

REVIEW

Drug cessation in complex older adults: time for action

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Abstract

Background: general opinion is growing that drug cessation in complex older patients is warranted in certain situations. From a clinical viewpoint, drug cessation seems most warranted in four situations, i.e., falls, delirium, cognitive impairment and end-of-life situations. To date, little information about the effects of drug cessation in these four situations is available.

Objectives: to identify the effects and effectiveness of drug cessation on falls, delirium and cognitive impairment. For end-of-life situations, we reviewed cessation of inappropriate drug use.

Methods: electronic databases were searched using MeSH terms and relevant keywords. Studies published in English were included if they evaluated the effects of drug cessation in older persons, aged ≥ 65 years, with falls, delirium or cognitive impairment; or cessation of inappropriate drug use in end-of-life situations.

Results: we selected seven articles for falls, none for delirium, two for cognition and two for end-of-life situations. Withdrawal of psychotropics reduced fall rate; a prescribing modification programme for primary care physicians reduced fall risk. Withdrawal of psychotropics and a systematic reduction of polypharmacy resulted in an improvement of cognition. Very little rigorous research has been conducted on reducing inappropriate medications in patients approaching end of life.

Conclusion: little research has focussed on drug cessation. Available studies showed a beneficial impact of cessation of psychotropic drugs on falls and cognitive status. More research in this field is needed. The issue of systematic drug withdrawal in end-of-life cases is controversial, but is increasingly relevant in the face of rising numbers of older people of this clinical status.

Keywords: older adults, drug cessation, falls, delirium, cognitive impairment, end of life, older people

Introduction

Older patients are particularly prone to adverse drug reactions (ADR) because age is associated with changes in pharmacokinetics and pharmacodynamics that may alter drug metabolism. Multimorbidity and polypharmacy are common, but protocols for stopping medication in these circumstances are scarce.

In an evaluation of the applicability of clinical practice guidelines (CPGs) to the care of older individuals with several comorbid diseases, Boyd *et al.* [1] indicate that in the

complex patient with multimorbidity, interactions can also occur from adherence, such as interactions between a medication and a disease other than the target disease; medications for different diseases; medications and food. Consequently, adhering to current CPGs in caring for an older person with several comorbidities may have undesirable effects [1].

While the impact of drug use on health outcomes in older patients is quite well known, the impact of drug use on functional outcomes, such as falls, delirium and cognitive impairment, is less well known.

General opinion is growing that cessation of drugs in complex older patients should be considered in certain situations, where cessation rather than prescribing might be beneficial.

We believe that, from a clinical point of view, the principle of drug cessation is most warranted in four situations, i.e. in older adults presenting with falls, delirium or cognitive impairment and in end-of-life situations. To date, information about the effects of drug cessation in these four situations is scarce.

Therefore, we conducted a literature review on the effects of drug cessation on falls, delirium and cognitive impairment. In addition, we reviewed the literature for articles on drug cessation at the end of life.

Methods

We identified falls, delirium, cognitive impairment and end-of-life situations as high-risk situations for ADR in complex older adults.

Electronic databases (Medline, EMBASE, Cochrane Library, CINAHL, PsychLit) were searched for meta-analyses, reviews and recent large RCTs, using MeSH terms and relevant keywords. Studies published in English between 1 January 2008 and 1 May 2013 were included if they evaluated the effects of cessation of drug use in older adults, aged ≥ 65 years, with falls, delirium or cognitive impairment and studies that reviewed cessation of inappropriate drug use in end-of-life situations.

As keywords we used ‘drug cessation’, ‘medication cessation’, ‘drug withdrawal’, ‘medication withdrawal’, ‘drug discontinuation’, ‘medication discontinuation’, ‘polypharmacy reduction’, ‘falls’, ‘delirium’, ‘cognitive impairment’ and ‘end-of-life’.

For end of life, we also searched for ‘inappropriate drug use’ or ‘inappropriate medication’ and ‘end-of-life’. Two authors conducted the review process (TISCHA JM VAN DER CAMMEN and CAROLYN S STERKE).

Subjects at risk (I): older fallers

Falls among the older population are associated with a high morbidity and mortality. Approximately 30% of community-dwelling persons ≥ 65 years fall at least once a year. About half of these fallers (15%) fall more than once a year. Falls are more common in nursing home residents, with an incidence approaching 50%. The incidence of falls is age-related and increases with age, with the highest incidence in the oldest old.

Falls in older persons are usually of multifactorial origin. In the complex situation of multimorbidity and polypharmacy, which in older persons is often ‘the rule rather than the exception’, drug use may present an additive risk or contributing factor to falls (=‘excess risk’), i.e. in cases of pre-existent poor homeostasis (i.e., psychotropic drugs further impairing balance in patients with a previous stroke or polyneuropathy).

In the past decade, drugs that increase fall risk have been identified, initially in the meta-analysis by Leipzig *et al.* [2, 3], followed by a new meta-analysis by Woolcott *et al.* [4]. The drug classes predominantly associated with falls in older adults were the psychotropics, defined as antipsychotics, benzodiazepines (anxiolytics, hypnotics and sedatives) and antidepressants [2–4].

On the topic of polypharmacy and fall risk we found one article describing the association between total drug burden and falls in residential aged care facilities [5].

The authors used the Drug Burden Index (DBI), a measure of a person’s total exposure to anticholinergic and sedative medications that includes principles of dose–response and maximal effect and is associated with impaired physical function in community-dwelling older people, and evaluated the association between the DBI and falls in residents of residential aged care facilities. They found a significant and independent association between the DBI and falls in older people living in residential aged care facilities and recommend interventional studies, to determine whether reducing DBI, through dose reduction or cessation of anticholinergic and sedative drugs can prevent falls [5].

Evidence for the effects of drug cessation on falls

We found 48 reviews and 210 RCTs. We selected five reviews [6–10] and two specific articles [11, 12] included in the reviews, which demonstrated the effectiveness of drug cessation on falls in older adults [11, 12] (Box 1 and 2).

In the Cochrane Database Syst Rev 2009 [6], in the WITHDRAWN review [7] and in the most recent update of the Cochrane Database Syst Rev 2009 [8], the current body of knowledge is summarised. Medication review and modification were not effective in reducing rate of falls or risk of falling [8]. Risk of falling was expressed by the risk ratio,

Box 1. Summary on the effectiveness of drug cessation on falls

Withdrawal of psychotropics is effective in reducing rate of falls [6–11].

A prescribing modification programme for primary care physicians significantly reduced risk of falling [8, 12].

Box 2. Summary on the effectiveness of drug cessation on delirium and cognitive impairment

No studies available on drug cessation in delirium.

Withdrawal of psychotropics is associated with improved cognition [10].

Systematic reduction of polypharmacy in community-dwelling older adults can result in an improvement of cognitive function [18].

which compares the number of people who fall once or more; rate of falling was expressed by falls per person year [8]. Gradual, stepwise withdrawal of psychotropic medication in a placebo-controlled trial (CT) significantly reduced rate of falls, but not risk of falling [6–8, 11]. A prescribing modification programme for primary care physicians significantly reduced risk of falling [8, 12]. This programme included a major educational component for family physicians, with a face-to-face education by a clinical pharmacist and feedback on prescribing practices, as well as financial rewards. This, combined with self-assessment of medication use by their patients and subsequent medication review and modification, resulted in a significantly reduced risk of falling [8, 12].

A review [9] of the literature specifically relating to the effect of psychotropic medications on falls in older people, and with a particular focus on evidence supporting minimisation of their use to reduce risk of falls, confirmed the evidence [11] that gradual, stepwise withdrawal of psychotropic medication reduced rate of falls, but not risk of falling [9, 11].

In a systematic review [10] of the benefits and risks of medication withdrawal in older people as documented in published trials of medication withdrawal of specific classes of medications in patient populations with a mean age of ≥ 65 years, withdrawal of psychotropics was associated with a reduction in falls [10].

Summary on the effectiveness of drugs cessation in falls

Withdrawal of psychotropics is effective in reducing rate of falls [6–11].

A prescribing modification programme for primary care physicians significantly reduced risk of falling [8, 12].

Subjects at risk (2): older persons with delirium or cognitive impairment

The risk of drug-induced delirium is high in frail older people, and in those with dementia. In addition to polypharmacy, altered pharmacokinetics and pharmacodynamics and associated co-morbidities have an additive or synergistic role with drugs in causing delirium.

Medications are considered responsible for up to 39% of delirium cases in older people [13].

Many drugs have been associated with delirium, but certain classes of drugs are more commonly viewed as causative agents for delirium, including psychotropics, anticonvulsants, antiparkinson agents, opioid analgesics, gastrointestinal agents, i.e. antispasmodics, cimetidine, cardiovascular medications, i.e. antiarrhythmics, digoxin, antihypertensives (β -blockers, methyl-dopa), steroids [14].

The anticholinergic properties of these drugs probably play a causative role [14].

Rudolph *et al.* [15] developed the Anticholinergic Risk Scale (ARS), a ranked categorical list of commonly prescribed medications with anticholinergic potential. Higher

ARS scores were associated with significantly increased risk of anticholinergic adverse effects in older patients [15].

The authors recommend the ARS as a tool for identifying patients at risk of anticholinergic toxic reactions and as an educational aid for clinicians to identify medications with anticholinergic adverse effects so that they might avoid prescription [15].

For polypharmacy and delirium, Inouye and Charpentier [16] identified the addition of more than three medications during hospitalisation (RR, 2.9; 95% CI, 1.6–5.4) as one of five independent precipitating factors for delirium in older hospitalised patients [16].

For drug-induced cognitive impairment, we found one review article [17] reporting that non-amnestic mild cognitive deficits are consistently induced by first-generation antihistamines and tricyclic antidepressants, while BZD provoke combined amnestic and non-amnestic impairments [17]. The authors recommend that risk-benefit considerations are discussed with patients in order to enable an informed choice about drug discontinuation or substitution to potentially reverse cognitive adverse effects [17].

Evidence for the effects of drug cessation on delirium and cognitive impairment

We found 26 reviews and 59 RCTs addressing drug-induced delirium. We found no articles on the effects of drug cessation in delirium, which is understandable, given its multifactorial origin and complexity.

We found one review article [13] with specific recommendations for a medication review in older patients presenting with delirium, advising a thorough medication history, in order to determine if any new medications have been initiated, if medications have been discontinued, and the details of any recent dosage adjustments that have taken place [13].

When using cognitive impairment as a keyword, we found one systematic review [10] of published trials of medication withdrawal demonstrating that withdrawal of psychotropics was associated with improved cognition, and one prospective cohort study [18] on systematic reduction of polypharmacy demonstrating that reduction of polypharmacy led to improved cognition in 56 out of 64 patients.

In this prospective cohort study [18], an algorithm was applied for a trial of discontinuation of all drug therapies not immediately essential for life. The study included consecutive older community-dwelling patients referred by their family physician or family for comprehensive geriatric assessment in a Geriatric-Palliative Department. Drug cessation was recommended in 64 patients. In three out of 64 patients (ages 84, 85 and 73 years) a substantial improvement of cognitive impairment was observed (increases in absolute Mini-Mental State Examination score from 14 to 24, from 14 to 23 and from 14 to 30 points at 6–8 weeks after discontinuation of 7, 7 and 6 drugs, respectively). In total, in 56 (out of 64) patients improvements of cognitive impairment were reported; all occurred in the first couple of months following drug cessation and were maintained throughout

follow-up assessments (mean follow-up 19.2 months, SD \pm 11.4 months) [18].

However, the existing evidence for restoration of previous level of cognitive functioning after drug cessation is scarce, and articles or patient series on drug cessation as an intervention for cognitive impairment, dementia or drug-induced delirium are lacking in the literature.

Summary on the effectiveness of drug cessation in delirium and cognitive function

No articles were available on the effects of drug cessation on delirium.

Withdrawal of psychotropics is associated with improved cognition [10].

Systematic reduction of polypharmacy can result in an improvement of cognitive function [18].

Drug cessation at the end of life

In medicine, nursing and the allied health professions, end-of-life care refers to health care, not only of patients in the final hours or days of their lives, but more broadly care of all those with a terminal illness or terminal condition that has become advanced, progressive and incurable. End-of-life care requires a range of decisions, including questions of palliative care, patients' right to self-determination, medical experimentation, the ethics and efficacy of extraordinary or hazardous medical interventions and the ethics and efficacy even of continued routine medical interventions [19].

Among older adults with limited life expectancy, clinical benefits derived from use of multiple drugs and in particular those aimed at prolonging life or preventing clinical events, are negligible and do not counterbalance the risk of iatrogenic illness. Discontinuation of drugs in end-of-life care is not standard practice and clear guidelines on drug use to treat chronic and acute diseases at the end of life are not available so far. Avoiding or discontinuing drugs aimed at prolonging life or preventing clinical events may seem reasonable when the time needed to obtain the expected benefits from the drugs is longer than the estimated life expectancy of a particular individual, and when they do not offer symptomatic benefits [20]. O'Mahony recently suggested the conversion of major polypharmacy to 'oligopharmacy' (i.e. \leq 5 daily drugs), to avoid the onset of serious adverse drug events in patients with limited life expectancy [21].

For recommendations on medication review in end-of-life care, we found one review article [22] and one CT [23]. In the review article [22], the authors provide an ethically sound, evidence based discussion of the benefits and harms of medications commonly used in primary care among older patients. They point out that in frail older patients, who often have multimorbidity and functional impairments, symptom control, maintaining function and addressing end-of-life issues become the main priorities. "Thinking through the medication list" should be applied in patients at the end of life [22].

In the CT [23] on end-of-life care, the circumstances related to end-stage care of non-cancer nonagenarians (with end-stage congestive heart failure or dementia) in an acute care hospital were compared with those from a sample of younger patients; a prospective assessment was carried out of the written instructions for the following actions: do not resuscitate orders, the graduation of therapeutic decisions, information provided to relatives about prognosis, total withdrawal of normal drug therapy and provision of palliative care. Drug therapy was withdrawn in 66% of cases and terminal palliative care was initiated in 69%. The authors conclude that there is room for improvement in end-of-life care for the oldest-old patients with end-stage non-cancer chronic diseases [23].

For cessation of inappropriate medication and end of life, we found six reviews, two fulfilled the selection criteria [24,25], one systematic review [24] and one narrative review [25].

In the systematic review [24] of the literature for overuse of inappropriate medications in frail older adults with limited life expectancy, 21 studies were identified that used implicit criteria to identify inappropriate medications (including drugs without indication, unnecessary duplication and lack of effectiveness) [24]. Overall intervention effect sizes could not be determined due to heterogeneity of study designs, samples and measures. The authors conclude that very little rigorous research has been conducted on reducing inappropriate medications in frail older adults or patients approaching the end of life [24].

The narrative review [25] addressed medication use in persons with limited life expectancy; the authors found that a considerable proportion of individuals with a known terminal condition continued to take chronic disease preventive medications until death, despite questionable benefit. As death approached, there was an indication that a shift from a curative to palliative goal of care translated into a shift in medication use. The authors conclude that there is a need to develop consensus criteria to assess appropriate versus inappropriate medication use, specifically for individuals at the end of life [25].

Summary for medication use in end-of-life situations

Very little rigorous research has been conducted on reducing inappropriate medications in frail older adults or patients approaching end of life [24].

Box 3. Summary for medication use in end-of-life situations

Very little rigorous research has been conducted on reducing inappropriate medications in frail older adults or patients approaching end of life [24].

There is a need to develop consensus criteria to assess appropriate versus inappropriate medication use, specifically for individuals at the end of life [25].

There is a need to develop consensus criteria to assess appropriate versus inappropriate medication use, specifically for individuals at the end of life [25] (Box 3).

Conclusions

Medical complexity of older adults may have a great role in the onset of ADR and should always be considered before prescribing a pharmacological treatment in older patients [26].

Drug cessation in complex older patients is warranted in certain situations, where cessation rather than prescribing might be beneficial.

We reviewed the literature for effects of drug cessation on falls, delirium and cognitive impairment, and for cessation of inappropriate medication in end-of-life situations. There is evidence that withdrawal of psychotropics is effective in reducing rate of falls [6–11], and that a prescribing modification programme for primary care physicians can reduce risk of falling [8, 12].

Withdrawal studies in delirium are lacking. Withdrawal of psychotropics was associated with improved cognition [10]; a systematic reduction of polypharmacy in community-dwelling older adults resulted in an improvement of cognitive function in a considerable number of patients [18].

For end-of-life situations, very little rigorous research has been conducted on reducing inappropriate medications in frail older adults or patients approaching end of life [24]; there is a need to develop consensus criteria to assess appropriate versus inappropriate medication use [25]; the conversion of major polypharmacy to ‘oligopharmacy’ in patients with limited life expectancy deserves attention [21].

At the end of life, careful assessment of medication is necessary, in order to avoid inappropriate treatments and potentially serious ADR and events.

Conflict of interest

None declared.

Key points

- Effects of drug cessation on falls.
- Effects of drug cessation on delirium.
- Effects of drug cessation on cognitive impairment.
- Cessation of inappropriate medication in end-of-life situations.

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