STOPPFrail [Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy]: Consensus validation

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STOPPFrail [Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy]: Consensus validation

Abstract

Objective

To validate STOPPFrail, a list of explicit criteria for potentially inappropriate medication (PIM) use in frail older adults with limited life expectancy.

Design

A Delphi consensus survey of an expert panel comprising academic geriatricians, clinical pharmacologists, palliative care physicians, old age psychiatrists, general practitioners and clinical pharmacists.

Setting

Ireland.

Subjects

Seventeen panellists.

Methods

STOPPFrail criteria were initially created by the authors based on clinical experience and literature appraisal. Criteria were organised according to physiological system; each criterion accompanied by an explanation. Using Delphi consensus methodology, panellists ranked their agreement with each criterion on a 5-point Likert scale and provided written feedback. Criteria with a median Likert response of 4/5 (agree/strongly agree) and a 25^{th} centile of ≥4 were included in the final list.

Results

All panellists completed 3 Delphi rounds. Thirty criteria were proposed; 27 were accepted. The first two criteria suggest deprescribing medications without indication or where compliance is poor. The remaining 25 criteria include lipid-lowering therapies, alpha-blockers for hypertension, anti-platelets, neuroleptics, memantine, proton-pump-inhibitors, H2-receptor antagonists, anti-spasmodic agents, theophylline, leukotriene antagonists, calcium supplements, bone anti-resorptive therapy, selective oestrogen receptor modulators, non-steroidal anti-inflammatories, corticosteroids, 5-alpha-reductase inhibitors, alpha-1-selective blockers, muscarinic antagonists, oral diabetic agents, ACE-inhibitors, angiotensin receptor blockers, systemic oestrogens, multivitamins, nutritional supplements and prophylactic antibiotics. Consensus could not be reached on the inclusion of acetyl-cholinesterase inhibitors. Full consensus was reached on exclusion of anticoagulants and anti-depressants from the list.

Conclusion

STOPPFrail comprises 27 criteria relating to medications that are potentially inappropriate in frail older patients with limited life expectancy. STOPPFrail may assist physicians in deprescribing medications in these patients.

Keywords

Frail, life expectancy, deprescribing, polypharmacy, explicit criteria

Key points

STOPPFrail comprises 27 criteria for potentially inappropriate medications in frail older adults with limited life expectancy.

STOPPFrail may serve to assist physicians in deprescribing medications in a structured fashion in this group.

STOPPFrail can be applied in frail older adults with limited life expectancy in any healthcare setting.

Introduction

Population demographics are changing globally, with the greatest proportional increases seen in those aged ≥70 years [**1**]**.** Many older people are surviving longer with complex co-morbid illnesses including dementia, chronic kidney disease, cardiovascular disease, chronic lung disease and cancer, many of which contribute to frailty and poor survival prognosis [**2**, 3]. Chronic illnesses coupled with normal physiological ageing can have a negative impact on cognition and functional ability. In such patients, the final months of life are often characterised by frailty and increased dependency thus requiring re-evaluation of treatment goals, particularly medications intended to have long-term preventative effects such as lipid lowering drugs, anti-diabetic agents and cognitive enhancing drugs.

Nursing home residents are usually frail, with high levels of functional dependency, multiple co-morbid illnesses and high levels of medication use [**4, 5**]. In Ireland, 6% of adults aged ≥65 years live in nursing homes, increasing to 12% in those 80 to 84 years and 25% in those over 85 years [**6**]. In the United States [US], similar figures are seen with approximately 5% of adults' ≥67 years living in institutional care [**7**]. These proportions are likely to increase with current demographic trends. Currently, the median length of time from nursing home admission to death in the US is five months and within 1 year of admission, 65% of residents have died [**8**]. Clearly, the majority of older patients requiring admission to nursing homes have a limited life expectancy compared to those residing in the community. However, this frail group represents some of the highest consumers of prescription medications, despite a clearly reduced likelihood of long-term clinical benefit. The SHELTER study reports the rate of polypharmacy (5 – 9 drugs) and excessive polypharmacy (≥10 drugs) in nursing home residents to be 48.7% and 24.3% respectively [**9**].

Inappropriate prescribing (IP) is also prevalent in older adults. IP pertains to the mis-prescribing, overprescribing and under prescribing of medications in the context of a person's co-morbidities, full medication regime, functional and cognitive status as well as treatment goals and life expectancy [10]. In one US study of nursing home residents with dementia, more than half

received at least one daily drug of questionable benefit [**11**]. Polypharmacy and IP in older adults are linked to adverse drug events (ADEs), which can have a negative impact particularly on frail, multi-morbid nursing home residents [12]

Despite the high prevalence rates of polypharmacy and IP in the nursing home population, there is a paucity of evidence regarding the deprescribing of medications in older frail people with poor survival prognosis. Deprescribing refers to the process of tapering or stopping medications, aimed at reducing polypharmacy and improving patient outcomes. Although healthcare professionals, patients and their relatives all acknowledge the burden of polypharmacy for older people including administration time, adverse effects and cost, all groups display passivity towards deprescribing [**13**]. General Practitioners (GPs) cite many challenges to deprescribing including organisational factors, suboptimal medical and pharmacy records, limited time and limited training of nursing staff. Consequently, less than half use a consistent approach to deprescribing [**14**]. The National Institute for health and Care Excellence (NICE) recommend annual medication reviews in care home residents, during which appropriateness of medications should be optimised including deprescribing where necessary [**15**]. For community dwelling older adults with chronic diseases, no time frame is suggested [16, 17].

Although frailty is sometimes difficult to define, it is common in later life and increases with age [**18**]. Over 50% of nursing home residents [**4**] and 17% of community dwelling older adults are considered frail [19]. In the United Kingdom (UK) 14% of hospital admissions have at least one frailty syndrome [**20**]. Not all patients who are frail have a limited life expectancy, however, numerous studies link frailty to worsening disability, hospitalisation and death [**21**]. In patients with frailty and limited life expectancy, medication review should primarily focus on deprescribing and symptom management, rather than aggressive preventative strategies.

Numerous explicit prescribing tools aim to guide clinicians on cessation of PIMs including Beers [**22**], STOPP/START [**23**] and FORTA criteria [**24**]. STOPP/START criteria have been shown to improve medication appropriateness [**25, 26**] and reduce the incidence of adverse drug reactions

(ADRs) in hospitalised older adults [**27**]. However, these comprehensive tools are designed to detect common and preventable PIMs in the general older population and not specifically in frailer people with limited life expectancy. Indeed, STOPP/START criteria have limited applicability in this cohort. For instance patients with limited life expectancy would be unlikely to survive long enough to derive benefit from most medication listed in the START criteria. Furthermore, STOPP criteria do not suggest discontinuing major drugs classes that are least likely to have benefits in the last year of life e.g. statins. Therefore, with the accepted need for deprescribing in the frail older population, there is a clear associated need for specific explicit criteria to guide the prescriber. To date, no explicit guidelines exist for deprescribing in frailer older people with limited life expectancy, other than NORGEP-NH criteria, which are specific to the nursing home population [**28]**.

We aimed to develop an explicit tool, called STOPPFrail, to assist clinicians with deprescribing medications in frailer older adults with limited life expectancy in all healthcare settings.

Methods

Draft STOPPFrail criteria

The authors, all of whom have recognised expertise in geriatric pharmacotherapy, compiled the initial draft of STOPPFrail indicators and arranged them according to physiological systems, similar to STOPP/START criteria. We then identified the target for whom these criteria would be applicable i.e. (i) end-stage irreversible pathology, (ii) poor one year survival prognosis, (iii) severe physical functional impairment or cognitive impairment of both, (iv) symptom control is the priority rather than prevention of disease. Since the most consistent predictors of mortality are co-morbidities and functional impairment [**29**], our definition of patients who are appropriate for deprescribing according to STOPPFrail criteria was based on these essential indicators, rather than the presence of specific diseases, such as dementia or cancer. Also Incorporated in the tool are

challenges associated with medication use in this population, such as administration time and physical discomfort, as these have been reported by healthcare professionals, patients and their families to be of concern [**13**].

Following this, the evidence base for each drug or drug class was checked using the British National Formulary and an extensive literature review, limited to the last 20 years. Literature searches of PubMed, Cinahl and Google Scholar were undertaken. Searches included the drug in question with key words such as “life expectancy”, “frailty”, “older adults”, “poor prognosis”, “deprescribing”, “inappropriate prescribing” and “adverse drug events”. The draft criteria were agreed on a consensus basis by the authors and subsequently distributed to a panel of experts for validation by the Delphi technique [**30**], an established method for achieving consensus. The Delphi method was used for this research because of the lack of rigorous randomised controlled evidence supporting the long term benefits of preventive drugs in frailer older adults with complex co-morbidities and limited life expectancy; such patients are commonly excluded from clinical trials of drug therapies [**31**].

Expert panel selection

In June 2015, twenty five experts, were invited to participate in the Delphi process. Panellists were selected on the basis of their recognised academic credentials, clinical practice, experience and geographical diversity. After the study design and aims were explained to each participant, seventeen agreed to participate. The panel consisted of consultant geriatricians [n=6], clinical pharmacologists [n=3], old age psychiatrists [n=1], palliative care physicians [n=3], as well as senior academic primary care physicians [n=2] and clinical pharmacists with an interest in geriatric pharmacotherapy [n=2]. All of the panellists were affiliated with Irish university teaching hospitals (two in Northern Ireland). The panel was provided with an electronic repository containing supporting references for the proposed STOPPFrail criteria. Panellists’ competed the Delphi process between July 2015 and February 2016.

Data Collection and Analysis

Each round was sent to the panellists using an online survey [SurveyMonkey®]. The first Delphi round consisted of 30 criteria. Each criterion was presented in the same format i.e. a drug or drug class deemed potentially inappropriate followed by an explanatory sentence. Panellists rated their agreement with each statement on a 5-point Likert scale, where 5 = strongly agree, 4 = agree, 3 = neutral, 2 = disagree, 1 = strongly disagree, 0 = unable to offer an opinion [**32**]. In round 1, panellists were also asked to offer suggestions or comments (including new drugs) as appropriate.

Statistical analysis

For each statement, consensus was based on the median Likert response and interquartile range. A median value of 4 or 5 with a 25th centile of ≥4 was accepted for inclusion in the tool i.e. only statements with at least 75% of respondents agreeing or strongly agreeing were included. Proposed criteria with a median value of ≤3 were rejected: those with a median value of 4 or 5 and a 25th centile of < 4 were rephrased in accordance with panellists' suggestions and included in the next Delphi round. Statistical analysis was performed using IBM SPSS® Statistics version 22.

Results

All panellists completed the Delphi validation process in three rounds (**Figure 1**); 27 criteria comprise the final STOPPFrail tool (**Table 1**). Full statistical analysis (i.e. the phrasing of criteria and the distribution of the responses for each round) is available in supplementary data

In round 1, twenty criteria were accepted. The first proposed criterion included in STOPPFrail was a general statement that any drug prescribed without a clinical indication should be discontinued. The remaining 19 criteria accepted included lipid-lowering agents, alpha-blockers for hypertension, neuroleptics, proton pump inhibitors, theophyllines, leukotriene receptor antagonists, selective estrogen receptor modulators, non-steroidal anti-inflammatories, steroids, 5-alpha reductase inhibitors and alpha-blockers in catheterised patients, muscarinic antagonists, diabetic

oral agents, Angiotension-converting-enzyme inhibitors, Angiotensin receptor antagonists, multivitamins and nutritional supplements.

Two criteria were rejected in round 1. The first was the prescription of anticoagulants as a preventative measure. Our research group proposed discontinuation of as we considered that the bleeding risk and cost of treating outweighed the potential benefits to patients in whom cognition and function were poor. Panellists agreed that in the majority of people meeting the criteria for STOPPFrail, anticoagulants should be stopped, however this criterion was rejected due to their concern over the minority of patients in whom stopping anticoagulants would be potentially inappropriate. Specifically, the majority considered that, regardless of frailty and life expectancy, stroke was an unfavourable outcome. Both panellists and the authors agreed that individual clinical judgement should be applied based on individual preferences and priorities with regards to anti-coagulation. In recent years, anticoagulation has become easier, safer and more efficient due to novel anticoagulant drugs. Therefore panellists felt that in patients receiving anti-coagulants with minimal side effects, continuation was warranted.

The second criterion rejected in round 1 was the use of anti-depressants in patients with advanced dementia. Reasons for rejection included possible benefits outside anti-depressant effects such as analgesic effects, appetite stimulation and anxiolytic properties. Feedback suggested that cessation in patients with severe dementia was a reasonable approach, but not in all patients with limited life expectancy. Panellists feared that antidepressant therapy could be stopped in patients who derived benefit from treatment and that the risk of relapse outweighed the potential benefit of discontinuation.

Eight criteria were deemed inconclusive after round 1. The first was a general criterion of deprescribing any drug with which patients fail to comply. Feedback suggested that the explanatory sentence should remind users to try all appropriate measures to improve compliance before deprescribing; this criterion was rephrased accordingly for round 2. Other drugs for which there was

uncertainty among the panel were anti-platelets, memantine, acetylcholinesterase inhibitors, H2-receptor antagonists, calcium and vitamin D supplements, bone anti-resorptive/anabolic agents and prophylactic antibiotics. Feedback was incorporated into rephrasing the criteria for round 2.

Panellists agreed with the inclusion of anti-platelet agents, but raised concerns over their cessation when their indication was secondary prevention. Similar to the feedback for anti-coagulation, panellists were concerned about the minority of patients were deprescribing may be inappropriate. It was felt that secondary prevention should incorporate specialist judgement, and that a generalised statement would not be appropriate. Hence it was decided that primary prevention should be the focus of this criterion. Panellists welcomed the inclusion of calcium supplementation and anti-resorptive therapy in STOPPFrail, but asked for clarity around the explanatory sentence i.e. cessation where the indication was osteoporosis and not malignancy. Evidence is lacking on whether long term use of calcium is beneficial due to methodological flaws in studies and high dropout rates [**33**]. Patient compliance with calcium supplements is poor; those most likely to be non-compliant have a history of smoking, poor mobility and previous fractures [34]. Anti-resorptive medications are challenging to administer, have a less favourable side effect profile and in some cases have been shown to continue to have clinical benefits after cessation e.g. bisphosphonates. For these reasons the panellists agreed to cessation in those with limited life expectancy,

Consensus could not be reached on two criteria after round 2 i.e. cessation of (i) memantine and (ii) acetylcholinesterase inhibitors in advanced dementia. A third Delphi round was therefore prepared for circulation. In this round, consensus was obtained for memantine and it was included in the STOPPFrail tool. Consensus was not achieved for acetylcholinesterase inhibitors with no trend towards acceptance (**Table 2**). Panellists reported that the evidence base for acetylcholinesterase inhibitors in advanced dementia was still developing and the possibility that unrecognised benefits existed could not be dismissed. The DOMINO-AD trial was cited to support their exclusion [**35, 36**].

This trial suggests that in patients where acetylcholinesterase inhibitors are stopped, the admission rate to nursing homes in the following year is increased compared to those who continue acetylcholinesterase inhibitors. However, this difference is only seen in the first year following cessation. After three rounds, no additional concerns were raised by the panel and it was decided by the authors not to proceed to thus a fourth Delphi round was deemed unnecessary.

The final consensus STOPPFrail criteria are presented in **table 1**. An explanatory sentence to aid the decision to deprescribe the medication in question is present for clarification purposes, particularly to guide deprescribing drugs which cannot be stopped abruptly i.e. neuroleptics and long term steroids.

Discussion

STOPPFrail is an explicit list of 27 PIMs in frail older adults with limited life expectancy. The criteria are not designed to replace clinical judgement, but rather to assist clinicians with medication reviews and assessment of treatment goals in this specific patient cohort. Recognition of those patients to whom STOPPFrail is applicable may be challenging for less experienced physicians; in these circumstances, the use of simple mortality predictive tools may be helpful to guide life expectancy e.g. the Walter Index [**37**] or the CIRS-geriatric scale [38]. However, we anticipate that the majority of clinicians who will use this tool will be experienced in recognising patients who are appropriate for its application i.e. general practitioners or senior hospital specialists with prognostic knowledge of the diseases they manage. In the interest of simplicity and for the tool to be user friendly we did not want STOPPFrail to be contingent on the use of another tool to determine eligibility.

Polypharmacy is a well described problem in this cohort. This research aims to put a framework on the guiding principle of deprescribing in late life i.e. that the benefits of many preventive medications are negligible in those with a limited life expectancy. Although many IP explicit tools exist, there has been an unmet need for a concise explicit tool to assist deprescribing in

this specific patient cohort. STOPPFrail is short tool, focusing on 27 key indicators, suggesting that it will be easy to use, time efficient and therefore more likely to be implemented. Like STOPP/START criteria [**23**], STOPPFrail criteria are listed according to physiological system, thereby allowing users to structure their approach to deprescribing. We aimed for a concise set of criteria that can be easily deployed in paper and electronic format. Electronic application medication assessment criteria is challenging and the discussion of their potential benefits and implementation is beyond the scope of this paper. However, electronic implementation of the STOPP/START criteria is the focus of the SENATOR clinical trial (***39***), currently recruiting patients, and similarly there is the potential for the electronic implementation of STOPPFrail criteria.

Developing this tool required discussing many controversial treatments e.g. hypertension. The authors and panellists agreed that a generalised statement about discontinuing all anti-hypertensives would be contentious. Therefore, it was decided to focus on the drug class least likely to be prescribed as a first line agent and most likely to cause orthostatic hypotension and falls in an older cohort i.e. alpha-blockers.

Inevitably, explicit STOPPFrail criteria will be compared with implicit deprescribing criteria designed for use in older populations, such as the Garfinkel algorithm [40] and the CEASE criteria [41, 42], which have small-scale clinical trial evidence to support their efficacy. Despite this evidence, implicit criteria for prescribing and deprescribing have not come into routine clinical practice. It remains to be seen whether STOPPFrail, as the first systematic set of explicit deprescribing criteria designed specifically for older people with advanced frailty and poor survival prognosis, holds a greater likelihood of being applied in the routine clinical situation than implicit criteria sets.

Finally appropriate use of STOPPFrail criteria may have pharmaco-economic benefits. Older frail adults with a poor survival prognosis account for a growing proportion of the population and a disproportionately high level of medication consumption. Implementation of safe, evidence-based deprescribing in this population, may improve patients' quality of life through reduced ADEs, related

hospitalisations and mortality. The true value of STOPPFrail will need to be tested by means of randomised controlled trials examining its impact as an intervention on patient quality of life, healthcare utilization, medication costs and mortality.

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Disclaimer & Intellectual property of STOPPFrail

STOPPFrail recommendations are based partly on evidence base and partly on expert consensus and are intended to guide prescribers and others who routinely review the medication of older people with advanced frailty (physical and/or cognitive) and poor survival prognosis. As such, the STOPPFrail criteria are offered as a clinical tool to assist the process of considered deprescribing in this particular patient population. STOPPFrail criteria are not meant to over-ride the clinical judgement of the prescriber/medication reviewer in individual cases and do not replace the responsibility of the prescriber/medication reviewer in the matter of medication selection or deselection for individual patients.

STOPPFrail criteria, now published and in the public domain, may be used by any appropriately trained person as an assistive tool in the process of medication review of this particular cohort of older people. STOPPFrail criteria are not constrained by copyright and in themselves are not patentable as intellectual property. The term 'STOPPFrail' is however protected by copyright and cannot be used for commercial purposes except by University College Cork, Ireland or with the expressed written consent of University College Cork, Ireland

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Table 1: Final STOPPFrail criteria

STOPP frail 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 impairment 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. Risk of the medication outweighing the benefit
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: Cardiovascular system

B1. Lipid lowering therapies [statins, ezetimibe, bile acid sequestrants, 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 [43, 44, 45]

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 [46]

Section C: Coagulation system

C1: Anti-platelets

Avoid anti-platelet agents for primary [as distinct from secondary] cardiovascular prevention [no evidence of benefit] [47]

Section D: Central Nervous System

D1. Neuroleptic antipsychotics

Aim to reduce dose and gradually 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] [48, 49, 50, 51, 52]

D2: Memantine

Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved behavioural and psychological symptoms of dementia [BPSD] [specifically in frail patients who meet the criteria above] [53, 54, 55, 56]

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 [57]

E2: H2 receptor antagonist

H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose [57]

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 [57]

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 [58, 59, 60]

F2. Leukotriene antagonists [Montelukast, Zafirlukast]

These drugs have no proven role in COPD, they are indicated only in asthma [61]

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]**

Unlikely to be of any benefit in the short term

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 [57]

G4. **Long-term oral NSAIDs**

Increased risk of side effects [peptic ulcer disease, bleeding, worsening heart failure etc.] when taken regularly for ≥ 2 months [62, 63, 64]

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 gradual discontinuation [65]

Section H: Urogenital System

H1. 5-alpha reductase inhibitors

No benefit with long term urinary bladder catheterisation [66, 67]

H2. Alpha blockers

No benefit with long term urinary bladder catheterisation [66, 67]

H3. Muscarinic antagonists

No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity [66, 67]

Section I: Endocrine System

I1. Diabetic oral agents

Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary [68]

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 [69]

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 [69]

I4. Systemic oestrogens for menopausal symptoms

Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms [57]

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 [70]

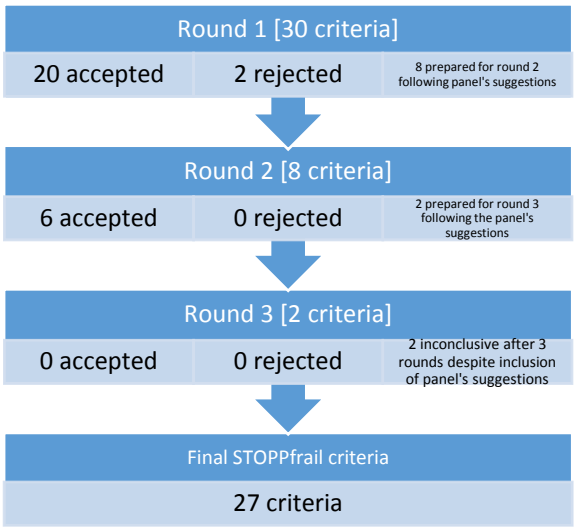
J3: Prophylactic Antibiotics

No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs [71, 72, 73]

Table 2: Acetyl Cholinesterase Inhibitors Delphi Results

	Acetyl Cholinesterase Inhibitor		
	Round 1	Round 2	Round 3
Median	4.000	4.000	4.000
25th centile	3.250	3.000	3.250

Figure 1: Flow chart of Delphi Process



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Supplementary Data

Table1: Round 1 results

STOPP frail 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:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- 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:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

Criteria sent to panel	Median	25th centile	75th Centile	Outcome
Section A: General				
A1. Any drug that the patient persistently fails to comply with for any reason	4.000	3.500	5.000	Inconclusive
A2. Any drug without clear clinical indication	5.000	5.000	5.000	Accepted
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 outweighs the potential benefits.	5.000	4.000	5.000	Accepted
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.	5.000	4.000	5.000	Accepted

Section C: Coagulation System **C1. Anticoagulants (warfarin/novel oral anticoagulants)** Anticoagulation as a preventative measure (e.g. with atrial fibrillation) as distinct from treatment of acute venous thromboembolic (VTE) disease.	3.000	2.000	4.000	Rejected
C2. Anti-platelet agents No role for anti-platelet agents in primary cardiovascular prevention, only beneficial for secondary cardiovascular prevention, therefore discontinue unless there is a previous history of ischaemic heart disease, cerebrovascular disease or arterial stent insertion.	4.000	3.000	5.000	Inconclusive
Section D: Central Nervous System **D1. Memantine** Discontinue unless it has been prescribed for behavioural and psychological symptoms of dementia (BPSD) in patients with Alzheimers disease and has been shown to improve symptoms.	4.000	2.250	5.000	Inconclusive
D2. Acetylcholinesterase inhibitors There is no significant clinical benefit from continuation of these drugs in those with advanced Alzheimers disease (Mini-Mental State Examination score <10/30 *and* functionally dependent). No role in other dementia syndromes in the advanced stages.	4.000	3.250	5.000	Inconclusive
D3. Anti-depressants There is no proven role for anti-depressants in advanced dementia (MMSE <10/30 and functionally dependent).	3.000	2.000	4.000	Rejected
D4. 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).	5.000	4.000	5.000	Accepted
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.	4.000	4.000	5.000	Accepted

E2. H2 Receptor Antagonists H2 Receptor Antagonists at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms or symptoms reoccur after discontinuation.	4.000	3.500	5.000	Inconclusive
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.	4.000	4.000	5.000	Accepted
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 adverse drug events (ADEs).	5.000	4.000	5.000	Accepted
F2. Leukotriene antagonists (Montelukast, Zafirlukast) These drugs have no proven role in COPD, they are indicated only in asthma.	5.000	4.000	5.000	Accepted
Section G: Musculoskeletal System				
G1. Calcium and vitamin D supplementation Unlikely to be of any benefit in the short term.	4.000	3.000	5.000	Inconclusive
G2. Anti-resorptive/bone anabolic drugs for osteoporosis (bisphosphonates, strontium, teriparatide, denosumab) Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated adverse drug events.	4.000	3.000	5.000	Inconclusive
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.	5.000	4.000	5.000	Accepted
G4. Long-term oral NSAIDs Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months.	5.000	4.000	5.000	Accepted
G5. Long-term oral steroids	5.000	4.000	5.000	Accepted

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 with urinary catheter** 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.	 5.000 5.000 5.000	 4.000 4.000 4.000	 5.000 5.000 5.000	 Accepted Accepted Accepted
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.	 4.000 4.000 4.000 4.000	 4.000 4.000 4.000 4.000	 4.500 5.000 5.000 5.000	 Accepted Accepted Accepted Accepted
Section J: Miscellaneous **J1. Multi-vitamin combination supplements** Discontinue when prescribed for prophylaxis rather than treatment.	 5.000	 4.000	 5.000	 Accepted

J2. Nutritional supplements (other than vitamins) Discontinue when prescribed for prophylaxis rather than treatment.	5.000	4.000	5.000	Accepted
J3. Prophylactic antibiotics No firm evidence for a role for prophylactic antibiotics for recurrent cellulitis or recurrent UTI.	4.000	3.000	5.000	Inconclusive

Round 2 Results

STOPP frail 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:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- 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:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

Criteria sent to panel	**Median**	**25th centile**	**75th centile**	**Outcome**
Section A: General A1. Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations	5.000	4.000	5.000	Accepted
Section C: Coagulation System **C2. Anti-platelet agents**				

Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit).	5.000	4.000	5.000	Accepted
Section D: Central Nervous System **D1. Memantine** Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD. **D2. Acetylcholinesterase inhibitors** Discontinue and monitor in patients with severe dementia.	4.000 4.000	3.500 3.000	5.000 5.000	Inconclusive Inconclusive
Section E: Gastrointestinal System **E2. H2 Receptor Antagonists** H2 Receptor Antagonists at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose.	4.000	4.000	5.000	Accepted
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**)	5.000 4.000	4.000 4.000	5.000 5.000	Accepted Accepted
Section J: Miscellaneous **J3. Prophylactic antibiotics** No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTI.	4.000	4.000	5.000	Accepted

Round 3 Results

STOPP frail 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:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- 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:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

Criteria sent to Panel	Median	25th centile	75th centile	Outcome
Section D: Central Nervous System				
D1: Memantine Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved behavioural and psychological symptoms of dementia (BPSD) (specifically in frail patients who meet the criteria above)	4.000	4.000	5.000	Accepted
D2. Acetylcholinesterase inhibitors Discontinue and monitor in patients with severe dementia (specifically in frail patients who meet the criteria above)	4.000	3.250	5.000	Inconclusive

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