Published in final edited form as:
J Am Geriatr Soc. 2008 October ; 56(10): 1946–1952. doi:10.1111/j.1532-5415.2008.01916.x.

Discontinuing Medications: A Novel Approach for Revising the Prescribing Stage of the Medication-Use Process

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Abstract

Thousands of Americans are injured or die each year from adverse drug reactions, many of which are preventable. The burden of harm conveyed by the use of medications is a significant public health problem and, therefore, improving the medication-use process is a priority. Recent and ongoing efforts to improve the medication-use process focus primarily on improving medication prescribing, and not much emphasis has been put on improving medication discontinuation. A formalized approach for rationally discontinuing medications is a necessary antecedent to improving medication safety and improving the nation's quality of care. This paper proposes a conceptual framework for revising the prescribing stage of the medication-use process to include

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Author Contribution:
All authors have equally approved the manuscript.
All authors have contributed to the content of the paper and the conception and design; and critical revision of the manuscript for important intellectual content
Acquisition of data: KTB
Analysis and interpretation of data: KTB, HMH, MHB, SGP
Drafting of the manuscript: KTB, HMH, SMH, SGP
Administrative, technical, or material support: SMH
Supervision: KTB, SMH

discontinuing medications. This framework has substantial practice and research implications, especially for the clinical care of older persons, who are particularly susceptible to the adverse effects of medications.

Keywords

discontinuing medications; drug withdrawal; medication-use process; adverse drug withdrawal events; older adults

INTRODUCTION

Every medication has associated risk. Adverse drug reactions (ADRs), defined 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 physiologic function,"1 are a costly risk associated with medication use. Adverse drug reactions are between the fourth and sixth leading cause of death in the U.S.2 It has been estimated that 5% of national health expenditures are attributable to ADRs, costing between $37.6 and $50 billion annually.3 These and other data argue persuasively for an urgent need to develop preventative strategies that reduce ADRs.

The medication-use process as traditionally conceived comprises a series of five stages including prescribing, communicating orders, dispensing, administering, and monitoring.4 Most often, preventable ADRs occur at the prescribing stage of the process in acute and ambulatory care.5, 6 Many approaches have been evaluated to improve the prescribing stage, including drug regimen reviews by pharmacists and computerized physician order entry or electronic prescribing. Various approaches have targeted the prescribing stage, although most approaches tend to be narrow in scope. Some interventions have mainly focused on improving underprescribing while others have tried to improve medication choice or dose.

Prescribing must not occur in isolation; rather, the prescribing stage of the medication-use process must integrate the processes of prescribing and deprescribing (or discontinuing) medications. The possibility of rationally discontinuing medications also needs to be assessed as an approach to improve prescribing and prevent potential ADRs. There is a growing body of evidence showing that discontinuing specific medications in certain patient populations does not worsen outcomes,7–9 decreases the risk of ADRs,10 and reduces costs attributable to medications.11 Therefore, strategies to improve discontinuing medications and integrate the discontinuation process into the health care system must be a top priority.

This paper proposes a conceptual framework for revising the prescribing stage of the medication-use process to include discontinuing medications. This framework has substantial practice and research implications, especially for the clinical care of older persons, who are particularly susceptible to the adverse effects of medications. The purpose of this paper is to bring much needed attention to medication discontinuation and to provide information to guide clinicians about the steps and challenges associated with discontinuing medications.

THE PRESCRIBING STAGE REVISED

Taking into account the medication-use process employed in practice, we developed an algorithmic approach to the process that expands the prescribing stage to include discontinuing medications (Figure 1). The process begins when a patient comes in contact

with the health care system. A clinician then performs an assessment that varies in comprehensiveness according to the circumstances and may include a review of the medical history, physical examination, and review of medications. Once a patient assessment has been performed, a decision is made to initiate a new medication, change the current regimen, continue therapy as prescribed, and/or discontinue a medication. This decision represents a key transition point in the prescribing stage.

The steps associated with starting a new medication or changing the drug regimen have been well-described.12 Indications that may warrant initiating a new medication include new symptom or condition, timely need for prevention, and lack of clinical improvement despite optimal treatment with other therapies, among others. Indications that may warrant changing the drug regimen include worsening symptom or condition, medication-related adverse effect, poor medication adherence or compliance, excessive out-of-pocket expenditures, and mandated therapeutic substitution, among others. If a new medication or change in the drug regimen is not warranted, the clinician may continue the current regimen or decide whether a medication or medications can or should be discontinued. Sometimes, it may be necessary to stop medications when a new medication is prescribed or the drug regimen is changed, as when drug-drug interactions require discontinuing a medication or when the new medication is being substituted for the old one. Therefore, Figure 1 represents an iterative process, whereby prescribing and discontinuing medications are not mutually exclusive and the clinician can go through many cycles of the process.

Discontinuing Medications

There are four distinct steps associated with discontinuing medications: (1) recognizing an indication for discontinuing a medication; (2) identifying and prioritizing the medication(s) to be targeted for discontinuation; (3) discontinuing the medication along with proper planning, communicating, and coordinating with the patient and in concert with the care of other clinicians; and, (4) monitoring the patient for beneficial or harmful effects.13 Indications that may warrant discontinuing a medication include (i) diminished benefit, such as cases of clinical improvement or stabilization, or (ii) increased risk, such as medication-related adverse effects, drug interactions, and unsafe use such as high-risk drugs in older adults. Sometimes, a new or worsening medical condition makes it necessary to stop a medication that otherwise would be continued. Other times, it is acceptable to discontinue a medication to test the hypothesis that the medication is no longer needed. In the nursing home setting, a gradual dose reduction is required for certain medications, including psychopharmacological medications.14 This process involves the stepwise tapering of a dose to determine if symptoms, conditions, or risks can be managed by a lower dose or if the dose or medication can be discontinued. This guideline emphasizes the importance of seeking an appropriate dose and duration for each medication and minimizing the risk of potential ADRs.

Once the decision is made to discontinue a medication, the clinician needs to consider how best to proceed with discontinuation. This process can be guided by considering both the underlying patient (e.g., age, co-morbid conditions) and medication (e.g., pharmacokinetics) characteristics. Failure to account for these characteristics can result in an adverse drug withdrawal event (ADWE), defined as “a clinically significant set of symptoms or signs caused by the removal of a drug.”15 The clinical manifestations of an ADWE may include a true physiological withdrawal reaction (e.g., rebound hypertension after discontinuing therapy with an alpha-antagonist antihypertensive), an exacerbation of the underlying condition for which the medication was originally prescribed (e.g., worsening edema after withdrawing diuretic therapy for heart failure), or a new set of symptoms (e.g., nausea and weakness after stopping therapy with corticosteroids).15

Table 1 shows medications frequently associated with ADWEs. The most common medications associated with ADWEs are those from the cardiovascular and central nervous system drug classes.15, 18 Within the cardiovascular drug class, the most common medications associated with ADWEs are beta-blockers, and most ADWEs involving these medications are attributable to physiological withdrawal reactions or exacerbations of the underlying condition.15 Within the central nervous system drug class, the most common medications associated with ADWEs are benzodiazepines, and most ADWEs involving these medications are attributable to physiological withdrawal reactions (e.g., anxiety), which may mimic the underlying condition.15

To reduce the likelihood of an ADWE, we recommend that many medications be tapered over the course of days to weeks, particularly medications used on a long-term basis. In other words, when discontinuing a medication "stop slow as you go low." Unfortunately, the best rate of taper cannot easily be predicted by pharmacokinetics alone. Some medications alter receptor binding and cause post-receptor changes. The activity produced is a function of the medication's binding affinity and receptor activation as well as the dose prescribed and duration of use. For example, prolonged systemic administration of supraphysiologic doses of a steroid can lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. However, duration of therapy and cumulative dose only roughly predict HPA axis suppression. Glucocorticoid potency and current dosage are also known to correlate with risk for HPA axis suppression. Because no prospective studies have defined optimal methods of dosage reduction for steroids, empirically, patients who have been on any long-term, systemic steroid therapy should have their steroid slowly tapered toward physiologic doses over weeks until the drug is stopped.22 Thus, as this exemplar situation demonstrates, when discontinuing a medication, consideration should be given to pharmacokinetics, pharmacodynamics, dose, and duration of use. Furthermore, while it may be possible to discontinue several medications concurrently, it is recommended that discontinuation be performed sequentially so that any withdrawal event(s) can be easily attributed to the medication ceased.13 Using these basic principles, studies have consistently demonstrated that the overwhelming majority of medications can be discontinued safely and effectively without causing an ADWE.15, 18

Case Example

An 84-year old woman was admitted to a nursing home for acute rehabilitation following surgery for a hip fracture that was sustained during a recent fall. Her medications on transfer to the nursing home included atenolol, duloxetine, losartan, lovastatin, metformin, enoxaparin, and omeprazole. Upon careful review of the medical records accompanying the resident, all of the medications had an appropriate indication with the exception of omeprazole. Omeprazole was apparently started for "stress ulcer prophylaxis" while in the hospital and continued upon discharge. The physician and pharmacist taking care of the resident agreed that omeprazole did not have an appropriate indication, and discussed the literature suggesting that medications in this class have recently been associated with *C. difficile* colitis, community acquired pneumonia, vitamin B12 deficiency, and even with hip fracture.23–25 Consequently, omeprazole was identified and prioritized for discontinuation. The plan was to abruptly withdraw omeprazole, since this medication is rarely associated with an ADWE. The nursing staff was also told to monitor the resident and notify the physician if the resident had complaints of reflux or abdominal pain.

IMPLICATIONS FOR PRACTICE AND RESEARCH

Geriatric and Other Special Populations

It is especially important to consider a medication's risk-benefit ratio in certain patient populations that have a greater need for having medications discontinued. Since older people experience more medical problems than younger people and often receive multiple medications, there is increased concern about geriatric polypharmacy, defined as "the use of excessive and frequently inappropriate medications."26 The clinical consequences of geriatric polypharmacy are numerous and can be quite serious, including ADRs, medication errors, medication nonadherence, and excessive costs to both the individual and society.26 Rationally discontinuing medications in older adults is a logical approach to mitigate polypharmacy. Future research should examine the clinical, humanistic, and economic impact of systematically discontinuing medications for the burgeoning geriatric population.

Even more than the general geriatric population, the more than 1.6 million nursing-home residents in the U.S. take a disproportionate number of medications,27 placing them at exceptionally high risk for ADRs. The incidence of ADRs in nursing homes ranges from 1.2 to 7.3 per 100 resident-months.27 Appropriately discontinuing medications in nursing-home residents is likely to result in more judicious medication use and will therefore reduce ADRs and costs attributable to medications. For instance, the interpretive guidelines for nursing-home surveyors, released in December 2006 by the Centers for Medicare & Medicaid Services,14 reflect the trade-off between benefits and risks associated with medication use in nursing homes. The federal guidelines require that nursing-home residents who receive any medication have a specific indication for the medication, a plan for monitoring for efficacy and toxicity that is clearly stated, and a specific reason for continuing, adjusting, or discontinuing the medication.14 Research to determine the most effective ways to monitor and discontinue medications are particularly needed in the nursing home setting because of the disproportionate amount of medication use and consequent high frequency of ADRs that occur in this setting. Such research is likely to have a substantial impact on the quality and cost of medical care provided to a significant number of vulnerable older adults.

Hospice patients also represent another population likely to benefit from the rational discontinuation of medications, especially those that are not being used for palliation or to improve quality of life – the goal that is often the most important for hospice patients. Medications are carefully reviewed upon admission to hospice and, based upon payment issues or changing goals of care and ideally in accordance with the needs and wishes of the patient and family, some medications are discontinued, often abruptly. On the other hand, because of the complexity of the coexisting medical and psychological needs in dying patients, at some point during their hospice care, most patients will have medications added to their already complex regimens.28 Therefore, one serious challenge in hospice care is that medications are frequently prescribed – initiated and discontinued. Appropriately discontinuing medications for hospice patients, whether or not new medications are added, is likely to reduce burdens at the end of life and decrease the risk of ADRs, thereby contributing to overall quality of life.

Barriers to Discontinuing Medications

There are many challenges to successfully discontinuing medications, including patient-, clinician-, and system-related barriers. From a patient's perspective, having medications prescribed is a familiar intervention that occurs throughout the person's lifespan. Patients often become psychologically attached to a medication they have been taking for years to manage a chronic condition, and discontinuing this medication may be disconcerting to the patient. The patient and, in many cases, his/her family may perceive the medication

discontinuation as substandard care or feel abandoned and that their condition is now terminal, treatment is futile, and death is imminent. Convincing patients and their families that a medication prescribed to manage a chronic condition is no longer essential and, in fact, could be harmful is challenging. When feasible, clinicians should try to emphasize the positive: the patient no longer needs the medication because his/her condition has improved. Furthermore, patients may become physically dependent on a medication, which may preclude the complete discontinuation of therapy.

From a clinician's perspective, once a medication is initiated it may be difficult to stop. On the one hand, clinicians are concerned with patients' resistance to change. Further, the act of prescribing a medication is a socially understood expression of the clinician-patient relationship that may be perceived as a demonstration of the clinician's caring and concern. Thus, clinicians may be reluctant to discontinue a medication, because of fear that doing so would damage this relationship. In addition, clinicians are concerned with other clinicians' resistance to change; they are often unwilling or feel uncomfortable discontinuing a medication that another clinician has prescribed.29 Clinicians too should take solace in the positive: the patient is at greater risk from taking the medication than from not taking it. Future research should explore barriers to discontinuing medications from the clinician's perspective.

In contrast to initiating medications, which ideally is guided by evidence from randomized controlled trials, discontinuing medications is often empiric because clinical trials are not designed to routinely or rigorously demonstrate the effects of medication discontinuation once a predetermined outcome has been achieved. In many randomized controlled trials, the consequences of medication discontinuation are reported only in subjects who stop the medication due to adverse effects or nonadherence. Other studies of medication discontinuation are prompted by concerns regarding adverse effects or withdrawal syndromes that occur in the post-marketing phase.30, 31 Although post-marketing data may suggest the feasibility and rationale for stopping a medication, conducting a randomized discontinuation trial once a medication is widely used to treat a chronic disease can be ethically and logistically problematic.32 An alternative is to incorporate a double-blind, randomized discontinuation phase into an early clinical trial, a design used in early-phase trials for cytostatic chemotherapy to detect sustained benefits as well as adverse discontinuation effects in initial responders.32

Therefore, from a system's perspective, there is a paucity of data about discontinuing many medications; data may only be available from less robust findings in observational or retrospective studies. For many chronic disease states with maintenance therapies, persistence of benefit may be present even after stopping a medication. For example, an extended placebo-controlled trial of a bisphosphonate demonstrated that the reduction in fractures achieved in an initial five-year treatment period was sustained for an additional five years off of therapy despite increased bone turnover.9 In contrast, discontinuing other chronic disease medications, such as acetylcholinesterase inhibitors in dementia, may worsen the chronic disease in patients who initially responded to the medication.33 Unfortunately, due to the lack of a double-blind, randomized discontinuation phase in trials for acetylcholinesterase inhibitors, much uncertainty remains regarding the proper duration of therapy and method of discontinuation. Thus, a systematic process that focuses on discontinuing medications and that becomes integrated into a truly interested health system can help to address this conspicuous gap in care.

COMMENT

To optimally solve critical deficits in the medication-use process for most Americans, especially the vulnerable elderly, efforts to improve medication discontinuation must be coupled to efforts to improve medication initiation. Improving medication discontinuation is complex but feasible and indeed necessary to promote the health and safety of the public. Multilevel approaches to improve both the initiation and discontinuation of medications are consistent with the Institute of Medicine's mission to design a safer health care system.4

For one, our present health care system provides little incentive for patients or providers to stop therapy. Consistent with patient-centered care, it is essential that the patient and, where relevant, the patient's caregiver are fully informed of and participate in the discontinuation process, including follow-up with providers. Further, patients should be taught and encouraged to inform all of their providers about medications that have been recently discontinued or initiated, especially self-initiated medications, supplements, or other therapies. Prescribers are in a key position to recognize an indication for discontinuing a medication, identify and prioritize medications to be targeted for discontinuation, and discontinue the medication with appropriate subsequent monitoring. Prescribers need to realize that it is sometimes appropriate and necessary to stop a medication that another prescriber initiated. More importantly, prescribers should communicate this information in a way that facilitates the process. Efforts to teach prescribers the skills of shared decision making are sorely needed.

Pharmacists are important resources for prescribers and patients. Pharmacists provide information both to prescribers on a medication's properties and how to taper or discontinue a medication and to patients about medication discontinuation, such as information about ADRs and ADWEs. Further, pharmacists are often the most accessible of health care providers and, therefore, they are in key positions to monitor patients. Strategies to improve pharmacists' involvement in the medication discontinuation process should be explored. Nurses bring to the discontinuation process their particular expertise in working with individual patients and patient's families to facilitate learning, adjustment, and behavior change. Other health care professionals, such as advanced practitioners, also contribute their special expertise in managing and monitoring patients during the discontinuation process. Similarly, strategies to improve nurses' and other health care professionals' involvement in the medication discontinuation process should be investigated.

The documentation of information on medications between care settings is particularly poor. 34 Better documentation in patients' medical records, especially at key points during transitions in care, will undoubtedly improve medication discontinuation by reducing unnecessary continuation of potentially harmful medications and preventing medications from getting inadvertently discontinued or restarted after discontinuation. As evidenced by the case example, documenting all of the medications' indications will improve continuity of care by helping to identify medications that could potentially be discontinued.

Finally, although most efforts to change behavior and practice need to be directed at the patient and clinician to have the greatest effect, to be successful, systems that improve all stages of the medication-use process and provide more effective protection against errors need to be developed. Technology such as computerized physician order entry has been advocated as one of the most effective means of improving the prescribing stage, particularly medication initiation. Technology may also be used to improve medication discontinuation. Clinical decision support systems, for example, can recognize medication indications and identify high-risk or unnecessary medications that should be targeted for discontinuation. When used in concert with the health care team, these support systems can

also facilitate patient care planning and assist with monitoring.35 Technological systems deserve additional research to elucidate their value in potentially improving the medication discontinuation process.

While we have purposely not included all the features that would be expected to improve medication discontinuation, such as determining which and when medications should be targeted for discontinuation, these are equally urgent considerations. Also, an important question is whether a systematic approach to discontinuing medications improves patient outcomes. Before the relationship between the discontinuation process and outcomes can be examined, it is necessary to have a workable approach to discontinuing medications and to have at least a preliminary understanding of the process for doing so. Such a process as we propose should, therefore, be regarded as a necessary first step in programmatic outcomes-based research of discontinuing medications.

In summary, the prescribing stage of the medication-use process must incorporate the related challenges of discontinuing medications as well as prescribing them. Reevaluating the prescribing stage in these terms is important to improve the quality of patient care and reduce the costs attributable to medications. Medication discontinuation warrants further attention to understand best practices and the effect on health outcomes. A formalized approach for rationally discontinuing medications is a necessary antecedent to building a safer health care system.

Acknowledgments

Dr. Handler is supported by Grant No. 1 KL2 RR024154-01 from the National Institutes of Health (NIH Roadmap Multidisciplinary Clinical Research Career Development Award Grant) and a Merck/AFAR Junior Investigator Award in Geriatric Clinical Pharmacology.

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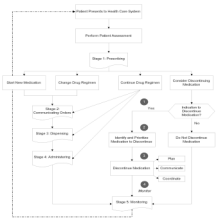

Figure 1.
The medication-use process, illustrating the prescribing stage revised to include discontinuing medications. See text for listing of indications for either initiating or changing or for discontinuing medications. Numbers denote the steps in the discontinuation process.

Table 1

Medications Commonly Associated with Adverse Drug Withdrawal Events (ADWEs)*

Medications[15–21]	Type of Withdrawal Reaction	Withdrawal Event
Alpha-antagonist antihypertensives	P	Agitation, headache, hypertension, palpitations
Angiotensin converting-enzyme inhibitors	P, D	Heart failure, hypertension
Antianginals	D	Angina (myocardial ischemia)
Anticonvulsants	P, D	Anxiety, depression, seizures
Antidepressants	P, D	Akathisia, anxiety, chills, coryza, gastrointestinal distress, headache, insomnia, irritability, malaise, myalgia, recurrence of depression
Antiparkinson agents	P, D, N	Hypotension, psychosis, pulmonary embolism, rigidity, tremor
Antipsychotics	P	Dyskinesias, insomnia, nausea, restlessness
Baclofen	P, N	Agitation, anxiety, confusion, depression, hallucinations, hypertonia, insomnia, mania, nightmares, paranoia, seizures
Benzodiazepines	P	Agitation, anxiety, confusion, delirium, insomnia, seizures
Beta-blockers	P, D	Angina, anxiety, hypertension, myocardial infarction, tachycardia
Corticosteroids	P, N	Anorexia, hypotension, nausea, weakness
Digoxin	D	Heart failure, palpitations
Diuretics	D	Heart failure, hypertension
Histamine-2 blockers	D	Recurrence of esophagitis and indigestion symptoms
Narcotic analgesics	P	Abdominal cramping, anger, anxiety, chills, diaphoresis, diarrhea, insomnia, restlessness
Nonsteroidal anti-inflammatory drugs	D	Recurrence of arthritis and gout symptoms
Sedative/hypnotics (e.g., barbiturates)	P	Anxiety, dizziness, muscle twitches, tremor
Statins	D, N	Cardiogenic shock, early neurological deterioration, heart failure, myocardial infarction, ventricular arrhythmia

Abbreviations: P, physiological withdrawal; D, exacerbation of underlying condition; N, new set of symptoms.

*Modified from Hanlon JT, Lindblad CI, Maher RL et al. Geriatric pharmacotherapy. In: Tallis RC, Fillit HM, eds. Brocklehurst's textbook of geriatric medicine and gerontology. New York: Churchill Livingstone, 2003, pp 1289–1296.1