CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Deprescribing in multi-morbid older people with polypharmacy: agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases
Authors	Curtin, Denis;Dukelow, Tim;James, Kirstyn;O'Donnell, Desmond;O'Mahony, Denis;Gallagher, Paul F.
Publication date	2018-11-12
Original Citation	Curtin, D., Dukelow, T., James, K., O'Donnell, D., O'Mahony, D. and Gallagher, P. (2018) 'Deprescribing in multi-morbid older people with polypharmacy: agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases', European Journal of Clinical Pharmacology. doi: 10.1007/s00228-018-2598-y
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1007/s00228-018-2598-y
Rights	© 2018, Springer-Verlag GmbH Germany, part of Springer Nature. All rights reserved. The final publication is available at Springer via https://dx.doi.org/10.1007/s00228-018-2598-y
Download date	2026-11-04 04:55:01
Item downloaded from	https://hdl.handle.net/10468/7152

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Title: Deprescribing in multi-morbid older people with polypharmacy: Agreement between STOPPFrail explicit criteria and Gold Standard deprescribing using 100 standardized clinical cases.

Denis Curtin [1, 2], Tim Dukelow[1], Kirstyn James[1], Desmond O'Donnell[1], Denis O'Mahony[1, 2], Paul Gallagher[1, 2].

1. Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland, T12 DC4A.
2. Department of Medicine, University College Cork, Ireland.

Corresponding Author:

Denis Curtin

Address: Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland, T12 DC4A

Email: DenisCurtin@physicians.ie

Abstract

Purpose - Older people with advanced frailty are among the highest consumers of medications. When life expectancy is limited, some of these medications are likely to be inappropriate. The aim of this study was to compare STOPPFrail, a concise, easy-to-use, deprescribing tool based on explicit criteria, with gold standard, systematic geriatrician-led deprescribing.

Methods– 100 standardized clinical cases involving 1024 medications were prepared. Clinical cases were based on anonymized hospitalized patients aged ≥65 years, with advanced frailty (Clinical Frailty Scale ≥6), receiving ≥5 regular medications, who were selected from a recent observational study. Level of agreement between deprescribing methods was measured by Cohen's Kappa coefficient. Sensitivity and positive predictive value of STOPPFrail-guided deprescribing relative to gold standard deprescribing was also measured.

Results – Overall, 524 medications (51.2%) of medications prescribed to this frail, elderly cohort were potentially inappropriate by gold standard criteria. STOPPFrail-guided deprescribing led to the identification of 70.2% of the potentially inappropriate medications. Cohen's kappa was 0.60 (95% confidence interval 0.55 -0.65; p<0.001) indicating moderate agreement between STOPPFrail-guided and gold standard deprescribing. The positive predictive value of STOPPFrail was 89.3% indicating that the great majority of deprescribing decisions aligned with gold standard care.

Conclusions - STOPPFrail removes an important barrier to deprescribing by explicitly highlighting circumstances where commonly used medications can be safely deprescribed in older people with advanced frailty. Our results suggest that in multi-morbid older patients with advanced frailty, the use of STOPPFrail criteria to address inappropriate polypharmacy may be reasonable alternative to specialist medication review.

Keywords

STOPPFrail, deprescribing, frailty, polypharmacy, multimorbidity

Introduction

An important principle when caring for older people with multi-morbidity is to carefully align the medication regimen to the condition and goals of care of the individual patient.[1] This is particularly important for patients approaching end of life where symptom management usually takes priority over stringent chronic disease control. Polypharmacy is common in this cohort and many of these patients are prescribed medications that are probably futile.[2] Yet physicians commonly forego the opportunity to deprescribe because of fear of negative consequences (i.e symptom relapse, clinical deterioration).[3, 4] This is despite evidence indicating that deprescribing can be achieved without compromising patient safety or wellbeing [5-7].

The complexity associated with frailty, multi-morbidity and polypharmacy necessitates a systematic approach to deprescribing. Scott and colleagues have recently proposed a 5-step deprescribing protocol (CEASE –**C**onfirm current medications; **E**stimate risk of drug-related harm; **A**ssess each medication for decontinuation; **S**ort/ prioritize medications for discontinuation; **E**liminate medications according to agreed deprescribing plan). The third step –assessing each medication for discontinuation - requires the user to answer a series of questions about each medication in the patient's regimen (**Figure 1**).[8] While comprehensive and patient-centred, the outcome of this step will depend on the knowledge, attitudes and experience of the user. Implicit approaches, such as CEASE, are usually time-consuming, thereby greatly limiting their integration into routine clinical practice.[9] More recently, the STOPPFrail criteria (**Table 1**), a list of 27 indicators to assist physicians with deprescribing decisions in frail older individuals with poor 1 year survival prognosis, have been validated.[10] Of the 27 indicators, 26 are explicit (i.e. clearly defined statements highlighting the potentially inappropriate use of particular drug/ drug classes in a particular clinical situation) and one is implicit (i.e. A2: Stop any drug without a clear clinical indication). STOPPFrail criteria, which are organized according to physiological system, are concise, have substantial inter-rater reliability,[11] and are designed to be used by physicians of all disciplines who provide care for frailer older people on a routine basis.

The primary aim of the present study is to compare the utility of the structured predominantly explicit STOPPFrail criteria with a gold standard comparitor in frail older people with poor 1-year survival prognosis. Of the available published deprescribing guides, the CEASE protocol has the strongest evidence of efficacy and physician acceptabilty,[12] and therefore, its use by a physician with expertise in clinical pharmacotherapy is an appropriate gold standard for deprescribing. If STOPPFrail reproduces the results of this gold standard, then it's brevity and easy usability may make it a more appropriate method of deprescribing in routine clinical practice for this particular population of older people. The secondary aim was to determine which inappropriate or unnecessary medications are not identified by STOPPFrail. This information could inform future iterations of the STOPPFrail criteria.

Methodology

Clinical cases

To ensure that the comparison between the two deprescribing methods was valid, it was important to minimize external sources of variability.[13] For this reason, structured clinical cases were prepared to ensure timely and equal access to information relevant to the deprescribing decision (**supplementary appendix 1**). These clinical cases were based on anonymized patients included in a recent observational study that examined the prevalence of potentially inappropriate medications in the discharge prescriptions of older people hospitalized in the year prior to their death.[2] Each structured clinical case included a list of diagnoses, regular medications, functional and cognitive status and routine blood tests results prior to hospital discharge. All clinical cases were based on patients aged ≥65 years, prescribed ≥5 regular medications with moderate to severe frailty (Clinical Frailty Score ≥6 [14]). For each of the clinical cases, it was assumed that:

i. The patient was medically stable
ii. The patient had a poor 1 year survival prognosis
iii. The list of diagnoses was complete and correct
iv. Laxatives (unless potentially part of a prescribing cascade) and paracetamol were appropriate
v. There were no difficulties with medication administration (e.g. dysphagia, poor inhaler technique etc.) unless explicitly stated
vi. The patient's nutritional status was satisfactory unless otherwise stated
vii. Behavioural and psychological symptoms of dementia were present only if explicitly stated

Application of deprescribing methods

Four physicians, all trained in geriatric medicine, reviewed the clinical cases and identified medications that were potentially eligible for deprescribing. Two physicians (DC and DOD) rigidly applied STOPPFrail criteria while the other physicians (KJ and TD), who were not familiar with STOPPFrail criteria, identified drugs to be deprescribed using step 3 of the CEASE protocol (hereafter referred to as Scott's deprescribing algorithm; **figure 1**). The physicians were instructed to document the primary reason for each deprescribing decision. Drugs that were not eligible for deprescribing were classified as 'important'. The physicians initially worked independently and then resolved any discrepancies in pairs to produce a final consensus list for each deprescribing method.

Sample size calculation and statistical analysis

A sample size of 100 was chosen to detect with 80% probability a Cohen's kappa coefficient of 0.70 under the alternative hypothesis when Cohen's kappa under the null hypothesis was 0.6. This sample size would also allow for more than 500 medications to be evaluated. Cohen's kappa

coefficient was interpreted as poor if ≤0.2, fair if 0.21–0.40, moderate if 0.51–0.6, substantial if 0.61–0.8 and almost perfect if 0.81–1.00.[15] Statistical analysis was performed using SPSS® version 21.

Results

Clinical cases

The mean number of medications per clinical case was 10.2 (standard deviation 3.3). The total number of medications to be evaluated (when paracetamol was excluded) was 994. Most medications were taken orally (88.7%), while the remainder were administered by inhaled (5.1%), transdermal (3%), topical (2%), or subcutaneous/ intramuscular (1.3%) routes.

Agreement between methods

The physicians using the Scott's deprescribing algorithm identified 524 medications (52.7% of the total) as potentially eligible for deprescribing; the physicians using STOPPFrail criteria identified 412 medications for deprescribing (41.4%; see **Supplementary appendix 2**). Cohen's kappa co-efficient was 0.60 (95% confidence interval 0.55 -0.65; p<0.001) indicating moderate agreement between the methods. With Scott's deprescribing algorithm representing the gold standard, the sensitivity of STOPPFrail (i.e. the proportion of *inappropriate* medications correctly identified by STOPPFrail) was 70.2%. The specificity (i.e. the proportion of *important* medications that were correctly continued by the physicians using STOPPFrail) was 90.6%. The positive predictive value of STOPPFrail (i.e. the proportion of medications deemed *inappropriate* by the physicians using STOPPFrail that were actually inappropriate) was 89.3% while the negative predictive value (i.e. the proportion of medications deemed *important* by the physicians using STOPPFrail that were actually important) was 73.2%.

The primary reasons for the deprescribing decisions are summarized in **Supplementary appendix 3**. 'No valid indication' was the primary reason for 50% of the deprescribing decisions made by the physicians using Scott's deprescribing algorithm and in 42.7% of the decisions made by the physicians using STOPPFrail. Lipid lowering agents, proton pump inhibitors, calcium and anti-resorptive drugs for osteoporosis accounted for 33% of the medications deprescribed using STOPPFrail.

Discrepancies between methods

The physicians using STOPPFrail did not identify 156 medications (29.7%) that were potentially eligible for deprescribing (**Table 2**). Antihypertensive agents, vitamin D supplements and laxatives

(prescribed as part of a prescribing cascade) accounted for 54.4% of the potentially inappropriate medications that were not identified by the physicians using STOPPFrail. The physicians using STOPPFrail deprescribed calcium supplements and continued vitamin D preparations in all cases while the physicians guided by Scott's algorithm were more selective and generally continued these medications when a history of osteoporosis, fractures or recurrent falls was included in the patients' medical history.

Discussion

This study is important because it shows that approximately half of all the medications prescribed to older people approaching end of life may be unnecessary or inappropriate. Many people with advanced frailty and polypharmacy will not have the benefit of a comprehensive specialist medication review. In this study, application of STOPPFrail -a novel, concise explicit deprescribing tool designed for all physicians who commonly provide care for older adults approaching end of life - demonstrated moderate agreement with gold-standard specialist geriatrician-led deprescribing.

A major barrier to deprescribing is the difficulty associated with balancing risk and benefit of a specific medication for a particular patient. STOPPFrail addresses this difficulty by explicitly highlighting circumstances where commonly used medications can be safely discontinued. There is good evidence that people are much more likely to follow through on tasks that they see value in *when* those tasks are made easier for them.[16 -18] It is therefore likely that providing explicit criteria will make the task of deprescribing more accessible to non-specialist physicians who care for older, adults approaching end of life.

The physicians using the STOPPFrail criteria identified 70.2% of medications that were potentially eligible for deprescribing according to gold standard assessment. When medications for deprescribing were identified by the physicians using STOPPFrail, these medications were *actually* inappropriate in 89.3% of cases. While the use of STOPPFrail does not 'catch all' potentially inappropriate medications, it is very reassuring that the great majority of the deprescribing decisions appear to align with gold standard care.

For both methods, the most common reason for deprescribing was 'no valid indication'. This emphasizes the importance, during a medication review, of ensuring that each drug is linked to a diagnosis or active symptom. While STOPPFrail explicit criteria largely address step 2 (harm outweighs benefit) and step 4 (preventive drugs –benefit unlikely to be realized) of Scott's deprescribing algorithm, future iterations may need to go further to address aspects of step 3 (symptom or disease control drugs). For example, STOPPFrail does not prompt the physician to review symptoms such as pain which may be over-treated with potentially problematic medications. Furthermore, symptoms such as poor appetite, nausea, altered bowel habit, sedation and gait disturbance, which may represent the adverse effects of drugs, are not targeted. Finally, antihypertensive therapies and vitamin D supplements were the most common inappropriate or unnecessary medications that were not identified by the physicians using STOPPFrail. These drugs

are commonly prescribed yet evidence of clear benefit, as well as specific guidance for use in people with advanced frailty, is lacking.[19 22] In the absence of high quality clinical trial evidence, explicit criteria based on expert consensus opinion may enable physicians to make clinically sound decisions about the use of these medications in this particular expanding patient population.

All structured clinical cases in this study were derived from data collected from a cohort of hospitalized patients who died within 1 year of their hospital admission. A CFS score ≥6 was used to select frail patients from this cohort which would ensure that the deprescribing task was credible and that a short term risk of death was not unforseeable. It is important to emphasize that, in everyday clinical practice, we do not recommend using a CFS score ≥6 to select patients for STOPPFrail –guided deprescribing. STOPPFrail is intended for older people approaching end of life for whom the goal of care is to enhance quality of life and minimize the risk of drug-related complications. In the absense of sensitve and reliable prediction models,[23] identifiying older people who are approaching end of life will depend largely on physician experience and judgement.[10]

Our study has some potential limitations. Firstly, it was a theoretical exercise using structured clinical cases. While derived from real patient data, the structured clinical cases do not reflect the complexities and nuances of real clinical care. However, we contend that standardization was necessary because external sources of variability (e.g. inequality of information) could have invalidated the primary aim of the study which was to compare the two methods of deprescribing.[13] Secondly, two physicians trained in geriatric medicine, arriving at deprescribing decisions through consensus, using Scott's deprescribing algorithm, represented 'gold standard' deprescribing in this study. It is important to emphasize that 'gold standard' does not necessarily mean 'perfect' but rather 'best available'.[24] We believe the method used in this study is likely to be very close to the 'best available' deprescribing for this population of patients in most hospitals.

In summary, the results of this study indicate that the STOPPFrail criteria can assist physicians in making appropriate deprescribing decisions and that, reassuringly, these decisions align closely with gold standard deprescribing. In everyday clinical practice, where frail older people approaching end of life are commonly encountered by attending physicians with variable expertise, STOPPFrail guided deprescribing may be a reasonable alternative to specialist medication review. Future iterations of STOPPFrail should include guidance on antihypertensive therapy discontinuation as well as prompts to the physician to explore particular symptoms which may represent adverse drug events.

Acknowledgements

Conflict of interest

O'Mahony and Gallagher were involved in the development of the STOPPFrail Criteria.

Author contributions

Curtin, O'Mahony, Gallagher: study concept and design. Curtin, Dukelow, James, O'Donnell: application of deprescribing methods. Curtin, O'Mahony, Gallagher: preparation of manuscript. All authors: critical revision and final approval of manuscript.

Sponsor's role

Curtin and O'Mahony are supported by the European Union's Horizon 2020 research and innovation programme (grant number 634238). The sponsor had no role in the design, conduct or reporting of this study.

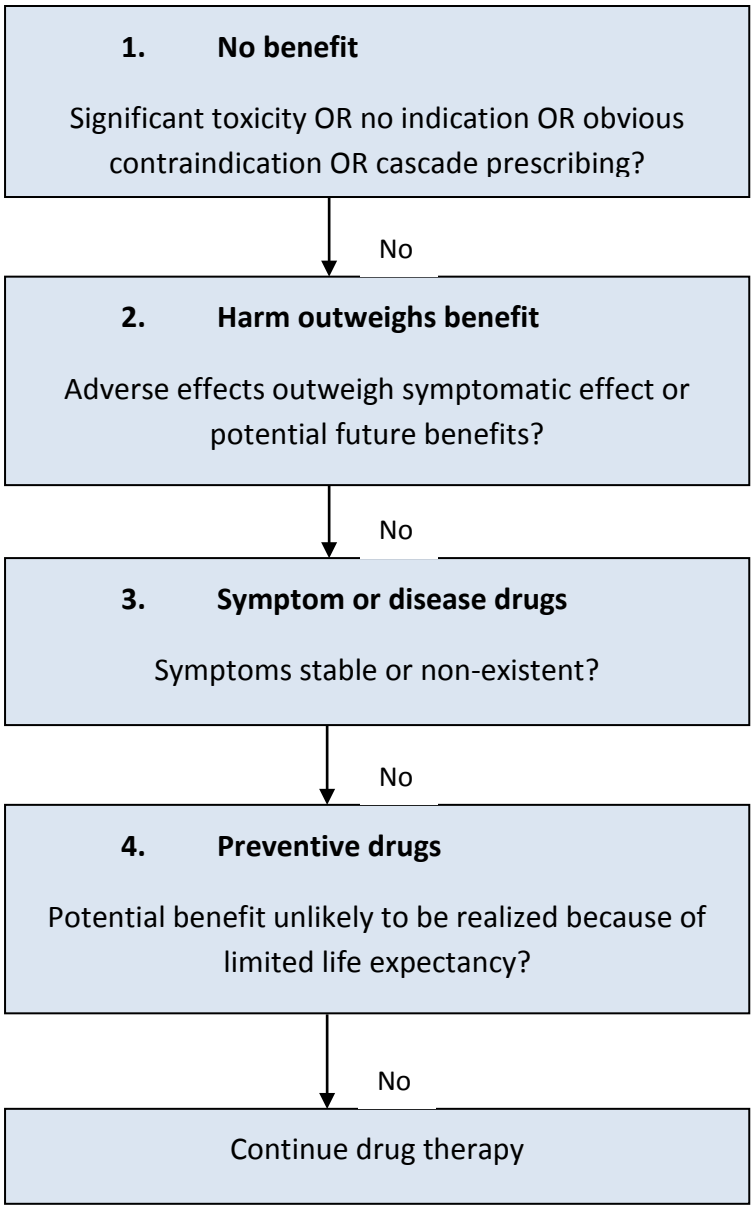


Figure 1: Step 3 of the CEASE protocol: Scott's deprescribing algorithm

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:

1) **End-stage irreversible pathology**
2) **Poor one year survival prognosis**
3) **Severe functional or severe cognitive impairment or both**
4) **Symptom control is the priority rather than prevention of disease progression**

The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:

1) **Drug adherence/compliance is difficult**
2) **Administration of the medication is challenging**
3) **Monitoring of the medication effect is challenging**
4) **Drug adherence/ compliance is difficult**

Section A: General

A1: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations.
A2: Any drug without clear clinical indication.

Section B: Cardiology system

B1. Lipid lowering therapies (statins, ezetimibe, bile acid sequestrans, fibrates, nicotinic acid and acipimox)
These medications need to be prescribed for a long duration to be of benefit. For short-term use, the risk of adverse drug events (ADEs) outweighs the potential benefits
B2. Alpha-blockers for hypertension
Stringent blood pressure control is not required in very frail older people. Alpha blockers in particular can cause marked vasodilatation, which can result in marked postural hypotension, falls and injuries

Section C: Coagulation system

C1: Anti-platelets
Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit)

Section D: Central Nervous System

D1. Neuroleptic antipsychotics
Aim to reduce dose and discontinue these drugs in patients taking them for longer than 12 weeks if there are no current clinical features of behavioural and psychiatric symptoms of dementia (BPSD)
D2: Memantine
Discontinue and monitor in patients with moderate to severe dementia, unless
memantine has clearly improved BPSD (specifically in frail patients who meet the criteria above)

Section E: Gastrointestinal System

E1. Proton Pump Inhibitors
Proton Pump Inhibitors at full therapeutic dose ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
E2: H2 receptor antagonist
H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
E3. Gastrointestinal antispasmodics
Regular daily prescription of gastrointestinal antispasmodics agents unless the patient has frequent relapse of colic symptoms because of high risk of anti-cholinergic side effects

Section F: Respiratory System

F1. Theophylline.
This drug has a narrow therapeutic index, requires monitoring of serum levels and interacts with other commonly prescribed drugs putting patients at an increased risk of ADEs
F2. Leukotriene antagonists (Montelukast, Zafirlukast)
These drugs have no proven role in COPD, they are indicated only in asthma (50)

Section G: Musculoskeletal System

G1: Calcium supplementation
Unlikely to be of any benefit in the short term
G2: Anti-resorptive/bone anabolic drugs *FOR OSTEOPOROSIS* (**bisphosphonates, strontium, teriparatide, denosumab)**
G3. Selective Estrogen Receptor Modulators (SERMs) for osteoporosis
Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated ADEs particularly venous thromboembolism and stroke
G4. Long-term oral NSAIDs
Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months
G5. Long-term oral steroids
Increased risk of side effects (peptic ulcer disease etc.) when taken regularly for ≥ 2 months. Consider careful dose reduction and discontinuation

Section H: Urogenital System

H1. 5-alpha reductase inhibitors
No benefit with long term urinary bladder catheterisation
H2. Alpha blockers
No benefit with long term urinary bladder catheterisation
H3. Muscarinic antagonists
No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity

Section I: Endocrine System

I1. Diabetic oral agents
Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary
I2. ACE-Inhibitors for diabetes
Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis
I3. Angiotensin Receptor Blockers (ARBs)
Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis
I4. Systemic oestrogens for menopausal symptoms
Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms

Section J: Miscellaneous

J1. Multi-vitamin combination supplements
Discontinue when prescribed for prophylaxis rather than treatment
J2. Nutritional supplements (other than vitamins)
Discontinue when prescribed for prophylaxis rather than treatment
J3: Prophylactic Antibiotics
No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs

Disclaimer (STOPPFrail)

Whilst every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence-based, it is emphasized that the final decision to avoid or initiate any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that prescribing decisions should take account of current published evidence in support of or against the use of drugs or drug classes described in STOPPFrail.

Table 1: The STOPPFrail criteria [12]

Potentially inappropriate or unnecessary drugs which were not identified by STOPPFrail (N=156)	N	(%)	Drugs inappropriately identified for deprescribing using STOPPFrail criteria (N=44)	N	(%)
Antihypertensive agents	32	(20.5%)	Calcium supplements	11	(25%)
Vitamin D supplements	31	(19.8%)	Anti-resoptive/ bone anabolic drugs	12	(27.3%)
Laxatives (as part of prescribing cascade)	22	(14.1%)	Memantine	6	(13.6%)
Harm outweighs benefit	16	(10.2%)	Prednisolone	3	(6.8%)
Antiplatelets in patients with advanced frailty/ remote history of vascular events	16	(10.2%)	Miscellaneous	12	(27.3%)
Cholinesterase inhibitors in patients with advanced dementia	4	(2.6%)			
Miscellaneous	35	(22.4%)			

Table 2: Discrepancies between the deprescribing methods: STOPPFrail guided-deprescribing evaluated against 'gold standard' deprescribing

References

1. Steinman MA, Hanlon JT (2010) Managing medications in clinically complex elders: "There's got to be a happy medium". JAMA;304:1592.
2. Curtin D, O'Mahony D, Gallagher P (2018) Drug consumption and futile medication prescribing in the last year of life: an observational study. Age and Ageing; 47:749-753.
3. Jansen J, Naganathan V, Carter SM, et al (2016) Too much medicine in older people? Deprescribing through shared decision making. BMJ;353:I2893.
4. Anderson K, Freeman C, Stowasser D, Scott I (2014) Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. BMJ Open;4:e006544.
5. Wouters H, Scheper J, Koning H et al (2017) Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 167(9):609-617.
6. Potter K, Flicker L, Page A, et al (2016) Deprescribing in Frail Older People: A Randomised Controlled Trial. PLoS One. 11(3).
7. Garfinkel D (2018) Poly-de-prescribing to treat polypharmacy: efficacy and safety. *Ther Adv Drug Saf*; 9(1) 25–43.
8. Scott IA, Hilmer SN, Reeve E, et al (2015) Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med.;175(5):827-34.
9. Spinewine A, Schmader KE, Barber N, et al (2007) Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet.;370(9582):173-84.
10. Lavan AH, Gallagher P, Parsons C, O'Mahony D (2017) STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age and Ageing; 0: 1–8.
11. Lavan AH, Gallagher P, O'Mahony D (2017) Inter-rater reliability of STOPPFrail [Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy] criteria amongst 12 physicians. Eur J Clin Pharmacol. doi: 10.1007/s00228-017-2376-2. [Epub ahead of print]
12. Scott I, Anderson K, Freeman C. Review of structured guides for deprescribing. Eur J Hosp Pharm 2017; 24:51-57.
13. Watson PF, Petrie A (2010) Method agreement analysis: a review of correct methodology. Theriogenology.;73(9):1167-79.
14. Rockwood K, Song X, MacKnight C, et al (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ; 173:489–495.
15. Landis JR, Koch GG (1977). The measurement of observer agreement for categorical data. Biometrics;33:159–74.

16. Leventhal, H (1965). Effects of Fear and Specificity of Recommendation upon Attitudes and Behavior. J Pers Soc Psychol.2(1):20-29.
17. Bucher T, Collins C, Rollo ME, et al (2016) Nudging consumers towards healthier choices: a systematic review of positional influences on food choice. Br J Nutr;115(12):2252-63.
18. Bednall TC, Bove LL (2011) Donating blood: a meta-analytic review of self-reported motivators and deterrents. Transfus Med Rev.;25(4):317-34.
19. Benetos A, Rossignol P, Cherubini A, et al (2015). Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians. JAMA.;14;314(2):170-80.
20. Autier P, Mullie P, Macacu A, et al (2017) Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol.;5(12):986-1004.
21. Zheng Y, Zhu J, Zhou M, Cui L, Yao W, Liu Y (2013) Meta-analysis of long-term vitamin D supplementation on overall mortality. PLoS One.;8(12):e82109.
22. Hill TR, Aspray TJ (2017) The role of vitamin D in maintaining bone health in older people. Ther Adv Musculoskelet Dis. 2017;9(4):89-95.
23. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. JAMA. 2012;307(2):182-92.
24. Versi E (1992) "Gold standard" is an appropriate term. BMJ; 305(6846):187.