HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

J Am Geriatr Soc. 2022 September ; 70(9): 2738–2741. doi:10.1111/jgs.17883.

Deprescribing Trials: A Focus on Adverse Drug Withdrawal Events

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Pharmacotherapy is often essential for many older adults to prevent and treat diseases/syndromes. Unfortunately, too often older adults can experience adverse drug events or an injury due to a drug.[1] Adverse drug reactions, a subset of adverse drug events, are defined by the World Health Organization as a response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.[2] Adverse drug reactions are a common cause of hospitalization, with a meta-analysis of 42 studies reporting that adverse drug reactions accounted for 9% of all hospitalizations in older adults.[3] Of note from one third to one half of adverse drug reactions are preventable.[3]

Another important medication-related problem, and subset of adverse drug events, is adverse drug withdrawal events (ADWEs) characterized as “a clinical set of symptoms or signs that are related to the discontinuation of a drug”.[4,5] There are two major types of ADWEs: 1) physiological withdrawal reaction (Table 1), and 2) a return of the underlying disease. Physiological ADWEs are more likely to be experienced immediately whereas the latter can occur up to four months after discontinuation. Return of the underlying disease is the most common type of withdrawal event. Clinicians caring for older patients with polypharmacy and multimorbidity are hesitant to deprescribe for them because of the risk of ADWEs. It is interesting to note that, except for anticonvulsants, benzodiazepine receptor agonists, and corticosteroids, most drugs can be safely tapered over a 4-to-6-week period. These three classes of medications should be tapered slowly and may take as long as a 6-to-12-month period. ADWEs can be avoided and minimized if adequate tapering and monitoring is conducted. Several excellent review articles and resources are available to guide safe deprescribing with the goal of avoiding and minimizing ADWEs.[6,7]

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Author contributions: All authors contributed to the writing of this article and approved the final version before submission.

Conflict of Interest: The authors have no conflicts of interest to declare.

The incidence and severity of ADWEs in older adults has not been well studied. The three seminal obervational studies that used a causality algorithm to ascertain ADWEs are described below. Data from a national study of older Veterans showed that 1.2% of all non-elective hospital admissions was due to ADWEs with 90% deemed to be preventable.[8] Gerety et al. investigated ADWEs in a single nursing home in Texas over an 18-month time period and found that 62 nursing home patients experienced a total of 94 ADWEs (mean 0.54 per patient) corresponding to an incidence of 0.32 reactions per patient-month.[9] Only one ADWE was associated with hospitalization. Graves et al conducted a study of 124 ambulatory older adults and found that 38 patients had 72 ADWEs.[10] Overall, 26 ADWEs (36%) resulted in hospitalization or other health care visit. Cardiovascular (37% to 62%) and central nervous system (10% to 30%) drug classes were the most frequently implicated.[8–10]

The literature has proliferated with trials examining deprescribing interventions since this concept was first described in 2003.[11–13] The assessment of ADWEs, along with adverse drug events, is a critical outcome to include in deprescribing trials to understand the potential harm and whether interventions vary regarding ADWE occurrence. However, several challenges exist to identifying and measuring ADWEs as the methodology is not well developed. Ross et al. reviewed adjudication methods for adverse drug event ascertainment for deprescribing trials, and concluded no method evaluated was designed or validated for deprescribing studies and most methods do not inherently capture ADWEs.[14] Sources of information for ADWE assessment may include patient self-report, chart review, and electronic methods, each with their advantages and disadvantages. The first step in identifying an ADWE is to identify whether the patient is experiencing an *adverse event*, followed by determining if the symptom(s) are related to existing drug therapy (i.e., adverse drug event) or related to a recently discontinued medication (i.e., ADWE). ADWE assessment is established by using a causality algorithm that reduces variability between raters using clinical judgement alone. The Naranjo adverse drug reaction probability scale has been adapted to assess the probability that the symptom(s) are related to drug withdrawal and has excellent rater reliability between two clinical pharmacists (kappa statistic of 0.81; Table 2).[8] Challenges to ADWE assessment include lack of validated self-reported measurements, underestimation of ADWEs if utilizing emergency department or hospitalization records as few ADWEs are serious, difficulty in identifying ADWEs that present as a constellation of symptoms (selective serotonin reuptake inhibitor syndrome), and causality algorithms (i.e. Naranjo) include some criteria that are unlikely to be routinely assessed (e.g., reaction reappear when drug was rewithdrawn).[15] Given the challenges of ADWE detection, moderate ADWEs (e.g. not requiring hospitalization) will likely remain undetected. Nonetheless, moderate withdrawal events will be important to characterize as these may result in patient distress, less willingness to discontinue medications in the future,[16] and increased office visits.

We recently conducted a comprehensive review of the literature since 2016 to update a prior meta-analysis focused on interventions to reduce adverse drug reactions.[17] We discovered only three deprescribing studies measured ADWEs as an outcome, all published in 2022. McDonald et al published the results of a cluster randomized controlled trial whose objective was to evaluate the effect of an electronic deprescribing decision support tool on older adults with polypharmacy on adverse drug events (including ADWEs) following hospital

discharge.[18] Two clinicians independently reviewed medical records and used a Likert scale to determine adverse drug events and ADWEs with a third clinician resolving any discordances. They found that while deprescribing was higher in the intervention group as compared to the control group, there was no difference between groups in the occurrence of ADEs within 30 days following hospital discharge (adjusted risk difference [aRD] −0.8% (95% CI, −2.9% to 1.3%). Moreover, deprescribing did not lead to more ADWEs in the intervention compared to the control group (aRD −0.1%; 95% CI, −1.2% to 1.0%). Overall, there were 49 ADWEs, representing 19.7% of the 249 adverse drug events.

Bayliss et al conducted a study to examine the effectiveness of increasing patient and clinician awareness about the potential to deprescribe unnecessary or risky medications among patients with dementia or mild cognitive impairment.[19] Safety monitoring included manually adjudicated medical records for all mortality events and every third hospitalization preceded by a primary care encounter with a medication discontinuation. About 30% in each group were using a potentially inappropriate medication at baseline. At six months, the rates of intervention and control groups taking one or more potentially inappropriate medications were similar (17.8% vs 20.9%; P=0.08*).* They also found that there was no pattern of adverse drug withdrawal events with the intervention. No further details about the measurement of ADWEs were provided, however, a safety paper from this trial is forthcoming (personal communication with Dr. Bayliss).

A study by McCarthy et al. was designed to investigate the effect of a general practitioner-delivered, individualized medication review in reducing polypharmacy and potentially inappropriate prescriptions in community-dwelling older patients with multimorbidity in primary care.[20] General practitioners in the intervention arm were asked to report any possible ADWE following the medication review. An adapted version of the Naranjo drug withdrawal algorithm was used to assess ADWE causality. Self-reported possible ADWEs were collected from patient follow-up questionnaires. At six months, there was no significant effect on the odds of having at least one potentially inappropriate prescription in the intervention versus control group (odds ratio [OR] 0.39, 95% CI: 0.14 −1.06). They also found that only 15 ADWEs occurred out of 826 stopped drugs in intervention patients (1.81%), 10 of which were considered probable. ADWEs were not measured in the control group for comparison. Only one of the ADWEs was categorized as serious (i.e., a severe depressive episode requiring inpatient admission eight weeks after discontinuing a serotonin–norepinephrine reuptake inhibitor).

These three studies are an important step in providing estimates for the incidence and severity of ADWEs in deprescribing trials. Strengths included rigorous study design, methods and large sample sizes. However, despite enrolling thousands of participants, these studies were likely underpowered to find a difference in ADWEs due to the low numbers reported. This exemplifies the challenge in understanding the effect of deprescribing interventions on this important outcome. Methods of ADWE detection and causality assessment varied (Likert scale vs. Naranjo scale) across these studies.

In summary, ADWEs are less common than adverse drug reactions and are preventable and minimized with careful tapering. At the time of deprescribing a medication, clinicians

should use a shared decision-making approach with their patient and provide information regarding possible withdrawal events, a clear outline of what to expect, and discuss strategies to minimize this temporary reaction. We encourage the development of ADWE methodology and for future deprescribing research to not only measure ADWEs in both intervention and control groups but to consider using an explicit causality algorithm when feasible. It is also important for studies to report number of ADWEs within the context of how many medications were discontinued in order estimate the extent of the problem.

ACKNOWLEDGEMENTS

Funding Sources:

This work was supported in part by the National Institute on Aging (U19AG066567), Centers for Disease Control and Prevention (U01CE002967) and a VA Health Services Research and Development Service Merit Award (IIR 18-228)

Sponsor's Role:

None.

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Table 1.

Drugs with Physiological Adverse Drug Withdrawal Events

Drugs	**Withdrawal syndrome**
Alpha blockers for hypertension	hypertension, palpitations, headache, agitation
Anticholinergics	irritability, anxiety, insomnia, sweating and nausea
Anticonvulsants	seizures
Antidepressants	akathisia, anxiety, irritability, gastrointestinal distress, malaise, myalgia, headache, coryza, chills, insomnia
Antiparkinsonian agents	rigidity, tremor, pulmonary embolism, psychosis, hypotension
Antipsychotics	dyskinesias, cholinergic overactivity, super sensitivity psychosis
Baclofen	hallucinations, paranoia, insomnia, nightmares, mania, depression, anxiety, agitation, confusion, seizures, hypertonia
Benzodiazepine receptor agonists	agitation, confusion, delirium, seizures, insomnia
Beta blockers	angina, myocardial infarction, anxiety, tachycardia, hypertension
Corticosteroids (chronic oral)	nausea, fever, anorexia, lethargy, arthralgias, postural hypotension
Histamine 2 receptor antagonists	heartburn, reflux, dyspepsia, epigastric pain, weight loss
Nitrates	myocardial ischemia
Opioid analgesics	restlessness, anxiety, anger, insomnia, chills, abdominal cramping, diarrhea, diaphoresis
Proton pump inhibitors	heartburn, reflux, dyspepsia, epigastric pain, weight loss
Sedative/Hypnotics (e.g., barbiturates)	anxiety, muscle twitches, tremor, dizziness

Table 2.

Naranjo's Adverse Drug Withdrawal Event Causality Algorithm

Questions	YES	NO	Don't Know
1.Previous conclusive reports on this reaction?	+1	0	0
2. Event appear after the drug was withdrawn?	+2	−1	0
3. Improve when the drug was readministered?	+1	0	0
4. Reaction reappear when drug was rewithdrawn?	+2	−1	0
5. Alternative causes for reaction?	−1	+2	0
6. Reaction appear after placebo discontinued?	−1	+1	0
7. Did patient previously use drug chronically?	+1	0	0
8. Reaction less severe when dose increased or more when decreased?	+1	0	0
9. Similar reaction to previous exposure to similar drugs?	+1	0	0
10. Adverse event confirmed by objective evidence?	+1	0	0

Scoring: < 1 no withdrawal event; 1 to 4 possible; 5 to 8 probable; >8 definite