Science of the Total Environment 443 (2013) 324–337

Contents lists available at SciVerse ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Lower-dose prescribing: Minimizing "side effects" of pharmaceuticals on society and the environment

Christian G. Daughton [a,*], Ilene Sue Ruhoy [b,1]

[a] Environmental Sciences Division, National Exposure Research Laboratory, U.S. Environmental Protection Agency, 944 East Harmon Avenue, Las Vegas, NV 89119, USA
[b] Pediatric Neurology Resident, Seattle Children's Hospital, University of Washington, Seattle, WA 98105, USA

HIGHLIGHTS

- Sustainable medication prescribing treats patient and environment as integral whole.
- Medication dose can often be reduced while still achieving therapeutic targets.
- Reduced dose translates into lower environmental loadings of excreted drug residues.
- Reduced dose can help prevent adverse side effects, drug diversion, and poisonings.
- Reduced dose can lessen cost of health care and reduce need for waste treatment.

ARTICLE INFO

Article history:
Received 17 September 2012
Received in revised form 25 October 2012
Accepted 25 October 2012
Available online 29 November 2012

Keywords:
Active pharmaceutical ingredient (API)
Reduced dose
Sustainable prescribing
Prudent prescribing
Off-label prescribing
Environmental impact

ABSTRACT

The prescribed use of pharmaceuticals can result in unintended, unwelcomed, and potentially adverse consequences for the environment and for those not initially targeted for treatment. Medication usage frequently results in the collateral introduction to the environment (via excretion and bathing) of active pharmaceutical ingredients (APIs), bioactive metabolites, and reversible conjugates. Imprudent prescribing and non-compliant patient behavior drive the accumulation of unused medications, which pose major public health risks from diversion as well as risks for the environment from unsound disposal, such as flushing to sewers. The prescriber has the unique wherewithal to reduce each of these risks by modifying various aspects of the practice of prescribing. By incorporating consideration of the potential for adverse environmental impacts into the practice of prescribing, patient care also could possibly be improved and public health better protected.

Although excretion of an API is governed by its characteristic pharmacokinetics, this variable can be somewhat controlled by the prescriber in selecting APIs possessing environment-friendly excretion profiles and in selecting the lowest effective dose. This paper presents the first critical examination of the multi-faceted role of drug dose in reducing the ambient levels of APIs in the environment and in reducing the incidence of drug wastage, which ultimately necessitates disposal of leftovers. Historically, drug dose has been actively excluded from consideration in risk mitigation strategies for reducing ambient API levels in the environment. Personalized adjustment of drug dose also holds the potential for enhancing therapeutic outcomes while simultaneously reducing the incidence of adverse drug events and in lowering patient healthcare costs. Optimizing drug dose is a major factor in improving the sustainability of health care. The prescriber needs to be cognizant that the "patient" encompasses the environment and other "bystanders," and that prescribed treatments can have unanticipated, collateral impacts that reach far beyond the healthcare setting.

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1. Introduction

Pharmaceuticals play a major and growing role in therapeutic interventions practiced in Western allopathic medicine. Assuming that the most efficacious drug is selected by the prescriber, the major variable in achieving successful outcomes is *dose*. It is a well accepted medical practice to alter dose based on desired clinical response coupled with avoidance of adverse reactions. Less well known is that dose also plays a major role in a wide spectrum of collateral but largely hidden effects extending far beyond the immediate patient. Dose determines the quantities of active pharmaceutical ingredients (APIs) that are continually released to the environment via excretion, bathing (as a result of topical administration and excretion via sweat), and disposal of unwanted leftovers. Despite its critical role and the ramifications that derive from strictly adhering to "approved" usage, dose receives

Abbreviations: APIs, active pharmaceutical ingredients; FDA, U.S. Food and Drug Administration; ADRs, adverse drug reactions; DDD, defined daily dose; PBT, persistent, bioaccumulative, toxic; SSRI, selective serotonin reuptake inhibitor.

* Corresponding author. Tel.: +1 702 798 2207; fax: +1 702 798 2142.
E-mail addresses: daughton.christian@epa.gov (C.G. Daughton), iruhoy@u.washington.edu (I.S. Ruhoy).
[1] Tel.: +1 206 987 2078; fax: +1 206 987 2649.

0048-9697/$ – see front matter. Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.scitotenv.2012.10.092

disproportionately little attention as a parameter that could be better optimized.

Drug dose has long been actively excluded from risk mitigation strategies for achieving reductions in ambient API levels in the environment. Drug dose has long been mistakenly assumed to be a parameter not amenable to control. By reducing dose (to levels below on-label guidelines), therapeutic goals can often still be met — or sometimes even exceeded (by minimizing adverse effects and thereby facilitating compliant patient behavior) — and patient expense can be reduced.

Dose is the major focus of this discourse. Presented is the first critical examination of the multi-faceted role that optimal drug dose could play in reducing the ambient levels of APIs in the environment and in reducing the incidence of drug wastage, which ultimately necessitates disposal of leftovers. Provided is the first framework for how a rational approach to dose selection during prescribing/dispensing could greatly assist in reducing the multiple and interconnected adverse impacts of medication usage on human health, cost of medical care, public safety, and the environment.

Strategies for addressing environmental problems resulting from the practice of health care have historically failed to incorporate sustainable solutions because they involve the communication and collaboration of two disparate professions that rarely interact — namely health care and environmental science. A major objective of this paper is to bridge the disconnect between medicine and environmental science — to foster communication and collaboration between medical care professionals and environmental scientists. It is important for both disciplines to understand the unique challenges faced by both — particularly how the practice of medication prescribing could be improved by incorporating some of the principles of environmental sustainability.

2. Background and rationale: bystander and environmental impacts of prescribing

Imprudent or inappropriate prescribing — including over-prescribing, mis-prescribing, and "marginal medicine" (Hoffman and Pearson, 2009) — includes unsupported off-label ("unapproved") indications, higher-than-necessary dose strengths (which can also overlap with the on-label dose range), and larger-than-needed dose quantities or longer-than-needed durations. All of these can contribute to the accumulation by the patient of unused medications (as a result of non-compliant or non-adherent patient behavior — partly driven by adverse drug reactions or patient confusion caused by polypharmacy). The patient is then faced with the frustration of wasted investment and burdened by the added responsibility, hazards, and liabilities associated with either storing or disposing of the wasted medications — all made worse in the U.S. by the absence of a nationwide approach for safe, efficient, and timely disposal (Daughton, 2010a).

Unused, accumulated medications promote drug diversion to others (with attendant abuse, misuse, and other risks posed by self-medication). Their unsecured storage by consumers facilitates unintended poisonings for others (a leading cause of overall poisonings among children, including mortality). Their imprudent disposal can amplify the introduction of APIs to the environment (with attendant societal costs imposed by the need for mitigation or remediation). They often represent significant wasted healthcare resources. And they can serve as a stark measure of failure to achieve treatment goals (Daughton and Ruhoy, 2011). Some of these concerns are becoming better recognized by the healthcare community (e.g., see: Donini-Lenhoff, 2012). The far-reaching effects of imprudent prescribing are discussed elsewhere in the literature and are beyond the scope of this paper. Supporting evidence for prudent prescribing can usually be found in authoritative, peer-reviewed sources and clinical trials, often made more accessible in updated compilations such as drug bulletins (Olsson and Pal, 2006).

Large and chemically diverse arrays of APIs compose the armamentarium of medications and diagnostic agents available to the large spectrum of healthcare professions. The expanding universe of biochemical targets (Imming et al., 2006) will continue to drive the development of numerous, new small-molecule drug entities (Reymond and Awale, 2012). Small-molecule pharmaceuticals are ubiquitous throughout society (Ruhoy and Daughton, 2008), as shown by a complex network of sources and ultimate fates of APIs in the environment (Daughton, 2008; see Fig. 1 therein, illustration also available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf). This will exacerbate the growing concerns surrounding environmental stewardship and public health and safety — the imperative to prevent drug diversion, abuse, overuse/misuse, and unintended poisonings (Daughton, 2010a). Environmental stewardship for drugs partly involves the need to reduce the incidence of APIs as ubiquitous contaminants of water resources, aquatic wildlife, the terrestrial environment, and food sources. An additional environmental burden of APIs (especially antibiotics and hormones) emanates from their frequent use in agriculture (especially confined animal feeding operations and aquaculture) (e.g., Bartelt-Hunt et al., 2011). Absent, however, is a cohesive strategy for ensuring that the processes feeding these pathways are optimized to reduce the entry of APIs to our immediate and ambient environments — strategies focused on waste reduction and pollution prevention. Such a strategy is required to create a sustainable, unified system for the optimally effective use of pharmaceuticals.

We propose that the fundamental cause for this disconnect and inefficiencies is the failure to recognize that the practices governing the use of pharmaceuticals in health care could be re-designed to lessen all of the downstream burdens. These strategies would yield reductions in: (i) the release to sewers of administered APIs — primarily via excretion and secondarily via bathing and (ii) the generation of leftover medications. Two strategies in particular have long been discounted as infeasible or imprudent: (1) prescribing lower doses and (2) evidence-based selection of APIs guided in part by their excretion profiles (prescribing those APIs displaying minimal excretion of the parent drug, bioactive products, or reversible metabolic conjugates) (Daughton and Ruhoy, 2011). This discussion focuses on the first strategy; the second strategy requires considerably more supporting data and effort to present and is the possible subject of a future paper.

Impudent use of medication undoubtedly plays a significant role in three of the six primary categories of waste in the U.S. healthcare system identified by a recent administrator of the Centers for Medicare and Medicaid Services, namely: (1) failures of care delivery, (2) failures of care coordination, and (3) overtreatment (Berwick and Hackbarth, 2012). These three categories compose a portion of the minimum estimated 20% waste of healthcare resource expenditures in the U.S. This is corroborated by a 2011 survey of U.S. primary care physicians, where 42% of respondents felt that the patients in their own practices received too much care (Sirovich and Woloshin, 2011); undoubtedly, an unknown portion of this directly involved over-treatment with medications. A portion of over-treatment may well derive from unfounded patient demands, partly driven by misinformed beliefs of patients regarding drug effectiveness and safety. For example, a recent U.S. survey of the public's knowledge of the drug approval process revealed that 39% believed that the U.S. Food and Drug Administration (FDA) approves only "extremely effective drugs" and 25% believed that the FDA approves only "drugs lacking serious side effects" (Schwartz and Woloshin, 2011).

Despite its association with off-label use, prudent low-dose prescribing could have major positive outcomes by: (i) reducing the loadings of APIs in the environment, (ii) protecting public health by reducing drug diversion (and the profound problems with attendant abuse of certain drugs and misuse of others) and unintended poisonings by drugs (especially infants, toddlers, and children), (iii) improving public trust — by reducing hidden and unwelcomed exposure of humans to trace levels of numerous APIs via potable water and contaminated foods, and (iv) improving health care — with more efficient attainment