Deprescribing in cognitively vulnerable older people: development and validation of STOPPCog criteria.

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Abstract

Objective: To validate STOPPCog, a list of explicit criteria for potentially inappropriate medication (PIM) use in cognitively vulnerable older adults.

Design: A Delphi consensus survey of an expert panel comprising academic geriatricians, old age psychiatrists, general practitioners, and clinical pharmacists.

Setting: Ireland.

Subjects: Nine panellists.

Methods: STOPPCog criteria were initially created by the authors based on clinical experience and literature appraisal. Criteria were organised according to drug/drug class. 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 value of 1 or 2 (strongly agree/agree) and a 25th centile value of ≤2 were included in the final list.

Results: All panellists completed two Delphi consensus validation rounds. Twenty-five criteria were proposed initially, twenty were accepted. One criterion was rejected (multi-vitamin supplements), and four criteria were rephrased (two of these were combined to one criterion for greater clarity). The final list comprised 23 criteria that are arranged in six subgroups i.e. (i) drugs with anticholinergic properties taken daily; (ii) drugs with sedative properties taken daily; (iii) drugs that may exacerbate psychotic symptoms in patients with alpha-synuclein pathology; (iv) drugs used for chronic pain; (v) drugs without proven efficacy for dementia taken daily; (vi) drugs that are of no proven benefit in advanced stage dementia i.e. clinical dementia rating (CDR) of 3.0 where palliation may be appropriate.

Conclusion: STOPPCog comprises 23 criteria relating to medications that are potentially inappropriate in cognitively vulnerable older adults. STOPPCog may assist physicians in deprescribing medications in this patient population.

Keywords: polypharmacy, deprescribing, cognition, dementia, potentially inappropriate medication (PIM), older people.

Keypoints:

- STOPPCog was designed to assist clinicians with deprescribing decisions.
- STOPPCog consists of 23 deprescribing criteria.
- Older people are commonly prescribed multiple medications, some of which may be contributing to cognitive vulnerability.

Introduction

In frail older adults, delirium represents the failure of a vulnerable brain to show resilience in response to an acute stressor [1]. Although delirium is a multifactorial process, it is estimated that medications alone may account for 12%–39% of all cases [2–4]. Appropriate prescribing of medications is of critical importance in promoting patient safety, optimising therapeutic outcomes, and preventing adverse drug events [5]. This is particularly true in the delivery of healthcare to older people where the interaction between multiple drugs, increasing burden of co-morbidity and the emergence of frailty characteristics create an environment of complexity and greater risk to patient safety. The correlation between inappropriate prescribing and adverse outcomes in older adults is firmly established [6–8]. Polypharmacy is linked to increased risk of falls, adverse drug reactions, excess hospitalisation and higher mortality among older individuals [9]. Additionally, some studies have indicated a connection between polypharmacy and dementia [10,11]. Similarly, higher overall burden of drug-related anticholinergic effects, quantitatively assessed using scales like the anticholinergic burden (ACB) scale and the Drug Burden Index (DBI), are associated with elevated risks of mortality, cognitive decline, hospitalisation, and functional impairment in older adults [12,13].

The term 'potentially inappropriate medications' (PIMs) refers to particular medications for which the associated risk often outweighs the potential benefits, especially when other alternatives are available [14]. Numerous explicit prescribing tools aim to guide clinicians on cessation of PIMs including Beers criteria [15], STOPP/START criteria [16] and FORTA criteria [17]. The most recent iteration of Beers criteria includes a section comprising two lists of drugs that are to be avoided in patients with delirium or dementia, unless safer alternatives are unavailable [18]. The drugs considered potentially inappropriate in delirium and dementia in Beers criteria include anticholinergics, antipsychotics, H2-receptor antagonists, Z-drug hypnotics and opioids. Corticosteroids are also listed as potentially inappropriate in delirium. MATCH-D criteria for medications to avoid or curtail in older people with dementia were created and validated by an Australian group in 2016 [19]. Whilst MATCH-D criteria provide evidence-based direction to prescribers on medication prescribing and deprescribing in patients across the spectrum of dementia severity, the criteria deal more in the principles of medication management in dementia rather than providing explicit criteria per se that might be applied in routine medication review of dementia patients. In addition, MATCH-D criteria deal specifically with prescribing and deprescribing in patients with dementia and do not refer to medication management in cases of delirium.

Evidence to support deprescribing as a beneficial intervention in older people with dementia is currently not robust [12,20] and deprescribing of certain medications such as long-term preventive drugs in older people approaching end of life may be difficult for both prescribers and patients [21]. However, there is no clear evidence that deprescribing is detrimental in older patients with severe dementia and may be beneficial [22]. STOPP/START criteria when used as an intervention have been shown to improve medication appropriateness [23] and to reduce the incidence of adverse drug reactions in hospitalised older adults [24]. However, STOPP/START criteria are designed to detect common and preventable PIMs in the general older population and not specifically in cognitively vulnerable older adults. The most recent iteration of STOPP/START criteria (i.e. version 3) contains separate sections relating to potentially inappropriate prescribing relating to drugs/drug classes that act primarily on the central nervous system and drugs/drug classes that increase antimuscarinic/anticholinergic drug burden [16]. However, it does not include criteria dealing specifically with PIMs that may exacerbate delirium or dementia in older people. Similarly, whilst STOPPFrail version 2 criteria has a section dealing with drugs for consideration for deprescribing in older people with severe frailty and poor survival prognosis, that section only deals with memantine and antipsychotics [25].

Cognitive impairment is most commonly encountered in older people, with approximately 5% of people aged ≥65 years in developed countries suffering from dementia [26] and a further 20% having mild cognitive impairment [27]. Delirium occurs with an incidence varying between 11% and 42% in older people with acute illness [28]. Older people with cognitive impairment have increased susceptibility to adverse central nervous system effects of medications, especially sedatives and anticholinergics [29]. Studies show that patients with delirium have a 39% higher risk of death and a 3-fold higher risk of incident dementia than patients without delirium when followed up, and that each additional delirium episode is associated with a 20% increased risk of dementia [30]. As mentioned above, medications alone can be a significant risk factor for delirium in older adults. Therefore, avoiding potentially problematic drugs in a population of patients who are cognitively vulnerable is important. In this article, the term ’cognitively vulnerable’ refers to those who may have a history of cognitive impairment not amounting to overt dementia, clinically overt dementia, or previous episodes of delirium. In relation to dementia severity, there is a particular need to avoid drugs that are likely to exacerbate cognitive impairment or drugs that have no clinical efficacy in severe dementia i.e. clinical dementia rating (CDR) scale 3 [31]. For this reason, we aimed to develop an explicit tool, called STOPPCog, to assist clinicians with deprescribing medications in cognitively vulnerable older adults in all healthcare settings.

Methods

We compiled the initial draft of STOPPCog indicators and arranged them according to certain drug properties. Following this, we examined the evidence base for each drug or drug class using the British National Formulary volume 81 and a literature review, limited to the previous 20 years (see Appendix 1 in Supplementary Data section). Literature searches of PubMed, Cinahl and Google Scholar databases were also undertaken. Searches included the drug in question with key words including 'cognition', 'cognitive impairment', 'delirium', 'older adults', 'dementia', 'deprescribing', 'IP' (inappropriate prescribing) and 'ADEs'. The draft criteria were agreed by the authors following the literature review and subsequently distributed to a panel of experts for validation using the validation Delphi process [32], an established method for achieving consensus.

In September 2023, nine experts were invited to participate in the Delphi process based on their recognised academic and clinical credentials. The expert panel consisted of physicians in geriatric medicine (n = 3), clinical pharmacists with a special interest in geriatric pharmacotherapy (n = 2), old age psychiatrists (n = 2), and senior academic primary care physicians (n = 2). All the panellists were affiliated with Irish university teaching hospitals and working in senior staff positions. The panel was provided with an electronic repository containing supporting references for the proposed STOPPCog criteria. Panellists completed the Delphi process between February and April 2024.

Each iteration of draft STOPPCog criteria was sent to the Delphi panellists using an online survey platform (SurveyMonkey®). The first Delphi validation round consisted of 25 draft 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 level of agreement/disagreement with each statement on a 5-point Likert scale, where 1 = strongly agree; 2 = agree; 3 = neutral; 4 = disagree; and 5 = strongly disagree [33]. In Round 1, panellists were also asked to offer suggestions or comments on specific criteria (including new drugs) as appropriate.

For each statement, consensus was based on the median Likert scale response and interquartile range. A median value of 1 or 2 and a 25th centile value of ≤2 (i.e. at least 75% of panel members agreed or strongly agreed) were required for the criterion to be included. Criteria with a median value of 1 or 2 but a 25th centile value of >2 were held over to be rephrased according to the panel member suggestions and entered the next Delphi validation round.

Results

In round 1 of the Delphi process, twenty-five criteria were submitted to the expert panel for evaluation. Twenty of these 25 proposed criteria had median Likert scores of 1 or 2 with 75th centile values of ≤ 2 and were retained as validated criteria. One criterion was rejected (daily multi-vitamin supplements), and four criteria had a median value of 1 or 2 but a 25th centile value of >2 and were rephrased for greater clarity according to the panel member suggestions and entered in the next Delphi validation round. Two of the four criteria suggested for rephrasing were combined into one criterion to improve ease of use (i.e. nootropics and ginkgo biloba). One criterion (tricyclic antidepressants) had achieved validation in round 1 but was rephrased to include additional drug examples in round 2. All clarified and rephrased criteria were accepted in round 2. An additional table was provided within STOPPCog criteria to provide drug examples relating to each criterion to facilitate ease of use (see Table 2).

All panellists completed the Delphi validation process in two rounds; the final STOPPCog tool (see Table 1) consisted of 23 validated criteria. STOPPCog is comprised of six PIM categories: i) drugs with anticholinergic properties taken daily, ii) drugs with sedative properties taken daily, iii) drugs that may exacerbate psychotic symptoms in patients with alpha-synuclein pathology, iv) drugs used for chronic pain, v) drugs without proven efficacy for dementia taken daily, and vi) drugs that are of no proven benefit in severe/advanced stage dementia. Full analysis (i.e. the phrasing of criteria and the distribution of the responses for each round) is available in a supplementary data file (see Appendix 2 in Supplementary Data section).

Discussion

The central aim of STOPPCog criteria is to provide clinicians with a practical, patient-centred, and evidence-based tool that facilitates deprescribing of potentially inappropriate drugs in cognitively vulnerable older people. It comprises 23 explicit criteria which aim to assist clinicians with medication review and to facilitate the avoidance of potentially inappropriate treatment in these patients. While Beers criteria and STOPP/START criteria both include PIMs relevant to patients with cognitive impairment, STOPPCog aims to consolidate these alongside other recommendations. There is a high prevalence of PIMs amongst patients with cognitive impairment and dementia which is associated with excess all-cause mortality [34–37]. Medication assessment tools such as the anticholinergic burden (ACB) scale [38] and the Drug Burden Index (DBI) [39] provide useful indicators of potentially detrimental medication in older people with cognitive impairment but may not provide enough specific guidance when used in isolation.

Prevention of delirium in older people is of paramount importance in any clinical setting. One recent large-scale retrospective study demonstrated that over 75% of older hospitalised patients with delirium were taking medicines known or suspected to precipitate delirium prior to admission [40]. A systematic review showed that incident delirium in hospitalized older patients persisted at hospital discharge in 45% of cases and at 1 month post-discharge in 33% of cases [41]. As discussed earlier, delirium is a significant risk factor for incident dementia [30]. In patients with established dementia, a delirium episode is associated with accelerated cognitive decline. Gross et al. demonstrated that over half of a group of patients with a diagnosis of Alzheimer's disease developed delirium during hospitalisation, and that these patients experienced a more rapid rate of cognitive deterioration throughout a 5-year period following hospitalisation compared to Alzheimer's disease patients who did not become delirious during hospitalization [42]. While the cause of delirium is often multifactorial, there is evidence indicating that medications may be an important predisposing factor [40] and precipitating factor for delirium [2–4]. This underlines the importance of screening for potentially problematic medications as a potentially modifiable factor to prevent future delirium episodes in at-risk individuals.

Older adults often experience polypharmacy as a direct result of multimorbidity. Older people with physical or mental frailty are at heightened risk from associated polypharmacy, such as adverse drug-drug interactions, drug-disease adverse effects, and impaired medication adherence [43]. Older adults with cognitive impairment are also more susceptible to the adverse effects of medications due to age-related physiological changes, decreased rate of metabolism, and altered drug sensitivity [44,45]. In addition, cognitive impairment may adversely affect an individual's ability to adhere to complex medication regimens, increasing the risk of missed drug doses or medication errors that may result in worsening of cognitive function [46,47]. Although PRN use of drugs in the STOPPCog list may result in transient worsening of cognition, we have focused particularly on the daily continuous use of drugs with adverse cognitive effects where the risks of such adverse effects are more likely and more severe. Also, the evidence for adverse cognitive effects relates more to continuous daily use rather than PRN use. Rationalising medication regimens in cognitively impaired patients through the application of STOPPCog criteria during routine medication review should improve treatment outcomes. Effective management of medications can also favourably impact the quality of life of older adults with cognitive impairment by minimising symptoms, preventing complications, and promoting independence [48,49]. Application of STOPPCog criteria may, at least in theory, facilitate this process through more effective avoidance of potentially adverse medications in cognitively impaired older people. Clearly, STOPPCog criteria as an intervention will need to be evaluated through randomised

controlled trials to fully assess its impact on important clinical outcomes in this growing population of older people.

There are significant strengths in STOPPCog criteria. Firstly, the Delphi panel was multidisciplinary and representative of healthcare professionals who routinely undertake medication review of older people with cognitive impairment in a variety of healthcare settings in Ireland. Secondly, STOPPCog criteria are evidence-based and, like STOPP/START criteria, arranged according to physiological systems for ease of use. Thirdly, the list of drugs in STOPPCog is inclusive of the main drugs/drug classes likely to cause or adversely affect cognition in cognitively impaired older people. Finally, STOPPCog criteria are relatively succinct, a feature that should facilitate their application in routine medication review. For these reasons, we contend that STOPPCog criteria are likely to be both representative of opinions of multidisciplinary clinicians in Ireland and generalizable internationally in relation to facilitating the avoidance of drugs that may be particularly inappropriate in older people with cognitive vulnerability through having overt dementia or previous episodes of delirium.

There are also some limitations to this study related to the Delphi process and the use of online surveys. Firstly, the selection and design of the questions by the authors might have influenced some panellists' responses such that they might have interpreted certain proposed criteria somewhat differently. However, no panellist sought removal of draft criteria during the Delphi process, indicating general agreement with the proposed criteria. Secondly, there were no face-to-face meetings with the panel members due to feasibility constraints which might have allowed for better use of the panellists' expertise. However, the on-line validation process prevented the opinions of individual panellists from dominating a face-to-face discussion which can, in theory, result in biased interpretation of certain proposed criteria and their evidence base. Another limitation is that we did not conduct formal systematic reviews to inform individual criteria due to resource constraints.

Conclusion

Arising from this Delphi validation exercise, we present STOPPCog criteria as a clinical tool designed to facilitate medication reviewers to identify drugs/drug classes that are known to worsen cognition in older people with cognitive vulnerability resulting from overt dementia, current delirium or previous history of delirium. STOPPCog criteria are arranged according to concurrent clinical conditions for ease of use. Further studies are required to evaluate the clinical impact of STOPPCog as an intervention in older people at risk of medication-related exacerbation of cognitive function.

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Table 1. STOPPCog criteria (final version).

STOPPCog is a list of drugs and drug classes that are considered potentially problematic or ineffective or with an adverse risk/benefit ratio in older people with a history of cognitive impairment, dementia, or previous episodes of delirium. While some of the drugs listed below may have a valid indication, the risk-benefit trade-off should be carefully considered in this patient group.	
Section A: Drugs with anticholinergic properties taken daily	1. Specific antidepressants: tricyclic anti-depressants, paroxetine and phenelzine 2. Bladder antimuscarinics that cross the blood brain barrier (BBB) [see Table 2] 3. Gastrointestinal antimuscarinics that cross the BBB [see Table 2] 4. First generation antihistamines 5. First- and second-generation antipsychotics 6. Any drug or drug combination with an anti-cholinergic burden (ACB) score ≥2
Section B: Drugs with sedative properties taken daily	1. Benzodiazepine hypnotics 2. Benzodiazepine anxiolytics 3. Z-drug hypnotics
Section C: Drugs that may exacerbate psychotic symptoms in patients with alpha-synuclein pathology (i.e. Parkinson's disease and Dementia with Lewy Bodies)	1. Anticholinergic drugs for Parkinson's disease tremor 2. Amantadine 3. Dopamine receptor agonists 4. Monoamine Oxidase Type B inhibitors 5. Catechol-O-methyltransferase (COMT) inhibitors
Section D: Drugs used for chronic pain	1. Opioids 2. Gabapentinoids 3. Anti-epileptic drugs, especially topiramate 4. Anti-spasticity drugs that cross the BBB [see Table 2]
Section E: Drugs without proven efficacy for dementia taken daily	1. Specific nootropics (see table)
Section F: Drugs that are of no proven benefit in *advanced stage* dementia i.e. Clinical Dementia Rating (CDR) of 3.0 where palliation may be appropriate	1. Acetylcholinesterase inhibitors 2. Memantine 3. Beta-amyloid reducing monoclonal antibodies 4. Long-term preventive drugs for conditions other than dementia without intrinsic symptom relief properties (e.g. statins, antiplatelet agents, anticoagulants, antihypertensives, bisphosphonates)
Disclaimer (STOPPCog): While every effort has been made to ensure that the potentially inappropriate deprescribing criteria listed in STOPPCog are accurate and evidence-based, it is emphasized that the final decision to deprescribe 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 STOPPCog may change after the time of publication of these criteria. Therefore, it is advisable that deprescribing decisions should take account of current published evidence in support of or against the use of drugs or drug classes described in STOPPCog.	

Table 2. Drug examples based on STOPPCog criteria.

Criteria	Drug Names/Classes	Mechanism
A1	amitriptyline, nortriptyline, doxepin, clomipramine, imipramine, desipramine, amoxapine, protriptyline, trimipramine Paroxetine Phenelzine	Anticholinergic effects
A2	trospium chloride, tolterodine, fesoterodine, oxybutynin, solifenacin, darifenacin	Anticholinergic effects
A3	dicyclomine hydrochloride, hyoscine hydrobromide	Anticholinergic effects
A4	diphenhydramine, promethazine, dimenhydrinate, chlorpheniramine	Anticholinergic effects
A5	**First generation**: chlorpromazine, flupenthixol, fluphenazine, haloperidol, loxapine, pimozide, sulpiride, trifluoperazine, zuclopenthixol, levomepromazine **Second generation**: olanzapine, quetiapine, clozapine, aripiprazole, risperidone	Anticholinergic effects & sedative effects
A6	See **https://www.acbcalc.com/** See ACBCalc® scorecard below	Anticholinergic effects
B1	triazolam, lormetazepam, lorprazolam, nitrazepam, temazepam, flurazepam	Sedative effects
B2	alprazolam, chlordiazepoxide, diazepam, oxazepam, clonazepam, clobazam	Sedative effects
B3	zopiclone, zolpidem, zaleplon	Sedative effects
C1	benztropine, trihexyphenidyl, procyclidine, biperidin	Anticholinergic effects
C2	amantadine	Risk of psychosis
C3	pramipexole, ropinirole, apomorphine hydrochloride, rotigotine	Risk of psychosis
C4	rasagiline, selegiline, safinamide	Risk of psychosis
C5	entacapone, tolcapone, opicapone	Risk of psychosis
D1	oxycodone, morphine, codeine, fentanyl, tramadol, pethidine	Sedative effects
D2	pregabalin, gabapentin	Sedative effects
D3	topiramate, carbamazepine, clonazepam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, valproate	Sedative effects

D4	baclofen, tizanidine, pridinol, dantrolene	Sedative effects
E1	**Eugeroics:** modafinil **ADHD drugs**: methylphenidate, lisdexamphetamine, dexamphetamine **Nootropic supplements**: B vitamins, fish oil supplements, herbal supplements including ginkgo biloba **Nootropic racetams:** piracetam, aniracetam, etc.	No proven efficacy
F1	donepezil, rivastigmine, galantamine	No proven efficacy in severe dementia
F2	memantine	No proven efficacy in severe dementia
F3	lecanemab, aducanumab, donanemab	No proven efficacy in severe dementia
F4	statins, antiplatelet agents, anticoagulants, antihypertensives, bisphosphonates	No proven efficacy in severe dementia