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Avoiding Adverse Drug Withdrawal Events When Stopping Unnecessary Medications According to the STOPPFrail Criteria

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Abstract

OBJECTIVE: To provide clinicians with information about avoiding adverse drug withdrawal events (ADWEs) when discontinuing unnecessary medications as per the STOPPFrail criteria.

DATA SOURCES: Searches of MEDLINE (1970-June 2020), the Cochrane Database of Systematic Reviews (through June 2020), Google Scholar (through June 2020).

STUDY SELECTION: Reviews and original studies of ADWEs.

DATA EXTRACTION: Tapering protocols for specific drugs/ classes from randomized controlled deprescribing trials.

DATA SYNTHESIS: Six drug classes were identified as being high risk for physiological ADWEs.

CONCLUSION: The occurrence of ADWEs is rare in comparison to adverse drug reactions in older adults. Few drugs/classes have been reported to have physiological ADWEs with abrupt discontinuation. For these we provide information about tapering protocols and symptom monitoring to avoid ADWEs.

Keywords

Adverse drug withdrawal events; Aged; Deprescribing; End of life; STOPPFrail

Introduction

It is well known that polypharmacy is a common phenomenon in older patients.[1-3] The seminal conceptual work by Holmes et al. alerts clinicians to consider the transition of medication indications at end of life from curative to palliative in older patients.[4] At this

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transition point, the emphasis changes to optimize medications that may improve/maintain function and quality of life and minimize/discontinue medications whose indication is preventative.[4]

The question then is, what constitutes a drug that can be deprescribed? One such approach is the application of explicit criteria such as those developed for patients with severe dementia and cancer.[5,6] While these may be helpful for specific conditions, they leave one unsure of their universal application. To fill this void, a set of explicit criteria named the Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail) was published in 2017 by Lavan and collegues.[7] They are intended to be relevant to those patients with end-stage irreversible pathology, poor 1-year survival prognosis, severe physical functional impairment or cognitive impairment of both and those patients where symptom control is the priority rather than prevention of disease.[7] The STOPPFrail criteria note that for this set of end-of-life patients, the approach to medication uses or starting new medications should include the following considerations: (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; (5) lack of clear indication; and (6) intolerance of medication. We believe that an additional consideration should be whether the drug is high risk for physiological adverse drug withdrawal events (ADWEs). Since then, to the best of our knowledge, only 1 randomized controlled trial by Curtin et al. has targeted an intervention to reduce questionably beneficial medications per the STOPPFrail criteria.[8] The appendices of the manuscript by Curtain et al. gave advice regarding tapering methods for medications identified by the STOPPFrail criteria. However, they are limited by the lack of specificity and supporting citations, particularly for those discontinued medications that have an increased risk of physiological ADWEs that represent the return of the underlying disease. Given this background, this review aims to provide clinicians with information about avoiding ADWEs when discontinuing unnecessary medications per the STOPPFrail criteria.

Methods

Articles that assessed ADWEs and deprescribing interventions in older adults were identified through searches of MEDLINE (1970-June 2020), the Cochrane Database of Systematic Reviews (through June 2020), and Google Scholar (through June 2020). Additional publications were identified by a manual search of the reference lists of identified articles, the authors' own materials, published reviews, and Internet websites.

Data Synthesis

The literature search identified 6 seminal book chapters and reviews to identify those drugs when discontinued mentioned having physiological ADWEs.[9-14] We then reviewed primary ADWE study literature.[15-19] We then identified deprescribing randomized controlled trials to identify taper protocols.[20-32] Finally, we reviewed medication discontinuation algorithms that appear on national deprescribing organizations.[33-35]

Table 1 lists those STOPPFrail drugs that when discontinued are unlikely to result in physiological ADWEs. This differs slightly from those listed in the appendix of the Curtin et al. of possible ADWEs, which includes angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, estrogen, nutritional supplements, oral diabetic agents, or theophylline, drugs for which we could find no evidence from a literature review that when these drugs discontinued cause physiological ADWEs.[8]

Nonetheless, there are tapering algorithms for many of these drugs, including oral diabetes drugs as well as memantine on the Canadian deprescribing organization website, and for nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, statins, and calcium from the Tasmanian deprescribing organization website.[33,34] Further, though generally thought that rapid discontinuation of peripheral alpha-blockers can cause rebound hypertension, data from benign prostatic hypertrophy clinical trials show that abruptly stopping peripheral agents (ie, terazosin, prazosin, and doxazocin) is feasible and safe.[12]

For the remaining drugs in Table 1, specific tapering guidelines are lacking. To prevent ADWEs resulting from the underlying disease, clinicians should consider the dose, duration, and pharmacokinetics of medications.[9] Risk can be minimized or eliminated by slow, careful tapering of the medication over a prolonged period of time (eg, 4-6 weeks). This approach is similar to that taken in the initiation and titration of a new medication. Careful monitoring for early symptoms of the underlying disease (eg, knee pain after discontinuing NSAIDs) is advised.

Table 2 lists the medications that are part of the STOPPFrail criteria with an increased likelihood of physiological ADWEs. This table also list signs/symptoms seen with a typical physiological ADWE and tapering recommendations to avoid these physiological withdrawal reactions.

There is some literature that the abrupt withdrawal of the central alpha-blocker clonidine can cause rebound hypertension.[20] The average age of the 9 subjects studied was 62 years.[20] The mechanism is thought to result from increased peripheral sympathetic activity.[20] Data from antihypertensive deprescribing trials suggest a 3-to-6-week taper to be prudent especially when the patients is maintained on at least 1 other antihypertensive.[28,29]

We found only three deprescribing trials of anticholinergics that measured associated health outcomes in older adults.[21-23] None showed consistent improvement in neuropsychological testing, nor did they specify a tapering schedule or report withdrawal reactions.[21-23] However, since cholinergic rebound is theoretically possible, the New South Wales deprescribing website offers tapering guidelines (ie, wean gradually by 25%-50% of the daily dose every 1-4 weeks).[35]

Antipsychotics block a number of neurotransmitters, including dopamine, and thus rebound effects are possible.[27] None of the published deprescribing trials described an approach based on pharmacokinetic principles.[24,25] We recommend a 2-stage gradual dose-reduction protocol for tapering antipsychotic medications based on the log dose-response relationship; each stage was designed to result in 50% dose reductions prior to discontinuation, according to the specific half-life of each drug.[36] So, for example, someone taking long-term

risperidone 4 mg daily whose half-life is 3-20 hours of the parent compound and 21-30 hours of the active metabolite, one would first decrease the dose to 2 mg daily and then 2-3 weeks later decreased it further to 1 mg daily and again 2-3 weeks later to 0.5 mg daily before discontinuation.

It is well known that abrupt discontinuation of systemic corticosteroids taken in high doses for long durations can result in signs of adrenal insufficiency.[30] One study included older subjects (average age older than 68 years) taking greater than 5 mg/day continuously for pulmonary problems. They recommended tapering prednisone equivalent at a rate of 5 mg per week until 6-11 mg per day was reached. A well-known drug information source further suggested tapering of 0.5-1 mg/day in prednisone equivalent occur every 2-4 weeks and monitor over 6-12 months.[31]

Abrupt discontinuation of H_2 blockers/proton pump inhibitors (PPI) has been reported to cause rebound acid hypersecretion and related symptoms.[13] One study of 98 chronic PPI users without a history of peptic ulcer or esophagitis (median age 63 years) found that only 27% did not use PPIs during the year after discontinuation.[32] The Canadian deprescribing website offers practical guidelines for tapering that includes cutting the daily dosage in half for 1 month and use as-needed antacids and then discontinue.[33]

Discussion

To the best of our knowledge, this is the first review of ADWEs that might occur when discontinuing unnecessary drugs per the STOPPFrail criteria. It is important to note that this is not a comprehensive review of all possible ADWEs that can occur during deprescribing. In particular, serious physiological ADWEs can occur with abrupt discontinuation of antiepileptic drugs, baclofen, beta-blockers, and benzodiazepines, which are not part of the STOPPFrail criteria. Readers are encouraged to further review the following references for more information about withdrawing these drugs and others.[9-19]

It is interesting to note that, with the exception of corticosteroids, that most drugs can be safely tapered over a 4-6 week period. While this time period might be too prolonged/ complicated for some hospice patients, there is time for many hospice patients whose average length of stay is approximately 90 days.[39] Also, it is important to note that corticosteroids can be helpful for symptom control at end of life (eg, nausea and vomiting after palliative radiation) and should not always be considered unnecessary.

There are limitations to this review. It is not a systematic review and meta-analysis. In addition, the articles cited rarely included frail older adults. More studies such as the recent article by Niznik et al. are needed to determine the consequences (if any) of discontinuing medications at end of life.[40]

Conclusion

The occurrence of ADWEs is rare in comparison with adverse drug reactions in older adults.[9-13,37,38] Few drugs/classes have been reported to have physiological withdrawal reactions with abrupt discontinuation.[9-13,37,38] For these we provide insights as to what symptoms to

look for and information about tapering unnecessary medications to avoid ADWEs. Further empiric studies are needed to measure actual ADWE event rates of these protocols.

Addendum

Since the writing of this manuscript, version 2 of the STOPPfrail criteria has been published.[41] There are new criteria for deprescribing antihypertensives, antianginals (ie, nitrates, nicorandil, ranolazine), and vitamin D.[41] Regarding the first new criteria, recently reported were the results of a randomized controlled deprescribing trial of older adults taking multiple antihypertensives with a systolic blood pressure lower than 150 mm Hg.[42] They found that one antihypertensive could be discontinued without significant adverse outcomes or increases in blood pressure. Caution should still be taken to taper alpha (eg, clonidine) and beta-blockers (eg, propranolol) over 3 to 6 weeks as physiological adverse drug withdrawal events have been reported.[43,44] Discontinuation of antiantiginals should not be attempted in those with chest pain in the previous 6-12 months or in those with known coronary artery disease.[41] In those who have these antianginals deprescribed, 30 days of careful monitoring should be undertaken to look for relapse of anginal symptoms.[45] Finally, no particular precautions are necessary to abruptly discontinue vitamin D.

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ABBREVIATIONS:

ADWE	Adverse drug withdrawal events
NSAIDs	Nonsteroidal anti-inflammatory drugs
PPIs	Proton pump inhibitors
STOPPFrail	Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy

REFERENCES

1. Dwyer LL, Han B, Woodwell DA, et al. Polypharmacy in nursing home residents in the United States: results of the 2004 National Nursing Home Survey. Am J Geriatr Pharmacother. 2010;8:63–72. [PubMed: 20226393]
2. Charlesworth CJ, Smit E, Lee DS, et al. Polypharmacy among adults aged 65 years and older in the United States: 1988-2010. J Gerontol A Biol Sci Med Sci. 2015;70:989–95. [PubMed: 25733718]
3. Maher R, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Exp Opin Drug Saf. 2014;13:57–65.
4. Holmes HM, Hayley DC, Alexander GC, et al. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166:605–9. [PubMed: 16567597]

5. Holmes HM, Sachs GA, Shega JW, et al. Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc. 2008; 56:1306–11. [PubMed: 18482301]
6. Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer. 2015;23:71–8. [PubMed: 24975044]
7. Lavan A, Gallagher P, Parsons C, et al. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing 2017;45:1–12.
8. Curtin D, Jennings E, Daunt R, et al. Deprescribing in older people approaching end of life: a randomized controlled trial using STOPPFrail Criteria. J Am Geriatr Soc. 2020;68:762–9. [PubMed: 31868920]
9. Naples JN, Handler SM, Maher R, et al. Geriatric Pharmacotherapy and Polypharmacy. In: Fillit H, Rockwood K, Young J. (eds). Brocklehurst's Textbook of Geriatric Medicine. 8th ed. London, UK: Churchill Livingstone; 2016:849–54.
10. Bains K, Holmes H, Beers M, et al. Discontinuing medications: a novel approach for revising the prescribing stage of the medication use process. J Am Geriatr Soc. 2008;56:1946–52. [PubMed: 18771457]
11. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging. 2008;25:1021–31. [PubMed: 19021301]
12. Reidenberg MM. Drug discontinuation effects are part of the pharmacology of a drug. J Pharmacol Exp Ther. 2011;339:324–8. [PubMed: 21849624]
13. Reeve E, Moriarty F, Nahas R, et al. A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. Exp Opin Drug Saf. 2018;17:39–49.
14. Tjia J, Velten SJ, Parsons C, et al. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013:285–307 [PubMed: 23475597]
15. Gerety M, Cornell JE, Plichta D, et al.: Adverse events related to drugs and drug withdrawal in nursing home residents. J Am Geriatr Soc. 1993;41:1326–32. [PubMed: 8227915]
16. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. Arch Intern Med. 1997;157:2205–10. [PubMed: 9342997]
17. Kennedy JM, van Rij AM, Spears RA, et al. Polypharmacy in a general surgical unit and consequences of drug withdrawal. Br J Clin Pharmacol. 2000;49:353–62. [PubMed: 10759691]
18. Mita Y, Aksishta M, Tanaka K, et al. Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. Geriatr Gerontol Int. 2004;4:146–50.
19. Marcum ZA, Amuan ME, Pugh MJV, et al. Prevalence of potentially preventable unplanned hospitalizations caused by therapeutic failures and adverse drug withdrawal events among older veterans. J Gerontol Med Sci. 2012;67:867–74.
20. Reid JL, Campbell BC, Hamilton CA. Withdrawal reactions following cessation of central alpha-adrenergic receptor agonists. Hypertension. 1984;6(Suppl II):II-71–II-75. [PubMed: 6150002]
21. Kersten H, Molden E, Tolo IK, et al. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. J Gerontol Series A Biomedical. 2012;68:271–8.
22. Campbell NL, Perkins AJ, Khan BA, et al. Deprescribing in the pharmacologic management of delirium (DE-PMD): a randomized trial in the intensive care unit. J Am Geriatr Soc. 2019;67:695–702 [PubMed: 30664239]
23. Tollefson GD, Montague-Clouse J, Lancaster SP. The relationship of serum anticholinergic activity to mental status performance in an elderly nursing home population. J Neuropsychiatry Clin Neurosci. 1991;3:314–9. [PubMed: 1821247]
24. Ruths S, Straand J, Nygaard HA, et al. Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study--The Bergen District Nursing Home Study. Int J Gei Psych. 2008;23:889–95.
25. Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009;8:151–7. [PubMed: 19138567]

26. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev. 2017;CD011969. [PubMed: 28301676]
27. Chouinard G, Chouinard VA. Atypical antipsychotics: CATIE Study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. Psychother Psychosom. 2008;77:69–77. [PubMed: 18230939]
28. Hajjar I, Hart M, Wan SH, et al. Safety and blood pressure trajectory of short-term withdrawal of antihypertensive medications in older adults: experience from a clinical trial sample. J Am Soc Hypertension. 2013;7:289–93.
29. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of discontinuation of antihypertensive treatment in elderly people on cognitive functioning—the DANTE Study Leiden: a randomized clinical trial. JAMA Intern Med. 2015;175:1622–30. [PubMed: 26301603]
30. Rice K, Rubins J, Lebahn F, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD—a randomized trial. Am J Respir Crit Care Med. 2000;162:174–8. [PubMed: 10903238]
31. Furst DE, Saag KG. Glucocorticoid withdrawal. In: Wolters Kluwer UpToDate, Inc.; 2020
32. Björnsson E, Abrahamsson H, Simrén M, et al. Discontinuation of proton pump inhibitors in patients on longterm therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24:945–54. [PubMed: 16948806]
33. Canadian Deprescribing Guidelines and Algorithms. https://deprescribing.org/resources/deprescribing-guidelines-algorithms/ Accessed April 13, 2020.
34. Tasmania Deprescribing guides. https://www.primaryhealthtas.com.au/resources/deprescribing-guides/ Accessed April 13, 2020
35. New South Wales Deprescribing tools. http://www.nswtag.org.au/deprescribing-tools/ Accessed April 13, 2020.
36. Tjia J, Reidenberg MM, Hunnicutt JN, et al. Approaches to gradual dose reduction of chronic off-label antipsychotics used for behavioral and psychological symptoms of dementia. Consult Pharm. 2015;30:599–611. [PubMed: 26450142]
37. Coulson J, Routledge PA. Adverse reactions to drug withdrawal. Adverse Drug React Bull. 2008;252:967–70.
38. Reeve E, Shakib S, Hendrix I, et al. Review of deprescribing processes and development of an evidence-based, patient-centered deprescribing process. Br J Clin Pharmacol. 2014;78:738–47. [PubMed: 24661192]
39. Medicare Payment Advisory Commission. Hospice services: assessing payment adequacy and updating payments. In: Report to Congress, Medicare Payment Policy, 3 2016. http://www.medpac.gov/docs/default-source/reports/chapter-11-hospice-services-march-2016-report-.pdf. Accessed August 17, 2020.
40. Niznik JD, Zhao X, He M, et al. Risk for health events after deprescribing AChEIs in nursing home residents with severe dementia. J Am Geriatr Soc. 2020;68:699–707 [PubMed: 31769507]
41. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age and Ageing, 2020 (online) doi/10.1093/ageing/afaa159.
42. Sheppard JP, Burt J, Lown M, et al. The effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older: the OPTIMISE randomized controlled trial. JAMA. 2020;323:2039–51. [PubMed: 32453368]
43. Reid JL, Campbell BC, Hamilton CA. Withdrawal reactions following cessation of central alpha-adrenergic receptor agonists. Hypertension.1984;6(Suppl II):II-71–II-75. [PubMed: 6150002]
44. Ross PJ, Lewis MJ, Sheridan DJ, et al. Adrenergic hypersensitivity after beta-blocker withdrawal. Br Heart J. 1981;45:637–42 [PubMed: 6114739]
45. George J, Kitzis I, Zandorf D, et al. Safety of nitrate withdrawal in angina-free and hemodynamically stable patients with coronary artery disease. Chest. 2003;124:1652–7 [PubMed: 14605030]

Table 1.

STOPP-Frail Criteria Drugs without Physiological Withdrawal Reactions

Drugs/Classes
Angiotensin converting enzyme inhibitor to prevent diabetes nephropathy
Antibiotics, prophylactic
Alpha blockers in catheterized patients (i.e., terazosin, prazosin, doxazosin)
Angiotensin receptor blockers to prevent diabetic nephropathy
Antiplatelets
Bisphosphonates and other antiresorptives
Calcium
Diabetes oral drugs
Estrogen for menopausal symptoms
Five (5) alpha-reductase inhibitors (i.e., dutasteride, finasteride)
Lipid lowering agents
Leukotriene antagonists
Memantine
Multivitamins
Nonsteroidal anti-inflammatory drugs taken long term
Nutritional supplements
Selective estrogen receptor modulators
Theophylline

Table 2.

STOPPFrail Criteria Drugs with Physiological Withdrawal Reactions

Drugs/Classes	Typical Physiological Withdrawal Reactions	Tapering Recommendations to avoid Physiological Withdrawal Reactions
Central alpha blockers for hypertension (e.g., clonidine)	Rebound hypertension	Taper over 3 to 6 weeks[28-29]
Anticholinergic for colic symptoms or in those with urinary catheter	Cholinergic rebound symptoms including irritability, anxiety, insomnia, sweating and nausea	Taper over 4-8 weeks[35]
Antipsychotics used for behavioral and psychological symptoms of dementia	Dyskinesias, overactivity, super sensitivity psychosis	1st generation antipsychotic: 25%–50% daily dose reduction cholinergic every 1-2 days; 2nd generation antipsychotic: 25%–50% daily dose reduction every 2 weeks (except aripiprazole 25%–50% daily dose reduction every 2 months)[36]
Corticosteroids (oral) taken long term	Adrenal insufficiency including symptoms of nausea, fever, anorexia, lethargy, arthralgias, postural hypotension	Taper prednisone equivalent at a rate of 5 mg per week until reach 10 mg/day in prednisone equivalent. Then taper 0.5 mg-1 mg/day of prednisone equivalent every 2-4 weeks. May take 6-12 months to completely withdraw and see return of hypothalamic pituitary adrenal axis[30,31]
Histamine 2 receptor antagonists	Rebound gastric hypersecretion with symptoms of heartburn, reflux, dyspepsia, epigastric pain, weight loss	Half dose initially. Stop altogether in 1 month if no symptoms of dyspepsia[33]
Proton pump inhibitors	Rebound gastric hypersecretion with symptoms of heartburn, reflux, dyspepsia, epigastric pain, weight loss	Half dose initially. Stop altogether in 1 month if no symptoms of dyspepsia[33]