Deprescribing in Europe and other countries: current initiatives and ongoing activities.

Prof. Stephen Byrne
University College Cork, Ireland
October 2022

Declaration

Prof Stephen Byrne –
Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Ireland

Co-inventor/author of STOPP/START criteria, Have received funding from the HRB and EU-FP7, H2020 to investigate the impact of STOPP/START v2 in optimising prescribing in older patients

SENATOR:https://pubmed.ncbi.nlm.nih.gov/32484850/
OPERAM: https://pubmed.ncbi.nlm.nih.gov/34257088/
TRUST https://pubmed.ncbi.nlm.nih.gov/28402245/
iKASCADE project: **I**dentifying **K**ey Prescribing C**ASCAD**es in the **E**lderly: A Transnational Initiative on Drug Safety

Royal Cork Yacht Club, 1720

Titanic 1912

Queen's College, Cork. Founded 1845

ESCP Symposium Prague 2022

ESCP SIG- Deprescribing Members Meeting
Thursday 20 October 2022,
12.30 CET
Room: Ostrava

Potentially Inappropriate Prescribing (PIP)

- Prevalence of patients with PIP in secondary care: ~ 50%.
- Computerised interventions suggested as an effective strategy to reduce this.

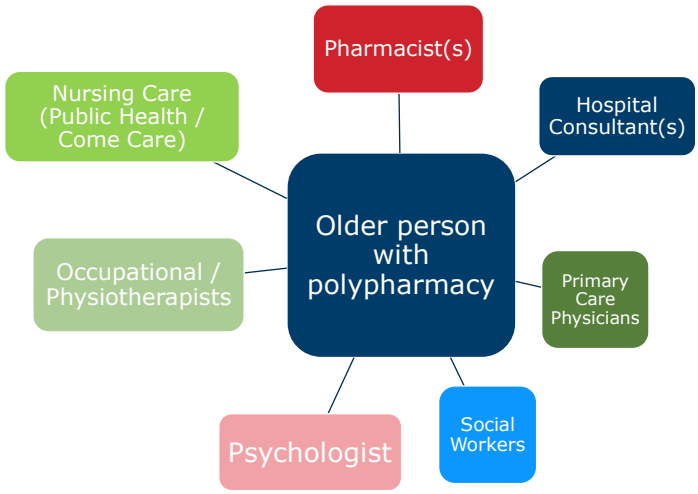
AGEING AND MULTIMORBIDITY

- By the year 2050 in Europe the number of citizens older than 65 years will be higher than those younger than 10 years
- More than two thirds of older people have two or more apparently unrelated diseases
- Older people with multimorbidity will be around 75 millions in 2060 in Europe (nearly 10% of the whole population)
- Multimorbidity is inevitably associated with **polypharmacy**

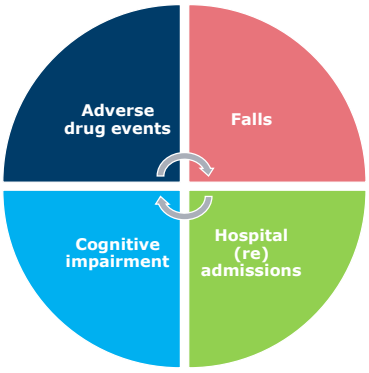
Marengoni A et al. Aging Research Review 2011;10:430

- ❖ It is not possible to have evidence-based guidelines for every possible combination of multiple concomitant diseases
- ❖ We need to be able to provide advice regarding medicines least likely to harm

The complex healthcare relationships



Polypharmacy is associated with an increased risk of inappropriate prescribing, which in turn leads to different negative outcomes:



Despite this there is limited evidence on interventions to improve medication appropriateness and lower the risk of adverse clinical outcomes

Sources: Davies et al. Journal of the American Medical Directors Association. 2020. | Liew et al. Annals of Family Medicine. 2019. | Mekonnen et al. Br J Clin Pharmacol. 2021. | Rochon et al. The Lancet. Health Longevity. 2021. | Xing et al. Ann Pharmacotherapy. 2019.

STRATEGIES TO HELP DEPRESCRIBING

- Clinical guidelines e.g. NICE guideline for the management of type 2 diabetes (2015): relaxation of HbA1c level for older or frail people with reduced life expectancy, risk of falling or those with significant comorbidities.
- Deprescribing guidelines and algorithms. e.g. Deprescribing of proton-pump inhibitors (Thompson 2016); Deprescribing protocol (Scott 2015).
- Lists or criteria for inappropriate precriptions or potentially inappropriate medications. E.g. Beers Criteria, STOPP/START criteria, EU(7)-PIM list, etc.

Systematic reviews on deprescribing in older people

- Thillainadesan et al. → older hospitalized patients (i.e. ≥65 years)

Drugs Aging. 2018;35(4):303-319

- Dills et al. → adult patients (aged ≥18 years) in outpatient, assisted living, nursing home and acute care settings

J Am Med Dir Assoc. 2018;19(11):923-935

- Shrestha et al. → older patients (i.e. ≥65 years) with life-limiting illnesses and reduced life expectancy

Br J Clin Pharmacol. 2019;10.1111/bcp.14113

  - Deprescribing can reduce polypharmacy and IP
  - Unclear if tangible benefits for ADRs, falls, re-hospitalization, quality of life and mortality

Multi-centre RCTs of Deprescribing

- **SENATOR** RCT (2012 – 2018): 6 European centres, 1,537 patients
(primary endpoint: hospital-acquired ADRs within 14 days/discharge)

O'Mahony D et al., *Age & Ageing* 2020; 49: 605–614

- **OPERAM** RCT (2015 – 2020): 4 European centres, 2,008 patients
(primary endpoint: drug-related readmissions within 12 months)

Blum M et al., *BMJ* 2021 Jul 13;374:n1585. doi: 10.1136/bmj.n1585

- **VALFORTA** RCT (2013 – 2014): 2 German centres, 409 patients
(primary endpoint: sum of medication errors i.e. over-, under- or mis-treatment)

Wehling M et al. *Age Ageing* 2016; 45: 262–267

- **OPTIMIST** RCT (2013 – 2015): 4 Danish centres, 1,467 patients
(primary composite endpoint: readmission or ED visits within 180 days)

Ravn-Nielsen LV et al., *JAMA Intern Med* 2018; 178(3): 375-382

- **MedSafer** RCT (2017 – 2020): 11 Canadian centres, 5,698 patients
(primary endpoint: ADEs within 30 days of hospital discharge)

McDonald EG et al. *JAMA Intern Med* 2022; 182(3):265-273.

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Available deprescribing tools

Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy: A Systematic Review

Wade Thompson, PharmD, MSc, Carina Lundby, MScPhm,†‡ Trine Graabæk, MScPhm, PhD,†‡ Dorthe S. Nielsen, RN, MHS, PhD,§‖¶ Jesper Ryg, MD, PhD,**†† Jens Sondergaard, MD, PhD,* and Anton Pottegård, MScPhm, PhD†‡*

Thompson W., et al. JAGS 2019; 67:172-180

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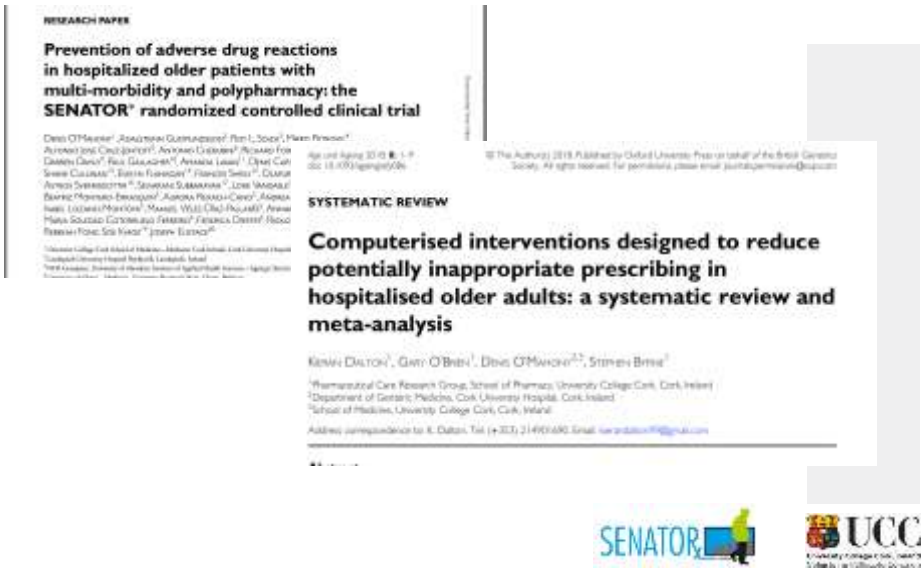
Available deprescribing tools

Tool name	Population	Description
Geriatric-Palliative algorithm	Nursing home resident with incurable disease	Identifies if a drug can be deprescribed based on indication, safety, and alternative therapies.
STOPPFrail	Frail older persons (end-stage irreversible pathology, poor 1-year survival prognosis, severe functional impairment, goal of symptom control)	List of criteria for specific medications and health conditions for which deprescribing can be considered; provides suggested monitoring parameters
LESS-CHRON	Older persons with multiple comorbidities, specifically frail older persons (criteria are medication specific)	List of drugs/conditions to consider for deprescribing; provides monitoring/follow-up guidance
Holmes et al.	Individuals with advanced dementia	List of medications to guide deprescribing; medications considered never appropriate, rarely appropriate, sometimes appropriate, always appropriate.

Available deprescribing tools contd'

Tool name	Population	Description
Pruskowski and Handler.	Individuals with limited life expectancy (with comfort-focused treatment plan), particularly older nursing home residents	List of medications to consider deprescribing
Frank and Weir.	Older persons, specific discussion of frail individuals and those with limited life expectancy (no specific criteria described)	Algorithm to guide deprescribing process for entire medication list
Scott et al. (a)		Ten-step framework to approach deprescribing process for entire medication list
Scott et al. (b)		Five-step approach and algorithm to guide deprescribing process for entire medication list

SENATOR



RESEARCH PAPER

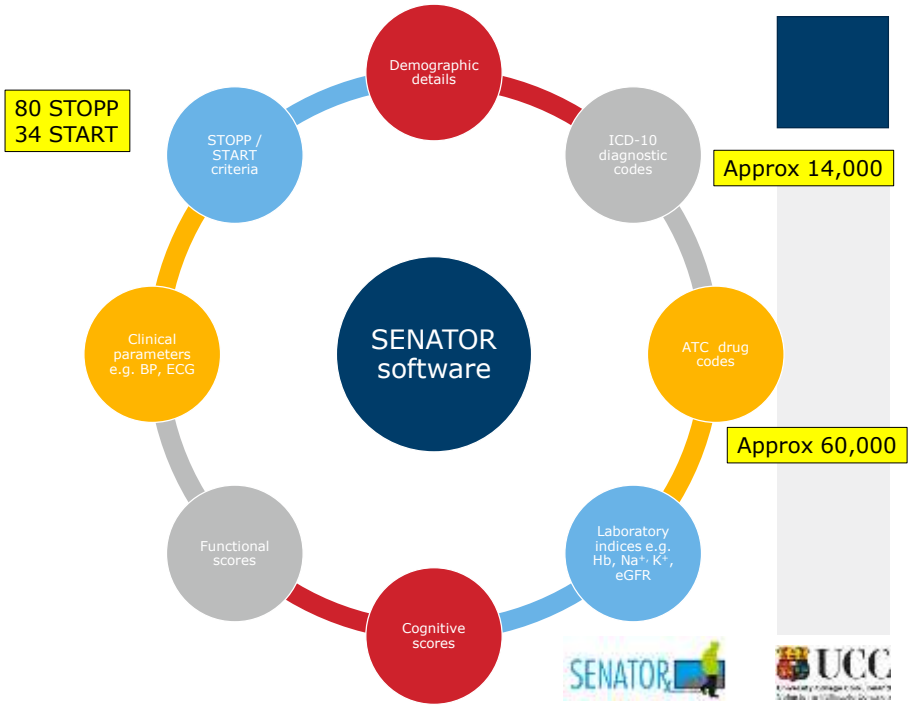
Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial

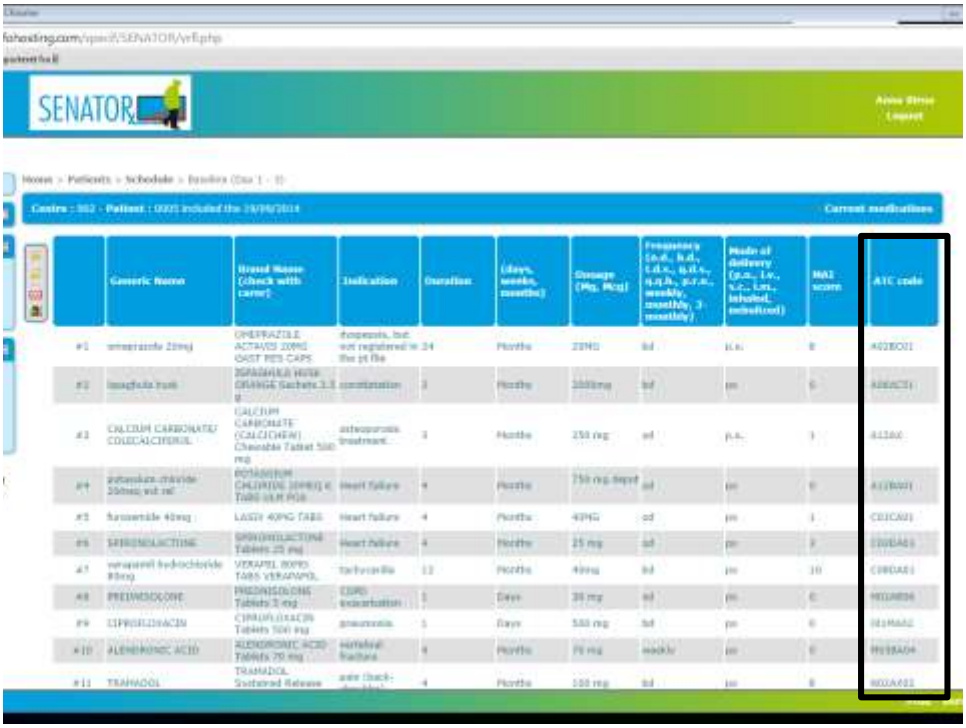
SYSTEMATIC REVIEW

Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis

SENATOR RCT

- Phase 1: Observational data in 800 patients (in order to estimate ADR rates in medical specialties in the 6 participating hospitals)
- Phase 2: Cluster-randomization of 1872 patients to 'normal' pharmaceutical care (n= 936) or SENATOR-guided pharmaceutical care (n= 936)
- **Primary outcome measure**:
- % of patients adjudicated as having at least one likely or definite, non-trivial hospital acquired ADR within 14 days of enrolment during index hospitalization.





ICD-10 codes in the software

ICD-10 coding	Name of condition with this ICD-10 code	Disease severity	Cause of admission
K57	Diverticular disease of intestine	☑ Mild ☐ Moderate ☐ Severe	☐ Yes ☑ No
I25.2	Old myocardial infarction	☑ Mild ☐ Moderate ☐ Severe	☐ Yes ☑ No
Z95.5	Presence of coronary angioplasty implant and graft	☑ Mild ☐ Moderate ☐ Severe	☐ Yes ☑ No
I95.1	Orthostatic hypotension	☑ Mild ☐ Moderate ☐ Severe	☐ Yes ☑ No
M81.9	Osteoporosis, unspecified	☑ Mild ☐ Moderate ☐ Severe	☐ Yes ☑ No
J22	Unspecified acute lower respiratory infection	☐ Mild ☑ Moderate ☐ Severe	☑ Yes ☐ No

SENATOR

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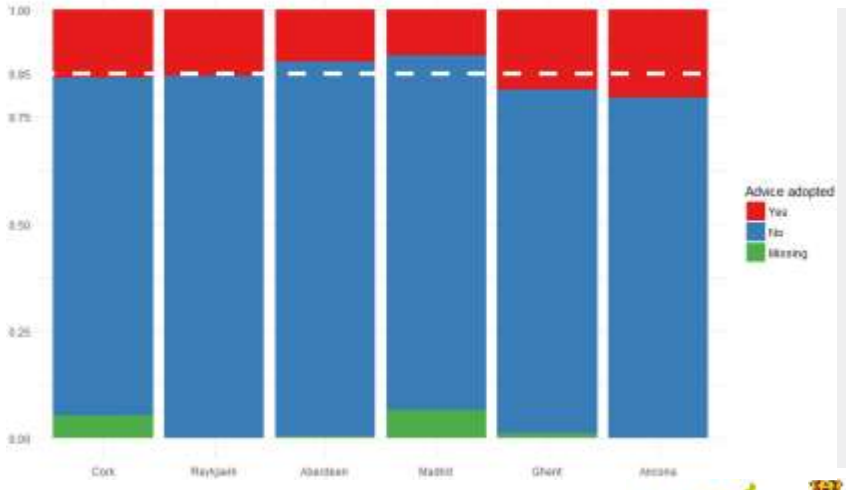
Uptake of SENATOR software medication advice points in each of the six participating centres.



Problems encountered in SENATOR

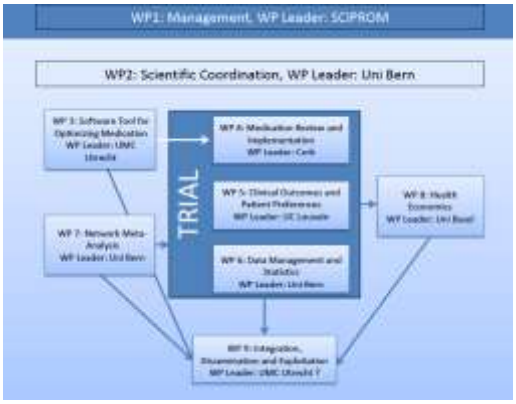
- Couldn't take into account all patient parameters – e.g. reason for admission
  - Suggested to start antithrombotic in a patient who may have presented with a bleed
- Some recommendations were falsely triggered - extra information would be required to prevent such false triggers in future applications
- Doesn't always consider route of administration e.g. IV vs PO corticosteroids

Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial

Blum MR; Sallevelt BTGM; Spinewine A; O'Mahony D; Moutzouri E; Feller M; Baumgartner C; Roumet M; Jungo KT; Schwab N; Bretagne L; Beglinger S; Aubert CE; Wilting I; Thevelin S; Murphy K; Huibers CJA; Drenth-van Maanen AC; Boland B; Crowley E; Eichenberger A; Meulendijk M; Jennings E; Adam L; Roos MJ; Gleeson L; Shen Z; Marien S; Meinders AJ; Baretella O; Netzer S; de Montmollin M; Fournier A; Mouzon A; O'Mahony C; Aujesky D; Mavridis D; Byrne S; Jansen PAF; Schwenkglenks M; Spruit M; Knol W; Dalleur O; Trelle S; Rodondi N

Blum et al. BMJ. 2022.

OPERAM – Across 4 Clinical Sites



Countries participating in the OPERAM trial

Source: https://www.operam-2020.eu/index.php?id=1502, accessed 26.08.2022

OPERAM study participants

Participants

- Adults aged **≥ 70 years**
- Admitted to a participating hospital ward
- **Multimorbidity** (≥ 3 chronic conditions)
- **Polypharmacy** (≥ 5 daily drugs)
- Few exclusion criteria to maximize generalizability

Intervention

- Cluster-randomisation at the level of attending hospital physicians
- 1:1 randomisation to the intervention or control arm
- Intervention performed by team of a doctor and a pharmacist
- Structured assessment of preadmission medication list

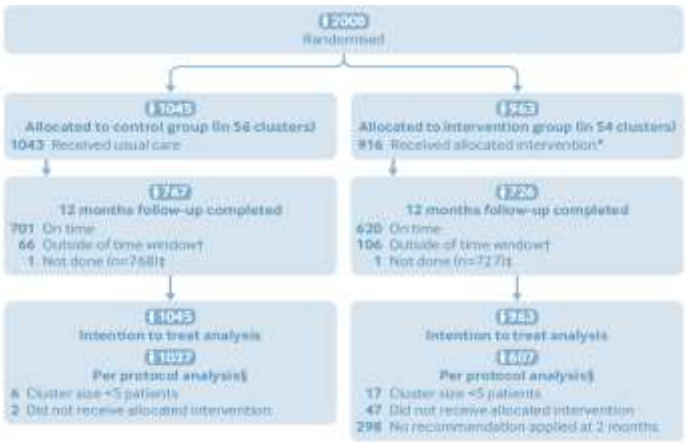
OPERAM Intervention *(contd')*

- Web-based evidence-based structured medication review using STRIP assistant
  - Based on the STOPP/START criteria
- Generation of patient specific prescribing recommendations
- Final report sent to general practitioners with all prescribing recommendations

Excerpt from the 'Systematic Tool to Reduce Inappropriate Prescribing' (STRIP) assistant

Sources: (1) O'Mahony et al. Age Ageing. 2015. | Drenth-van Maanen et al. J Eval Clin Pract. 2018. | Crowley et al. BMC Health Serv Res. 2020. | Adam et al. BMJ Open. 2019

OPERAM - Study Flow Chart



Source: Blum et al. BMJ. 2021.

- Total recruitment:
  - **54 clusters**
  - **2,008 patients**

OPERAM - Clinical Outcome

	Events (%)		Hazard ratio (95% confidence interval)
	Control	Intervention	
First drug related hospital admission	**234 (22.4)**	**211 (21.9)**	**0.95 (0.77 to 1.17)**
Death	203 (19.4)	172 (17.9)	0.90 (0.71 to 1.13)
First fall	263 (25.2)	237 (24.6)	0.96 (0.79 to 1.15)
First preventable DRA	100 (9.6)	84 (8.7)	0.89 (0.63 to 1.25)
First DRA in patients with ≥1 STOPP recommendation implemented at 2-month follow-up	156/875 (17.8)	64/398 (16.1)	0.88 (0.65 to 1.19)

DRA = drug-related hospital admission

Lessons learnt from OPERAM

Strengths:

- Enrolment of >2000 patients with multimorbidity with minimal exclusion criteria
- Few patients lost to follow-up
- Addressing limitations of previous trials through
  - Cluster randomisation
  - Maximized blinding
  - Adjudication of hospital readmissions

Limitations

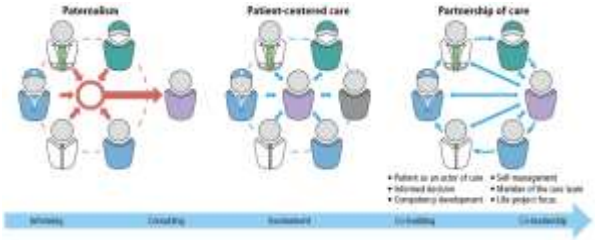
- Perhaps some medication changes in the control arm were similar to the intervention, potential bias
- Single timepoint intervention
- Cluster randomisation at the level of the doctor (not hospital), ? potential for contamination in control clusters

Frequency and acceptance of CDSS-generated STOPP/START signals

An expert team's involvement in translating population-based CDSS signals to individual patients is essential, **<u>as more than half of the signals for potential overuse, underuse and misuse were not deemed clinically appropriate in a hospital setting</u>**.


Frequency and Acceptance of Clinical Decision Support System-Generated STOPP/START Signals for Hospitalized Older Patients with Polypharmacy and Multimorbidity

Sallevelt et al. *Drugs Aging.* 2022



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Drugs & Aging (2022) 39:829–840
https://doi.org/10.1007/s40266-022-00964-9

ORIGINAL RESEARCH ARTICLE

ThinkCascades: A Tool for Identifying Clinically Important Prescribing Cascades Affecting Older People

Lisa M. McCarthy[1,2,3] · Rachel Savage[4,5] · Kieran Dalton[6] · Robin Mason[4,7] · Joyce Li[4] · Andrea Lawson[4] · Wei Wu[4] · Shelley A. Sternberg[8] · Stephen Byrne[6] · Mirko Petrovic[9] · Graziano Onder[10] · Antonio Cherubini[11] · Denis O'Mahony[12] · Jerry H. Gurwitz[13] · Francesco Pegreffi[14] · Paula A. Rochon[4,5,15,16]

Accepted: 22 June 2022 / Published online: 15 September 2022

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ThinkCascade

- 'Clinically important' prescribing cascades in older adults.

Drug A	Side effect	Drug B
Cardiovascular System (n=2)		
Calcium Channel Blocker →	Peripheral edema →	Diuretic
Diuretic →	Urinary incontinence →	Overactive bladder medication
Central Nervous System (n=4)		
Antipsychotic →	Extrapyramidal symptoms →	Antiparkinsonian agent
Benzodiazepine →	Cognitive impairment →	Cholinesterase inhibitor or memantine
Benzodiazepine →	Paradoxical agitation or agitation secondary to withdrawal →	Antipsychotic
SSRI / SNRI →	Insomnia →	Sleep agent
Musculoskeletal System (n=1)		
NSAID →	Hypertension →	Antihypertensive
Urogenital System (n=2)		
Urinary anticholinergics for overactive bladder →	Cognitive impairment →	Cholinesterase inhibitor or memantine
Alpha-1 receptor blocker →	Orthostatic hypotension, dizziness →	Vestibular sedatives

Challenges with deprescribing

Knowledge

- Identification of opportunities
- Knowing how to deprescribe

Fear of adverse drug withdrawal effects (ADWEs)

- These occur much less frequently than adverse drug effects

Responsibility

- Whose job is it anyway?

Time constraints

Overcoming challenges to deprescribing

Equip teams to become better deprescribers

- Geriatric pharmacotherapy education
- Explicit deprescribing criteria
  - Potential for software
- Deprescribing algorithms

Regular medication reviews

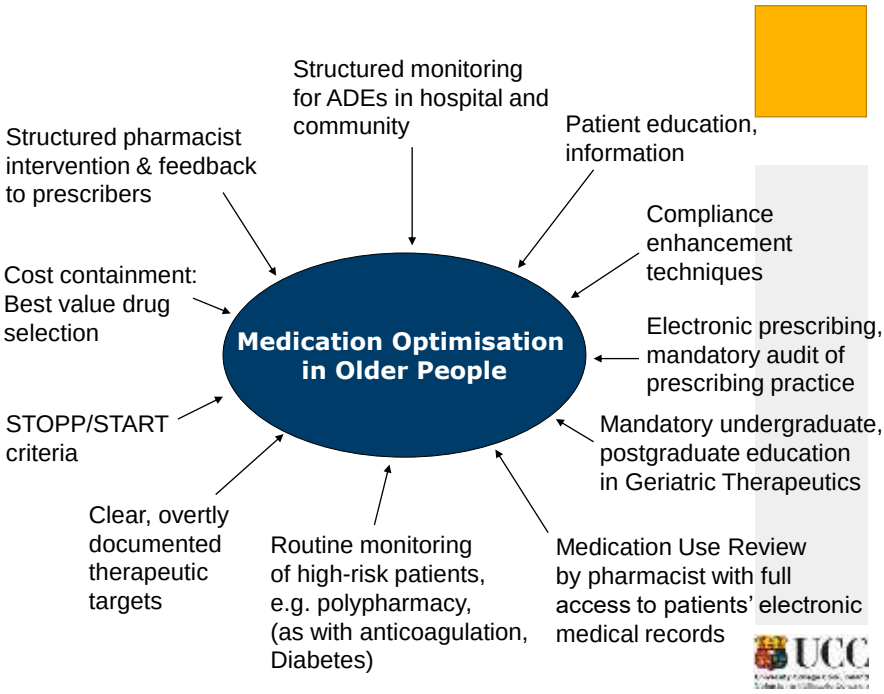
- Improving communication between levels of care

Patient involvement

- Education and empowerment
- Shared decision-making

Deprescribing Guideline Algorithms and Protocols

https://deprescribing.org/



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