor Professor **Marie-Laure Laroche**, who brought her encyclopaedic knowledge of geriatric pharmacology. You kindly accepted to be part of this journey, and you have always been supportive of my work and ideas. Thank you.

Many colleagues at the Aging Research Centre (ARC) have contributed, one way or another, to this thesis. **Jonas Wastesson**, with whom I have shared many discussions, publications, beers, and laughs over the past few years. You have taught me quite a bit and you have (sometimes reluctantly) been involved in many of my crazy epidemiological endeavours. I'm looking forward to our next 200 manuscripts together. I am also greatly indebted to **Amaia Calderon-Larrañaga**, for showing me what this job is really about: asking clinicians questions that matter in order to get answers that can help patients. Your compassionate and empathic way of bringing people together to do better research is truly inspiring. What a fantastic scientific leader you will be! **Louise Sundberg** deserves a special mention. You know how much I enjoyed our discussions, lunches and the occasional glass of rosé wine. What you maybe don't know is how much lighter and sweeter you made my time at ARC (despite your weird manners and your unpredictable dietary restrictions). Thank you for being this intelligent, perceptive and kind-hearted person; I am lucky to have you as a friend. **Neda Agahi** has also played an essential role during the past few years, both professionally and personally. You made me realise that there is indeed a way for the *Reds* to live happily alongside the *Yellows*, the *Blues* and even (sometimes) the *Greens*.

Thank you to **Stina Ek**, one of the most quick-witted persons I know. You reminded me now and again what "standing up for oneself" really means. Thank you to **Stefan Fors** for your unparalleled insight and your imperturbable gentleness, and for putting up with me despite our widely different personalities. Now that this thesis is wrapped up, I can finally go back to writing the manuscripts we talked about!

This PhD wouldn't have been the same without a solid crew of colleagues and friends, including **Davide Vetrano** (a promising geriatrician and a skilled Macarena dancer), **Giulia Grande** (seriously, though, who doesn't like Tarantino movies?), **Debora Rizzuto** (a ray of sunshine who also happens to be the most supportive biostatistician around), **Giola Santoni** (who always took the time to explain what was wrong with my mixed-effect models), **Anna Marseglia** (who made me dream about the wonders of Ostuni, the most magnificent city in Southern Italy; you are always welcome in our *guestaaaa roooooooom* in Paris), **Alexander Darin Mattsson** (who likes to talk nearly as much as I do) and **Lieke de Boer** for her sparkling intelligence and in-depth knowledge of the *Monty Python and the Holy Grail*. Others also deserve to be acknowledged: thank you to **Emerald Heiland**, **Mozhu Ding**, **Johan Rehberg**, **Gregoria Kalpouzos**, **Goran Papenberg**, **Kuan-Yu Pan**, **Christina Dintica**, **Josephine Heap**, **Harpa Sif Eyjólfsdóttir**, **Ying Shang**, **Yajun Liang**, **Rui Wang**, **Serhiy Dekhtyar**, **Isabelle Von Saenger**, and **Linnea Sjöberg**.

Thank you to Professor **Johan Fritzell**, for letting me sneak into the Social Gerontology group and for keeping a keen eye on my work. The only thing you're missing is a glamourous French scarf! *Grazie mille* to Professor **Laura Fratiglioni** for being supportive and for giving me the freedom to be an independent PhD student. We don't always see eye to eye, but you have always been very respectful of my way of doing things.

Other colleagues at Karolinska Institutet have played a positive role in my doctoral education. At the Department of Medical Epidemiology and Biostatistics (MEB), I would like to thank **Malin Eriksson** for reviewing this thesis and giving me much-needed feedback, **Sara Hägg**, **Ebba du Rietz**, **Juan-Jesus Carrero**, and **Arvid Sjölander** for their warm welcome and for the exciting collaborations that are coming up. Thank you also to Professor **Nancy Pedersen**, from whom I am learning a lot these days: her calm, kind, and down-to-earth approach to leading young researchers is a blessing. Last but not least, the last few months would not have been the same without the skilled and absolutely benevolent **Gunilla Sonnenbring**.

In France, I am especially thankful to Professor **Régis Aubry**, who has been my mentor for almost a decade. I owe him (for better or worse) most of my working habits and personal ethics. He will be happy and proud to know that a number of persons have complained that I was too pragmatic, not obsequious enough towards senior staff members, and that I worked both too much and too early in the morning. **Marie-Noëlle Belloir**, with whom I started in the field of palliative care in 2008, also had a considerable influence on me. She taught me one of the most important lessons of my professional life: "Whatever you do is pointless if it doesn't make a difference to the patients."

Collaborating with clinicians is without doubt the most enjoyable part of this job. They provide me with relevant research questions, they help me figure out a way to find useful answers, they are always available when I need some advice to interpret the results, and

they never miss an occasion to explain that "doctors aren't *that* bad, they are just caught up in tricky situations." Over the years, I have had the privilege of working with a remarkable group of oncologists, geriatricians, palliative care physicians, general practitioners and pharmacists who share a deep commitment to improving patient care at the end of life. I have learnt a great deal of what I know with Professor **Christophe Tournigand** and Dr **Emmanuelle Kempf** (Henri Mondor, Paris), Professor **François Goldwasser** (Hôpital Cochin, Paris), Dr **Philippe Rochigneux** (Institut Paoli Calmettes, Marseille), Dr **Yvan Beaussant** (Dana Farber Cancer Institute, Boston), **Barbara Roux** (CHU Limoges), Dr **Thomas Tannou** (CHU Besançon), Dr **Laurent Calvel** (CHU Strasbourg), Dr **Rémy Thirion** (CH Dinan), Dr **Stephen Barclay** (Cambridge University). I am deeply indebted to **Adam Todd** (University of Newcastle) for his encouragements, his expert advices and his friendship, and to Professor **Jean Kutner** (University of Colorado) for her thoughtful support, her unparalleled kindness, and for the stimulating discussions that we've have. My gratitude also goes to **Marie Tournigand** (Empreintes) and **Nancy Kentish-Barnes** (Hôpital Saint-Louis, Paris), with whom collaborating is always a treat.

Since its first meeting in Brussels in June 2017, the "Big data for end-of-life care research" task force of the European Association for Palliative Care has been a great success. A special mention to Professor **Joachim Cohen** (VU Brussels) and Professor **Bregje Onwuteaka-Philipsen** (Amsterdam UMC), with whom I share the coordination of this initiative. It is not only a pleasure but also a privilege to collaborate with them, in this atmosphere of trust, mutual respect, scientific rigor, and fun. Within the group, I would like to acknowledge and thank **Kim Beernaert**, **Tinne Smets**, **Robrecht De Schreye**, **Veerle Piette**, **Arno Maetens**, **Annicka Van der Plas**, and **Peter May**. I also want to express my gratitude to Professor **Lieve Van den Block** for her friendly support over the years and her refreshingly no-nonsense approach to research.

Spending a little over one month with the "Pharmaco- and Device epidemiology" research group at the University of Oxford has been a wonderful experience. Thank you to Professor **Daniel Prieto-Alhambra**, who is not only an exceptionally kind and generous person but also a razor-sharp researcher when it comes to discussing methods for causal inference in pharmacoepidemiology. "A good head and good heart are always a formidable combination", Nelson Mandela wrote. Dani also has impeccable taste in wine, which—as everyone knows—is paramount to entertain French collaborators. The whole team has been endearingly welcoming while I was in Oxford, especially **Samuel Hawley**, **Vicky Strauss**, **Paloma O'Dogherty Cordero** and **Mahkameh (Maki) Mafi.**

Finally, this journey would not have been possible without **Irène**. I honestly don't think I would have dared to get involved in academic research without your support and confidence in me. You are the most brilliant person I know. I will follow you anywhere, no matter how far, as long as we keep learning new things together. And the answer is yes.

REFERENCES

Please note that papers of special interest have been highlighted (•).

1. World Health Organization. *World Report on Ageing and Health*. Geneva; 2015.
2. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death. *Lancet*. 2018;392 (10159):2052-2090.
3. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections. *Lancet*. 2017;6736(16):1-13.
4. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. *Lancet*. 2015;385 (9967):540-548.
5. Statistics Sweden. The future population of Sweden 2015–2060. 2015:284.
6. United Nations. Department of Economic and Social Affairs. Population Division. *World Population Prospects: 2017 Revision*. 2017.
7. Raftery AE, Li N, Ševčíková H, Gerland P, Heilig GK. Bayesian probabilistic population projections for all countries. *Proc Natl Acad Sci*. 2012;109(35):13915-13921.
8. Dong X, Milholland B, Vijg J. Evidence for a limit to human lifespan. *Nature*. 2016;538 (7624):257-259.
9. Olshansky SJ. From Lifespan to Healthspan. *JAMA*. 2018;320(13):1323.
10. De Beer J, Bardoutsos A, Janssen F. Maximum human lifespan may increase to 125 years. *Nature*. 2017;546(7660):E16-E17.
11. Hughes BG, Hekimi S. Many possible maximum lifespan trajectories. *Nature*. 2017;546(7660):E8-E9.
12. Colchero F, Rau R, Jones OR, et al. The emergence of longevous populations. *Proc Natl Acad Sci*. 2016;113(48):E7681-E7690.
13. Oeppen J, Vaupel JW. Broken Limits to Life Expectancy. *Science*. 2002;296(5570):1029
14. Carnes BA, Olshansky SJ, Hayflick L. Can Human Biology Allow Most of Us to Become Centenarians? *Journals Gerontol Ser A Biol Sci Med Sci*. 2013;68(2):136-142.
15. Statistics Sweden. *The Future Population of Sweden 2018–2070*. Vol 1. Stockholm: Statistics Sweden; 2018.
16. Crimmins EM. Lifespan and healthspan: Past, present, and promise. *Gerontologist*. 2015; 55(6):901-911.
17. Lafortune G, Balestat G, Disability Study Expert Group. *Trends in Severe Disability Among Elderly People: Assessing the Evidence in 12 OECD Countries and the Future Implications*. 2007.
18. Smith AK, Walter LC, Miao Y, Boscardin WJ, Covinsky KE. Disability during the last two years of life. *JAMA Intern Med*. 2013;173 (16):1506-1513.
19. Ford JC, Ford JA. Multimorbidity: will it stand the test of time? *Age Ageing*. 2018;47(1):6-8.

20• Kingston A, Wohland P, Wittenberg R, et al. Is late-life dependency increasing or not? A comparison of the Cognitive Function and Ageing Studies (CFAS). *Lancet*. 2017;390 (10103):1676-1684.

21. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009;374(9696):1196-1208.
22. Sundberg L, Agahi N, Fritzell J, Fors S. Trends in health expectancies among the oldest old in Sweden, 1992-2011. *Eur J Public Health*. 2016;26(6):1069-1074.
23. Harper S. Economic and social implications of aging societies. *Science*. 2014;346(6209):587.
24. Gorina Y, Hoyert D, Lentzner H, Goulding M. Trends in causes of death among older persons in the United States. *Natl Cent Heal Stat*. 2006;(6):1-12.
25. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013. *Lancet*. 2015;385(9963):117-171.
26. Etkind SN, Bone AE, Gomes B, et al. How many people will need palliative care in 2040? Past trends, future projections and implications for services. *BMC Med*. 2017;15(1):1-10.
27. Glaser BG, Strauss AL. *Time for Dying*. Chicago: Aldine Publishing Company; 1968.
28. Mccormick TR, Conley BJ. Patients' perspectives on dying and on the care of dying patients. *West J Med*. 1995;163(3):236-243.
29. Institute of Medicine. *Approaching Death: Improving Care at the End of Life*. Washington, D.C.: The National Academies Press; 1997.

30. Lynn J. Serving patients who may die soon and their families: The role of hospice and other services. *JAMA*. 2001;285(7):925-932.

31. Morris JN, Suissa S, Sherwood S, Wright SM, Greer D. Last days: A study of the quality of life of terminally ill cancer patients. *J Chronic Dis*. 1986;39(1):47-62.

32. Lunney JR, Lynn J, Hogan C. Profiles of older medicare decedents. *J Am Geriatr Soc*. 2002;50(6):1108-1112.

33. Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of End of Life: A Systematic Review. *Journals Gerontol Ser B*. 2018;73(4):564.

34• Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. *JAMA*. 2003;289(18):2387-2392.

35. Lynn J, Adamson DM. *Living Well at the End of Life: Adapting Health Care to Serious Chronic Illness in Old Age*. Santa Monica, CA: RAND Corporation; 2003.

36• Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. *BMJ*. 2005;330(7498):1007-1011.

37. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A. Patterns of social, psychological, and spiritual decline toward the end of life in lung cancer and heart failure. *J Pain Symptom Manage*. 2007;34(4):393-402.

38. Lloyd A, Kendall M, Starr JM, Murray SA. Physical, social, psychological and existential trajectories of loss and adaptation towards the end of life for older people living with frailty: a serial interview study. *BMC Geriatr*. 2016; 16(1):176.

39• Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of Disability in the Last Year of Life. *N Engl J Med*. 2010;362(13):1173-1180.

40. Morgan DD, Tieman JJ, Allingham SF, Ekström MP, Connolly A, Currow DC. The trajectory of functional decline over the last 4 months of life in a palliative care population: A prospective, consecutive cohort study. *Palliat Med*. 2019;33(6):693-703.

41. Lunney JR, Albert SM, Boudreau R, et al. Mobility Trajectories at the End of Life: Comparing Clinical Condition and Latent Class Approaches. *J Am Geriatr Soc*. 2018;66(3):503.

42. Beernaert K, Pardon K, Van den Block L, et al. Palliative care needs at different phases in the illness trajectory: a survey study in patients with cancer. *Eur J Cancer Care*. 2016;25(4):534-543.

43. Morin L, Aubry R, Frova L, et al. Estimating the need for palliative care at the population level: A cross-national study in 12 countries. *Palliat Med*. 2017;31(6):526-536.

44. Chaudhry SI, Murphy TE, Gahbauer E, Sussman LS, Allore HG, Gill TM. Restricting symptoms in the last year of life: A prospective cohort study. *JAMA Intern Med*. 2013;173(16):1534-1540.

45. Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: The World Health Organization's global perspective. *J Pain Symptom Manage*. 2002;24(2):91-96.

46. Brereton L, Clark J, Ingleton C, et al. What do we know about different models of providing palliative care? Findings from a systematic review of reviews. *Palliat Med*. 2017;31(9):781.

47. Brown CRL, Hsu AT, Kendall C, et al. How are physicians delivering palliative care? A population-based retrospective cohort study describing the mix of generalist and specialist palliative care models in the last year of life. *Palliat Med*. 2018;32(8):1334-1343.

48. Quill TE, Abernethy AP. Generalist plus specialist palliative care—creating a more sustainable model. *N Engl J Med*. 2013;368 (13):1173-1175.

49. Clark D. From margins to centre: a review of the history of palliative care in cancer. *Lancet Oncol*. 2007;8(5):430-438.

50. Sallnow L, Paul S. New Public Health Approaches to End-of-Life Care. In: MacLeod RD, Block L Van den, eds. *Textbook of Palliative Care*. Cham: Springer; 2018:1-10.

51. Hughes MT, Smith TJ. The Growth of Palliative Care in the United States. *Annu Rev Public Health*. 2014;35(1):459-475.

52. Davies E. *What Are the Palliative Care Needs of Older People and How Might They Be Met ?* WHO Regional Office for Europe; 2004.

53. Van Mechelen W, Aertgeerts B, De Ceulaer K, et al. Defining the palliative care patient: A systematic review. *Palliat Med*. 2013;27(3):197.

54. Van Der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med*. 2014;28(3):197-209.

55. Blinderman CD, Billings JA. Comfort Care for Patients Dying in the Hospital. *N Engl J Med*. 2015;373(26):2549-2561.

56• Kelley AS, Morrison RS. Palliative Care for the Seriously Ill. *N Engl J Med*. 2015;373(8):747-755.

57. Murray SA, Kendall M, Mitchell G, Moine S, Amblàs-Novellas J, Boyd K. Palliative care from diagnosis to death. *BMJ*. 2017;356:j878.

58. World Health Assembly. *Strengthening of Palliative Care as a Component of Integrated Treatment throughout the Life Course*. Geneva: World Health Organization; 2014.

59. Institute of Medicine. *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life*. Washington, DC: The National Academies Press; 2015.

60• Temel JS, Greer J a, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733-742.

61. Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev*. 2017;CD011129.

62. Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol*. 2018;19(3):394-404.

63. Zimmermann C, Swami N, Krzyzanowska M, Early palliative care for patients with advanced cancer: cluster-randomised controlled trial. *Lancet*. 2014;383(9930):1721-30.

64. Hoerger M, Wayser GR, Schwing G, Suzuki A, Perry LM. Impact of Interdisciplinary Outpatient Specialty Palliative Care on Survival and Quality of Life in Adults With Advanced Cancer: A Meta-Analysis of Randomized Controlled Trials. *Ann Behav Med*. 2019;53 (7):674-685.

65. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35(1):96-112.

66• Hui D, Bruera E. Integrating palliative care into the trajectory of cancer care. *Nat Rev Clin Oncol*. 2016;13(3):159-171.

67. Kaasa S, Loge JH, Aapro M, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol*. 2018;2045(18):1-66.

68. Jordan K, Aapro M, Kaasa S, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. *Ann Oncol*. 2018;29(1):36-43.

69. Pardon K, Vanbutsele G. Palliative Care and Cancer. In: MacLeod RD, Block L Van den, eds. *Textbook of Palliative Care*. Springer; 2018.

70. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*. 4th ed. Richmond, VA: National Coalition for Hospice and Palliative Care; 2019.

71. Wells R, Stockdill ML, Dionne-Odom JN, et al. Educate, Nurture, Advise, Before Life Ends Comprehensive Heartcare for Patients and Caregivers (ENABLE CHF-PC): study protocol for a randomized controlled trial. *Trials*. 2018;19(1):422.

72. Scheerens C, Chambaere K, Pardon K, et al. Development of a complex intervention for early integration of palliative home care into standard care for end-stage COPD patients: A Phase 0-I study. *PLoS One*. 2018;13(9)e0203326

73. Smets T, Onwuteaka-Philipsen BBD, Miranda R, et al. Integrating palliative care in long-term care facilities across Europe (PACE): protocol of a cluster randomized controlled trial of the "PACE Steps to Success" intervention in seven countries. *BMC Palliat Care*. 2018;17(1):47.

74. Diop MS, Rudolph JL, Zimmerman KM, Richter MA, Skarf LM. Palliative Care Interventions for Patients with Heart Failure: A Systematic Review and Meta-Analysis. *J Palliat Med*. 2017;20(1):84-92.

75. Shinall MC, Karlekar M, Martin S, et al. COMPASS: A Pilot Trial of an Early Palliative Care Intervention for Patients With End-Stage Liver Disease. *J Pain Symptom Manage*. 2019; Epub doi: 10.1016/j.jpainsymman.2019.06.023

76. Higginson IJ, Costantini M, Silber E, Burman R, Edmonds P. Evaluation of a new model of short-term palliative care for people severely affected with multiple sclerosis: a randomised fast-track trial to test timing of referral and how long the effect is maintained. *Postgrad Med J*. 2011;87(1033):769-775.

77. ten Koppel M, Onwuteaka-Philipsen BD, Van den Block L, et al. Palliative care provision in long-term care facilities differs across Europe: Results of a cross-sectional study in six European countries (PACE). *Palliat Med*. 2019; Epub. Doi: 10.1177/0269216319861229

78. Rosenwax L, McNamara B, Blackmore A, Holman C. Estimating the size of a potential palliative care population. *Palliat Med*. 2005;19(7):556-562.

79. Murtagh FEM, Bausewein C, Verne J, Iris Groeneveld E, Kaloki YE, Higginson IJ. How many people need palliative care? A study developing and comparing methods for population-based estimates. *Palliat Med*. 2014;28(1):49-58.

80. Scholten N, Günther AL, Pfaff H, Karbach U. The size of the population potentially in need of palliative care in Germany – an estimation based on death registration data. *BMC Palliat Care*. 2016;15(1):1-7.

81. Kane PM, Daveson BA, Ryan K, McQuillan R, Higginson IJ, Murtagh FEM. The need for palliative care in ireland: A population-based estimate of palliative care using routine mortality data, inclusive of nonmalignant conditions. *J Pain Symptom Manage*. 2015; 49(4):726-733.

82• Sleeman KE, de Brito M, Etkind S, et al. The escalating global burden of serious health-related suffering: projections to 2060 by world regions, age groups, and health conditions. *Lancet Glob Heal*. 2019;7(7):e883-e892.

83. Gawande A. *Being Mortal: Medicine and What Matters in the End*. New York, NY: Metropolitan Books; 2014.

84. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. *JAMA*. 1947;135(15):985.

85. Zoll PM, Linenthal AJ, Gibson W, Paul MH, Norman LR. Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock. *N Engl J Med*. 1956;254(16):727-732.

86. Kouwenhoven WB, Milnor WR, Knickerbocker GG, Chesnut WR. Closed chest defibrillation of the heart. *Surgery*. 1957;42(3):550-561.

87. Elam JO, Brown ES, Elder JD. Artificial Respiration by Mouth-to-Mask Method. *N Engl J Med*. 1954;250(18):749-754.

88. Safar P. Ventilatory efficacy of mouth-to-mouth artificial respiration. *JAMA*. 1958;167(3):335.

89. Safar P, Escarraga LA, Elam JO. A Comparison of the Mouth-to-Mouth and Mouth-to-Airway Methods of Artificial Respiration with the Chest-Pressure Arm-Lift Methods. *N Engl J Med*. 1958;258(14):671-677.

90. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. *JAMA*. 1960;173(10):1064-1067.

91• Sladen A. Closed-Chest Massage, Kouwenhoven, Jude, Knickerbocker. *JAMA*. 1984;251(23):3137.

92. Trevelyan B, Smallman-Raynor M, Cliff AD. The Spatial Dynamics of Poliomyelitis in the United States: From Epidemic Emergence to Vaccine-Induced Retreat, 1910–1971. *Ann Assoc Am Geogr*. 2005;95(2):269-293.

93. Oshinsky DM. *Polio: An American Story*. New York, NY: Oxford University Press; 2005.

94. Sykes K. The Story of Artificial Ventilation. In: Eger EI, Saidman LJ, Westhorpe RN, eds. *The Wondrous Story of Anesthesia*. New York, NY: Springer; 2014:761-770.

95. Drinker P, McKhann CF. The use of a new apparatus for the prolonged administration of artificial respiration: a fatal case of poliomyelitis. *JAMA*. 1929;92(20):1658.

96. Drinker P, Shaw LA. An apparatus for the prolonged administration of artificial respiration. *J Clin Invest*. 1929;7(2):229-22947.

97. Dhawan N. Philip Drinker versus John Haven Emerson: Battle of the iron lung machines, 1928–1940. *J Med Biogr*. 2018;0(0):1-6.

98. Woollam CHM. The development of apparatus for intermittent negative pressure respiration. *Anaesthesia*. 1976;31(4):537-547.

99. Drinker PA, McKhann CF. The Iron Lung. First Practical Means of Respiratory Support. *JAMA*. 1986;255(11):1476.

100. Freyche MJ, Payne AM. Poliomyelitis in 1954. *Bull World Health Organ*. 1956;15(1-2):43-121.

101. Lassen HCA. The epidemic of poliomyelitis in Copenhagen, 1952. *Proc R Soc Med*. 1954;47(1):67-71.

102• Lassen HCA. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen, with special reference to the treatment of acute respiratory insufficiency. *Lancet*. 1953; 261(6749):37-41.

103. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. *Proc R Soc Med*. 1954; 47(1):72-74.

104. West JB. The physiological challenges of the 1952 Copenhagen poliomyelitis epidemic and a renaissance in clinical respiratory physiology. *J Appl Physiol*. 2005;99(2):424-432.

105. Berthelsen PG, Cronqvist M. The first intensive care unit in the world: Copenhagen 1953. *Acta Anaesthesiol Scand*. 2003;47(10):1190-1195.

106. Reisner-Sénélar L. The birth of intensive care medicine: Björn Ibsen's records. *Intensive Care Med*. 2011;37(7):1084-1086.

107. Kelly FE, Fong K, Hirsch N, Nolan JP. Intensive care medicine is 60 years old: the history and future of the intensive care unit. *Clin Med*. 2014;14(4):376-379.

108. Stromskag KE, G Brock-Utne J, Eklund J, Holmdahl M. A History of Nordic Anesthesia. In: Eger EI, Saidman LJ, Westhorpe RN, eds. *The Wondrous Story of Anesthesia*. New York, NY: Springer; 2014:417-428.

109. Engström CG. Treatment of severe cases of respiratory paralysis by the engström universal respirator. *BMJ*. 1954;2(4889):666-69.

110. Saffle JR. The 1942 fire at Boston's Cocoanut Grove nightclub. *Am J Surg*. 1993;166(6):581.

111. Rosengart MR, Pinsky MR. Origins of the Critically Ill: The Impetus for Critical Care Medicine. In: Scales DC, Rubenfeld GD, eds. *The Organization of Critical Care. An Evidence-Based Approach to Improving Quality*. New York, NY: Springer; 2014:9-24.

112. Carter LS. Critical concept. *Dartmouth Med*. 2005;29(3):40-48.

113. Mosenthal WT, Boyd DD. Special unit saves lives, nurses and money. *Mod Hosp*. 1957;89(6):83-86.

114. Ristagno G, Weil MH. History of Critical Care Medicine: The Past, the Present and the Future. In: Gullo A, Lumb PD, Besso J, Williams GF, eds. *Intensive and Critical Care Medicine*. Milano: Springer; 2009:3-17.

115. Safar P, Dekornfeld TJ, Pearson JW, Redding JS. The Intensive Care Unit. A three year experience at Baltimore City Hospitals. *Anaesthesia*. 1961;16(3):275-284.

116• Warraich H. *Modern Death: How Medicine Changed the End of Life*. New York, NY: St. Martin's Press; 2017.

117. Goulon M, Babinet P, Simon N. Brain Death or Coma Dépassé. In: *Care of the Critically Ill Patient*. London: Springer; 1983:765-771.

118• Mollaret P, Goulon M. Le coma dépassé. *Rev Neurol (Paris)*. 1959;101(1):3-15.

119. Wertheimer P, Jouvet M, Descotes J. À propos du diagnostic de la mort du système nerveux dans les comas avec arrêt respiratoire traités par respiration artificielle. *Press Médicale*. 1959;67(3):87-88.

120. Schwab RS, Potts F, Bonazzi A. EEG as an aid in determining death in the presence of cardiac activity ethical, legal, and medical aspects. *Electroencephalogr Clin Neurophysiol*. 1963; 15:147-148.

121. Hamlin H. Life or Death by EEG. *JAMA*. 1964;190(2):14-16.

122. Pius XII. En réponse à trois questions de morale médicale sur la réanimation. *Acta Apostolica Sedis*. 1957;49:1027–1033.

123. Pius XII. The Prolongation of Life: An Address of Pope Pius XII to an International Congress of Anesthesiologists (November 24, 1957). *Pope Speaks*. 1958;4(4):393-398.

124. Wertheimer P, de Rougemont J, Descotes J, Jouvet M. Données angiographiques relatives à la mort de l'encéphale au cours des comas avec arrêt respiratoire (Coma dites dépassés). *Lyon Chir*. 1960;56:641–648.

125. Jouvet M. Diagnostic électro-sous-cortico-graphique de la mort du système nerveux central au cours de certains comas. *Electroencephalogr Clin Neurophysiol*. 1959;11(4):805-808.

126• Settergren G. Brain death: An important paradigm shift in the 20th century. *Acta Anaesthesiol Scand*. 2003;47(9):1053-1058.

127. Crafoord CC. Cerebral Death and the Transplantation Era. *Dis Chest*. 1969;55(2):141-145.

128. Murray JE, Merrill JP, Harrison JH, Wilson RE, Dammin GJ. Prolonged Survival of Human-Kidney Homografts by Immunosuppressive Drug Therapy. *N Engl J Med*. 1963;268(24):1315.

129. Murray J, Gleason R, Bartholomay A. Fourth report of the Human Kidney Transplant Registry: 16 September 1964 to 15 March 1965. *Transplantation*. 1965;3(5):684-699.

130. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet*. 1963;117(6):659-676.

131. Hardy JD, Webb WR, Dalton ML, Walker GR. Lung Homotransplantation in Man. *JAMA*. 1963;186(12):811.

132. Legendre C, Kreis H. A tribute to Jean Hamburger's contribution to organ transplantation. *Am J Transplant*. 2010;10(11) 2392-2395.

133• Machado C. The first organ transplant from a brain-dead donor. *Neurology*. 2005;64(11) 1938-1942.

134. Squifflet JP. The history of transplantation at the Catholic University of Louvain Belgium 1963-2003. *Acta Chir Belg*. 2003;103(3):10-20.

135. Potter R. The Moment of Death. *Med Leg J*. 1963;31(3):195-196.

136. Giertz GB. Ethical Problems in Medical Procedures in Sweden. In: Wolstenholme GEW, O'Connor M, eds. *Ethics in Medical Progress: With Special Reference to Transplantation*. Boston: Little, Brown and Company; 1966:139-148.

137. Wasmuth CE, Stewart BH. Medical and Legal Aspects of Human Organ Transplantation. *Clevel State Law Rev*. 1965;14(3):442.

138. Ross LF, Thistlethwaite JR. The 1966 Ciba Symposium on Transplantation Ethics. *Transplantation*. 2016;100(6):1191-1197.

139• Wolstenholme GEW, O'Connor M. *Ethics in Medical Progress: With Special Reference to Transplantation*. Boston: Little, Brown and Company; 1966.

140. Wasmuth CE. The Medical, Legal, and Ethical Considerations of Human Organ Transplantations. *William Mary Law Rev*. 1970; 11(3):636-658.

141. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *South African Med J*. 1967;41(48):1271-1274.

142. Cooper DKC. Christiaan Barnard's defining moment. *Eur Heart J*. 2017;38(46):3400-3401.

143. Hoffenberg R. Christiaan Barnard: his first transplants and their impact on concepts of death. *BMJ*. 2001;323(7327):1478-1480.

144. Giacomini M. A change of heart and a change of mind? Technology and the redefinition of death in 1968. *Soc Sci Med*. 1997;44(10):1465.

145. Woodruff MFA, Robson JS. Transplantation of a Kidney From an Identical Twin. *Lancet*. 1961;277(7189):1245-1249.

146. Pallis CA. ABC of brain stem death. The arguments about the EEG. *BMJ*. 1983;286(6361):284-287.

147• Beecher HK. Ethics and Clinical Research. *N Engl J Med*. 1966;274(24):1354-1360.

148. Beecher HK. Ethical Problems Created by the Hopelessly Unconscious Patient. *N Engl J Med*. 1968;278(26):1425-1430.

149. Kaufman MT. Rights of a Man in Coma Pondered: doctor poses questions on medical transplant. *New York Times*. December 10, 1967

150. Wijdicks EFM. The neurologist and Harvard criteria for brain death. *Neurology*. 2003; 61(7):970-976.

151. Stone JL, Hughes JR. Early history of electroencephalography and establishment of the american clinical neurophysiology society. *J Clin Neurophysiol*. 2013;30(1):28-44.

152. Rosoff SE, Schwab RS. EEG in establishing brain death: 10-year report, with criteria and legal safeguards in 50 states. *Meeting of American Electroencephalographic Society*. June 8, 1967.

153• A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968;205:337-340.

154. Carol A. *Les Médecins et La Mort : XIXe-XXe Siècle*. Paris: Aubier; 2004.

155. de Gaudart d'Allaines F. Rapport au nom de la Commission des prélèvements d'organes. *Bull l'Académie Natl Médecine*. 1966;150(16):249-50.

156. Socialdepartementet. *Dödsbegreppet. SOU 1984:79*. Stockholm; 1982.

157. *Socialstyrelsens Cirkulär (MF 1973:29) om Prognos och Behandling Vid Totalt Och Oåterkalleligt Bortfall Av Hjärnfunktionerna*.

158. Ingvar D, Widen L. Hjärndöd: Sammanfattning av ett symposium [Brain death: Summary of a symposium]. *Lakartidningen*. 1972;69:3804-14.

159• Belkin GS. *Death Before Dying: History, Medicine, and Brain Death*. New York, NY: Oxford University Press; 2014.

160. Diagnosis of death: Memorandum issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 15 January 1979. *BMJ*. 1979;1(6159):332.

161. Silverman D, Saunders MG, Schwab RS, Masland RL. Cerebral Death and the Electro-encephalogram. *JAMA*. 1969;209(10):1505.

162. Silverman D, Masland RL, Saunders MG, Schwab RS. Irreversible coma associated with electrocerebral silence. *Neurology*. 1970; 20(6):525-525.

163. Mohandas A, Chou SN. Brain death: a clinical and pathological study. *J Neurosurg*. 1971; 35(2):211-218.

164. Walker AE, Diamond EL, Moseley J. The Neuropathological Findings in Irreversible Coma. *J Neuropathol Exp Neurol*. 1975; 34(4):295-323.

165. An appraisal of the criteria of cerebral death. A summary statement. A collaborative study. *JAMA*. 1977;237(10):982-986.

166. De Georgia MA. History of brain death as death: 1968 to the present. *J Crit Care*. 2014;29(4):673-678.

167. Korein J. Brain Death: Interrelated Medical and Social Issues. *Ann N Y Acad Sci*. 1983;315(1)

168. Black PM. Brain Death (First Part). *N Engl J Med*. 1978;299(7):338-344.

169. Black PM. Brain Death (Second Part). *N Engl J Med*. 1978;299(8):393-401.

170. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Appendix C (Statutes on the Determination of Death). In: *Defining Death. Medical, Legal and Ethical Issues in the Determination of Death*. Washington, D.C.: U.S. Government printing office; 1981:109-116.

171. Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976. *BMJ*. 1976;2(6045):1187-1188.

172. Wijdicks EFM. The transatlantic divide over brain death determination and the debate. *Brain*. 2012;135(4):1321-1331.

173. An appalling Panorama. *BMJ*. 1980;281:1028

174. Pallis CA. Medicine and the Media. *BMJ*. 1980;281(6247):1064-1064.

175• President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Defining Death. Medical, Legal and Ethical Issues in the Determination of Death*. Washington, D.C.: U.S. Government Printing Office; 1981.

176. Capron AM, Kass LR. A Statutory Definition of the Standards for Determining Human Death: An Appraisal and a Proposal. *Univ PA Law Rev*. 1972;121(1):87.

177. Capron AM, Kass LR. A Statutory Definition of the Standards for Determining Human Death. In: Humber JM, Almeder RF, eds. *Biomedical Ethics and the Law*. Boston, MA: Springer; 1979:555-588.

178. Bernat JL, Culver CM, Gert B. On the Definition and Criterion of Death. *Ann Intern Med*. 1981;94(3):389.

179. Guidelines for the Determination of Death: Report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *JAMA*. 1981;246(19):2184.

180. Wijdicks E. Determining brain death in adults. *Neurology*. 1995;(May):1003-1011.

181. Wijdicks EFM. The case against confirmatory tests for determining brain death in adults. *Neurology*. 2010;75(1):77-83.

182. Youngner SJ, Arnold RM, Schapiro R. *The Definition of Death : Contemporary Controversies*. Baltimore, MD: Johns Hopkins University Press; 1999.

183. Wijdicks EFM. Deliberating Death in the Summer of 1968. *N Engl J Med*. 2018; 379(5):412-415.

184. World Medical Association (WMA). Declaration of Sydney on Human Death. 22nd World Medical Assembly, Sydney, Australia. 1968.

185. Machado C, Korein J, Ferrer Y, et al. The declaration of Sydney on human death. *J Med Ethics*. 2007;33(12):699-703.

186. Medical A, Medical W, Council J. Ethical Guidelines for Organ Transplantation. *Judic Counc Am Med Assoc*. 1968;205(6):341.

187. Curran WJ. The Uniform Anatomical Gift Act. *N Engl J Med*. 1969;280(1):36-37.

188. de Gaudart d'Allaines F. Les problèmes posés par les prélèvements d'organes sur un mort en survie artificielle. *Bull Acad Natl Med*. 1966;150(1):6-8.

189. Vigouroux R. Colloque sur les états frontières entre la vie et la mort. *Marseille Chirurgical*. 1966;18(1):194.

190. Machado C, Korein J, Ferrer Y, Portela L, Garcia M de la C, Manerp JM. The concept of brain death did not evolve to benefit organ transplants. *J Med Ethics*. 2007;33(4):197-200.

191. Belkin GS. Brain death and the historical understanding of bioethics. *J Hist Med Allied Sci*. 2003;58(3):325-361.

192. Descotes J, Jouvet M. Les limites de la réanimation respiratoire et le diagnostic de mort du système nerveux central dans les comas avec arrêt respiratoire. *Anesth Analg (Paris)*. 1959;16:344-348.

193. A way of dying. *The Atlantic Monthly*. January 1957:53-55.

194. Life-in-Death. *N Engl J Med*. 1957;256(16):760.

195. Ayd FJ. The Hopeless Case. Medical and Moral Considerations. *JAMA*. 1962;181(13):1099.

196• Rydvall A. *Withold or Withdraw Futile Treatment in Intensive Care. Arguments Supported by Physicians and the General Public*. Umeå: Umeå University, Sweden; 2016.

197. Stone HB. Limitations of surgery in the treatment of malignant diseases. *AMA Arch Surg*. 1951;63(1):2-3.

198. Stone HB. The limitations of radical surgery in the treatment of cancer. *Surg Gynecol Obstet*. 1953;97(2):129-134.

199. Rynearson EH. "You Are Standing at the Bedside of a Patient Dying of Untreatable Cancer." *CA Cancer J Clin*. 1959;9(3):85-87.

200. Symposium on Terminal Care. *CA Cancer J Clin*. 1960;10(1):12-24.

201. Fitts WT. What philadelphia physicians tell patients with cancer. *JAMA*. 1953;153(10):901.

202. Oken D. What to Tell Cancer Patients: A Study of Medical Attitudes. *JAMA*. 1961;175(13):1120

203. Symmers WS. Not allowed to die. *BMJ*. 1968;1(5589):442-442.

204. Emrys-Roberts M. Death and resuscitation. *BMJ*. 1969;4(5679):364-365.

205. Escoffier-Lambiotte C. Les tourments du crépuscule. *Le Monde*. May 6, 1975.

206. Neasden memorandum on resuscitation. *BMJ*. 1967;3(5569):858-859.

207. Vital Decision. *BMJ*. 1967;4(5573):235.

208. Lodge B. Resuscitation of the elderly. *BMJ*. 1967;4(5570):53-54.

209. Grand Jury of the Supreme Court of the State of New York (Queens County). DNR Procedures: Purple Dots Revisited. *Conn Med*. 1985;49:367-376.

210. Sullivan R. Hospital's data faulted in care of terminally ill. *The New York Times*. March 21, 1984:30.

211. Sullivan R. Law Proposed for Withholding Emergency Care. *The New York Times*. April 20, 1986:38.

212. Sullivan R. New York State Drafts Right-to-Die Guidelines. *The New York Times*. August 13, 1987:36.

213• Bedell SE, Delbanco TL, Cook EF, Epstein FH. Survival after Cardiopulmonary Resuscitation in the Hospital. *N Engl J Med*. 1983;309(10):569.

214. McGrath RB. In-house cardiopulmonary resuscitation - after a quarter of a century. *Ann Emerg Med*. 1987;16(12):1365-1368.

215. Peschin A, Coackley CS. A Five Year Review of 734 Cardiopulmonary Arrests. *South Med J*. 1970;63(5):506-510.

216. Lemire JG, Johnson AL. Is Cardiac Resuscitation Worthwhile? *N Engl J Med*. 1972;286(18):970-72

217. Johnson AL, Tanser PH, Ulan RA, Wood TE. Results of cardiac resuscitation in 552 patients. *Am J Cardiol*. 1967;20(6):831-835.

218. Gazelle G. The Slow Code — Should Anyone Rush to Its Defense? *N Engl J Med*. 1998; 338(7):467-469.

219. Shuster E. Fifty Years Later: The Significance Of The Nuremberg Code. *N Engl J Med*. 1997; 337(20):1436-1440.

220. Human Experimentation: Code of Ethics of the World Medical Association. *BMJ*. 1964; 2(5402):177-177.

221. Beauchamp TL. Informed consent: Its history, meaning, and present challenges. *Cambridge Q Healthc Ethics*. 2011;20(4):515-523.

222• Capron AM. Where did informed consent for research come from? *J Law, Med Ethics*. 2018;46(1):12-29.

223. Luce JM, White DB. A History of Ethics and Law in the Intensive Care Unit. *Crit Care Clin*. 2009; 25(1):221-237.

224. Lepore J. The Politics of Death. *The New Yorker*. November 30, 2009.

225. Supreme Court of New Jersey. *In the Matter of Karen Quinlan, an Alleged Incompetent*. 70 N.J. 10; 355 A.2d 647; 1976 N.J. LEXIS 181; 79 A.L.R.3d 205(1976).

226. Clinical Care Committee of the Massachusetts General Hospital. Optimum Care for Hopelessly Ill Patients. *N Engl J Med*. 1976; 295(7):362-364.

227. Rabkin MT, Gillerman G, Rice NR. Orders Not to Resuscitate. *N Engl J Med*. 1976;295(7):364-6.

228. Fried C. Terminating Life Support: Out of the Closet! *N Engl J Med*. 1976;295(7):390-391.

229. Standards for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC). *JAMA*. 1974;227(7):833-867.

230• President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Deciding to Forego Life-Sustaining Treatment. Ethical, Medical, and Legal Issues in Treatment Decisions*. Washington, D.C.: U.S. Government printing office; 1983.

231. Grenvik A, Powner DJ, Snyder J V., Jastremski MS, Babcock RA, Loughhead MG. Cessation of therapy in terminal illness and brain death. *Crit Care Med*. 1978;6(4):284-290.

232. Grenvik A. "Terminal weaning"; discontinuance of life-support therapy in the terminally ill patient. *Crit Care Med*. 1983;11(5):394-395.

233. NIH workshop summary. Withholding and withdrawing mechanical ventilation. *Am Rev Respir Dis*. 1986;134(6):1327-1330.

234. Schneiderman LJ, Spragg RG. Ethical Decisions in Discontinuing Mechanical Ventilation. *N Engl J Med*. 1988;318(15):984-988.

235. United States Supreme Court. Cruzan v. Director, Missouri Department of Health (497 U.S. 261, June 25, 1990). *Supreme Court Report*. 1990;110:2841-2892.

236. Lo B. Beyond the Cruzan Case: The U.S. Supreme Court and Medical Practice. *Ann Intern Med*. 1991;114(10):895.

237. Barrocas A, Geppert C, Durfee SM, et al. A.S.P.E.N. Ethics Position Paper. *Nutr Clin Pract*. 2010;25(6):672-679.

238• Volkert D, Beck AM, Cederholm T, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr*. 2019;38(1):10-47.

239. Williams MA, Gordon J, Bacon D. Position statement on laws and regulations concerning life-sustaining treatment, including artificial nutrition and hydration, for patients lacking decision-making capacity. *Neurology*. 2008;70(3):242-243.

240. Wanzer SH, Adelstein SJ, Cranford RE, et al. The Physician's Responsibility toward Hopelessly Ill Patients. *N Engl J Med*. 1984;310(15):955-959.

241. Jecker NS, Pearlman RA. Medical futility. Who decides? *Arch Intern Med*. 1992;152(6):1140-44.

242. Hubinek M, Voogd JJ. Rights of the sick and dying. Report to the Social, Health and Family Affairs Committee. *Counc Eur Parliam Assem*. 1976;3699. Strasbourg: Council of Europe

243. Pellegrino ED, Thomasma DC. The conflict between autonomy and beneficence in medical ethics: proposal for a resolution. *J Contemp Health Law Policy*. 1987;3(1):23-46.

244. Gillon R. Autonomy and the principle of respect for autonomy. *BMJ*. 1985;290:1806-08.

245. Tolle SW, Teno JM. Lessons from Oregon in Embracing Complexity in End-of-Life Care. *N Engl J Med*. 2017;376(11):1078-1082.

246• Tolle SW, Black L, Meier D, End-of-Life Advance Directive. *N Engl J Med*. 2015;372(7):667-670.

247. Martin DK, Emanuel LL, Singer PA. Planning for the end of life. *Lancet*. 2000;356(9242):1672-1676.

248. Gillick MR. Advance Care Planning. *N Engl J Med*. 2004;350(1):7-8.

249. Svenska Läkaresällskapets delegation för medicinsk etik. *Läkaren Och Den Svårt Sjuke Patienten. Rapport Från Utredningen Rörande Vissa Frågor Beträffande Sjukvård i Livets Slutskede [The Doctor and the Seriously Ill Patient. Report from the Inquiry on Healthcare at the End of Life]*. Stockholm: Socialdepartementet; 1978.

250. Socialstyrelsen. *Livsuppehållande Åtgärder i Livets Slutskede [Life-Sustaining Therapy near the End of Life]*. Stockholm: Allmänna förlaget; 1992.

251. Socialstyrelsen. Socialstyrelsens föreskrifter och allmänna råd om livsuppehållande behandling [National Board of Health and Welfare regulations and general advice on life-sustaining treatments]. *SOSFS 2011:7*. 2011:8.

252. Socialstyrelsen. *Om Att Ge Eller Inte Ge Livsuppehållande Behandling [Whether or Not to Give Life-Sustaining Treatment]*. Stockholm: Allmänna förlaget; 2011.

253. British Medical Association Medical Ethics Committee. *Withholding and Withdrawing Life-Prolonging Medical Treatment*. Oxford, UK: Blackwell Publishing; 1999.

254. Ashraf H. BMA address the issue of withholding and withdrawing treatment. *Lancet*. 1999;353(9171):2220.

255. Luttrell S. Withdrawing or withholding life prolonging treatment. A new BMA report fills an ethical vacuum. *BMJ*. 1999;318(7200):1709.

256. Loi n° 2005-370 du 22 avril 2005 relative aux droits des malades et à la fin de vie. *JORF n°95 du 23 avril 2005 page 7089*. 2005.

257. Baumann A, Audibert G, Claudot F, Puybasset L. Ethics review: End of life legislation—the French model. *Crit Care*. 2009;13(1):204.

258. Youngner SJ, O'Toole E. Withdrawing Treatment in the Persistent Vegetative State. *N Engl J Med*. 1994;331(20):1382-1383.

259• Smedira NG, Evans BH, Grais LS, et al. Withholding and withdrawal of life support from the critically ill. *N Engl J Med*. 1990; 322(5):309-315.

260. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med*. 1997;155(1):15-20.

261. Luce JM, Prendergast TJ. The Changing Nature of Death in the ICU. In: Curtis JR, Rubenfeld GD, eds. *Managing Death in the ICU: The Transition from Cure to Comfort*. New York, NY: Oxford University Press; 2001:19-29.

262. Wong WT, Phua J, Joynt GM. Worldwide end-of-life practice for patients in ICUs. *Curr Opin Anaesthesiol*. 2018;31(2):172-178.

263. McPherson K, Carlos WG, Emmett TW, Slaven JE, Torke AM. Limitation of Life-Sustaining Care in the Critically Ill: A Systematic Review of the Literature. *J Hosp Med*. 2019;14(5):303-310.

264. Vincent J-L, Parquier J-N, Preiser J-C, Brimioulle S, Kahn RJ. Terminal events in the intensive care unit. *Crit Care Med*. 1989;17(6):530-533.

265• Van Der Heide A, Deliens L, Faisst K, et al. End-of-life decision-making in six European countries: Descriptive study. *Lancet*. 2003; 362(9381):345-350.

266. Bosshard G, Nilstun T, Bilsen J, et al. Forgoing treatment at the end of life in 6 European countries. *Arch Intern Med*. 2005;165(4):401-7.

267. Van Delden JJM, Löfmark R, Deliens L, et al. Do-not-resuscitate decisions in six European countries. *Crit Care Med*. 2006;34(6):1686-1690.

268. Chambaere K, Cohen J, Robijn L, Bailey SK, Deliens L. End-of-life decisions in individuals dying with dementia in Belgium. *J Am Geriatr Soc*. 2015;63(2):290-296.

269. Wendrich-van Dael AE, Pivodic L, Cohen J, Deliens L, Van den Block L, Chambaere K. End-of-Life Decision Making for People Who Died of Dementia: A Mortality Follow-Back Study Comparing 1998, 2007, and 2013 in Flanders, Belgium. *J Am Med Dir Assoc*. 2019:Epub. Doi: 10.1016/j.jamda.2019.04.004

270. Cardona-Morrell M, Kim JCH, Turner RM, Anstey M, Mitchell IA, Hillman K. Non-beneficial treatments in hospital at the end of life: A systematic review on extent of the problem. *Int J Qual Heal Care*. 2016;28(4):456-9.

271. Luta X, Maessen M, Egger M, Stuck AE, Goodman D, Clough-Gorr KM. Measuring intensity of end of life care: A systematic review. *PLoS One*. 2015;10(4):1-16.

272. Barnato AE, McClellan MB, Kagay CR, Garber AM. Trends in Inpatient Treatment Intensity among Medicare Beneficiaries at the End of Life. *Health Serv Res*. 2004;39(2):363-375.

273. Wennberg JE, Fisher ES, Stukel TA, Skinner JS, Sharp SM, Bronner KK. Use of hospitals, physician visits, and hospice care during last six months of life among cohorts loyal to highly respected hospitals in the United States. *BMJ*. 2004;328(7440):607.

274• Teno JM, Gozalo P, Trivedi AN, et al. Site of death, place of care, and health care transitions among US medicare beneficiaries, 2000-2015. *JAMA*. 2018;320(3):264-271.

275• Bekelman JE, Halpern SD, Blankart CR, et al. Comparison of site of death, health care utilization, and hospital expenditures for patients dying With cancer in 7 developed countries. *JAMA*. 2016;315(3):272-283.

276. Kwok AC, Semel ME, Lipsitz SR, et al. The intensity and variation of surgical care at the end of life: A retrospective cohort study. *Lancet*. 2011;378(9800):1408-1413.

277. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol*. 2004;22(2):315-321.

278. Barbera L, Paszat L, Qiu F. End-of-Life Care in Lung Cancer Patients in Ontario: Aggressiveness of Care in the Population and a Description of Hospital Admissions. *J Pain Symptom Manage*. 2008;35(3):267-274.

279. Rochigneux P, Raoul JL, Beaussant Y, et al. Use of chemotherapy near the end of life: What factors matter? *Ann Oncol*. 2017;28(4):809-817.

280. Liu TW, Chang WC, Wang HM, et al. Use of chemotherapy at the end of life among Taiwanese cancer decedents, 20012006. *Acta Oncol (Madr)*. 2012;51(4):505-511.

281. Näppä U, Lindqvist O, Rasmussen BH, Axelsson B. Palliative chemotherapy during the last month of life. *Ann Oncol*. 2011;22(11):2375-2380.

282. Fang P, Jagsi R, He W, et al. Rising and Falling Trends in the Use of Chemotherapy and Targeted Therapy Near the End of Life in Older Patients With Cancer. *J Clin Oncol*. 2019;37(20):1721-1731.

283. Bekelman JE, Halpern SD, Blankart CR, et al. Comparison of site of death, health care utilization, and hospital expenditures for patients dying With cancer in 7 developed countries. *JAMA*. 2016;315(3):272-283.

284. De Schreye R, Smets T, Annemans L, et al. Applying quality indicators for administrative databases to evaluate end-of-life care for cancer patients in Belgium. *Health Aff*. 2017;36(7):1234-1243.

285. Gallais Sérézal I, Beaussant Y, Rochigneux P, et al. End-of-life care for hospitalized patients with metastatic melanoma in France: a nationwide, register-based study. *Br J Dermatol*. 2016;175(3):583-592.

286. Law AC, Stevens JP, Walkey AJ. Gastrostomy Tube Use in the Critically Ill, 1994-2014. *Ann Am Thorac Soc*. 2019;16(6):724-730.

287. Kempf E, Tournigand C, Rochigneux P, Aubry R, Morin L. Discrepancies in the use of chemotherapy and artificial nutrition near the end of life for hospitalised patients with metastatic gastric or oesophageal cancer. A countrywide register-based study. *Eur J Cancer*. 2017;79:31-40.

288. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36(1):11-48.

289. Mitchell SL, Teno JM, Roy J, Kabumoto G, Mor V. Clinical and Organizational Factors Associated With Feeding Tube Use Among Nursing Home Residents With Advanced Cognitive Impairment. *JAMA*. 2003;290(1):73.

290• Mitchell S, Mor V, Gozalo P, Servadio J, Teno J. Tube Feeding in US Nursing Home Residents With Advanced Dementia, 2000-2014. *JAMA*. 2016;316(7):769-770.

291. Teno JM, Mitchell SL, Gozalo PL, et al. Hospital characteristics associated with feeding tube placement in nursing home residents with advanced cognitive impairment. *JAMA*. 2010;303(6):544-550.

292. American Geriatrics Society Ethics Committee and Clinical Practice and Models of Care Committee. American Geriatrics Society feeding tubes in advanced dementia position statement. *J Am Geriatr Soc*. 2014;62(8):1590.

293. Volkert D, Wirth R, Chourdakis M, et al. ESPEN guidelines on nutrition in dementia. *Clin Nutr*. 2015;34(6):1052-1073.

294. Sampson EL, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia. *Cochrane Database Syst Rev*. 2009;(2):CD007209

295. Wang S, Aldridge MD, Gross CP, Canavan M, Cherlin E, Bradley E. End-of-Life Care Transition Patterns of Medicare Beneficiaries. *J Am Geriatr Soc*. 2017;65(7):1406-1413.

296. Xing J, Mukamel DB, Temkin-Greener H. Hospitalizations of nursing home residents in the last year of life. *J Am Geriatr Soc*. 2013;61(11):1900-1908.

297. Kelfve S, Wastesson J, Fors S, Johnell K, Morin L. Is the level of education associated with transitions between care settings in older adults near the end of life? A nationwide, retrospective cohort study. *Palliat Med*. 2018;32(2):366-375.

298. Abarshi E, Echteld M, Van Den Block L, Donker G, Deliens L, Onwuteaka-Philipsen B. Transitions between care settings at the end of life in the Netherlands: Results from a nation-wide study. *Palliat Med*. 2010;24(2):166-74.

299• Van den Block L, Deschepper R, Bilsen J, Van Casteren V, Deliens L. Transitions Between Care Settings at the End of Life in Belgium. *JAMA*. 2007;298(14):1635.

300. Pivodic L, Pardon K, Miccinesi G, et al. Hospitalisations at the end of life in four European countries: A population-based study via epidemiological surveillance networks. *J Epidemiol Community Health*. 2015;70(5):430-6.

301. De Roo ML, Francke AL, Van den Block L, et al. Hospitalizations of cancer patients in the last month of life: quality indicator scores reveal large variation between four European countries in a mortality follow-back study. *BMC Palliat Care*. 2014;13(1):54.

302. Goldsbury DE, O'Connell DL, Girgis A, et al. Acute hospital-based services used by adults during the last year of life in New South Wales, Australia: a population-based retrospective cohort study. *BMC Health Serv Res*. 2015;15(1):537.

303. Qureshi D, Tanuseputro P, Perez R, Seow H. Place of Care Trajectories in the Last Two Weeks of Life: A Population-Based Cohort Study of Ontario Decedents. *J Palliat Med*. 2018;21(11):1588-1595.

304. Pivodic L, Pardon K, Morin L, et al. Place of death in the population dying from diseases indicative of palliative care need: A cross-national population-level study in 14 countries. *J Epidemiol Community Health*. 2016;70(1):17-24.

305. Cohen J, Pivodic L, Miccinesi G, et al. International study of the place of death of people with cancer: A population-level comparison of 14 countries across 4 continents using death certificate data. *Br J Cancer*. 2015;113(9):1397-1404.

306. Reyniers T, Deliens L, Pasman HR, et al. International variation in place of death of older people who died from dementia in 14 European and non-European countries. *J Am Med Dir Assoc*. 2015;16(2):165-171.

307. Houttekier D, Cohen J, Bilsen J, Addington-Hall J, Onwuteaka-Philipsen BD, Deliens L. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc*. 2010;58(4):751-756.

308. Aldridge MD, Bradley EH. Epidemiology and patterns of care at the end of life: Rising complexity, shifts in care patterns and sites of death. *Health Aff*. 2017;36(7):1175-1183.

309• Bone AE, Gomes B, Etkind SN, et al. What is the impact of population ageing on the future provision of end-of-life care? Population-based projections of place of death. *Palliat Med*. 2018;32(2):329-336.

310. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: A systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430-9.

311. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet*. 2012; 380(9836):37-43.

312. van den Akker M, Buntinx F, Knottnerus J. Comorbidity or multimorbidity : what's in a name ? A review of literature. *Eur J Gen Pract*. 1996;2(June):65-70.

313. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases - A systematic review on existing multimorbidity indices. *Journals Gerontol Ser A Biol Sci Med Sci*. 2011;66 A(3):301-311.

314. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology. *Ann Fam Med*. 2012;10(2):142-151.

315. Sinnige J, Braspenning J, Schellevis F, Stirbu-Wagner I, Westert G, Korevaar J. The prevalence of disease clusters in older adults with multiple chronic diseases--a systematic literature review. *PLoS One*. 2013;8(11):e79641.

316. France EF, Wyke S, Gunn JM, Mair FS, McLean G, Mercer SW. Multimorbidity in primary care: a systematic review of prospective cohort studies. *Br J Gen Pract*. 2012;62(597):e297-307.

317. Salive ME. Multimorbidity in older adults. *Epidemiol Rev*. 2013;35(4):75-83.

318. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. *J Clin Epidemiol*. 2014;67(3):254-266.

319. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One*. 2014;9(7):e102149.

320• Calderón-Larrañaga A, Vetrano DL, Onder G, et al. Assessing and Measuring Chronic Multimorbidity in the Older Population: A Proposal for Its Operationalization. *Journals Gerontol A*. 2017;72(10):1417-1423.

321. Rosella L, Kornas K, Huang A, Bornbaum C, Henry D, Wodchis WP. Accumulation of chronic conditions at the time of death increased in Ontario from 1994 to 2013. *Health Aff*. 2018;37(3):464-472.

322. Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2016;67:130-8.

323. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA*. 2015; 314(1):52-60.

324. Rizzuto D, Melis RJF, Angleman S, Qiu C, Marengoni A. Effect of Chronic Diseases and Multimorbidity on Survival and Functioning in Elderly Adults. *J Am Geriatr Soc*. 2017; 65(5):1056-1060.

325. Tetzlaff J, Muschik D, Epping J, Eberhard S, Geyer S. Expansion or compression of multimorbidity? 10-year development of life years spent in multimorbidity based on health insurance claims data of Lower Saxony, Germany. *Int J Public Health*. 2017;62(6):679-86.

326. Tetzlaff J, Junius-Walker U, Muschik D, Epping J, Eberhard S, Geyer S. Identifying time trends in multimorbidity—defining multimorbidity in times of changing diagnostic practices. *J Public Heal*. 2017;25(2):215-222.

327. Cho H, Klabunde CN, Yabroff KR, et al. Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. *Ann Intern Med*. 2013; 159(10):667-676.

328. Dugoff EH, Canudas-Romo V, Buttorff C, Leff B, Anderson GF. Multiple chronic conditions and life expectancy: A life table analysis. *Med Care*. 2014;52(8):688-694.

329. Schneider KM, O'Donnell BE, Dean D. Prevalence of multiple chronic conditions in the United States' Medicare population. *Health Qual Life Outcomes*. 2009;7(1):82.

330. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013; 381(9868):752-762.

331. Rockwood K, Mitnitski A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. *Clin Geriatr Med*. 2011; 27(1):17-26.

332• Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *Journals Gerontol Ser A Biol Sci Med Sci*. 2007;62(7):722-727.

333• Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *Journals Gerontol Ser A Biol Sci Med Sci*. 2001;56(3):M146-M157.

334. Morley JE, Vellas B, Abellan van Kan G, et al. Frailty consensus: A call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397.

335. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. *J Am Geriatr Soc*. 2012;60(8):1487-1492.

336. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *Journals Gerontol Ser A Biol Sci Med Sci*. 2009;64(6):675-681.

337. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2015;16(11):940

338. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med*. 2006;166(4):418-423.

339. Herr M, Arvieu JJ, Ankri J, Robine JM. What is the duration of life expectancy in the state of frailty? Estimates in the SIPAF study. *Eur J Ageing*. 2018;15(2):165-173.

340. Pollack LR, Goldstein NE, Gonzalez WC, et al. The Frailty Phenotype and Palliative Care Needs of Older Survivors of Critical Illness. *J Am Geriatr Soc*. 2017;65(6):1168-1175.

341. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of end-of-life care provided to patients with different serious illnesses. *JAMA Intern Med*. 2016;176(8):1095-1105.

342• Singer AE, Meeker D, Teno JM, Lynn J, Lunney JR, Lorenz KA. Symptom trends in the last year of life from 1998 to 2010: A cohort study. *Ann Intern Med*. 2015;162(3):175-183.

343. Gómez-Batiste X, Martínez-Muñoz M, Blay C, et al. Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population. *Palliat Med*. 2014;28(4):302-311.

344. Mohile SG, Xian Y, Dale W, et al. Association of a cancer diagnosis with vulnerability and frailty in older medicare beneficiaries. *J Natl Cancer Inst*. 2009;101(17):1206-1215.

345. Monfardini S, Basso U. Oncological causes of frailty in older cancer patients. *Eur J Cancer*. 2007;43(8):1230-1231.

346. Lee JSW, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *J Am Med Dir Assoc*. 2014;15(4):281-286.

347. Sourdet S, Lafont C, Rolland Y, Nourhashemi F, Andrieu S, Vellas B. Preventable Iatrogenic Disability in Elderly Patients During Hospitalization. *J Am Med Dir Assoc*. 2015;16(8):674-681.

348. Veronese N, Stubbs B, Noale M, et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. *J Am Med Dir Assoc*. 2017;18(7):624-628.

349. Saum KU, Schöttker B, Meid AD, et al. Is Polypharmacy Associated with Frailty in Older People? Results From the ESTHER Cohort Study. *J Am Geriatr Soc*. 2017;65(2):e27-e32.

350• Gill TM, Gahbauer EA, Han L, Allore HG. The role of intervening hospital admissions on trajectories of disability in the last year of life: prospective cohort study of older people. *BMJ*. 2015;350:h2361.

351. Shahrokni A, Wu AJ, Carter J, Lichtman SM. Long-term Toxicity of Cancer Treatment in Older Patients. *Clin Geriatr Med*. 2016;32(1):63.

352• Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol*. 2015;26(6):1091-1101.

353. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *Journals Gerontol Ser A Biol Sci Med Sci*. 2004;59(3):M255-M263.

354. Theou O, Rockwood MRH, Mitnitski A, Rockwood K. Disability and co-morbidity in relation to frailty: how much do they overlap? *Arch Gerontol Geriatr*. 2012;55(2):e1-8.

355. Cesari M, Pérez-Zepeda MU, Marzetti E. Frailty and Multimorbidity: Different Ways of Thinking About Geriatrics. *J Am Med Dir Assoc*. 2017;18(4):361-364.

356. Bernabei R, Martone AM, Vetrano DL, Calvani R, Landi F, Marzetti E. Frailty, Physical Frailty, Sarcopenia: A New Conceptual Model. *Stud Health Technol Inform*. 2014;203:78-84.

357. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: Two sides of the same coin. *Front Aging Neurosci*. 2014; 6(July):192.

358. Walston J, Bandeen-Roche K, Buta B, et al. Moving Frailty Toward Clinical Practice: NIA Intramural Frailty Science Symposium Summary. *J Am Geriatr Soc*. 2019;67(8):1559.

359. Boyd KJ, Murray SA. Worsening disability in older people: a trigger for palliative care. *BMJ*. 2015;350:h2439.

360. Amblàs-Novellas J, Murray SA, Espaulella J, et al. Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories. *BMJ Open*. 2016;6(9):e012340.

361• Covinsky KE, Eng C, Lui L-Y, Sands LP, Yaffe K. The last 2 years of life: functional trajectories of frail older people. *J Am Geriatr Soc*. 2003;51(4):492-498.

362. Chen J, Chan DD, Kiely DK, Morris JN, Mitchell SL. Terminal trajectories of functional decline in the long-term care setting. *Journals Gerontol Ser A Biol Sci Med Sci*. 2007;62(5):531-536.

363. Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: a longitudinal population-based study. *BMC Med*. 2018;16(1):171.

364• Stow D, Spiers G, Matthews FE, Hanratty B. What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. *Palliat Med*. 2019;33(4):399-414.

365. Boockvar KS, Meier DE. Palliative Care for Frail Older Adults. *JAMA*. 2006;296(18):2245.

366. Koller K, Rockwood K. Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med*. 2013;80(3):168-174.

367. Van Lancker A, Velghe A, Van Hecke A, et al. Prevalence of symptoms in older cancer patients receiving palliative care: A systematic review and meta-analysis. *J Pain Symptom Manage*. 2014;47(1):90-104.

368. Moens K, Higginson IJ, Harding R. Are There Differences in the Prevalence of Palliative Care-Related Problems in People Living With Advanced Cancer and Eight Non-Cancer Conditions? A Systematic Review. *J Pain Symptom Manage*. 2014;48(4):660-677.

369. Janssen DJA, Spruit MA, Wouters EFM, Schols JMGA. Daily symptom burden in end-stage chronic organ failure: A systematic review. *Palliat Med*. 2008;22(8):938-948.

370. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011; 12(2):160-174.

371. Murtagh FEM, Addington-Hall J, Higginson IJ. The Prevalence of Symptoms in End-Stage Renal Disease: A Systematic Review. *Adv Chronic Kidney Dis*. 2007;14(1):82-99.

372. Solano J, Gomes B, Higginson I. A Comparison of Symptom Prevalence in Far Advanced Cancer , AIDS , Heart Disease , Chronic Obstructive Pulmonary Disease and Renal Disease. *J Pain Symptom Manage*. 2006;31(1):58-69.

373. Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HCJM, Voest EE, de Graeff A. Symptom Prevalence in Patients with Incurable Cancer: A Systematic Review. *J Pain Symptom Manage*. 2007;34(1):94-104.

374• Van Den Beuken MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on Prevalence of Pain in Patients with Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage*. 2016;51(6):1070.e9.

375. Lokker ME, Van Zuylen L, Van Der Rijt CCD, Van Der Heide A. Prevalence, impact, and treatment of death rattle: A systematic review. *J Pain Symptom Manage*. 2014;47(1):105-122.

376. Guyatt GH. Evidence-based medicine. *Am Coll Physicians J Club*. 1991;114:A16.

377. Guyatt G. Evidence-Based Medicine. A New Approach to Teaching the Practice of Medicine. *JAMA*. 1992;268(17):2420.

378. Institute of Medicine (Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E) *Clinical Practice Guidelines We Can Trust*. Washington, D.C.: National Academies Press; 2011.

379. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.

380. Boyd CM, Vollenweider D, Puhan MA. Informing Evidence-Based Decision-Making for Patients with Comorbidity: Availability of Necessary Information in Clinical Trials for Chronic Diseases. Boutron I, ed. *PLoS One*. 2012;7(8):e41601.

381• Jadad AR. Consideration of Multiple Chronic Diseases in Randomized Controlled Trials. *JAMA*. 2011;306(24):2670.

382. Du Vaure CB, Dechartres A, Battin C, Ravaud P, Boutron I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: A systematic review of registration details. *BMJ Open*. 2016;6(9):4-11.

383. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16(1):1-14.

384. Tinetti ME, Bogardus ST, Agostini J V. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med*. 2004;351:2870-2874.

385. Guthrie B, Boyd CM. Clinical Guidelines in the Context of Aging and Multimorbidity. *Public Policy Aging Rep*. 2018;28(4):143-149.

386. Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ*. 2012; 345(7878):e6341.

387• Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA*. 2005;294(6):716-724.

388. Okeowo D, Patterson A, Boyd C, Reeve E, Gnjidic D, Todd A. Clinical practice guidelines for older people with multimorbidity and life-limiting illness: what are the implications for deprescribing? *Ther Adv Drug Saf*. 2018; 9(11):619-630.

389. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol*. 2012;65(9):989-995.

390. Fincke BG, Snyder K, Cantillon C, et al. Three complementary definitions of polypharmacy: Methods, application and comparison of findings in a large prescription database. *Pharmacoepidemiol Drug Saf*. 2005;14(2):121-8.

391. Mortazavi SS, Shati M, Keshtkar A, Malakouti SK, Bazargan M, Assari S. Defining polypharmacy in the elderly: a systematic review protocol. *BMJ Open*. 2016;6(3):e010989.

392. Charlesworth CJ, Smit E, Lee DSH, Alramadhan F, Odden MC. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988–2010. *Journals Gerontol Ser A Biol Sci Med Sci*. 2015;70(8):989-995.

393. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314(17):1818-1831.

394. Morin L, Johnell K, Laroche M-L, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. *Clin Epidemiol*. 2018; 10:289-298.

395. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in Nursing Home in Europe : Results From the SHELTER Study. 2012;(6):698.

396• Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opin Drug Saf*. 2018;17(12):1185

397. Wise J. Polypharmacy: a necessary evil. *BMJ*. 2013;347:f7033.

398. Duerden M, Avery T, Payne R. *Polypharmacy and Medicines Optimisation. Making It Safe and Sound*. London: The King's Fund; 2013.

399. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium". *JAMA*. 2010;304(14):1592-1601.

400. Cadogan CA, Ryan C, Hughes CM. Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many. *Drug Saf*. 2016;39(2):109-116.

401. Poudel A, Peel NM, Nissen LM, Mitchell CA, Gray LC, Hubbard RE. Adverse Outcomes in Relation to Polypharmacy in Robust and Frail Older Hospital Patients. *J Am Med Dir Assoc*. 2016;17(8):767.e9-767.e13.

402. Sganga F, Landi F, Ruggiero C, et al. Polypharmacy and health outcomes among older adults discharged from hospital: Results from the CRIME study. *Geriatr Gerontol Int*. 2015;15(2):141-146.

403. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. *J Am Geriatr Soc*. 2014;62(12):2261-2272.

404. Nightingale G, Skonecki E, Boparai MK. The Impact of Polypharmacy on Patient Outcomes in Older Adults With Cancer. *Cancer J*. 2017;23(4):211-218.

405. George C, Verghese J. Polypharmacy and Gait Performance in Community–dwelling Older Adults. *J Am Geriatr Soc*. 2017;65(9):2082-2087.

406• Montero-Odasso M, Sarquis-Adamson Y, Song HY, Bray NW, Pieruccini-Faria F, Speechley M. Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study. *J Am Geriatr Soc*. 2019;67(6):1182-1188.

407. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf*. 2007; 30(10):911-918.

408. Mallet L, Spinewine A, Huang A. Prescribing In Elderly People 2 The challenge of managing drug interactions in elderly people. 2007:185.

409. Shi S, Mörike K, Klotz U. The clinical implications of ageing for rational drug therapy. *Eur J Clin Pharmacol*. 2008;64(2):183.

410. Sera LC, McPherson ML. Pharmacokinetics and Pharmacodynamic Changes Associated with Aging and Implications for Drug Therapy. *Clin Geriatr Med*. 2012;28(2):273-286.

411. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69(3):319-326.

412. Davies EA, O'Mahony MS. Adverse drug reactions in special populations — the elderly. *Br J Clin Pharmacol*. 2015;80(4):796-807.

413. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2003;57(1):6-14.

414. Atkin PA, Veitch PC, Veitch EM, Ogle SJ. The epidemiology of serious adverse drug reactions among the elderly. *Drugs and Aging*. 1999;14(2):141-152.

415. Calderón-Larrañaga A, Poblador-Plou B, González-Rubio F, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Multimorbidity, polypharmacy, referrals, and adverse drug events: Are we doing things well? *Br J Gen Pract*. 2012;62(605):821-826.

416• Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002-2012.

417. Alhawassi TM, Krass I, Bajorek B V, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging*. 2014;9:2079-2086.

418. Laflamme L, Monárrez-Espino J, Johnell K, Elling B, Möller J. Type, number or both? A population-based matched case-control study on the risk of fall injuries among older people and number of medications beyond fall-inducing drugs. *PLoS One*. 2015;10(3).

419. Bennett A, Gnjidic D, Gillett M, et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. *Drugs Aging*. 2014; 31(3):225-232.

420. Morin L, Calderon Larrañaga A, Welmer A-K, Rizzuto D, Wastesson J, Johnell K. Polypharmacy and injurious falls in older adults: a nationwide nested case-control study. *Clin Epidemiol*. 2019;11:483-493.

421. Kuijpers MAJ, Van Marum RJ, Egberts ACG, Jansen PAF. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol*. 2008;65(1):130-133.

422. Calderón-Larrañaga A, Diaz E, Poblador-Plou B, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Non-adherence to antihypertensive medication: The role of mental and physical comorbidity. *Int J Cardiol*. 2016;207:310-316.

423• Johnell K, Fastbom J, Rosén M, Leimanis A. Inappropriate drug use in the elderly: A nationwide register-based study. *Ann Pharmacother*. 2007;41(7-8):1243-1248.

424. Morin L, Fastbom J, Laroche M-L, Johnell K. Potentially inappropriate drug use in older people: a nationwide comparison of different explicit criteria for population-based estimates. *Br J Clin Pharmacol*. 2015;80(2):315.

425• Fialová D, Topinková E, Gambassi G, et al. Potentially inappropriate medication use among elderly home care patients in Europe. *JAMA*. 2005;293(11):1348-1358.

426. Nothelle SK, Sharma R, Oakes AH, Jackson M, Segal JB. Determinants of Potentially Inappropriate Medication Use in Long-Term and Acute Care Settings: A Systematic Review. *J Am Med Dir Assoc*. 2017;18(9):806.e1-806.e17.

427. Scottish Government Polypharmacy Model of Care Group. *Polypharmacy Guidance, Realistic Prescribing*. 3rd ed. (Mair A, Leitch J, Calderwood C, eds.). Edinburgh: Scottish Government; 2018.

428. Santanasto AJ, Goodpaster BH, Kritchevsky SB, et al. Body Composition Remodeling and Mortality: The Health Aging and Body Composition Study. *Journals Gerontol Ser A Biol Sci Med Sci*. 2017;72(4):513-519.

429. Institute of Medicine. *Pharmacokinetics and Drug Interactions in the Elderly: Workshop Summary*. Washington, D.C.: National Academies Press; 1997.

430. Aalami OO. Physiological Features of Aging Persons. *Arch Surg*. 2003;138(10):1068.

431. Reeve E, Wiese MD, Mangoni A a. Alterations in drug disposition in older adults. *Expert Opin Drug Metab Toxicol*. 2015;11(4):491-508.

432. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011; 12(7):601-610.

433. Wehling M. Age-Associated General Pharmacological Aspects. In: Wehling M, ed. *Drug Therapy for the Elderly*. Vienna: Springer; 2013:21-34.

434• Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet*. 2007;370(9582):173-184.

435. Samsa GP, Hanlon JT, Schmader KE, et al. A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity. *J Clin Epidemiol*. 1994;47(8):891-896.

436. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992; 45(10):1045-1051.

437. Hanlon JT, Schmader KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. *Drugs Aging*. 2013;30(11):893-900.

438. Galván-Banqueri M, De La Higuera-Vila L, Vega-Coca MD, Nieto Martín MD, Pérez-Guerrero C, Santos-Ramos B. Reliability of a questionnaire for pharmacological treatment appropriateness in patients with multiple chronic conditions. *Eur J Intern Med*. 2013; 24(5):420-424.

439. Chang C-B, Chan D-C. Comparison of published explicit criteria for potentially inappropriate medications in older adults. *Drugs Aging*. 2010;27(12):947-957.

440. Dimitrow MS, Airaksinen MSA, Kivelä SL, Lyles A, Leikola SNS. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: A systematic review. *J Am Geriatr Soc*. 2011;59(8):1521-1530.

441. Levy HB, Marcus EL, Christen C. Beyond the beers criteria: A comparative overview of explicit criteria. *Ann Pharmacother*. 2010; 44(12):1968-1975.

442. Santos APAL, da Silva DT, dos Santos Júnior GA, et al. Evaluation of the heterogeneity of studies estimating the association between risk factors and the use of potentially inappropriate drug therapy for the elderly: a systematic review with meta-analysis. *Eur J Clin Pharmacol*. 2015;71(9):1037-1050.

443. Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PLoS One*. 2012;7(8).

444. Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol*. 2015;71(12):1415.

445. Morin L, Laroche ML, Texier G, Johnell K. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. *J Am Med Dir Assoc*. 2016;17(9):862.e1-862.e9.

446. Dedhiya SD, Hancock E, Craig BA, Doebbeling CC, Thomas J. Incident use and outcomes associated with potentially inappropriate medication use in older adults. *Am J Geriatr Pharmacother*. 2010;8(6):562-570.

447. Lau DT, Kasper JD, Potter DEB, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. *Arch Intern Med*. 2005;165(1):68-74.

448. Pugh MJ V., Marcum ZA, Copeland LA, et al. The quality of quality measures: HEDIS® quality measures for medication management in the elderly and outcomes associated with new exposure. *Drugs and Aging*. 2013;30(8):645-54.

449. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674.

450. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *Eur J Clin Pharmacol*. 2015;71(7):861.

451. Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) List: International Consensus Validation of a Clinical Tool for Improved Drug Treatment in Older People. *Drugs and Aging*. 2018;35(1):61-71.

452. Laroche M-L, Charmes J-P, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur J Clin Pharmacol*. 2007;63(8):725-731.

453. Maio V, Del Canale S, Abouzaid S. Using explicit criteria to evaluate the quality of prescribing in elderly Italian outpatients: a cohort study. *J Clin Pharm Ther*. 2010;35(2):219-229.

454. McLeod PJ, Huang a R, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *C Can Med Assoc J*. 1997;156(3):385-391.

455. Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. *Scand J Prim Health Care*. 2009;27(3):153-159.

456. Nyborg G, Straand J, Klovning A, Brekke M. The Norwegian General Practice-Nursing Home criteria (NORGEP-NH) for potentially inappropriate medication use: A web-based Delphi study. *Scand J Prim Health Care*. 2015;33(2):134-141.

457. Holt S, Schmiedl S, Thürmann P a. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int*. 2010;107(31-32):543-551.

458. 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):213-218.

459• 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;74(3):331-338.

460. Swedish National Board of Health and Welfare. *Indikatorer För God Läkemedelsterapi Hos Äldre*. Stockholm; 2010.

461. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med*. 1991;151(9):1825-1832.

462. Beers MH. Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly. *Arch Intern Med*. 1997;157(14):1531.

463. 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):2716-2724.

464. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616.

465. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015; 63(11):2227-2246.

466. Wehling M. Critical Extrapolation of Guidelines and Study Results: Risk-Benefit Assessment for Patients with Reduced Life Expectancy and a New Classification of Drugs According to Their Fitness for the Aged. In: Wehling M, ed. *Drug Therapy for the Elderly*. Vienna: Springer; 2013:35-42.

467. Kuhn-Thiel AM, Weiß C, Wehling M. Consensus validation of the FORTA (Fit for the Aged) List: A clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. *Drugs and Aging*. 2014.

468. Pazan F, Weiss C, Wehling M. The FORTA (Fit fOR The Aged) List 2015: Update of a Validated Clinical Tool for Improved Pharmacotherapy in the Elderly. *Drugs and Aging*. 2016;33(6):447-49.

469. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): Application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing*. 2008;37(6):673.

470. Muhlack DC, Hoppe LK, Weberpals J, Brenner H, Schöttker B. The Association of Potentially Inappropriate Medication at Older Age With Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies. *J Am Med Dir Assoc*. 2017; 18(3):211-220.

471. Skoldunger A, Fastbom J, Wimo A, Fratiglioni L, Johnell K. Impact of Inappropriate Drug Use on Hospitalizations, Mortality, and Costs in Older Persons and Persons with Dementia: Findings from the SNAC Study. *Drugs Aging*. 2015;32(8):671-678.

472• Cahir C, Bennett K, Teljeur C, Fahey T. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. *Br J Clin Pharmacol*. 2014;77(1):201-210.

473. Endres HG, Kaufmann-Kolle P, Steeb V, Bauer E, Böttner C, Thürmann P. Association between potentially inappropriate medication (PIM) use and risk of hospitalization in older adults: An observational study based on routine data comparing PIM use with use of PIM alternatives. *PLoS One*. 2016;11(2):1-15.

474. Ruggiero C, Dellaquila G, Gasperini B, et al. Potentially inappropriate drug prescriptions and risk of hospitalization among older, italian, nursing home residents: The ulisse project. *Drugs and Aging*. 2010;27(9):747-758.

475. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: A population-based study of the very old. *Drugs and Aging*. 2005;22(1):69-82.

476. Hyttinen V, Taipale H, Tolppanen AM, et al. Incident Use of a Potentially Inappropriate Medication and Hip Fracture in Community-Dwelling Older Persons With Alzheimer's Disease. *Ann Pharmacother*. 2017;51(9):725-34.

477. Johnell K. Inappropriate Drug Use in People with Cognitive Impairment and Dementia: A Systematic Review. *Curr Clin Pharmacol*. 2015; 10(3):178-184.

478. Patel T, Slonim K, Lee L. Use of potentially inappropriate medications among ambulatory home-dwelling elderly patients with dementia: A review of the literature. *Can Pharm J / Rev des Pharm du Canada*. 2017;150(3):169-183.

479. O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. *Age Ageing*. 2011;40(4):419.

480. Cruz-Jentoft AJ, Boland B, Rexach L. Drug therapy optimization at the end of life. *Drugs and Aging*. 2012;29(6):511-521.

481• Stevenson J, Abernethy AP, Miller C, Currow DC. Managing comorbidities in patients at the end of life. *BMJ*. 2004;329(7471):909-912.

482. Bain KT, Weschules DJ. Medication inappropriateness for older adults receiving hospice care: a pilot survey. *Consult Pharm*. 2007;22(11):926-934.

483. Holmes HM. Rational prescribing for patients with a reduced life expectancy. *Clin Pharmacol Ther*. 2009;85(1):103-107.

484. Akinbolade O, Husband A, Forrest S, Todd A. Deprescribing in advanced illness. *Prog Palliat Care*. 2016;24(5):268-271.

485. Lee SP, Bain KT, Maio V. Appropriate discontinuation of medications at the end of life: A need to establish consensus criteria. *Am J Med Qual*. 2007;22(6):393-394.

486. van der Cammen TJM, Rajkumar C, Onder G, Sterke CS, Petrovic M. Drug cessation in complex older adults: time for action. *Age Ageing*. 2014;43(1):20-25.

487. Mangin D, Bahat G, Golomb BA, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. *Drugs and Aging*. 2018;35(7):575-587.

488• Chassin MR. Is Health Care Ready for Six Sigma Quality? *Milbank Q*. 1998;76(4):565-591.

489. Morgan DJ, Dhruva SS, Wright SM, Korenstein D. Update on Medical Practices That Should Be Questioned in 2015. *JAMA Intern Med*. 2015; 175(12):1960-1964.

490. Youngner SJ. Who defines futility? *JAMA*. 1988;260(14):2094-2095.

491. Murphy DJ. Do-Not-Resuscitate Orders. Time for Reappraisal in Long-term-Care Institutions. *JAMA*. 1988;260(14):2098.

492. Van Scoy-Mosher MB. Cancer Chemotherapy: Ethical Dilemmas. *J Clin Oncol*. 1989;7(5):687.

493. Emanuel EJ, Young-Xu Y, Levinsky NG, Gazelle G, Saynina O, Ash AS. Chemotherapy Use among Medicare Beneficiaries at the End of Life. *Ann Intern Med*. 2003;138(8):639-644.

494. Earle CC, Venditti LN, Neumann PJ, et al. Who gets chemotherapy for metastatic lung cancer? *Chest*. 2000;117(5):1239-1246.

495• Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: Is it a quality-of-care issue? *J Clin Oncol*. 2008;26(23):3860-3866.

496. Martoni AA, Tanneberger S, Mutri V. Cancer chemotherapy near the end of life: The time has come to set guidelines for its appropriate use. *Tumori*. 2007;93(5):417-422.

497• Harrington SE, Smith TJ. The Role of Chemotherapy at the End of Life. *JAMA*. 2008;299(22):2667.

498. Hong JH, Rho S-Y, Hong YS, J.H. H, S.-Y. R. Trends in the Aggressiveness of End-of-Life Care for Advanced Stomach Cancer Patients. *Cancer Res Treat*. 2013;45(4):270-275.

499. Ho TH, Barbera L, Saskin R, Lu H, Neville B a, Earle CC. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. *J Clin Oncol*. 2011;29(12):1587-1591.

500• Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. *JAMA Oncol*. 2015;1(6):778-784.

501. Wright AA, Zhang B, Keating NL, Weeks JC, Prigerson HG. Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: Prospective cohort study. *BMJ*. 2014;348:g1219.

502. Schnipper LE, Smith TJ, Raghavan D, et al. American society of clinical oncology identifies five key opportunities to improve care and reduce costs: The top five list for oncology. *J Clin Oncol*. 2012;30(14):1715-1724.

503. Lyu H, Xu T, Brotman D, et al. Overtreatment in the United States. *PLoS One*. 2017;12(9):1-11.

504. Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D. 2018 Update on Medical Overuse. *JAMA Intern Med*. 2019;179(2):240.

505• Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet*. 2017;390(10090) 156-168.

506. Moynihan R. Too much medicine? *BMJ*. 2002;324(7342):859-860.

507. Hensher M, Tisdell J, Zimitat C. "Too much medicine": Insights and explanations from economic theory and research. *Soc Sci Med*. 2017;176:77-84.

508• Gawande A. Overkill. *New Yorker*. May 11, 2015.

509. Epstein D. When Evidence Says No, but Doctors Say Yes. *The Atlantic*. February 2, 2017.

510. Kale MS, Korenstein D. Overdiagnosis in primary care: Framing the problem and finding solutions. *BMJ*. 2018;362:k2820.

511. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613.

512. Bulliard JL, Chiolero A. Screening and overdiagnosis: Public health implications. *Public Health Rev*. 2015;36(1):1-5.

513. Bhatia RS, Bouck Z, Ivers NM, et al. Electrocardiograms in Low-Risk Patients Undergoing an Annual Health Examination. *JAMA Intern Med*. 2017;177(9):1326.

514. Johansson M, Jørgensen KJ, Brodersen J. Harms of screening for abdominal aortic aneurysm: Is there more to life than a 0·46% disease-specific mortality reduction? *Lancet*. 2016;387(10015):308-310.

515. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(4):279.

516. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness. *N Engl J Med*. 2016;375(15):1438-1447.

517. Qaseem A, Lin JS, Mustafa RA, Horwitch CA, Wilt TJ. Screening for Breast Cancer in Average-Risk Women: A Guidance Statement From the American College of Physicians. *Ann Intern Med*. 2019;170(8):547.

518. Oeffinger KC, Fontham ETH, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk. 2015 Guideline Update From the American Cancer Society. *JAMA*. 2015; 314(15):1599.

519. Wolfe HR, Gupta A, Sadeghi N. Unnecessary Staging Imaging in Early-Stage Breast Cancer. *JAMA Intern Med*. 2017;177(10):1516.

520. Koch C, Roberts K, Petruccelli C, Morgan DJ. The Frequency of Unnecessary Testing in Hospitalized Patients. *Am J Med*. 2018; 131(5):500-503.

521• Korenstein D, Chimonas S, Barrow B, Keyhani S, Troy A, Lipitz-Snyderman A. Development of a Conceptual Map of Negative Consequences for Patients of Overuse of Medical Tests and Treatments. *JAMA Intern Med*. 2018;178(10) 1401-1407.

522. Schwartz AL, Landon BE, Elshaug AG, Chernew ME, McWilliams JM. Measuring low-value care in Medicare. *JAMA Intern Med*. 2014; 174(7):1067-1076.

523. Mcalister FA, Lin M, Bakal J, Dean S. Frequency of low-value care in Alberta, Canada: A retrospective cohort study. *BMJ Qual Saf*. 2018; 27(5):340-346.

524• Panagioti M, Khan K, Keers RN, et al. Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis. *BMJ*. 2019;366:l4185.

525. Blanco-Reina E, Ariza-Zafra G, Ocaña-Riola R, León-Ortíz M, Bellido-Estévez I. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? *Eur J Clin Pharmacol*. 2015;71(2):199.

526. Gruber-Baldini AL, Zimmerman S, Roth M, et al. Medication undertreatment in assisted living settings. *Arch Intern Med*. 2004;164(18) 2031-2037.

527. Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E, et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. *Eur J Clin Pharmacol*. 2018;74(7):961-970.

528. Cherubini A, Corsonello A, Lattanzio F. Underprescription of beneficial medicines in older people: Causes, consequences and prevention. *Drugs and Aging*. 2012;29(6):463.

529. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med*. 1998;338(21):1516-1520.

530. Glasziou P, Straus S, Brownlee S, et al. Evidence for underuse of effective medical services around the world. *Lancet*. 2017; 390(10090):169-177.

531. Schneiderman LJ, Jecker NS. *Wrong Medicine Doctors, Patients, Futile Treatment: Second Edition*. Baltimore: Johns Hopkins University Press; 2011.

532. Graham J. End-of-Life Medications Draw More Attention, Greater Scrutiny. *JAMA*. 2015;313(3):231.

533. Todd A, Holmes HM. Recommendations to support deprescribing medications late in life. *Int J Clin Pharm*. 2015;37(5):678-681.

534. Fede A, Miranda M, Antonangelo D, et al. Use of unnecessary medications by patients with advanced cancer: Cross-sectional survey. *Support Care Cancer*. 2011;19(9):1313-1318.

535. Raijmakers NJH, van Zuylen L, Furst CJ, et al. Variation in medication use in cancer patients at the end of life: a cross-sectional analysis. *Support Care Cancer*. 2013;21(4):1003-1011.

536. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. *Support Care Cancer*. 2009;17(6):745-748.

537. Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the "OncPal deprescribing guideline". *Support Care Cancer*. 2015;23(1):71-78.

538. Suhrie EM, Hanlon JT, Jaffe EJ, Sevick MA, Ruby CM, Aspinall SL. Impact of a geriatric nursing home palliative care service on unnecessary medication prescribing. *Am J Geriatr Pharmacother*. 2009;7(1):20-25.

539. Domingues PGD, Carneiro R, Costa I, et al. Therapeutic futility in cancer patients at the time of palliative care transition: An analysis with a modified version of the Medication Appropriateness Index. *Palliat Med*. 2015;29(7):643-651.

540• Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166(6):605-609.

541. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating palliative medicine into the care of persons with advanced dementia: Identifying appropriate medication use. *J Am Geriatr Soc*. 2008;56(7):1306-1311.

542. Holmes HM, Min LC, Yee M, et al. Rationalizing prescribing for older patients with multimorbidity: Considering time to benefit. *Drugs and Aging*. 2013;30(9):655-666.

543. Van der Linden L, Hias J, Spriet I, Walgraeve K, Flamaing J, Tournoy J. Medication review in older adults: Importance of time to benefit. *Am J Heal Pharm*. 2019;76(4):247-250.

544• Boyd C, Smith CD, Masoudi FA, et al. Decision Making for Older Adults With Multiple Chronic Conditions: Executive Summary for the American Geriatrics Society Guiding Principles on the Care of Older Adults With Multimorbidity. *J Am Geriatr Soc*. 2019; 67(4):665-673.

545. Kerr EA, Kullgren JT, Saini SD. Choosing Wisely: How to fulfill the promise in the next 5 years. *Health Aff*. 2017;36(11):2012-2018.

546. Malhotra A, Maughan D, Ansell J, et al. Choosing Wisely in the UK: The Academy of Medical Royal Colleges' initiative to reduce the harms of too much medicine. *BMJ*. 2015;350(May):10-13.

547. AGS Choosing Wisely Workgroup. American Geriatrics Society identifies five things that healthcare providers and patients should question. *J Am Geriatr Soc*. 2013;61(4):622-631.

548. AGS Choosing Wisely Workgroup. American Geriatrics Society identifies another five things that healthcare providers and patients should question. *J Am Geriatr Soc*. 2014;62(5):950-960.

549. Fischberg D, Bull J, Casarett D, et al. Five things physicians and patients should question in hospice and palliative medicine. *J Pain Symptom Manage*. 2013;45(3):595-605.

550. Onder G, Liperoti R, Foebel A, et al. Polypharmacy and mortality among nursing home residents with advanced cognitive impairment: results from the SHELTER study. *J Am Med Dir Assoc*. 2013;14(6):450.e7-12.

551. 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):107-112.

552. Morgan NA, Rowett D, Currow DC. Analysis of drug interactions at the end of life. *BMJ Support Palliat Care*. 2015;5(3):281-286.

553. Russell BJ, Rowett D, Abernethy AP, Currow DC. Prescribing for comorbid disease in a palliative population: Focus on the use of lipid-lowering medications. *Intern Med J*. 2014;44(2):177-184.

554. Sera L, McPherson ML, Holmes HM. Commonly Prescribed Medications in a Population of Hospice Patients. *Am J Hosp Palliat Med*. 2014;31(2):126-131.

555. Tjia J, Cutrona SL, Peterson D, Reed G, Andrade SE, Mitchell SL. Statin discontinuation in nursing home residents with advanced dementia. *J Am Geriatr Soc*. 2014;62(11):2095.

556. Todd a., Nazar H, Pearson H, Andrew L, Baker L, Husband A. Inappropriate prescribing in patients accessing specialist palliative day care services. *Int J Clin Pharm*. 2014;36(3):535-543.

557. Turner JP, Shakib S, Singhal N, et al. Prevalence and factors associated with polypharmacy in older people with cancer. 2014:1727-1734.

558. 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):590-595.

559. Kotlinska-Lemieszek A, Paulsen Ø, Kaasa S, Klepstad P. Polypharmacy in patients with advanced cancer and pain: A european cross-sectional study of 2282 patients. *J Pain Symptom Manage*. 2014;48(6):1145-1159.

560. Barcelo M, Torres O, Ruiz D, Casademont J. Appropriateness of medications prescribed to elderly patients with advanced heart failure and limited life expectancy who died during hospitalization. *Drugs and Aging*. 2014;31(7):541-546.

561. Chen I, Liu M, Twu F, Yuan C. Use of Medication by Nursing Home Residents Nearing End of Life : A Preliminary Report. 2010;18(3):199-205.

562. Cruikshank RP, Stafford B, Jones L. Polypharmacy in the terminally ill. *Med J Aust*. 2013;199(1):29.

563. Dwyer LL, Lau DT, Shega JW. Medications That Older Adults in Hospice Care in the United States Take, 2007. *J Am Geriatr Soc*. 2015;63(11):2282-2289.

564. Hui D, Li Z, Chisholm GB, Didwaniya N, Bruera E. Changes in medication profile among patients with advanced cancer admitted to an acute palliative care unit. *Support Care Cancer*. 2014;23(2):427-432.

565. Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: An epidemiologic study in nursing homes. *Scand J Prim Health Care*. 2014;32(4):187-192.

566. Grande G, Morin L, Vetrano DL, Fastbom J, Johnell K. Drug Use in Older Adults with Amyotrophic Lateral Sclerosis Near the End of Life. *Drugs Aging*. 2017;34(7):529-533.

567. Matlow JN, Bronskill SE, Gruneir A, et al. Use of Medications of Questionable Benefit at the End of Life in Nursing Home Residents with Advanced Dementia. *J Am Geriatr Soc*. 2017;65(7):1535-1542.

568. Morin L, Vetrano DL, Grande G, Fratiglioni L, Fastbom J, Johnell K. Use of Medications of Questionable Benefit During the Last Year of Life of Older Adults With Dementia. *J Am Med Dir Assoc*. 2017;18(6):551.e1-551.e7.

569. Oliveira L, Ferreira MO, Rola A, Magalhães M, Ferraz Gonçalves J. Deprescription in Advanced Cancer Patients Referred to Palliative Care. *J Pain Palliat Care Pharmacother*. 2016;30(3):201-205.

570• Tjia J, Briesacher BA, Peterson D, Liu Q, Andrade SE, Mitchell SL. Use of medications of questionable benefit in advanced dementia. *JAMA Intern Med*. 2014;174(11):1763-1771.

571. West E, Costantini M, Pasman H, Onwuteaka-Philipsen B. A comparison of drugs and procedures of care in the Italian hospice and hospital settings: the final three days of life for cancer patients. *BMC Health Serv Res*. 2014; 14(1):496.

572. Tjia J, Rothman MR, Kiely DK, et al. Daily Medication Use in Nursing Home Residents with Advanced Dementia. *J Am Geriatr Soc*. 2010;58(5):880-888.

573. Chuang H-Y, Wen Y-W, Chen L-K, Hsiao F-Y. Medication appropriateness for patients with dementia approaching the end of their life. *Geriatr Gerontol Int*. 2017;17:65-74.

574. Dewhurst F, Baker L, Andrew I, Todd A. Blood pressure evaluation and review of antihypertensive medication in patients with life limiting illness. *Int J Clin Pharm*. 2016; 38(5):1044-1047.

575. Fahlman C, Lynn J, Finch M, Doberman D, Gabel J. Potentially inappropriate medication use by Medicaid+Choice beneficiaries in the last year of life. *J Palliat Med*. 2007;10(3):686-95.

576. Fahlman C, Lynn J, Doberman D, Gabel J, Finch M. Prescription Drug Spending for Medicare+Choice Beneficiaries in the Last Year of Life. *J Palliat Med*. 2006;9(4):884-893.

577. Lee HR, Yi SY, Kim DY. Evaluation of prescribing medications for terminal cancer patients near death: Essential or futile. *Cancer Res Treat*. 2013;45(3):220-225.

578. Ma G, Downar J. Noncomfort Medication Use in Acute Care Inpatients Comanaged by Palliative Care Specialists Near the End of Life: A Cohort Study. *Am J Hosp Palliat Med*. 2014;31(8):812-819.

579. Agar M, Currow D, Plummer J, Seidel R, Carnahan R, Abernethy AP. Changes in anticholinergic load from regular prescribed medications in palliative care as death approaches. *Palliat Med*. 2009;23(3):257-265.

580. Huisman BAA, Geijteman ECT, Dees MK, van Zuylen L, van der Heide A, Perez RSGM. Better drug use in advanced disease: an international Delphi study. *BMJ Support Palliat Care*. November 2018:Epub.

581. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Med*. 2015;12(10).

582• Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*. 2018;363:k3532.

583. Ludvigsson JF, Almqvist C, Bonamy AKE, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016;31(2):125-136.

584. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773.

585. Wilmoth JR, Deegan LJ, Lundström H, Horiuchi S. Increase of maximum life-span in Sweden, 1861-1999. *Science*. 2000;289(5488):2366-68.

586. Socialstyrelsen. *Dödsorsaksstatistik – Historik, Produktionsmetoder Och Tillförlitlighet. Komplement till Rapporten Dödsorsaker 2008*. Stockholm; 2010.

587. World Health Organization (WHO). *International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Volume 2 – Instruction Manual*. 5th ed. Geneva: WHO Library; 2016.

588. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007; 16(7):726-735.

589. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register – A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol*. 2016;119(5):464-469.

590. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11(1):450.

591. Social Services Act - SFS 2001:453. *Sven Författningssamling*. 2001;12(453):1-21.

592. Anell A, Glenngård AH, Merkur S. Sweden: Health system review. *Health Syst Transit*. 2012;14(5):1-159.

593. Halldén K. The Swedish educational system and classifying education using the ISCED-97. In: Schneider SL, ed. *The International Standard Classification of Education: An Evaluation of Content and Criterion Validity for 15 European Countries*. Mannheim: University of Mannheim; 2008:253-267.

594. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol*. 2019;34(4):423-437.

595. Martin H. Calculating the standard of living of a household: one or several equivalence scales? *Econ Stat*. 2017;(491-492):101-117.

596. Hagenaars AJM, Zaidi AM, de Vos K. *Poverty Statistics in the Late 1980s: Research Based on Micro-Data.* Luxembourg: Statistical Office of the European Communities; 1994.

597. Sinnott S-J, Polinski JM, Byrne S, Gagne JJ. Measuring drug exposure: concordance between defined daily dose and days' supply depended on drug class. *J Clin Epidemiol*. 2016; 69:107-113.

598. Lau HS, De Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*. 1997; 50(5):619-625.

599• Tanskanen A, Taipale H, Koponen M, et al. Drug exposure in register-based research - An expert-opinion based evaluation of methods. Eller K, ed. *PLoS One*. 2017;12(9):e0184070.

600. Nielsen LH, Løkkegaard E, Andreasen AH, Keiding N. Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. *Pharmacoepidemiol Drug Saf*. 2008;17(4):384-388.

601. Wallerstedt SM, Fastbom J, Johnell K, Sjöberg C, Landahl S, Sundström A. Drug Treatment in Older People before and after the Transition to a Multi-Dose Drug Dispensing System: A Longitudinal Analysis. *PLoS One*. 2013;8(6):1-8.

602. Johnell K, Fastbom J. Comparison of prescription drug use between community-dwelling and institutionalized elderly in Sweden. *Drugs and Aging*. 2012;29(9):751-758.

603• 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.

604. Diewert W. Harmonized Indexes of Consumer Prices: Their Conceptual Foundations. *Swiss J Econ Stat*. 2002;138(IV).

605. Eurostat. *Harmonised Index of Consumer Prices (HICP). Methodological Manual*. (Eurostat, ed.). Luxembourg: European Union; 2018.

606. Schneider SL. *The International Standard Classification of Education 2011*. Vol 30.; 2013.

607. Fischer M, Karlsson M, Nilsson T, Schwarz N. *The Long-Term Effects of Long Terms Compulsory Schooling Reforms in Sweden*. Stockholm; 2017.

608. Marengoni A, Roso-Llorach A, Vetrano DL, et al. Patterns of Multimorbidity in a Population-Based Cohort of Older People: Sociodemographic, Lifestyle, Clinical, and Functional Differences. *Journals Gerontol A*. May 2019:Epub. Doi: 10.1093/gerona/glz137

609. Dekhtyar S, Vetrano DL, Marengoni A, et al. Association Between Speed of Multimorbidity Accumulation in Old Age and Life Experiences: A Cohort Study. *Am J Epidemiol*. 2019;(10). Epub. Doi: 10.1093/aje/kwz101

610. Juul-Larsen HG, Christensen LD, Andersen O, Bandholm T, Kaae S, Petersen J. Development of the "chronic condition measurement guide": a new tool to measure chronic conditions in older people based on ICD-10 and ATC-codes. *Eur Geriatr Med*. 2019;10(3):431-444.

611• Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records. *Lancet*. 2018;391(10132):1775-1782.

612. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing*. 2016;45(3):353-360.

613. Tolson D, Rolland Y, Katz PR, Woo J, Morley JE, Vellas B. An International Survey of Nursing Homes. *J Am Med Dir Assoc*. 2013;14(7):459-62.

614. Onder G, Carpenter I, Finne-Soveri H, et al. Assessment of nursing home residents in Europe: the Services and Health for Elderly in Long TERm care (SHELTER) study. *BMC Health Serv Res*. 2012;12(1):5.

615. Socialstyrelsen. *Öppna Jämförelser 2018 – Vård Och Omsorg Om Äldre. Jämförelser Mellan Kommuner Och Län*. Stockholm: Socialstyrelsen; 2019.

616. Socialstyrelsen. *10 År Med Öppna Jämförelser "Vård Och Omsorg Om Äldre". Jämförelser under Åren 2007–2016*. Stockholm: Sveriges Kommuner och Landsting; 2017.

617. Sanford AM, Orrell M, Tolson D, et al. An International Definition for "Nursing Home." *J Am Med Dir Assoc*. 2015;16(3):181-184.

618. Winblad U, Blomqvist P, Karlsson A. Do public nursing home care providers deliver higher quality than private providers? Evidence from Sweden. *BMC Health Serv Res*. 2017;17(1):487.

619. Deb P, Norton EC. Modeling Health Care Expenditures and Use. *Annu Rev Public Health*. 2018;39(1):489-505.

620. Malehi AS, Pourmotahari F, Angali KA. Statistical models for the analysis of skewed healthcare cost data: a simulation study. *Health Econ Rev*. 2015;5(1):11.

621. Beyerlein A. Quantile Regression--Opportunities and Challenges From a User's Perspective. *Am J Epidemiol*. 2014;180(3):330-1.

622. Koenker R. *Quantile Regression*. Cambridge: Cambridge University Press; 2010.

623. Manning WG, Basu A, Mullahy J. Generalized modeling approaches to risk adjustment of skewed outcomes data. *J Health Econ*. 2005; 24(3):465-488.

624. Manning W. Dealing with Skewed Data on Costs and Expenditures. In: Jones A, ed. *The Elgar Companion to Health Economics, Second Edition*. Edward Elgar Publishing; 2012.

625• Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. *Can Med Assoc J*. 2012;184(8):895-899.

626. Dalkey NC, Helmer-Hirschberg O. *An Experimental Application of the Delphi Method to the Use of Experts*. Santa Monica, CA: RAND Corporation; 1962.

627. Dalkey NC. *The Delphi Method: An Experimental Study of Group Opinion*. Santa Monica, CA: RAND Corporation; 1969.

628. Helmer-Hirschberg O. *Systematic Use of Expert Opinions*. Santa Monica, CA: RAND Corporation; 1967.

629. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: A systematic overview of published assessment tools. *Eur J Clin Pharmacol*. 2014;70(1):1-11.

630• Marriott J, Stehlik P. A critical analysis of the methods used to develop explicit clinical criteria for use in older people. *Age Ageing*. 2012;41(4):441-450.

631. Fried TR, Niehoff K, Tjia J, Redeker N, Goldstein MK. A Delphi process to address medication appropriateness for older persons with multiple chronic conditions. *BMC Geriatr*. 2016;16(1):1-8.

632. Curtin D, Gallagher PF, O'Mahony D. Explicit criteria as clinical tools to minimize inappropriate medication use and its consequences. *Ther Adv Drug Saf*. 2019; 10:Epub. Doi:10.1177/2042098619829431

633. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and Reporting the Delphi Method for Selecting Healthcare Quality Indicators: A Systematic Review. Wright JM, ed. *PLoS One*. 2011;6(6):e20476.

634. Maddison AR, Fisher J, Johnston G. Preventive medication use among persons with limited life expectancy. *Prog Palliat Care*. 2011; 19(1):15-21.

635• 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

636• Jünger 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.

637. World Medical Association (WMA). World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191.

638. Coughlin SS. Informed Consent in Public Health Research. In: *Case Studies in Public Health Ethics*. 2nd ed. American Public Health Association; 2009:21-26.

639. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 7th ed. Oxford: Oxford University Press; 2012.

640. Beauchamp TL. Methods and principles in biomedical ethics. *J Med Ethics*. 2003;29(5):269.

641. Metcalfe C, Martin RM, Noble S, et al. Low risk research using routinely collected identifiable health information without informed consent: encounters with the Patient Information Advisory Group. *J Med Ethics*. 2008;34(1):37-40.

642. Ballantyne A, Schaefer GO. Consent and the ethical duty to participate in health data research. *J Med Ethics*. 2018;44(6):392-396.

643. Hepgul N, Sleeman KE, Firth AM, et al. In response to Ballantyne and Schaefer's 'Consent and the ethical duty to participate in health data research.' *J Med Ethics*. 2019;45(5):351-352.

644. Fiske ST, Hauser RM. Protecting human research participants in the age of big data. *Proc Natl Acad Sci*. 2014;111(38):13675-13676.

645. Nuffield Council on Bioethics. *The Collection, Linking and Use of Data in Biomedical Research and Health Care: Ethical Issues*. London; 2015.

646. Vayena E, Salathé M, Madoff LC, Brownstein JS. Ethical Challenges of Big Data in Public Health. Bourne PE, ed. *PLOS Comput Biol*. 2015;11(2):e1003904.

647. Robling MR, Hood K, Houston H, Pill R, Fay J, Evans HM. Public attitudes towards the use of primary care patient record data in medical research without consent: a qualitative study. *J Med Ethics*. 2004;30(1):104-109.

648. Skovgaard LL, Wadmann S, Hoeyer K. A review of attitudes towards the reuse of health data among people in the European Union: The primacy of purpose and the common good. *Health Policy (New York)*. 2019;123(6):564-571.

649. Price WN, Cohen IG. Privacy in the age of medical big data. *Nat Med*. 2019;25(1):37-43.

650. El Emam K, Jonker E, Arbuckle L, Malin B. A Systematic Review of Re-Identification Attacks on Health Data. Scherer RW, ed. *PLoS One*. 2011;6(12):e28071.

651. Reeve E, Trenaman SC, Rockwood K, et al. Pharmacokinetic and pharmacodynamic alterations in older people with dementia. *Expert Opin Drug Metab Toxicol*. 2017;13(6):651.

652• Franken LG, de Winter BCM, van Esch HJ, et al. Pharmacokinetic considerations and recommendations in palliative care, with focus on morphine, midazolam and haloperidol. *Expert Opin Drug Metab Toxicol*. 2016;12(6):669.

653. Smith BS, Yogaratnam D, Levasseur-franklin KE, Forni A. Introduction to Drug Pharmacokinetics in the Critically Ill Patient. *Chest*. 2012;141(5):1327-1336.

654. Masman AD, Tibboel D, Baar FPM, van Dijk M, Mathot RA., van Gelder T. Prevalence and Implications of Abnormal Laboratory Results in Patients in the Terminal Phase of Life. *J Palliat Med*. 2016;19(8):822-829.

655. Trobec K, Kos MK, Von Haehling S, Springer J, Anker SD, Lainscak M. Pharmacokinetics of drugs in cachectic patients: A systematic review. *PLoS One*. 2013;8(11):e79603.

656. Tan J, Eastment J, Poudel A, RE H. Age-Related Changes in Hepatic Function: An Update on Implications for Drug Therapy. *Drugs Aging*. 2015;32(12):999-1009.

657. Bader F, Atallah B, Brennan LF, Rimawi RH, Khalil ME. Heart failure in the elderly: ten peculiar management considerations. *Heart Fail Rev*. 2017;22(2):219-228.

658. Geist M, Bardenheuer H, Burhenne J, Mikus G. Alteration of drug-metabolizing enzyme activity in palliative care patients: Microdosed assessment of cytochrome P450 3A. *Palliat Med*. 2019;33(7):850-855.

659. Olyaei AJ, Bennett WM. Drug Dosing in the Elderly Patients with Chronic Kidney Disease. *Clin Geriatr Med*. 2009;25(3):459-527.

660. Bowie MW, Slattum PW. Pharmacodynamics in Older Adults: A Review. *Am J Geriatr Pharmacother*. 2007;5(3):263-303.

661. Corsonello A, Pedone C, Incalzi R. Age-Related Pharmacokinetic and Pharmacodynamic Changes and Related Risk of Adverse Drug Reactions. *Curr Med Chem*. 2010;17(6):571-584.

662. Turnheim K. When drug therapy gets old: Pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol*. 2003;38(8):843-853.

663. Strouse TB. Pharmacokinetic Drug Interactions in Palliative Care: Focus On Opioids. *J Palliat Med*. 2009;12(11):1043-1050.

664. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: An appraisal. *BMC Med*. 2017;15(1):112.

665. Saver JL, Lewis RJ. Number Needed to Treat: Conveying the Likelihood of a Therapeutic Effect. *JAMA*. 2019;321(8):798-799.

666. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;(1):CD004816.

667. Reuben DB. Medical care for the final years of life: "When you're 83, it's not going to be 20 years". *JAMA*. 2009;302(24):2686-2694.

668. Ray KK, Cannon CP. Time to Benefit. *Crit Pathways Cardiol A J Evidence-Based Med*. 2005;4(1):43-45.

669. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. *JAMA*. 2014;312:1136-1144.

670• van de Glind EMM, Willems HC, Eslami S, et al. Estimating the Time to Benefit for Preventive Drugs with the Statistical Process Control Method: An Example with Alendronate. *Drugs and Aging*. 2016;33(5):347-353.

671. Braithwaite RS, Concato J, Chang CC, Roberts MS, Justice AC. A framework for tailoring clinical guidelines to comorbidity at the point of care. *Arch Intern Med*. 2007;167(21):2361-2365.

672. Braithwaite RS, Fiellin D, Justice AC. The payoff time: A flexible framework to help clinicians decide when patients with comorbid disease are not likely to benefit from practice guidelines. *Med Care*. 2009;47(6):610-617.

673• Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, Walter LC. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ*. 2013;346(January):e8441.

674. Lee SJ, Leipzig RM, Walter LC. Incorporating Lag Time to Benefit Into Prevention Decisions for Older Adults. *JAMA*. 2013;310(24):2609-10.

675. Taksler GB, Keshner M, Fagerlin A, Hajizadeh N, Braithwaite RS. Original Research Personalized Estimates of Benefit From Preventive Care Guidelines. 2013.

676. Lee SJ, Boscardin WJ, Kirby KA, Covinsky KE. Individualizing life expectancy estimates for older adults using the gompertz law of human mortality. *PLoS One*. 2014;9(9).

677. Cruz M, Covinsky K, Widera E, Stijacic-Cenzer I, Lee S. Predicting 10 year mortality for older adults. *Jama*. 2013;309(9):875-876.

678. Schonberg MA, Breslau ES, Hamel MB, Bellizzi KM, McCarthy EP. Colon cancer screening in U.S. adults aged 65 and older according to life expectancy and age. *J Am Geriatr Soc*. 2015; 63(4):750-756.

679. Tang V, Boscardin WJ, Stijacic-Cenzer I, Lee SJ. Time to benefit for colorectal cancer screening: survival meta-analysis of flexible sigmoidoscopy trials. *BMJ*. 2015;350:h1662.

680• Holmes HM, Todd A. The Role of Patient Preferences in Deprescribing. *Clin Geriatr Med*. 2017;33(2):165-175.

681. Malhotra C, Farooqui MA, Kanesvaran R, Bilger M, Finkelstein E. Comparison of preferences for end-of-life care among patients with advanced cancer and their caregivers: A discrete choice experiment. *Palliat Med*. 2015; 29(9):842-850.

682. Hamel L, Wu B, Brodie M. *Life Medical Care in Japan, Italy, the United States, and Brazil: A Cross-Country Survey*. Washington, DC: Kaiser Family Foundation; 2017.

683. Khandelwal N, Curtis JR, Freedman VA, et al. How Often Is End-of-Life Care in the United States Inconsistent with Patients' Goals of Care? *J Palliat Med*. 2017;20(12):1400-1404.

684. Teno JM, Fisher ES, Hamel MB, Coppola K, Dawson N V. Medical care inconsistent with patients' treatment goals: Association with 1-year Medicare resource use and survival. *J Am Geriatr Soc*. 2002;50(3):496-500.

685. Harris-Wehling J. Medicare Conditions of Participation and Accreditation for Hospitals. In: Lohr KN, Committee to Design a Strategy for Quality Review and Assurance in Medicare I of M, eds. *Medicare: A Strategy for Quality Assurance, Volume II: Sources and Methods (1990)*. Washington, DC: The National Academies Press; 1990:116-139.

686. Steffen G. Quality medical care. A definition. *JAMA*. 1988;260(1):56-61.

687. Teno JM, Price RA, Makaroun LK. Challenges Of Measuring Quality Of Community-Based Programs For Seriously Ill Individuals And Their Families. *Health Aff*. 2017;36(7):1227-1233.

688. Reuben DB, Tinetti ME. Goal-oriented patient care—an alternative health outcomes paradigm. *N Engl J Med*. 2012;366(9):777-779.

689. Jecker NS, Pearlman RA. Medical futility. Who decides? *Arch Intern Med*. 1992;152(6):1140-44.

690. Bayliss EA, Bonds DE, Boyd CM, et al. Understanding the context of health for persons with multiple chronic conditions: Moving from what is the matter to what matters. *Ann Fam Med*. 2014;12(3):260-269.

691• Auriemma CL, Nguyen CA, Bronheim R, et al. Stability of end-of-life preferences: A systematic review of the evidence. *JAMA Intern Med*. 2014;174(7):1085-1092.

692. Reeve E, Denig P, Hilmer SN, ter Meulen R. The Ethics of Deprescribing in Older Adults. *J Bioeth Inq*. 2016;13(4):581-590.

693. Tjia J, Givens J. Ethical Framework for Medication Discontinuation in Nursing Home Residents with Limited Life. *CGM*. 2012; 28(2):255-272.

694. Sokol DK. "First do no harm" revisited. *BMJ*. 2013;347:f6426.

695. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet*. 2017;389(10085):2239-2251.

696. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med*. 2015;175(3):356-362.

697. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: A systematic review of approaches, rates and outcomes. *Diabetes Obes Metab*. 2019;21(7):1668-1679.

698. Abdelhafiz AH, Sinclair AJ. Deintensification of hypoglycaemic medications-use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. *J Diabetes Complications*. 2018;32(4):444-450.

699. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. *JAMA Intern Med*. 2015;175(12):1942-1949.

700. Hamada S, Gulliford MC. Drug prescribing during the last year of life in very old people with diabetes. *Age Ageing*. 2017;46(1):147-151.

701. Tardy B, Picard S, Guirimand F, et al. Bleeding risk of terminally ill patients hospitalized in palliative care units: the RHESO study. *J Thromb Haemost*. 2017;15(3):420-428.

702. Noble S, Banerjee S, Pease NJ. Management of venous thromboembolism in far-advanced cancer: current practice. *BMJ Support Palliat Care*. 2019:Epub. Doi: 10.1136/bmjspcare-2019-001804

703. Noble S, Sui J. The treatment of cancer associated thrombosis: does one size fit all? Who should get LMWH/warfarin/DOACs? *Thromb Res*. 2016;140:S154-S159.

704• White C, Noble SIR, Watson M, et al. Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. *Lancet Haematol*. 2019; 6(2):e79-e88.

705• Steinman MA, Zullo AR, Lee Y, et al. Association of β -Blockers With Functional Outcomes, Death, and Rehospitalization in Older Nursing Home Residents After Acute Myocardial Infarction. 2016;94121:1-9.

706. Zullo AR, Olean M, Berry SD, Lee Y, Tjia J, Steinman MA. Patient-Important Adverse Events of β-blockers in Frail Older Adults after Acute Myocardial Infarction. *Journals Gerontol Ser A Biol Sci Med Sci*. 2019;74(8):1277-1281.

707. Tjia J, Lapane K. Guideline-Based Prescribing in Frail Elderly Patients. *JAMA Intern Med*. 2017;177(2):262.

708. Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: towards evidence-based deprescribing of drugs in older populations. *Evid Based Med*. 2013;18(4):121-4.

709. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med*. 2010;170(18):1648-1654.

710. Rodríguez-Pérez A, Alfaro-Lara ER, Albiñana-Perez S, et al. Novel tool for deprescribing in chronic patients with multimorbidity: List of Evidence-Based Deprescribing for Chronic Patients criteria. *Geriatr Gerontol Int*. 2017;17(11):2200-2207.

711. Reeve E, Thompson W, Farrell B. Deprescribing: A narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. *Eur J Intern Med*. 2017;38:3-11.

712. Gnjidic D, Couteur DGL, Hilmer SN. Discontinuing drug treatments. *BMJ*. 2014;349:g7013-g7013.

713. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. *Br J Clin Pharmacol*. 2015;80(6):1254.

714• Scott I a., Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015; 175(5):827-834.

715• Krishnaswami A, Steinman MA, Goyal P, et al. Deprescribing in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol*. 2019; 73(20):2584-2595.

716• Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: The EMPOWER cluster randomized trial. *JAMA Intern Med*. 2014;174(6):890-898.

717• Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a Pharmacist-Led Educational Intervention on Inappropriate Medication Prescriptions in Older Adults The D-PRESCRIBE Randomized Clinical Trial. *JAMA*. 2018;320(18):1889-1898.

718• Kutner JS, Blatchford PJ, Taylor DH, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness a randomized clinical trial. *JAMA Intern Med*. 2015;175(5):691-700.

719. Luymes CH, van der Kleij RMJJ, Poortvliet RKE, de Ruijter W, Reis R, Numans ME. Deprescribing Potentially Inappropriate Preventive Cardiovascular Medication: Barriers and Enablers for Patients and General Practitioners. *Ann Pharmacother*. 2016; 50(6):446-454.

720. Gnjidic D, Le Couteur DG, Kouladjian L, Hilmer SN. Deprescribing Trials: Methods to Reduce Polypharmacy and the Impact on Prescribing and Clinical Outcomes. *Clin Geriatr Med*. 2012; 28(2):237-253.

721. Page AT, Potter K, Clifford R, Etherton-Beer C. Deprescribing in older people. *Maturitas*. 2016; 91:115-134.

722. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in Frail Older People: A randomised controlled trial. *PLoS One*. 2016; 11(3):1-21.

723. Parsons C. Withdrawal of Antidementia Drugs in Older People: Who, When and How? *Drugs and Aging*. 2016;33(8):545-556.

724. Howard R, McShane R, Lindesay J, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: Secondary and post-hoc analyses. *Lancet Neurol*. 2015; 14(12):1171-1181.

725. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;6736(17).

726. Kimbell B, Murray SA, MacPherson S, Boyd K. Embracing inherent uncertainty in advanced illness. *BMJ*. 2016;354(613):i3802.

727. Viganò A, Dorgan M, Buckingham J, Bruera E, Suarez-Almazor ME. Survival prediction in terminal cancer patients: a systematic review of the medical literature. *Palliat Med*. 2000; 14(5):363-374.

728. Mackillop WJ, Quirt CF. Measuring the accuracy of prognostic judgments in oncology. *J Clin Epidemiol*. 1997;50(1):21-29.

729. Chow E, Harth T, Hruby G, Finkelstein J, Wu J, Danjoux C. How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally III cancer patients? A systematic review. *Clin Oncol*. 2001;13(3):209-218.

730. Gwilliam B, Keeley V, Todd C, et al. Prognosticating in patients with advanced cancer--observational study comparing the accuracy of clinicians' and patients' estimates of survival. *Ann Oncol*. 2013;24(2):482-488.

731• Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ*. 2003; 327(7408):195-198.

732. Glare P, Sinclair C, Downing M, Stone P, Maltoni M, Vigano A. Predicting survival in patients with advanced disease. *Eur J Cancer*. 2008;44(8):1146-1156.

733. White N, Reid F, Harris A, Harries P, Stone P. A systematic review of predictions of survival in palliative care: How accurate are clinicians and who are the experts? *PLoS One*. 2016;11(8).

734. Hole B, Salem J. How long do patients with chronic disease expect to live? A systematic review of the literature. *BMJ Open*. 2016; 6(12):e012248.

735. Moss AH, Ganjoo J, Sharma S, et al. Utility of the "Surprise" question to identify dialysis patients with high mortality. *Clin J Am Soc Nephrol*. 2008; 3(5):1379-1384.

736. Gibbins J, Bloor S, Reid C, Burcombe M, McCoubrie R, Forbes K. The use of a modified 'surprise' question to identify and recruit dying patients into a research project in an acute hospital setting. *BMJ Support Palliat Care*. 2012; 2(Suppl 1):A8.2-A8.

737. Murray S, Boyd K. Using the "surprise question" can identify people with advanced heart failure and COPD who would benefit from a palliative care approach. *Palliat Med*. 2011;25(4):382.

738. Downar J, Goldman R, Pinto R, Englesakis M, Adhikari NKJ. The "surprise question" for predicting death in seriously ill patients: a systematic review and meta-analysis. *Can Med Assoc J*. 2017;189(13):E484-E493.

739. White N, Kupeli N, Vickerstaff V, Stone P. How accurate is the 'Surprise Question' at identifying patients at the end of life? A systematic review and meta-analysis. *BMC Med*. 2017;15(1):139.

740• Yourman LC, Lee SJ, Schonberg M a, Widera EW, Smith AK. Prognostic Indices for Older Adults: A Systematic Review. *JAMA*. 2012; 307(2):182-192.

741. Han PKJ, Lee M, Reeve BB, et al. Development of a prognostic model for six-month mortality in older adults with declining health. *J Pain Symptom Manage*. 2012;43(3):527-539.

742. Schonberg MA, Li V, Marcantonio ER, Davis RB, McCarthy EP. Predicting Mortality up to 14 Years Among Community-Dwelling Adults Aged 65 and Older. *J Am Geriatr Soc*. 2017; 65(6):1310-1315.

743. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA*. 2006;295(7):801-808.

744. Levy C, Kheirbek R, Alemi F, et al. Predictors of six-month mortality among nursing home residents: Diagnoses may be more predictive than functional disability. *J Palliat Med*. 2015;18(2):100-106.

745. Brown MA, Sampson EL, Jones L, Barron AM. Prognostic indicators of 6-month mortality in elderly people with advanced dementia: A systematic review. *Palliat Med*. 2013;27(5):389.

746. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA*. 2004;291(22):2734-2740.

747. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med*. 2009;361(16):1529-1538.

748. Lee M, Chodosh J. Dementia and Life Expectancy: What Do We Know? *J Am Med Dir Assoc*. 2009;10(7):466-471.

749. Van Riet Paap J, Mariani E, Chattat R, et al. Identification of the palliative phase in people with dementia: a variety of opinions between healthcare professionals. *BMC Palliat Care*. 2015;14(1):1-6.

750. Mitchell SL, Miller SC, Teno JM, Davis RB, Shaffer ML. The Advanced Dementia Prognostic Tool: A Risk Score to Estimate Survival in Nursing Home Residents with Advanced Dementia. *J Pain Symptom Manage*. 2010;40(5):639-651.

751• Mitchell SL, Miller SC, Teno JM, Kiely DK, Davis RB, Shaffer ML. Prediction of 6-Month Survival of Nursing Home Residents With Advanced Dementia Using ADEPT vs Hospice Eligibility Guidelines. *JAMA*. 2010;304(17):1929.

752. Drazen JM, Yialamas MA. Certain about Dying with Uncertainty. *N Engl J Med*. 2017; 377(3):208-209.

753. Ridley S, Fisher M. Uncertainty in end-of-life care. *Curr Opin Crit Care*. 2013;19(6):642-647.

754• Fried TR. Shared Decision Making — Finding the Sweet Spot. *N Engl J Med*. 2016;374(2):104.

755. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. *BMJ*. 2016; 353(June):1-6.

756. Todd A, Holmes H, Pearson S, et al. 'I don't think I'd be frightened if the statins went': a phenomenological qualitative study exploring medicines use in palliative care patients, carers and healthcare professionals. *BMC Palliat Care*. 2016;15(1):13.

757. Ailabouni NJ, Nishtala PS, Mangin D, Tordoff JM. Challenges and Enablers of Deprescribing: A General Practitioner Perspective. *PLoS One*. 2016;11(4):e0151066.

758. van Soest-Poortvliet MC, van der Steen JT, de Vet HCW, Hertogh CMPM, Onwuteaka-Philipsen BD, Deliens LHJ. Factors Related to Establishing a Comfort Care Goal in Nursing Home Patients with Dementia: A Cohort Study among Family and Professional Caregivers. *J Palliat Med*. 2014;17(12):1317-1327.

759• Bernacki RE, Block SD. Communication about serious illness care goals: A review and synthesis of best practices. *JAMA Intern Med*. 2014;174(12):1994-2003.

760. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA*. 2000;284(19):2476-2482.

761. Casarett D, Crowley R, Stevenson C, Xie S, Teno J. Making difficult decisions about hospice enrollment: What do patients and families want to know? *J Am Geriatr Soc*. 2005;53(2):249.

762. Trice ED, Prigerson HG. Communication in End-Stage Cancer: Review of the Literature and Future Research. *J Health Commun*. 2009;14(sup1):95-108.

763. Bynum JPW, Barre L, Reed C, Passow H. Participation of Very Old Adults in Health Care Decisions. *Med Decis Mak*. 2014;34(2):216-230.

764. Brodie LHBWM. *Views and Experiences with End-of-Life Medical Care in Japan , Italy , the United States , and Brazil : Across-Country Survey*. Vol 1. Washington, DC: Kaiser Family Foundation; 2017.

765. Clayton JM, Butow PN, Tattersall MHN. The needs of terminally ill cancer patients versus those of caregivers for information regarding prognosis and end-of-life issues. *Cancer*. 2005;103(9):1957-1964.

766. Fallowfield LJ, Jenkins V a, Beveridge H a. Truth may hurt but deceit hurts more: communication in palliative care. *Palliat Med*. 2002;16(4):297-303.

767. Hagerty RG, Butow PN, Ellis PM, et al. Communicating with realism and hope: Incurable cancer patients' views on the disclosure of prognosis. *J Clin Oncol*. 2005;23(6):1278-1288.

768. Hancock K, Clayton JM, Parker SM, et al. Truth-telling in discussing prognosis in advanced life-limiting illnesses: A systematic review. *Palliat Med*. 2007;21(6):507-517.

769. Wright A a, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*. 2008;300(14):1665-1673.

770. Gattellari M, Voigt KJ, Butow PN, Tattersall MHN. When the treatment goal is not cure: Are cancer patients equipped to make informed decisions? *J Clin Oncol*. 2002;20(2):503-513.

771. Emanuel EJ, Fairclough DL, Wolfe P, Emanuel LL. Talking with terminally ill patients and their caregivers about death, dying, and bereavement: Is it stressful? Is it helpful? *Arch Intern Med*. 2004;164(18):1999-2004.

772. Pollard S, Bansback N, Bryan S. Patient Education and Counseling Physician attitudes toward shared decision making : A systematic review. *Patient Educ Couns*. 2015;98(9):1046-1057.

773. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Ann Intern Med*. 2001;134(12):1096-105.

774. Costantini M, Morasso G, Montella M, et al. Diagnosis and prognosis disclosure among cancer patients. Results from an Italian mortality follow-back survey. *Ann Oncol*. 2006; 17(5):853-859.

775. Parker SM, Clayton JM, Hancock K, et al. A Systematic Review of Prognostic/End-of-Life Communication with Adults in the Advanced Stages of a Life-Limiting Illness: Patient/ Caregiver Preferences for the Content, Style, and Timing of Information. *J Pain Symptom Manage*. 2007;34(1):81-93.

776• Schoenborn NL, Bowman TL, Cayea D, Pollack CE, Feeser S, Boyd C. Primary care practitioners' views on incorporating long-term prognosis in the care of older adults. *JAMA Intern Med*. 2016;176(5):671-678.

777. Sharp T, Moran E, Kuhn I, Barclay S. Do the elderly have a voice? Advance care planning discussions with frail and older individuals: a systematic literature review and narrative synthesis. *Br J Gen Pract*. 2013;63(615):e657-68.

778. Kale MS, Ornstein KA, Smith CB, Kelley AS. End-of-Life Discussions with Older Adults. *J Am Geriatr Soc*. 2016;64(10):1962-1967.

779. Abarshi E, Echteld M, Donker G, Van den Block L, Onwuteaka-Philipsen B, Deliens L. Discussing End-of-Life Issues in the Last Months of Life: A Nationwide Study among General Practitioners. *J Palliat Med*. 2011; 14(3):323-330.

780. Evans N, Costantini M, Pasman HR, et al. End-of-life communication: A retrospective survey of representative general practitioner networks in four countries. *J Pain Symptom Manage*. 2014;47(3):604-619.

781. Houben CHM, Spruit MA, Schols JMGA, Wouters EFM, Janssen DJA. Patient-Clinician communication about end-of-life care in patients with advanced chronic organ failure during one year. *J Pain Symptom Manage*. 2015;49(6):1109-1115.

782. Reinke LF, Slatore CG, Uman J, et al. Patient–Clinician Communication about End-of-Life Care Topics: Is Anyone Talking to Patients with Chronic Obstructive Pulmonary Disease? *J Palliat Med*. 2011;14(8):923-928.

783. Heyland DK, Dodek P, You JJ, et al. Validation of quality indicators for end-of-life communication: results of a multicentre survey. *CMAJ*. 2017;189(30):E980-E989.

784• Mack JW, Cronin A, Taback N, et al. End-of-Life Care Discussions Among Patients With Advanced Cancer. *Ann Intern Med*. 2012; 156(3):204-210.

785. Vicens C, Fiol F, Llobera J, et al. Withdrawal from long-term benzodiazepine use: Randomised trial in family practice. *Br J Gen Pract*. 2006;56(533):958-963.

786. Morin L, Johnell K, Van Den Block L, Aubry R. Discussing End-Of-Life issues in nursing homes: A nationwide study in France. *Age Ageing*. 2016;45(3):353-360.

787. Gjerberg E, Lillemoen L, Forde R, Pedersen R. End-of-life care communications and shared decision-making in Norwegian nursing homes - Experiences and perspectives of patients and relatives. *BMC Geriatr*. 2015;15(1):103.

788• Weeks JC, Catalano PJ, Cronin A, et al. Patients' Expectations about Effects of Chemotherapy for Advanced Cancer. *N Engl J Med*. 2012;367(17):1616-1625.

789. Chen CH, Kuo SC, Tang ST. Current status of accurate prognostic awareness in advanced/terminally ill cancer patients: a systematic review and meta-regression analysis. *Palliat Med*. 2017;31(5):406-418.

790. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: A prospective cohort study. *J Clin Oncol*. 2012;30(35):4387-4395.

791• Curtis JR, Downey L, Back AL, et al. Effect of a patient and clinician communication-priming intervention on patient-reported goals-of-care discussions between patients with serious illness and clinicians: A randomized clinical trial. *JAMA Intern Med*. 2018;178(7):930-940.

792. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: Predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol*. 2010; 28(7):1203-1208.

793. Ahluwalia SC, Tisnado DM, Walling AM, et al. Association of Early Patient-Physician Care Planning Discussions and End-of-Life Care Intensity in Advanced Cancer. *J Palliat Med*. 2015;18(10):834-841.

794. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA*. 1998;279(21):1709-1714.

795. Liu P-H, Landrum M, Weeks J, et al. Physicians' Propensity To Discuss Prognosis Is Associated with Patients' Awareness of Prognosis for Metastatic Cancers. *J Palliat Med*. 2014; 17(6):673-682.

796. Epstein AS, Prigerson HG, OReilly EM, Maciejewski PK. Discussions of Life Expectancy and Changes in Illness Understanding in Patients With Advanced Cancer. *J Clin Oncol*. 2016;34(20):2398-2403.

797. Enzinger AC, Zhang B, Schrag D, Prigerson HG. Outcomes of prognostic disclosure: Associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer. *J Clin Oncol*. 2015;33(32):3809-3816.

798. Heyland DK, Barwich D, Pichora D, et al. Failure to engage hospitalized elderly patients and their families in advance care planning. *JAMA Intern Med*. 2013;173(9):778-787.

799. Winkler EC, Reiter-Theil S, Lange-Rieß D, Schmahl-Menges N, Hiddemann W. Patient involvement in decisions to limit treatment: The crucial role of agreement between physician and patient. *J Clin Oncol*. 2009;27(13):2225-2230.

800. You JJ, Dodek P, Lamontagne F, et al. What really matters in end-of-life discussions? Perspectives of patients in hospital with serious illness and their families. *Can Med Assoc J*. 2014;186(18):E679-E687.

801. Back AL, Young JP, McCown E, et al. Abandonment at the end of life from patient, caregiver, nurse, and physician perspectives: loss of continuity and lack of closure. *Arch Intern Med*. 2009;169(5):474-479.

802. Gawande A. Quantity and quality of life: Duties of care in life-limiting illness. *JAMA*. 2016;315(3):267-269.

803. Arnold RL, Egan K. Breaking the "bad" news to patients and families: preparing to have the conversation about end-of-life and hospice care. *Am J Geriatr Cardiol*. 2004;13(6):307-312.

804. Meier DE. "I don't want Jenny to think I'm abandoning her": Views on overtreatment. *Health Aff*. 2014;34(5):895-898.

805. Gordon EJ, Daugherty CK. "Hitting you over the head": oncologists' disclosure of prognosis to advanced cancer patients. *Bioethics*. 2003;17(2):142-168.

806. Panagopoulou E, Mintziori G, Montgomery A, Kapoukranidou D, Benos A. Concealment of information in clinical practice: is lying less stressful than telling the truth? *J Clin Oncol*. 2008;26(7):1175-1177.

807. Bluhm M, Connell CM, De Vries RG, Janz NK, Bickel KE, Silveira MJ. Paradox of Prescribing Late Chemotherapy: Oncologists Explain. *J Oncol Pract*. 2016;12(12):e1006-e1015.

808. You JJ, Downar J, Fowler RA, et al. Barriers to goals of care discussions with seriously ill hospitalized patients and their families: A multicenter survey of clinicians. *JAMA Intern Med*. 2015;175(4):549-556.

809. Prod'homme C, Jacquemin D, Touzet L, Aubry R, Daneault S, Knoops L. Barriers to end-of-life discussions among hematologists: A qualitative study. *Palliat Med*. 2018;32(5):1021.

810. Ethier J, Paramsothy T, You JJ, Fowler R, Gandhi S. Perceived Barriers to Goals of Care Discussions With Patients With Advanced Cancer and Their Families in the Ambulatory Setting : A Multicenter Survey of Oncologists. 2018; *J Palliat Care.* 33(3):125-142.

811• Fulmer T, Escobedo M, Berman A, Koren MJ, Hernández S, Hult A. Physicians' Views on Advance Care Planning and End-of-Life Care Conversations. *J Am Geriatr Soc*. 2018; 66(6):1201-1205.

812. Centers for Medicare & Medicaid Services. *Since 1 January 2016, CMS Pays for Advance Care Planning under the Medicare Physician Fee Schedule (PFS) and the Hospital Outpatient Prospective Payment System (OPPS). CPT Codes 99497 and 99498*.; 2016.

813. Belanger E, Loomer L, Teno JM, Mitchell SL, Adhikari D, Gozalo PL. Early Utilization Patterns of the New Medicare Procedure Codes for Advance Care Planning. *JAMA Intern Med*. 2019;179(6):829.

814. Pelland K, Morphis B, Harris D, Gardner R. Assessment of First-Year Use of Medicare's Advance Care Planning Billing Codes. *JAMA Intern Med*. 2019;179(6):827.

815• Temel JS, Shaw AT, Greer JA. Challenge of prognostic uncertainty in the modern era of cancer therapeutics. *J Clin Oncol*. 2016; 34(30):3605-3608.

816. Myers J. Improving the quality of end-of-life discussions. *Curr Opin Support Palliat Care*. 2015;9(1):72-76.

817. Clayton JM, Butow PN, Tattersall MHN. When and how to initiate discussion about prognosis and end-of-life issues with terminally ill patients. *J Pain Symptom Manage*. 2005; 30(2):132-144.

818. Mitchell S, Loew J, Dale J, Millington-Sanders C. Providing end-of-life care in general practice: Findings of a national GP questionnaire survey. *Br J Gen Pract*. 2016;66(650):e647-e653.

819. Smith TJ, Dow LA, Virago E, Khatcheressian J, Lyckholm LJ, Matsuyama R. Giving honest information to patients with advanced cancer maintains hope. *Oncology*. 2010;24(6):521-525.

820. Clayton JM, Hancock K, Parker S, et al. Sustaining hope when communicating with terminally ill patients and their families: A systematic review. *Psychooncology*. 2008; 17(7):641-659.

821. Wenrich MD, Curtis JR, Shannon SE, Carline JD, Ambrozy DM, Ramsey PG. Communicating with dying patients within the spectrum of medical care from terminal diagnosis to death. *Arch Intern Med*. 2001;161(6):868-874.

822• Buiting HM, Rurup ML, Wijsbek H, van Zuylen L, den Hartogh G. Understanding provision of chemotherapy to patients with end stage cancer: qualitative interview study. *BMJ*. 2011;342(1):d1933.

823. Beaussant Y, Mathieu-Nicot F, Pazart L, et al. Is shared decision-making vanishing at the end-of-life? A descriptive and qualitative study of advanced cancer patient's involvement in specific therapies decision-making Cancer palliative care. *BMC Palliat Care*. 2015;14(1):61.
824. Salisbury H. The perils of deprescribing. *BMJ*. 2019;364:I666.
825. Laryionava K, Heußner P, Hiddemann W, Winkler EC. Framework for timing of the discussion about forgoing cancer-specific treatment based on a qualitative study with oncologists. *Support Care Cancer*. 2014;13(2):117-126.
826. Casarett DJ, Quill TE. "I'm not ready for hospice": strategies for timely and effective hospice discussions. *Ann Intern Med*. 2007;146(6):443-449.
827. Drought TS, Koenig BA. "Choice" in end-of-life decision making: researching fact or fiction? *Gerontologist*. 2002;42(S3):114-128.
828. Quill TE. Initiating End-of-Life Discussions With Seriously Ill Patients. *JAMA*. 2000;284(19):2502.
829. Maskrey N, Gordon A. Shared understanding with patients. *JAMA Intern Med*. 2017; 177(9):1247-1248.
830. Slort W, Blankenstein AH, Wanrooij BS, van der Horst HE, Deliens L. The ACA training programme to improve communication between general practitioners and their palliative care patients: development and applicability. *BMC Palliat Care*. 2012;11(1):9.
831. Walker S, Gibbins J, Barclay S, et al. Progress and divergence in palliative care education for medical students: A comparative survey of UK course structure, content, delivery, contact with patients and assessment of learning. *Palliat Med*. 2016;30(9):834-842.
832. Barclay S, Whyte R, Thiemann P, et al. An important but stressful part of their future work: Medical students' attitudes to palliative care throughout their course. *J Pain Symptom Manage*. 2015;49(2):231-242.
833. Oczkowski SJ, Chung H-O, Hanvey L, Mbuagbaw L, You JJ. Communication Tools for End-of-Life Decision-Making in Ambulatory Care Settings: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;11(4):e0150671.
834. Volandes AE. *The Conversation : A Revolutionary Plan for End-of-Life Care*. New York, NY: Bloomsbury U.S.; 2015.
835. Blumenthal-Barby JS, Krieger H. Cognitive Biases and Heuristics in Medical Decision Making. *Med Decis Mak*. 2015;35(4):539-557.
836• Casarett D. The Science of Choosing Wisely: Overcoming the Therapeutic Illusion. *N Engl J Med*. 2016;374(13):1203-1205.
837. Langer E. The illusion of control. *J Pers Soc Psychol*. 1975;32(2):311-328.
838. Presson PK, Benassi VA. Illusion of control: A meta-analytic review. *J Soc Behav Personal*. 1996;11(3):493-510.
839. McKenna FP. It won't happen to me: Unrealistic optimism or illusion of control? *Br J Psychol*. 1993;84(1):39-50.
840• Scott IA, Soon J, Elshaug AG, Lindner R. Countering cognitive biases in minimising low value care. *Med J Aust*. 2017;206(9):407-411.
841. Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: A systematic review. *JAMA Intern Med*. 2017;177(3):407-419.
842. Hoffmann TC, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med*. 2015;175(2):274-286.
843. Klein JG. Five pitfalls in decisions about diagnosis and prescribing. *BMJ*. 2005;330(7494):781-783.
844. Ayanian JZ, Berwick DM. Do physicians have a bias toward action? A classic study revisited. *Med Decis Making*. 1991;11(3):154-158.
845. Tsalatsanis A, Hozo I, Djulbegovic B. Acceptable regret model in the end-of-life setting: Patients require high level of certainty before forgoing management recommendations. *Eur J Cancer*. 2017;75:159.
846. Langer CJ. The "Lazarus response" in treatment-naive, poor performance status patients with non-small-cell lung cancer and epidermal growth factor receptor mutation. *J Clin Oncol*. 2009;27(9):1350-1354.
847. Braga S. Why do our patients get chemotherapy until the end of life? *Ann Oncol*. 2011;22(11):2345-2348.
848. Engelhardt EG, Pieterse AH, van der Hout A, et al. Use of implicit persuasion in decision making about adjuvant cancer treatment: A potential barrier to shared decision making. *Eur J Cancer*. 2016;66:55-66.
849. Ericson KMM, Fuster A. The Endowment Effect. *Annu Rev Econom*. 2014;6:555-579.
850. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: A systematic review. *Drugs and Aging*. 2013;30(10):793-807.

851. Farrell B, Pottie K, Rojas-Fernandez CH, Bjerre LM, Thompson W, Welch V. Methodology for developing deprescribing guidelines: Using evidence and GRADE to guide recommendations for deprescribing. *PLoS One*. 2016;11(8):1-12.

852. Bush SH, Kanji S, Pereira JL, et al. Treating an established episode of delirium in palliative care: Expert opinion and review of the current evidence base with recommendations for future development. *J Pain Symptom Manage*. 2014;48(2):231-248.

853. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: A randomized clinical trial. *JAMA Intern Med*. 2017;177(1):34-42.

854• Paque K, Vander Stichele R, Elseviers M, et al. Barriers and enablers to deprescribing in people with a life-limiting disease: A systematic review. *Palliat Med*. 2019;33(1):37-48.

855. Gonçalves F. Deprescription in Advanced Cancer Patients. *Pharmacy*. 2018;6(3):88.

856. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: A systematic review and thematic synthesis. *BMJ Open*. 2014;4(12).

857. Onder G, Nobili A, Marengoni A. Potentially Inappropriate Drug Prescribing and the "Never Change a Winning Team" Principle. *Journals Gerontol Ser A Biol Sci Med Sci*. 2016;71(11):1531-1532.

858. Irving G, Neves AL, Dambha-Miller H, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open*. 2017;7(10):e017902.

859. Lee W-C, Sumaya C V. Geriatric Workforce Capacity: A Pending Crisis for Nursing Home Residents. *Front Public Heal*. 2013;1(24):1-7.

860. U.S. Department of Health and Human Services. National and Regional Projections of Supply and Demand for Geriatricians: 2013-2025. *Natl Cent Heal Work Anal*. 2017;(April).

861. Bach PB, Schrag D, Begg CB. Resurrecting Treatment Histories of Dead Patients. A Study Design That Should Be Laid to Rest. *JAMA*. 2004;292(22):2765-2770.

862. Barnato AE, Cohen ED, Mistovich KA, Chang CCH. Hospital end-of-life treatment intensity among cancer and non-cancer cohorts. *J Pain Symptom Manage*. 2015;49(3):521-529.e5.

863. Cepeda MS, Fife D, Denarié M, Bradford D, Roy S, Yuan Y. Quantification of missing prescriptions in commercial claims databases: results of a cohort study. *Pharmacoepidemiol Drug Saf*. 2017;26(4):386-392.

864. Pottegård A, Hallas J. Assigning exposure duration to single prescriptions by use of the waiting time distribution. *Pharmacoepidemiol Drug Saf*. 2013;22(8):803-809.

865. Støvring H, Pottegård A, Hallas J. Determining prescription durations based on the parametric waiting time distribution. *Pharmacoepidemiol Drug Saf*. 2016;25(12)1451.

866. Støvring H, Pottegård A, Hallas J. Refining estimates of prescription durations by using observed covariates in pharmaco-epidemiological databases: an application of the reverse waiting time distribution. *Pharmacoepidemiol Drug Saf*. 2017;26(8):900-8.

867. Laugesen K, Sørensen HT, Petersen I, et al. Prescription duration and treatment episodes in oral glucocorticoid users: Application of the parametric waiting time distribution. *Clin Epidemiol*. 2017;9:591-600.

868. Tanskanen A, Taipale H, Koponen M, et al. From prescription drug purchases to drug use periods: a second generation method (PRE2DUP). *BMC Med Inform Decis Mak*. 2015;15(1):21.

869. Pottegård A, Christensen RD, Houji A, et al. Primary non-adherence in general practice: A Danish register study. *Eur J Clin Pharmacol*. 2014;70(6):757-763.

870. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: Analysis of 195,930 electronic prescriptions. *J Gen Intern Med*. 2010;25(4):284-290.

871. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005;58(4):323-337.

872. McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review. *Pharmacoepidemiol Drug Saf*. 2019;(July 2018):1-12.

873. Wilkinson T, Ly A, Schnier C, Rannikm K, Bush K. Identifying dementia cases with routinely collected health data : A systematic review. 2018;14:1038-1051.

874. Rizzuto D, Feldman AL, Karlsson IK, Dahl Aslan AK, Gatz M, Pedersen NL. Detection of dementia cases in two swedish health registers: A validation study. *J Alzheimer's Dis*. 2018;61(4):1301-1310.

875. Lunney JR, Albert SM, Boudreau R, Ives D, Newman AB, Harris T. Fluctuating Physical Function and Health: Their Role at the End of Life. *J Palliat Med*. 2019;22(4):424-426.

876. Gott M, Barnes S, Parker C, et al. Dying trajectories in heart failure. *Palliat Med*. 2007;21(2):95-99.

877. Eagar K, Watters P, Currow DC, Aoun SM, Yates P. The Australian Palliative Care Outcomes Collaboration (PCOC)--measuring the quality and outcomes of palliative care on a routine basis. *Aust Health Rev*. 2010;34(2):186-192.

878. Cronin KA, Lake AJ, Scott S, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. *Cancer*. 2018;124(13):2785-2800.

879. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023-1075.

880. Krok-Schoen JL, Fisher JL, Stephens JA, et al. Incidence and survival of hematological cancers among adults ages ≥75 years. *Cancer Med*. 2018;7(7):3425-3433.

881. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2012.

882. Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing Study Results. *Epidemiology*. 2017;28(4):553-561.

883. Bareinboim E, Pearl J. Causal inference and the data-fusion problem. *Proc Natl Acad Sci*. 2016;113(27):7345-7352.

884. Curtin D, O'Mahony D, Gallagher P. Drug consumption and futile medication prescribing in the last year of life: An observational study. *Age Ageing*. 2018; 47(5):749-753.

885. Roux B, Morin L, Papon A, Laroche M-L. Prescription and deprescription of medications for older adults receiving palliative care during the last 3 months of life: a single-center retrospective cohort study. *Eur Geriatr Med*. 2019;10(3):463-471.

886. Paque K, De Schreye R, Elseviers M, et al. Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. *Br J Clin Pharmacol*. 2019;85(4):827-837.

887. Narayan SW, Nishtala PS. Population-based study examining the utilization of preventive medicines by older people in the last year of life. *Geriatr Gerontol Int*. 2018;18(6):892-898.

888. Poudel A, Berry R, McCarthy A, Walpole E, Yates P, Nissen L. Medication use in older, terminally ill cancer patients: Are all medications appropriate? A longitudinal audit. *Palliat Med*. 2019. Epub

889. Heppenstall CP, Broad JB, Boyd M, et al. Medication use and potentially inappropriate medications in those with limited prognosis living in residential aged care. *Australas J Ageing*. 2016;35(2):E18-E24.

890. van der Meer HG, Taxis K, Pont LG. Changes in prescribing symptomatic and preventive medications in the last year of life in older nursing home residents. *Front Pharmacol*. 2018;8(January):1-7.

891. Todd A, Al-Khafaji J, Akhter N, et al. Missed opportunities: unnecessary medicine use in patients with lung cancer at the end of life - an international cohort study. *Br J Clin Pharmacol*. 2018;84(12):2802-2810.

892. Zueger PM, Holmes HM, Calip GS, Qato DM, Pickard AS, Lee TA. Medicare Part D Use of Older Medicare Beneficiaries Admitted to Hospice. *J Am Geriatr Soc*. 2018;66(5):937-944.

893. Zueger PM, Holmes HM, Calip GS, Qato DM, Pickard AS, Lee TA. Older Medicare Beneficiaries Frequently Continue Medications with Limited Benefit Following Hospice Admission. *J Gen Intern Med*. July 2019.

894. Hernán MA, Robin JM. *Causal Inference*. Boca Raton: Chapman & Hall/CRC (upcoming); 2019.

895. Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted Analyses in Studies Addressing Therapy and Harm: Users' Guides to the Medical Literature. *JAMA*. 2017;317(7):748-759.

896• Hernán MA, Hsu J, Healy B. A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. *CHANCE*. 2019;32(1):42.

897. Shi SM, Kim DH. The challenges of using the Hospital Frailty Risk Score. *Lancet*. 2018;392(10165):2692.

898. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf*. 2007;16(4):393.

899. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

900. Murray SA, Kendall M, Boyd K, Grant L, Highet G, Sheikh A. Archetypal trajectories of social, psychological, and spiritual wellbeing and distress in family care givers of patients with lung cancer. *BMJ*. 2010;340:c2581.

901. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: Propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ*. 2013;347:f6409.

902. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. *JAMA*. 2016;316(17):1818-1819.

903. Emilsson L, García-Albéniz X, Logan RW, Caniglia EC, Kalager M, Hernán MA. Examining bias in studies of statin treatment and survival in patients with cancer. *JAMA Oncol*. 2018;4(1):63-70.

904. Tannen RL, Weiner MG, Xie D. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: Comparison of database and randomised controlled trial findings. *BMJ*. 2009;338(7691):395-399.

905. Tannen R, Yu M. A new method to address unmeasured confounding of mortality in observational studies. *Learn Heal Syst*. 2016; 1(1):e10016.

906. Uddin MJ, Groenwold RHH, van Staa TP, et al. Performance of prior event rate ratio adjustment method in pharmaco-epidemiology. *Pharmacoepidemiol Drug Saf*. 2015;24(5):468-477.

907. Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. *BMJ*. 2016;355:i5813.

908. Suissa S. The case-time-control design. *Epidemiology*. 1995;6(3):248-253.

909. Schneeweiss S, Stürmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiol Drug Saf*. 1997; 6(Suppl 3):S51-9.

910. Sjölander A. The Case-time-control Method for Nonbinary Exposures. *Sociol Methodol*. 2017;47(1):182-211.

911. Moonen JEF, Foster-Dingley JC, Ce Ruijter W, et al. Effect of discontinuation of anti-hypertensive treatment in elderly people on cognitive functioning-the DANTE Study Leiden: A randomized clinical trial. *JAMA Intern Med*. 2015;175(10):1622-1630.

912• Luymes CH, Poortvliet RKE, van Geloven N, et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice — the ECSTATIC study: A cluster randomised non-inferiority trial. *BMC Med*. 2018;16(5):1-14.

913. Abduh Al-Shaqi M, Alami AH, Zahrani ASA-, Al-Marshad B, Muammar AB-, MZ A-S. The Pattern of Antimicrobial Use for Palliative Care In-Patients During the Last Week of Life. *Am J Hosp Palliat Med*. 2012;29(1):60-63.

914. Bayliss EA, Bronsert MR, Reifler LM, et al. Statin Prescribing Patterns in a Cohort of Cancer Patients with Poor Prognosis. *J Palliat Med*. 2013;16(4):412-418.

915. Kierner KA, Weixler D, Masel EK, Gartner V, Watzke HH. Polypharmacy in the terminal stage of cancer. *Support Care Cancer*. 2016;24(5):2067-2074.

916. Kwok AO, Yuen S -k., Yong DS, Tse DM. The Symptoms Prevalence, Medical Interventions, and Health Care Service Needs for Patients With End-Stage Renal Disease in a Renal Palliative Care Program. *Am J Hosp Palliat Med*. 2016;33(10):952-958.

917. McNeil MJ, Kamal AH, Kutner JS, Ritchie CS, Abernethy AP. The Burden of Polypharmacy in Patients Near the End of Life. *J Pain Symptom Manage*. 2016;51(2):178-183.e2.

918. Mullvain JA, Kozak KR, Moody JS, Campbell TC. Statin use in cancer patients with brain metastases: a missed communication opportunity at the end of life. *Support Care Cancer*. 2015;23(9):2643-2648.

919. Nauck F, Ostgathe C, Klaschik E, et al. Drugs in palliative care: results from a representative survey in Germany. *Palliat Med*. 2004; 18(2):100-107.

920. Sevilla-Sanchez D, Molist-Brunet N, Amblàs-Novellas J, Roura-Poch P, Espaulella-Panicot J, Codina-Jané C. Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. *Eur J Clin Pharmacol*. 2017;73(1):79.

921. Silveira MJ, Kazanis AS, Shevrin MP. Statins in the Last Six Months of Life: A Recognizable, Life-Limiting Condition Does Not Decrease their Use. *J Palliat Med*. 2008;11(5):685-693.

922. Van Den Noortgate NJ, Verhofstede R, Cohen J, Piers RD, Deliens L, Smets T. Prescription and Deprescription of Medication during the Last 48 Hours of Life: Multicenter Study in 23 Acute Geriatric Wards in Flanders, Belgium. *J Pain Symptom Manage*. 2016;51(6):1020-1026.

LIST OF TABLES AND FIGURES

LIST OF TABLES

LIST OF FIGURES

APPENDIX

Appendix Table. Summary of studies included in the scoping review

Please note that studies published after March 31, 2016 are indicated with an asterisk (*)

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
1.	Agar, 2009[579]	Australia	Cluster randomized controlled trial (secondary analysis)	Palliative patients (91% cancer) with pain who died during follow-up	304	71 (12)	Anticholinergic load rose as death approached, fueled mostly by the increasing use of medications for symptom management (e.g. oxycodone, morphine, fentanyl, dexamethasone, temazepam, clonazepam, butyl-scopolamine). Some medications for comorbid diseases also contributed to the anticholinergic load (e.g. furosemide, prednisolone, warfarin, digoxin). Increased anticholinergic load was associated with worse functional status and quality of life, and with enhanced symptoms (e.g. dry mouth).
2.	Al-Shaqi, 2012[913]	Saudi Arabia	Retrospective cohort, single-center	Terminally ill cancer patients who died in a palliative care unit	138	Median 50	63% of patients had ≥1 antimicrobial during their last week of life (including 46% antibiotics). Antimicrobials were mostly given systemically (79%, including 42% parenteral) rather than topically (21%). Most common antibiotics were metronidazole (J01XD01), ceftriaxone (J01DD04) and penicillin (J01C).
3.	Barcelo, 2014[560]	Spain	Retrospective cohort, single-center	Older patients with stage III–IV heart failure and limited life expectancy who died in acute geriatric ward	72	85 (12)	Mean Charlson index score 3.2. At admission, patients were prescribed an average of 8.6 drugs (SD 2.9), and 94.4 % of patients received five or more drugs. 85% of patients received at least one drug that was not for symptom management. Diltiazem or verapamil were prescribed to 10% of patients, which is considered inappropriate in patients with stage III-IV CHF. Other commonly prescribed drugs included loop diuretics (90%), aspirin or clopidogrel (50%), ACE/ARB (40%), oral anticoagulants (24%), iron supplement (26%), statins (19%), potassium-sparing agents (18%), beta-blockers (11%), antiosteoporotics (12%). Psychotropic drugs included antidepressants (33%, incl. 28% SSRIs), benzodiazepines (37%), and analgesics (22%, incl. 11% opioids).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
4.	Bayliss, 2013[914]	United States	Retrospective cohort, single-center	Patients receiving statins at time of cancer diagnosis who died during the observation period	496	Median 72	All patients had a low 5-year survival probability at time of diagnosis. Statins were prescribed for secondary prevention of pre-cancer conditions (64%, median survival time 131 days), or for primary prevention (36%, median survival time 231 days). 60% of patients had at least one refill of their statin prescription after cancer diagnosis, and 67% of patients alive after 24 months (n=87) were still on statins. Median time between the last refill and death was 63 days, with no significant difference between primary and secondary prevention (p= 0.45).
5.	Chen, 2010[561]	Taiwan	Retrospective cohort, single-center	Nursing home residents who died	31	83 (7.6)	Mean number of drugs prescribed at time of death was 7.9 (SD =3.3), compared with 6.8 (SD, 2.9) three months before death, and 6.5 (SD, 2.9) six months before death. A total of 8 (25%) residents were taking 10 or more medications at time of death. Most commonly prescribed medications were drugs for constipation (n=24), COPD (n=23), hypertension (n=21), gastrointestinal disorders (n=17) and antiplatelet agents (n=16).
6.	*Chuang, 2017[573]	Taiwan	Retrospective cohort, register-based	Older adults with dementia who died	6532	Median 85	Median Charlson index score 3 (IQR, 2-4). Most common causes of death were pneumonia, respiratory failure, and sepsis. The prevalence of medications deemed "never appropriate" (Holmes' criteria) decreased from 17.5% one year before death to 10.5% during the final month of life. These included antiplatelet agents (8%), statins (2%), AChEIs (1%) and memantine (0.3%). In addition, 21% of patients were using medications considered "rarely appropriate", including antispasmodics (9%), digoxin (4%), and antiarrythmics (3%).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
7.	Cruikshank, 2013[562]	Australia	Retrospective cohort, single-center	Older adults (≥65 years) who died in an inpatient palliative care unit	50	77 (SD Ø)	Overall, 21% of patients were prescribed ≥ 9 medications at time of admission (median time to death = 7 days). Mean number of drugs per patient was 8.5. Median number of drugs varied from 10 among patients aged 66-74 years to 7 among those aged 75 years and older. Within 72 hours after PCU admission, 67% of all prescribed drugs (n= 285 / 427) had been discontinued.
8.	Currow, 2007[558]	Australia	Cluster randomized controlled trial (secondary analysis)	Palliative care patients (96% cancer) who died during follow-up	260	71 (12) Median 73	Median time between palliative care referral and death was 93 days. At time of inclusion, number of medications was 4.9 (SD, 2.9), including 2.3 medications for symptom management and 2.6 medications for comorbid conditions. 15% of patients received ≥1medication considered "potentially inappropriate" according to Beers' criteria. The prevalence of polypharmacy (≥7) increased from 17% at time of inclusion to 27% at time of final assessment before death. Increase in the total number of medications was fueled by symptom-specific drugs, while there was a decrease in drugs for comorbid conditions.
9.	*De Schreye, 2017[284]	Belgium	Retrospective cohort, register-based	Adult who died from cancer	26 464	78 (SD Ø) 24% <65 y	During the final month before death, 17% of decedents received chemotherapy, 6.6% started using antidepressants, and 7% received blood transfusion. In addition, 67% of individuals received opioids.
10.	Dewhurst, 2016[574]	United Kingdom	Cross-sectional, single-center	Patients receiving care in a palliative service	54	NR	Average life expectancy, 18 months. 74% of patients with cancer. 26 patients had documented hypertension (mean BP 122/65 mmHg). Of these, all were treated with antihypertensives, but 25 / 26 were using the medication inappropriately.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
11.	Domingues, 2015[539]	Portugal	Prospective cohort, single-center	Patients with advanced cancer referred to a palliative care unit	71	68.2 (12)	42 patients (60%) had an ECOG ≥3. At time of palliative care referral, the mean number of medications was 8.9, with 86% of patients receiving 5 or more drugs and 27% receiving 10 or more drugs. Most common drugs were analgesics, psychotropics, antihypertensives, and antiacids. Using the Medication Appropriateness Index (MAI), physicians estimated that 23% of prescribed drugs did not have a clinical indication in palliative care, 7.2% were not effective, 10% had inappropriate posology or dosage, 3% presented significant risk of drug-drug interactions, 11% had significant risk of drug-disease interactions, 6% were duplicates, and 25% had an inappropriate duration (for chronic medications only).
12.	Dwyer, 2015[563]	United States	Retrospective cohort, survey	Older adults (≥65 years) receiving hospice care who died with cancer, dementia, debility, heart disease or lung disease.	2623	80% aged ≥75 years	During the final week of life, mean number of medications was 10.2, varying from 9.5 among decedents with dementia to 11.4 among those with lung disease. No significant difference across age groups. Most common medications included analgesics (98%, incl 91% opioids), antiemetics (78%), anxiolytic and sedatives (75%), antiepileptics (70%), laxatives (53%), antihypertensives (49%), antipsychotics (38%), bronchodilator (27%), PPIs (26%), anticoagulants (25%), antidepressants (24%), antiacids (19%), and antibiotics (18%).
13.	Fahlman, 2007[575,576]	United States	Retrospective cohort, register-based	Older adults (≥65 years) covered by the Medicare+Choice insurance who died	4602	55% aged ≥75 years	25% of decedents had ≥5 chronic comorbidities. During the final year of life, 44% of decedents received at least one drug considered “potentially inappropriate” according to Beer’s criteria, including propoxyphene (15.0%), zolpidem (3.8%), and amitriptyline (2.8%)

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
14.	Fede, 2011[534]	Brazil	Cross-sectional, single-center	Hospitalized patients with terminal cancer	87	Median 61	At time of inclusion (life expectancy < 6 months), median number of medications was 4. A total of 26% of patients self-reported drug-related adverse events. 21 patients (24%) were taking at least one unnecessary medication, including PPIs without history of GI bleeding or NSAID prescription. Other drugs considered unnecessary were statins without cardiovascular event in the last 12 months, antihypertensives with low blood pressure, and antidiabetics with hypoglycemia.
15.	*Grande, 2017[566]	Sweden	Retrospective cohort, register-based	Older adults (≥65 years) who died from Amyotrophic Lateral Sclerosis (ALS)	1603	76 (7)	43% of decedents had ≥4 chronic comorbidities. Mean number of drugs increased from 5.7 one year before death to 8.3 during the final month of life among community-dwellers, and from 7.5 to 9.7 among nursing home residents. The proportion of individuals exposed to 10 or more drugs increased from 19% during the 12th month before death to 37% during the last month. Psycholeptics (57%), analgesics (47%), laxatives (46%), psychoanaleptics (44%, incl. 42% antidepressants), and riluzol (45%) were the five most commonly used drug classes during the final months before death. Drugs of questionable benefit included statins (11%), mineral supplements (11%), calcium channel blockers (13%) and beta-blockers (27%).
16.	*Hamada, 2017[700]	United Kingdom	Retrospective cohort, register-based	Older adults (≥80 years) who died with diabetes mellitus	5324	Median 86	High burden of comorbidities, including cancer (35%), coronary heart disease (42%), stroke (15%), and dementia (13%). 15% of decedents had an estimated glomerular filtration rate <30, and 24% had an eGFR 30–44. During the final year of life, the number of prescribed drugs remained stable, with an average of 6.2 (SD 3.1). Overall, 73% of decedents received ≥5 drugs and 18% received ≥10 drugs;

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
17.	Heppenstall, 2016[889]	New Zealand	Prospective cohort, multicenter	Nursing home residents who died within 12 months	1582	85 (SD Ø)	At time of inclusion, nursing home residents were prescribed on average 7.4 drugs. Common medication classes included psychotropics (69%), analgesics (62%), antihypertensives (58%), antiplatelet agents (52%), diuretics (40%), statins (22%), bisphosphonates (16%), and antidiabetics (9%). Sub-analysis on 56 patients revealed that 13/33 were prescribed for primary prevention.
18.	Hui, 2015[564]	United States	Prospective cohort, single-center	Hospitalized patients with advanced cancer referred to a palliative care service	100	57 (13)	Average number of drugs changed from 9.2 (SD 4.5) before palliative care referral, to 10.1 at time of death (SD 3.8). Increase in the number of symptom-specific medications and decrease in the number of medications for comorbidities. Common drug classes included PPIs (82%), morphine (64%) and hydromorphone (57%), antidiabetics (30%), metoclopramide (55%), furosemide (24%), dexamethasone (68%), laxatives (81%), haloperidol (68%), and bronchodilators (75%)
19.	Jansen, 2014[565]	Norway	Retrospective cohort, multicenter (n=3)	Nursing home residents who died	524	Median 86	Most common chronic conditions included dementia (37%), CHF (30%), cancer (24%), and COPD (18%). Median length of stay, 103 days. At time of death, >99% of nursing home residents had active prescriptions. Mean number of medications was 9 (total of 4736 drugs). 28% of prescribed drugs were palliative, 51% were curative of preventive. Common drugs with clear palliative indication were morphine (71%), midazolam (55%), glycopyrronium (47%), and haloperidol (47%). Curative or preventive deaths included antithrombotics (24%), beta-blockers (18%), and ACE inhibitors (9%).
20.	Kierner, 2016[915]	Austria	Retrospective cohort, single-center	Hospitalized patients who died from advanced cancer	100	Median 63	Median number of drugs decreased from 11 to 6 between the 9th and the final day before death. During the final day of life, 60% of patients received 5 or more drugs. Most drugs were for chronic use.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
21.	Kotlinska-Lemieszek, 2014[559]	Multiple European countries	Cross-sectional, multicenter (n=17)	Patients with advanced cancer using Step-3 analgesics	2282	62 (12)	Patients were recruited in Norway (n=565), Italy (n=462), Germany (n=452), United Kingdom (n=295), Iceland (n=150), Sweden (n=135), Switzerland (n=115), Lithuania (n=54), Denmark (n=31), Finland (n=30) and Greece (n=5). Overall, 91% of patients had metastatic cancer. During the past 24 hours, patients used on average 7.8 medications, with 84% receiving ≥5 drugs and 28% receiving ≥10 drugs. 18% of patients received unnecessary drugs, including statins (6%), hormone replacement therapy (1%), and vitamins (12%). 33% of patients received potentially unnecessary drugs, including anticancer agents (5%), cardiovascular drugs (14%), GORDs, (29%), and allopurinol (2%).
22.	Kwok, 2016[916]	Hong Kong	Retrospective cohort, single-center	Patients with end-stage renal disease receiving palliative care	226	76 (9.7)	Mean number of comorbidities was 9.0 (SD 2.3), including hypertension (90%), diabetes (67%), ischemic heart disease (34%), congestive heart failure (34%), and stroke (30%). At time of advance care planning, average eGFR was 12.0 (SD 4.6). During the final 2 weeks of life, medications included antibiotics (53%), blood transfusion (30%), non-opioid analgesics (14%), strong opioids (21%), midazolam (5%), haloperidol (21%), and butylscopolamine (4.4%). In addition, 10% of patients started artificial nutrition (NG or percutaneous)
23.	Lee, 2013[577]	Korea	Retrospective cohort, multicenter (n=2)	Terminally ill cancer patients who died in hospitals	196	Median 67	Most commonly prescribed drugs included opioids (fentanyl, 62.2% and morphine, 44.3%), megestrol for anorexia (46%), metoclopramide for nausea (37%), tramadol (31%) and diclofenac (19%) for mild-to-moderate pain, morphine for dyspnea (23%), and gabapentin for neuropathic pain (22%). Butylscopolamine was used in only 6% of patients. Potentially futile medications were defined based on Riechelmann's and Fede's[534] approach. It included gastroprotectors (49%, including 25% futile), antihypertensives (28%, including 13% futile), antidiabetics (14%, including 1% futile), and statins (6%, including 4% futile).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
24.	Ma, 2014[578]	Canada	Retrospective cohort, multicenter (n=2)	Patients with poor prognosis referred to palliative care	70	76 (12.1)	During the last week before death (or the last week before PCU transition), patients were prescribed on average 6 medications for comfort, 4 medications "possibly for comfort" and 3 medications "definitely not for comfort." The latter category includes antihypertensives, antiplatelet agents, bisphosphonates, AChEI, hormone replacement, iron and vitamins, statins, and allopurinol. Not details about the prevalence of each drug class.
25.	*Matlow, 2017[567]	Canada	Retrospective cohort, register-based	Deceased nursing home residents with advanced dementia who received at least one medication of questionable benefit	9298	86.4 (6.7)	During the last 4 months of life, most common medications of questionable benefit were antidementia drugs (64%), statins (48%), antiplatelet agents excl. aspirin (18%) and sex hormones (2.1%). Overall, 45% of nursing home residents were still receiving ≥1 medication of questionable benefit during the final week of life. Less severe cognitive impairment as measured with the Cognitive Performance Score was associated with an increased likelihood of receiving medications of questionable benefit.
26.	McLean, 2013[551]	Ireland	Retrospective cohort, single-center	Patients referred to palliative care who died	52	Median 74.5	Mean time between palliative care referral and death was 10.8 weeks. Median number of comorbidities was 3, ranging from 0 to 7. During the final week of life, patients were prescribed a total of 10 medications. The number of medication for the management of comorbidities remained stable between the 3rd month before death and the final week of life (4–3), while the number of medications for symptom control increased from 4 to 7.2. Medications for comorbid conditions included aspirin (36%), beta-blockers (27%), statins (23%), ACE/ARB (15%), and calcium channel inhibitors (15%).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
27.	McNeil, 2015[917]	United States	Cluster randomized controlled trial (secondary analysis)	Adult patients with <12 months estimated prognosis taking a statin medication for primary prevention of cardio-vascular disease.	244	74.3 (11.5)	Mean time from inclusion to death was 264 days. 47% of patients had a diagnosis of cancer. Mean Charlson Comorbidity Index score 4.8 (SD 2.8). At time of enrollment, patients were prescribed on average 11.5 (SD 5) different medications, decreasing to 10.7 (SD 5) at time of death or end of follow-up. Most common drugs included antihypertensives (70%), bronchodilators (40%), laxatives (57%), antidepressants (54%), and gastroprotectors (60%).
28.	Morgan, 2015[552]	Australia	Retrospective cohort, multicenter (n=4)	Patients referred to palliative care who died	266	68.9 (13.2)	Primary diagnosis: solid tumor (89%), hematological malignancy (1.5%), neurodegenerative disease (1.5%), or organ failure (8%). During the last two weeks of life, patients were prescribed on average 10.8 (7.1) drugs (median 9, IQR 6–14). 72% of patients had at least one potential drug-drug interaction. Most frequent clinically significant potential DDIs involved haloperidol (n=185) or methadone (n=113).
29.	*Morin, 2017[568]	Sweden	Retrospective cohort, register-based	Older adults (≥75 years) who died with dementia	120 067	87.3 (5.6)	The prevalence of medications deemed “never appropriate” (Holmes’ criteria) decreased from 38.6% 12 months before death to 34.7% during the final month before death. After excluding antidementia drugs from the analysis, the prevalence of medications of questionable benefit during the final month of life was 19.1%. Most common medications of questionable benefit were antidementia drugs (20%), statins (8.3%), and sex hormones (10% of women). Institutionalization was independently associated with a 15% reduction of the likelihood to receive medications of questionable benefit.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
30.	Mullvain, 2015[918]	United States	Retrospective cohort, multicenter (n=2)	Adult patients with brain metastases	206	22% aged ≥70 years	Overall, 53/206 patients (26%) were prescribed with statins at the time of initial referral to whole-brain radiation therapy. 19 of them had a history of myocardial infarction or angina (secondary prevention). 13/53 patients discontinued statin therapy during follow-up. The authors propose a communication tool (scripted dialogue) to help physicians deprescribe preventive treatments.
31.	Nauck, 2004[919]	Germany	Prospective cohort, multicenter (n=55)	Patients hospitalized in palliative care units	1304	65.1 (12.8)	Most common drug classes were step-3 opioids (68%, including morphine 42% and fentanyl 28%), non-opioids- analgesics (59%), systemic corticosteroids (32%, including dexamethasone 27%), laxatives (31%), antiemetics (27%, including metoclopramide 21%), gastroprotective agents (24%), neuroleptics (19%), sedatives and anxiolytics (18%), antidepressants (16%) and diuretics (15%).
32.	Oliveira, 2016[569]	Portugal	Retrospective cohort, single-center	Patients referred to palliative care	448	Median 68	Median time from admission to death was 15 days. Comorbidities included hypertension (48%), high cholesterol (21%), venous thromboembolism (15%), and diabetes mellitus (20%). Potentially futile medications were defined based on Fede's approach.[534] 69 (15%) patients were prescribed with statins without any cardiovascular event in the previous 12 months, 125 (28%) patients were given gastroprotective agents deemed futile, 42 (9%) patients received antihypertensive treatments with either low BP or hypotension symptoms, and 9 patients received antidementia drugs.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
33.	Onder, 2013[550]	Multiple European countries	Cross-sectional, survey (SHELTER)	Nursing home residents with advanced dementia (CPS ≥5)	822	84.6 (8.0)	Nursing home residents from 8 different countries were included. 123 (15%) of residents had an Advanced Dementia Prognostic Tool (ADEPT) score ≥13.5, indicating limited life expectancy.[751] 14% of the overall study population had polypharmacy. Most commonly prescribed medications included laxatives (47%), gastroprotective agents (34%), antipsychotics (36%), benzodiazepines (33%), antidepressants (29%), antidementia drugs (13%), antiplatelet agents (34%), ACEi (16%), beta-blockers (16%), statins (8%), and calcium channel inhibitors (14%).
34.	Raijmakers, 2013[535]	Italy	Retrospective cohort, single-center	Patients who died from cancer	195	73 (SD Ø)	During the last 3 days of life, mean number of medication was 4.8 (SD 2.1), varying from 5.1 among hospitalized patients and 4.7 among hospice patients. Medications considered as "likely to be inappropriate" included iron and vitamin supplements (11%), replacement hormones (14%), bisphosphonates (1%), anticoagulants (26%), antihypertensives (13%), antiarrythmics (15%), gastroprotective agents (56%), antibiotics (31%), corticosteroids (65%), vasodilators (11%), and dopamine (7%). "Appropriate medications" included opioids (87%), midazolam (28%), haloperidol (46%), medications for pulmonary secretions (36%), and metoclopramide/levomepromazine for nausea (11%).
35.	Riechelmann, 2009[536]	Brazil	Retrospective cohort, single-center	Ambulatory patients with advanced cancer receiving palliative care	372	Median 66	More than 50% of patients received ≥6 drugs. Prevalence of futile medication was 22% before palliative care consultation. Most frequent unnecessary medications used by patients were statins (n=48), multivitamins (n=25), and allopurinol (n=4). Most common duplicate medications involved benzodiazepines (n=7).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
36.	Russell, 2014[553]	Australia	Prospective cohort, single-center	Adult patients with life-limiting illness referred to palliative care	203	72.9 (12.6)	Primary diagnosis was cancer for 68% of patients. Median Charlson Comorbidity Index score 8 (range 2–20). Mean number of medications at time of palliative care referral was 7.2 (SD 3.3), of which 5.3 (3.5) were for the management of chronic diseases and 1.9 (2.0) were for symptom control. Average number of medications was higher among patients with non-malignant disease (8.5 vs 6.6). 22% of patients were prescribed with statins, with no significant differences across disease groups or performance status scores.
37.	Sera, 2014[554]	United States	Retrospective cohort, multicenter	Hospice patients who died	4252	77.5 (14.3)	Patients were admitted to hospice in 11 different states. Most common primary diagnoses were cancer (35%), dementia (18%), lung disease (10%), and heart disease (10%). Average length of stay was 22 days. Mean number of medications at any time during hospice stay was 15.7, with ≥30 drugs. Most common prescribed drugs were paracetamol (86%), lorazepam (84%), morphine (84%), haloperidol (49%), and atropine (62%). Other commonly used medications included prochlorperazine (antiemetic, 47%), laxatives (e.g. docusate and bisacodyl, 29% and 26%), salbutamol (29%), scopolamine (25%), and furosemide (18%). Antihypertensives (33%), antiacid agents (35%), and antiplatelet agents (11%) were common among cancer patients.
38.	*Sevilla-Sanchez, 2017[920]	Spain	Cross-sectional, single-center	Hospitalized older adults identified as “palliative”	235	86.8 (5.4)	Moderate to severe cognitive impairment in 56.6% of patients. Mean number of drugs 9.5 (SD 3.8), with 47% of patients using 10 or more drugs. 19% of patients used cardiovascular medications, and 31% used medications for the central nervous system. Prevalence of inappropriate medications according to STOPP criteria was 88%. Overall, 25% of patients experienced at least one adverse drug event.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
39.	Silveira, 2008[921]	United States	Retrospective cohort, multicenter	VA patients treated with statins 6 months before death	1584	72-75 (9)	A total of 337 patients who died from life-limiting conditions (based on the Palliative Care Index), matched with 1247 patients who died without life-limiting condition. 99% male. At time of death, 51% of cases and 64% of controls were still receiving statins. Among patients who discontinued statins, discontinuation occurred on average 65 days (SD 50) before death.
40.	Suhrie, 2009[538]	United States	Retrospective cohort, single-center	VA patients who died in a geriatric palliative care unit	89	79.7 (7.8)	98% of patients were male. Primary diagnosis was mainly dementia (39%), followed by cancer (17%), and cardiovascular disease (11%). Mean number of chronic diseases was 8.4 (SD 4.3). At time of admission, mean number of prescribed medications was 9.7 (SD 4.3). Based on 3 items from the Medication Appropriateness Index (MAI), the proportion of patients with unnecessary medications was 74% at admission, and decreased to 39% at time of death (incl. 24% lack of effectiveness and 20% lack of indication).
41.	Tjia, 2014[555]	United States	Retrospective cohort, register-based	Nursing home residents with advanced dementia (CPS ≥6)	10 212	85.0 (7.3)	Inception cohort: nursing home residents are included at the time of transition to severe cognitive impairment. Common comorbid diseases included diabetes mellitus (29.6%), heart failure (20.8%), stroke (24.4%), hypertension (68%), renal failure (11%), and cancer (7.5). Overall, mean number of drugs at baseline was 7.1 (SD 4.8). 1699 (17%) of residents were using statins, of whom 632 (37.2%) discontinued their treatment during follow-up time. Among statin users who died during follow-up (n=924), 61.5% (n=568) were still using statins at time of death.
42.	Tjia, 2014[570]	United States	Cross-sectional, register-based	Nursing home residents with advanced dementia (CPS ≥5)	5406	Median 85	Common comorbid diseases included diabetes mellitus (28.5%), hypertension (70%), heart failure (16%), stroke (22%), osteoporosis (25%), and depression (47%). A total of 2911 residents (54%) received at least 1 medication deemed “never appropriate” (Holmes’ criteria) during the 90-day observation period. Most common medications of questionable benefit where AChEIs (36%), memantine (25%), and statins (22%).

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
43.	Tjia, 2010[572]	United States	Prospective cohort, multicenter (n=22)	Nursing home residents with advanced dementia (CPS ≥5)	323	85.3 (7.5)	A total of 177 residents (54.8%) died within 18 months. Most common comorbid conditions were hypertension (58.5%), osteoporosis (24.8%), coronary artery disease (18.6%), and diabetes mellitus (18.9%). Primary goal of care was comfort for 90% of residents. Mean number of drugs at baseline was 5.9 (SD 3.0). During the last week of life, mean number of drugs increased up to 6.3 (SD 3.3), including analgesics (60%), scopolamine (11%), antidiabetics (7.3%), beta-blockers (29.3%), ACE inhibitors (10%), calcium channel blockers (7.9%), statins (7.9%), diuretics (18.9%), laxatives (70.1%), PPIs (18.3%), antiplatelet agents (28%), antiosteoporotics (18.9%), antidepressants (37.2%, incl. 19.5% SSRIs), antipsychotics (20.1%), and antidementia drugs (7.9%).
44.	Todd, 2014[556]	United Kingdom	Prospective cohort, single-center	Adults patients attending a palliative care service and prescribed ≥1 drug	132	70	Most common life limiting diseases were cancer (82%), end-stage COPD (8%), end-stage CHF (6%) and Parkinson's disease (4%). Mean number of medications was 12 (range 1–21), varying from 10 among cancer patients to 14 among those with CHF. 16% of all medications (n= 238 / 1532) were deemed inappropriate in the context of limited life expectancy, affecting 70% of patients (n=92 / 132). Inappropriate medications included statins (27%), mineral supplements (24%), aspirin (20%), ACE inhibitors (20%), beta-blockers (19%), bisphosphonates (11%), vitamins (9%), calcium channel blockers (9%), and clopidogrel (5%). In addition, 267 potential drug–drug interactions were identified, including 112 considered clinically significant.

#	Author, year (ref)	Country	Study design	Study population	No.	Age, years	Main findings
45.	Turner, 2014[557]	Australia	Cross-sectional, single-center	Older adults (≥70 years) with cancer referred to an outpatient oncology clinic	385	76.7 (4.8)	Common cancer sites were GI (26%), lung (24%), and breast (11%). Comorbidities included hypertension (62%), arthritis (31%), diabetes (27%), COPD (26%), and coronary artery disease (18%). Mean number of medications was 5.7 (SD 3.7), with 57% of patients receiving 5 or more medications. Most commonly prescribed medications were ACE/ARBs (48%), statins (37%), antithrombotics (38%), antiacid agents (36%), analgesics (32%), beta-blockers (24%), calcium channel blockers (20%), antidiabetics (18%), and vitamins (17%). The authors distinguished between palliative and non-palliative patients, and found only little difference.
46.	Van Den Noortgate, 2016[922]	Belgium	Cross-sectional, multicenter (n=23)	Older adults who died in acute geriatric wards	290	85.7 (SD Ø)	Death was expected for 71% of patients Prevalence of dementia was 53%. At time of admission, common medications included antihypertensives (71%, incl. 27% treated until death), antiacid agents (59%, incl. 26% until death), diuretics (61%, incl. 23% until death), laxatives (44%, incl. 15% until death), aspirin (45%, incl. 13% until death), statins (21%, incl. 9% until death), and antidementia drugs (14%, incl. 6% until death). During the last 48 hours of life, 45% of patients had an anticipatory prescription of morphine, 15% of benzodiazepine, and 14% of scopolamine.
47.	West, 2014[571]	Italy	Retrospective cohort, multicenter (n=21)	Cancer patients who died	271	75 (SD Ø)	144 patients died in 16 hospitals, and 127 died in 5 hospices. Mean number of medications ranged 5.0–6.0. Drugs during the final 3 days of life were categorized as “potentially inappropriate” based on Raijmakers’ approach. 90% of patients received at least one drug of questionable benefit. It included antiacid (n=186), antibiotics (n=107), corticosteroids (n=161), anticoagulants (n=116), mineral and vitamin supplements (n=64), antihypertensives (n=51), replacement hormones (n=33), vasodilators (n=21), and dopamine (n=9).

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2019

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support.

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of aetiology and validity.
Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia.
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person.

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.
Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia.
Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above.

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above.
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.
Cornelius Christel. Drug use in the elderly. Risk or protection? Findings from the Kungsholmen project.
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.
Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.
Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.
Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)
Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.
Rehnman Jenny. The role of gender in face recognition. (Stockholm University)
Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?
Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)
Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.
Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.
Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.
Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)
Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.
Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.
Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.
Livner Åsa. Prospective and retrospective memory in normal and pathological aging.
Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.
Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.
Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.
Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.
Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.
Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.
Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.
Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.
Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.
Svärd Joakim. Emotional facial processing in younger and older adults.
Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.
Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.
Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.
Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.
Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.
Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.
Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.
Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.
Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.
Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.
Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.
Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.
Sjöberg Linnea. Using a life-course approach to better understand depression in older age.
Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence.
Berggren Rasmus. Cognitive development and educational attainment across the life span.
Liborio Vetrano Davide. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.
Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.
Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.
Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

A line is a dot that went for a walk (Paul Klee)

Karolinska
Institutet