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

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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.

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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.

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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

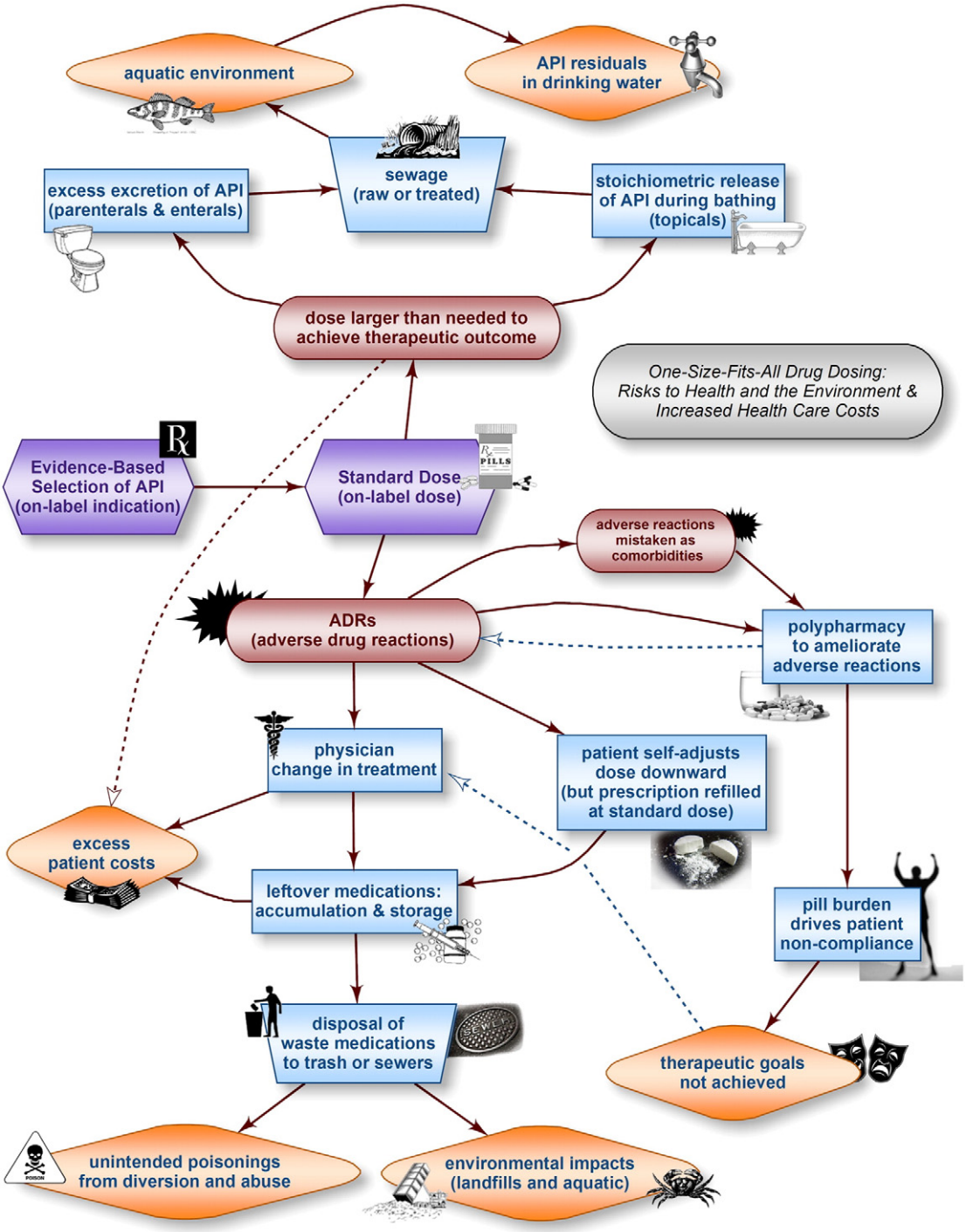

Fig. 1. One-size-fits-all drug dosing: risks to health and the environment, and increased health care costs.

of therapeutic outcomes, fewer adverse side (off-target) effects, and reduced patient costs. Although such an impressive list of collateral outcomes and goals might seem speculative, outlined here are the principles underlying a framework for their achievement.

A final note is important for perspective regarding the potential significance of APIs as contaminants in the ambient environment. Even though the levels of most APIs identified in the environment (especially the aquatic environment) are extremely low (many orders of magnitude lower than human plasma levels during therapeutic use), ecotoxicological research continually pushes the lowest observed effect levels (LOELs) even lower. One example of exquisite sensitivity is a study of the effects on freshwater snails by the antidepressants venlafaxine and citalopram. Exposure levels in the sub-nanogram per liter range or 10^{-12}M [up to 4 orders of magnitude below those known to occur in treated sewage effluent (e.g., see: Lajeunesse et al., 2012)] induced persistent foot detachment from the native substrate (Fong and Hoy, 2012). Such an alteration to behavior could prove adverse by affecting predator avoidance; many other examples of aquatic effects from exposures to low, ambient levels of APIs have been reported (see reviews: Corcoran et al., 2010; Santos et al., 2010). For humans, a parallel concern is those drugs with single-dose lethality to children. These drugs can be lethal to children in whole-body doses of

as little as a milligram; little appreciated is that these medications can be up to several orders of magnitude more potent than the most toxic pesticides currently available for consumer use (Daughton, 2010a).

3. Objectives of sustainable prescribing — beyond therapeutic outcomes and minimizing adverse effects

When prescribing a medication, it should provide the desired therapeutic outcome while minimizing adverse side effects and cost to the patient. The side effects, dosage, frequency and ease of administration, and other factors involved with the prescribed regimen must also not defeat compliance or discourage adherence by the patient. These goals can prove challenging to optimize because of competing trade-offs.

While this traditional decision process for prescribing might be complex, the complexity is largely lost in the day-to-day prescribing practices of healthcare providers because selection of medication type and dose is often based on an individual prescriber's experience with the use of particular medications in the context of a particular disease or somatic complaint. Consideration of large-scale studies, pharmacokinetics, other effective practices, and environmental stewardship are generally beyond the abilities of the time-restrained physicians.

For a truly sustainable system of healthcare, however, additional factors must be considered for a holistic, comprehensive, and prudent prescribing process (see Table 1). Of course, there are many additional fine points associated with each of these factors that serve to complicate generalizations. For example, although certain APIs are refractory to chemical alteration by engineered treatment systems used for upgrading or sanitizing sewage or drinking water [e.g., diclofenac, carbamazepine, and cetirizine (de Graaff et al., 2011)] or by a wide array of natural processes in the environment, other APIs are readily degraded and would pose lower potential for environmental impacts.

3.1. Prescribing to patients includes unintended prescribing to "bystanders"

Every prescription holds the potential for a downstream cascade of adverse impacts on the patient as well as others and the environment.

Table 1
Objectives of sustainable prescribing beyond therapeutic objectives and minimizing adverse effects.

Sustainable, environmentally sound prescribing should attempt to minimize
Continual entry of APIs into sewers (traces can later contaminate drinking waters and food supplies)
• Excretion of unmetabolized APIs via urine, feces, and sweat
• Excretion of bioactive metabolites
• Excretion of reversible metabolic conjugates (whose hydrolysis can liberate the API)
• Release of APIs via bathing (after topical application or excretion via sweating)
• Disposal of unused drugs and used delivery devices (such as transdermal patches)
Generation of leftover, unused medications
• Unnecessarily increases consumer expense
• Excessive prescribed quantities or complex regimens (exacerbated by polypharmacy) can promote non-compliant patient behavior
• May facilitate addiction, abuse, or misuse
• Facilitates storage/stockpiling, which may encourage diversion for second-hand use, including recreational use (such as pharm parties), drug sharing, and imprudent self-medication by others
• Imposes need for disposal of substantial quantities; disposal to sewers or trash can impose environmental or mitigation costs; prudent disposal via consumer take-back programs imposes societal infrastructure costs and increases environmental footprint (e.g., emissions from transportation and incineration)
Potential for accidental and unintended poisonings
• Risk exacerbated by practices that promote the generation of leftover medications (which may lead to unsecured storage or imprudent disposal)
• Morbidity and mortality are particularly problematic for infants, toddlers, children, and the elderly
• Certain drugs are acutely hazardous, possessing single-dose lethality for children
• Immediate surroundings and bystanders can be exposed to acutely toxic APIs (e.g., antineoplastics) via excretion (including sweat) from those undergoing treatment

Well documented as a major public health problem in the U.S. are the parallel but related problems of drug diversion (promoting abuse and addiction) and accidental poisonings (pharmaceuticals being a major cause of poisonings among children) (see references cited in: Daughton, 2010a; Daughton and Ruhoy, 2011). Even so, these two widely recognized problems are not sufficiently factored into the decision process used in prescribing. Efforts to reduce unintended poisonings, especially in children, would be greatly assisted if medications that are most frequently involved with accidental poisonings were flagged so that the appropriate precautions could be taken during the prescribing decision process. These include prescribing an alternative (especially if the targeted indication for the initial drug is off-label), prescribing quantities least likely to lead to unused leftovers, prescribing dose forms or formulations for adults that are less desirable or accessible to children, and ensuring that the patient understands the hazards involved with improper storage of unused medication as well as the imperative for prudent disposal of unwanted or used medication.

3.2. Prescribers' unintended impacts on bystanders

With each prescription issued for a targeted condition, prescribers should therefore keep in mind that they are essentially (albeit unintentionally):

- indiscriminately prescribing vanishingly small amounts of random medications to others beyond the patient (including those for whom the medication might be contraindicated — pregnant women or infants, or those with pronounced sensitivities);
- facilitating others to ingest trace levels of one or multiple "stealth" APIs without their knowledge or consent — perhaps on a chronic basis;
- creating the potential for making prescription-only medications freely available to those without a prescription — when leftovers are diverted (with the potential for increased morbidity and mortality via abuse and unintended poisonings);
- exposing others to significant levels of highly hazardous substances via excretion (such as family members of those prescribed antineoplastics) (Daughton, 2010a).

3.3. Minimizing the bystander impacts of prescribing

Clearly, given the realities of drug pharmacokinetics, unintended bystander exposures to even properly prescribed medications or their constituent APIs cannot be eliminated. But they can be reduced — by the prudent selection of API, dose, quantity, and duration of each prescribed medication regimen. Optimizing these variables should be attempted by using evidence-based off-label prescribing. Because of a lack of complete information (especially pharmacokinetics), optimizing each of these criteria is often a hypothetical exercise. We argue, however, that by paying attention to these criteria — and making the patient aware of the numerous stealth "side-effects" and "bystander effects" of medication use (beyond the known adverse drug reactions: ADRs) — a larger purpose could be served.

The current paradigm could be changed — where prescribers and patients alike resort to medication before alternative treatments. A variety of forces within the systems of health care often lead to a consideration of pharmaceuticals as the first line of treatment. Useful to consider would be alternative methods to treat chronic conditions that require control beyond acute and rapid corrections. Indeed, a more methodical, holistic approach may ultimately prove more efficacious, with fewer downstream effects. Acknowledging the many hidden side effects of medications may serve to catalyze an ongoing discussion and debate regarding society's complex relationship with drugs and how to design an environmentally sustainable system for their optimal use by the patient and society at large.

So what actions could be implemented now to optimize the prescriber's decision process?

The primary factor that promotes the entry of most APIs into the environment is excretion via urine and fecal material. Bathing has been identified as a secondary route of API release to sewers for those drugs whose primary use is via topical application and for many systemic APIs that are excreted via sweat (Daughton and Ruhoy, 2009). In contrast, disposal of leftover medications to sewers may be a major contributor only when the API would otherwise undergo extensive metabolism that does not result in reversible metabolic conjugates (Daughton and Ruhoy, 2009). Except for disposal, these routes of release to the environment have long been considered intractable to control via pollution prevention measures because they were viewed as natural, albeit unintended, consequences of medication use not amenable to alteration. And medications are viewed — rightly or wrongly — as essential for patient health, lifestyle, and well-being. This mind set has long impeded productive physician–patient conversations of non-pharmacologic, alternative interventions.

The multifaceted advantages of prudent prescribing are summarized in Table 2 and discussed further in the sections that follow.

3.4. Factors amenable to control for minimizing prescribing to bystanders

The initial dose determines the quantity of API excreted, even for those drugs that are extensively metabolized (resulting in the excretion of little of the unchanged parent API or its reversible conjugates); for topical drugs, the amount applied determines the amount released during bathing (excluding the portion systemically absorbed) (Daughton and Ruhoy, 2009). A certain portion of this prescribing is responsible for the unnecessary introduction of an excess quantity of APIs to the environment; this portion undoubtedly varies among APIs. This excess portion could be actively reduced by a number of strategies directly under the control or influence of the prescriber.

The only pollution prevention measure implemented to date is the control of drug disposal to sewers. This has been addressed mainly by the use of consumer collections called take-backs (Glassmeyer et al., 2009). But drug disposal is probably only a minor contributor to the levels of most APIs in the environment. Disposal might play a significant role only for those APIs that would otherwise be extensively metabolized and not yield reversible conjugates (Daughton and Ruhoy, 2009). Surprisingly, although the administered dose is recognized as the major variable responsible for most API release, it is widely discounted as one that is not amenable to control measures. In fact, environmental models that are designed to predict the concentrations of APIs in the aquatic environment almost always assume on-label doses (or assumptions regarding combined daily doses, such as the defined daily dose — DDD).

These assumptions retard the development and implementation of healthcare practices that could result in the most significant reductions of API loadings in the environment. To correct these ongoing assumptions, we examined the feasibility of controlling drug dose as a primary means for potentially reducing the entry of APIs to the environment. The problems that derive from failure to consider adjustment of doses to levels lower than the "standard" (on-label) dose are illustrated in Fig. 1. These problems result from the failure to consider patients, society at large, and the environment holistically — as an integral "patient" (Daughton and Ruhoy, 2011).

4. Off-label dosing as a key strategy in minimizing impacts on the environment and other bystanders

Captured in Fig. 1 are the major problems that can result from reliance on the standard (on-label) dose of a medication. The middle portions of the illustration pertain to concerns related to human health and safety. The upper and lower portions of the illustration relate respectively to impacts on the aquatic and terrestrial environments. The assumption is made in the illustration that the drug is being prescribed for an indicated (on-label) condition — as a "standard" dose has no formal meaning for an off-label condition, especially one not sufficiently supported by evidence.

Table 2
Multifaceted advantages of prudent prescribing — reducing adverse outcomes for patient health, public safety, and the environment.

Adverse outcome reduced	Resulting from	Reductions achieved via
Release of APIs to the environment	API excretion (urine and feces); release to sewers from bathing (APIs excreted in sweat and APIs concentrated in topical formulations); release in landfill leachate from disposal of leftovers to trash	Shorter regimens; lower doses (may avoid drug–drug interactions, which can lead to non-adherence and accumulation of leftovers)
Incidence of adverse events in patients	Caused by higher-than needed doses or longer-than needed durations of treatment	
Infrastructure costs to society	Disposal programs for leftover, unwanted drugs; additional treatment needed for wastewater and drinking water	
Cost to patients	Drug waste: leftover, unwanted, and unused medications	Eliminating need for self-adjustment of dose by skipping doses, dose-form modification (e.g., "pill splitting" or crushing), or measuring less (liquid dose-form); reducing physician change in treatment; reducing incidence of polypharmacy and non-compliance
Diversion, abuse, and unintended poisonings	Unsecured storage or imprudent disposal of new and unwanted drugs (and used delivery devices)	Informing patient of acute toxicity hazards (especially drugs lethal to children in a single dose)
Deterioration of physician–patient communication	Non-individualized, one-dose fits all prescribing	Involving patients in determining their personal optimal dose (shared decision-making may improve outcomes); low doses allow patient to possibly also benefit from the placebo response while avoiding ethical dilemmas that would normally be imposed on the physician (de Jong and Raz, 2011)
Unintended exposure of bystanders	API excretion via sweat followed by inter-dermal transfer (problematic for antineoplastics and other hazardous drugs) (Daughton and Ruhoy, 2009)	Informing patients of risks (both in writing and verbally)

The box in Fig. 1 labeled "ADRs" might be more accurately labeled "Preventable ADRs." Although ADRs for off-label indications can be frequently identified during post-market surveys, as the size of the treated population increases well beyond those used in clinical trials — and some of these ADRs eventually become well known (e.g., off-label use of fenfluramine-phentermine leading to cardiac valve damage) — the intent of the illustration is to show the potential benefits of off-label dosing (particularly doses lower than recommended) for indicated conditions. Note, however, that for a drug prescribed for an evidence-based off-label indication, the same principles involved with lower-dose prescribing can still apply. Many studies maintain that the large majority of ADRs derive from higher-than-necessary on-label dose rather than other aspects of prescribing such as an API's inherent pharmacodynamics, errors, or patient non-adherence (Cohen, 2001b; Lazarou

et al., 1998). The on-label, standard dose may simply be excessive for certain individuals.

For any API, the dose–response regime comprises targeted therapeutic effects and off-target, side effects (which subjectively may or may not be considered ADRs). The "optimal" dose (the best compromise between the two) is often determined by the patient in experimenting with self-dosing adjustments. The box labeled "patient self-adjusted dose" refers to the practice commonly used by patients who desire to either begin or maintain therapy at a dose below the on-label dose (e.g., to avoid ADRs) but the lower dose is not available from the manufacturer (or compounding pharmacy) or the patient does not want the physician to know about their non-adherence; cost savings may be another motivating factor. This practice involves pill splitting (or crushing) or other forms of "dose-form modification" (such as dividing the contents of emptied capsules), measuring less of a liquid dose-form, or using a less-frequent dosing schedule; for tablets amenable to splitting (using a well-designed splitter), the patient can often reproducibly create fractional doses ranging down to one-eighth. Although it is well-known that dose-form modification can pose problems for the patient (such as insufficient doses for conditions lacking symptoms that the patient can readily recognize; or the release of excessive API from dose-forms not intended for physical modification, such as time-release formulations), less appreciated is that dose-form modification can also pose hazards for bystanders. The physical alteration of medications holds the potential for unrecognized spillage of residues released from struggling to split or crush oddly shaped drugs or tablets designed to resist tampering. The released debris can later be accidentally contacted or consumed by children or pets (Daughton, 2010a); if the intent is to encourage patient experimentation with low doses, the prescriber might avoid oddly shaped drugs that make pill splitting difficult or time-released dose-forms or tablets designed to defeat tampering.

Supporting references for parts of Fig. 1 include: (i) uptake/bioconcentration of APIs by aquatic organisms (Daughton and Brooks, 2011; Meredith-Williams et al., 2012) and their impacts in the aquatic environment (Corcoran et al., 2010; Santos et al., 2010), (ii) occurrence and health ramifications of APIs in drinking water (Daughton, 2010b; Jelić et al., 2012), (iii) hazards of unintended human poisonings from mishandling of drugs (Daughton, 2010a), and (iv) overview of the issues surrounding patient non-compliance and various other patient/physician behaviors that lead to the accumulation and eventual need for disposing of unwanted, leftover drugs (Daughton, 2010a). Important to recognize is that the illustration focuses solely on the parent API with respect to environmental impact. Analogous concerns pertain to potential metabolites or transformation products, including: (i) labile, reversible metabolic conjugates, which can later undergo hydrolysis to return the parent API (Daughton and Ruhoy, 2009), (ii) environmental degradation products, many of which are the same as excreted metabolites (e.g., see: Celiz et al., 2009; Hernández et al., 2011), and (iii) transformation products, such as disinfection by-products (e.g., N-nitrosodimethylamine — NDMA) created during water chlorination (Pereira et al., 2011; Shen and Andrews, 2011).

The subject of drug dosing is widely misunderstood. As recently as 40 years ago, medicine was more an art than a science. Management of a patient was a culmination of the skills, experience, and observations of a physician along with patient specifics such as a demographics and family history. Largely as a result of the advent of statistically controlled clinical trials, prescribing of medications often now uses the "one size fits all" approach — rigidly adhering to the "standard" dose that is captured in the medication "label" (and reiterated in references such as the Physicians' Desk Reference, or PDR). Many erroneously assume that the standard dose should not be adjusted — to ensure therapeutic efficacy. Prescribers sometimes fear that adjusting the dose could lead to ethical or legal vulnerabilities (Rosoff and Coleman, 2011). This fear, however, is not well founded — as the standards of care for dosing of most commonly used classes of medicinal drugs are not established. Furthermore, the FDA does not prohibit off-label prescribing (one aspect of which is dose), as it does not regulate the practice of prescribing itself (Meadows and Hollowell, 2008); controlled substances are an exception where federal regulations do govern prescribing (Rosoff and Coleman, 2011). Note, however, that off-label prescribing may be viewed differently in other countries (e.g., see: Emmerich et al., 2012).

In fact, prudent off-label use is considered integral to the continual evolution and advancement of the accepted standard of care (Tomaszewski, 2006); prudent off-label use also plays a role in repurposing (or repositioning) drugs for new uses. For those clinicians hesitant to prescribe lower doses because of liability concerns, an alternative perspective is that universally prescribing the standard (on-label) dose invariably and necessarily means that one or more sub-populations are being over-medicated. These groups should instead be receiving lower doses because they display disproportionately higher responses at lower doses than indicated by the composite (average) dose–response curve from the general population. This recommendation inherently assumes that a physician is able to offer regular follow up, which may be in the form of a clinic visit or laboratory testing for evaluating a patient's response to a lower dose.

In this discussion, the assumption is made that all prescribing is for bona-fide indications — where the possibility of positive therapeutic outcomes is documented by sufficient evidence for the selected API. These include the indications covered by the label as well as those sufficiently supported for particular off-label uses. Prescribing for on-label indications involves drugs containing APIs that are commonly reported as environmental contaminants (e.g., see Supplementary Table S1). For those drugs prescribed for off-label indications lacking unambiguous evidence of efficacy in the absence of undue risk, avoidance of these uses would clearly result in a reduction in environmental API loadings.

5. The role of prudent, off-label prescribing

It is critical to distinguish prudent from imprudent prescribing. Off-label ("unapproved") prescribing includes bona-fide reasons to adjust parameters beyond those accommodated by the label, such as therapeutic indication (condition), dose strength and daily quantity, dose frequency (interval), duration (course), route of administration, age, or gender. Generally, this includes those variables not covered in the drug registration data (such as clinical trials), or those specifics that are actively excluded by the label (e.g., a specific contraindicated sub-population or drug–drug interaction).

Despite the restrictions implied by on-label use, off-label use (justified with sufficient supporting evidence) is a common and widely accepted prescribing practice (Radley et al., 2006), especially for children and other sub-populations that have historically been excluded from clinical trials. Only in the absence of supporting evidence (or the failure to acknowledge negative evidence) is off-label use considered imprudent, improper, problematic, or disapproved. Off-label use essentially serves as the major mechanism for continually updating the more limited knowledge base that existed at the time of licensing. This is tempered, however, by a possibly widespread misunderstanding among prescribers as to what exactly constitutes off-label use and the key role of supporting evidence (Chen et al., 2009). Growing numbers of resources provide access to information regarding evidence-based, off-label use (e.g., Baker, 2008; Chen et al., 2009; Largent et al., 2009; Stafford, 2012; Walton et al., 2008). Even with supporting evidence, however, the physician should document all off-label prescribing decisions to minimize liability vulnerabilities (Edersheim and Stern, 2009; Rosoff and Coleman, 2011).

Important to note is that the published literature on off-label prescribing focuses predominantly on off-label indications and sub-populations. Comparatively little attention is devoted to off-label dose.

6. Imprudent off-label prescribing versus conservative prescribing (less can be more)

In 2010, *The Archives of Internal Medicine* began publishing a series of articles ("Less Is More") on improving healthcare outcomes by avoiding the over-application of care, such as by imprudent prescribing (Grady and Redberg, 2010). Informal guidelines for less-is-more prescribing were outlined in one article from this series that presented two-dozen principles underlying what is becoming known as "conservative prescribing" (Schiff et al., 2011). These elements focused on more prudent, judicious prescribing, with an emphasis on restricting the types and numbers of medications prescribed to an individual patient. Absent, however, were considerations surrounding dose — or the attendant indirect effects regarding accidental or unintended exposure to others and the environment.

Imprudent prescribing includes purposeful use for off-label indications, as well as for on-label indications using parameters not covered by the label (e.g., excessive doses), in the absence of sufficient evidence or despite evidence to the contrary. Less appreciated is that it can also include adhering strictly to on-label use but resulting in unintended, unforeseen off-label use (such as particular mismatches resulting from uncoordinated polypharmacy contributed by multiple physicians). Indeed, one study involving measures striving to actively reduce or discontinue polypharmacy in elderly patients was shown to not result in significant risks, but rather to result in improved health for 84% of the patients (Garfinkel and Mangin, 2010). Particularly noteworthy with respect to geriatric medicine is the precaution needed in avoiding or reducing the dosage/duration of certain medications. The Beers Criteria — updated in 2012 (The American Geriatrics Society Beers Criteria Update Expert Panel, 2012) — were developed for informing the prescriber of medications that may pose unwarranted risks for older patients (AGS, 2012). Adherence to the Beers Criteria would result in immediate reductions in the environmental loadings of these age-inappropriate medications.

The magnitude of imprudent prescribing is reflected in any number of reports. One notable example is a report from the Office of Inspector General (Department of Health and Human Services) that documented widespread, imprudent, off-label prescribing for atypical antipsychotic drugs in nursing homes for the elderly (Levinson, 2011). This study targeted Medicare claims involving unnecessary use — defined in part as inappropriate indication (or contraindication), or excess dose or duration. In this case, patients were subjected to unnecessary risks, and healthcare was burdened by additional costs; API loadings to the environment were undoubtedly unnecessarily increased.

Of note is that off-label imprudent prescribing (i.e., unsupported by evidence) is not necessarily actively or uniformly regulated — except for certain controlled substances. Over the years, however, many arguments have been advanced for its regulation, including the larger issues of societal harm resulting from collateral adverse effects that lead to increased healthcare spending (e.g., Rosoff and Coleman, 2011).

All attempts to reduce imprudent prescribing clearly hold substantial potential for benefitting the patient and further protecting public safety (with reduced diversion and poisonings). But the arguments supporting the need to regulate imprudent, off-label prescribing could be augmented by emphasizing the increased probability that APIs are invariably and unnecessarily discharged to the environment — adding to the environmental loadings already resulting from prudent prescribing. Prohibition of imprudent prescribing could have a measurable and immediate impact on reducing the loadings of various types of APIs introduced to the environment.

Obvious drugs to first target for reduced prescribing are those frequently prescribed for off-label indications that have weak supporting evidence and which also have been identified as contaminants in the environment. As an example, some of the drugs highlighted in one off-label use study (Eguale et al., 2012) are summarized in Table 3. The records from 113 primary care physicians were examined for a 5-year period, entailing roughly a quarter million prescriptions for nearly 51,000 patients. These prescriptions involved 684 drugs. The incidence of prescription for off-label *indications* was 11%, and of these, 79% lacked supporting evidence considered to be strong. The 11 drugs listed in Table 3 are those with the highest off-label use for indications with the lowest incidence of strong supporting evidence — ranging from zero to less than 50%. Of these 11 drugs, eight were among the top 100 generic drugs prescribed in the U.S. in 2010 (Drug Topics, 2011).

Table 3
Examples of drugs prescribed for off-label indications with minimal strong supporting evidence and which have also been identified as contaminants in the environment.

Drug[a]	Evidence for occurrence of API as environmental contaminant[b]
Amitriptyline [#53] [c]	Wastewaters (Bisceglia et al., 2010; Unceta et al., 2010; Verlicchi et al., 2012); biosolids (Chari and Halden, 2012) [also see Table S1]
Azithromycin [#7]	Wastewater or sewage sludge (Miège et al., 2009; Radjenovic et al., 2009; Verlicchi et al., 2012); rivers or drinking water (Reif et al., 2012; Valcárcel et al., 2011); biosolids (Sabourin et al., 2012)
Celecoxib *(#74)*	Wastewater (MacLeod and Wong, 2010)
Citalopram [#19]	Wastewaters (Breitholtz et al., 2012; MacLeod and Wong, 2010; Metcalfe et al., 2010; Unceta et al., 2010); treated wastewaters and surface waters (Gros et al., 2012); rivers and drinking water (Valcárcel et al., 2011); aquatic organisms (Daughton and Brooks, 2011); sorbed to settleable particulates (Lahti, 2012; Lahti and Oikari, 2011)
Clonazepam [#28]	Sewage sludge (Fick et al., 2011) [lack of targeted monitoring in waters]
Diclofenac [#97]	Wastewaters (Stülten et al., 2008); treated wastewaters (Gros et al., 2012; Yu et al., 2012a); sewage sludge (Yu and Wu, 2012); fish (Lahti et al., 2012)
Gabapentin [#20]	Surface water (Ferrer and Thurman, 2012; Kasprzyk-Hordern et al., 2008); wastewater (Lai et al., 2011); surface water and drinking water (Morasch et al., 2010)
Olanzapine *(#195)*	Wastewaters and surface water (Bahr, 2009; Gracia-Lor et al., 2011)
Quinine [n.a.]	Acute toxicity hazard for children (Daughton, 2010a; references cited therein)
Risperidone [#80]	Fish (Fick et al., 2010); wastewaters (Bahr, 2009; Woldegiorgis et al., 2007)
Trazodone [#37]	Surface waters and wastewaters (Gros et al., 2012; Himmelsbach et al., 2006; Martínez Bueno et al., 2012)

[a] Drug frequently prescribed for off-label indications and which has weak supporting evidence (Eguale et al., 2012).
[b] Representative recent references documenting API occurrence in ambient waters, treated sewage effluent or sludge, sewage biosolids, or aquatic tissues.
[c] Number in square brackets indicates ranking of API among the top 200 most-frequently prescribed generic drugs in 2010 (Drug Topics, 2011); number in italicized parentheses indicates ranking of API among the combined top 200 most-frequently prescribed generic and branded drugs in 2011 (Bartholow, 2012). Lack of number indicates API is not among the most-frequently prescribed; note that this ranking does not include APIs from sales of OTC medications.

Other, widely accepted examples of imprudent prescribing include those highlighted in the Choosing Wisely Campaign, which was organized by the American Board of Internal Medicine Foundation in 2012 (http://choosingwisely.org/) in response to a proposal (Rosenbaum and Lamas, 2012) regarding the imperative and responsibility of physicians to factor cost — in the form of waste avoidance (Brody, 2012) — into their decision making. This campaign compiled lists of "Five Things Physicians and Patients Should Question" from each of nine U.S. medical specialty societies. Each of the 45 items on these nine lists represents a consensus, evidence-based recommendation. While the current lists focus almost exclusively on screening tests and procedures deemed imprudent under certain conditions (e.g., unnecessary diagnostic tests, "defensive medicine"), many of these tests lead to subsequent follow-up treatments that entail medications, often for long-term maintenance — a practice that particularly sustains and perpetuates environmental loadings of APIs.

Two examples highlighted by the Choosing Wisely Campaign specifically target imprudent prescribing of medication (over-treatment) and include avoiding antibiotics for certain sinusitis conditions and

the use of the lowest effective doses of proton pump inhibitors or histamine H-2 receptor antagonists for gastroesophageal reflux disease.

Indeed, both ranitidine (Castiglioni et al., 2006; Pedrouzo et al., 2011; Yu et al., 2012b) and omeprazole (Pedrouzo and Borrull, 2008; Rosal et al., 2010) have been reported in treated sewage effluent. And the imprudent use of antibiotics poses unique concerns from widespread contamination of the environment, especially in niches where residues accumulate and concentrate (such as soils and sediments). Concerns continue to emerge with respect to the selective pressure for antibiotic resistance (and for cell persistence) among bacteria of clinical concern from exposure to low, ambient levels of antibiotic APIs (Tello et al., 2012). Other examples of drugs frequently prescribed imprudently are those that pose acute risks for the elderly (e.g., Gloth, 2010).

A final example involves controlled substances (Schedules II, III, and IV) that are subject to doctor shopping and frequent abuse. These represent a particular group of drugs that experience high rates of imprudent prescribing with particularly strong adverse impacts on both patients and bystanders; they are also commonly identified as environmental contaminants (Bijlsma et al., 2012; Daughton, 2011). This prescribing could be substantially reduced by prescribers with more diligent and effective referral to prescription-drug monitoring programs (PDMPs) to track possible abuse by patients. Expansion of PDMPs and improved ease of access would greatly help (Daughton, 2010a; Perrone and Nelson, 2012).

7. The role of dose in mitigating APIs in the environment

Accounting for the potential impact of APIs on the environment as a new factor in guiding the drug selection process used in prescribing was conceptualized and introduced in Sweden in 2005 (Wennmalm and Gunnarsson, 2005); an assessment of this system (Swedish Environmental Classification and Information System for pharmaceuticals) has been made (Ågerstrand and Rudén, 2010). Three factors were considered in this first-ever environmental classification system for ranking an API's potential for adverse environmental impact: (i) resistance to microbial degradation (persistence), (ii) potential to bioaccumulate, and (iii) ability to elicit adverse effects on non-target organisms ([eco] toxicity) — PBT. An overview on integrating PBT as a consideration in the prescribing process is presented by Castensson et al. (2009).

Absent from the considerations of PBT were two primary but straightforward factors never before considered for guiding the practice of prescribing. These are: (i) the potential for the API to enter the environment to begin with (usually dictated by its pharmacokinetics, which governs excretion, and by its rate of non-compliance, which may reduce excretion but promote sewer disposal of leftovers), and (ii) reducing the entry to the environment of an API through simple dose reduction (when warranted by therapeutic evidence). The second approach (dose reduction) is the focus of this discussion. The complexities involved with the first factor were originally presented in Daughton and Ruhoy (2009); this first factor is important because regardless of how unfavorable PBT criteria might be, they are of little consequence if the potential for the API to enter the environment is low.

Many variables involving dose and its administration play roles not just in dictating the excretion of APIs but also in adverse drug reactions (ADRs), patient non-compliance, generation of leftovers, and in the disposal or diversion of leftovers and their consequences deriving from abuse and poisonings. The major variables are summarized in Table 4. Notably, most of these factors are interrelated in a network of complex feedback loops. A change to one factor will often impart changes to others. One factor that does not always negatively impact drug wastage but which is important with respect to patient health is the unintended forcing of non-compliant behavior by prescribing higher-than-needed doses of medications a patient cannot afford; in some of these cases, low-dose prescribing can promote compliance by making the prescription more affordable (e.g., Tseng et al., 2004). Increased compliance is also known to lead to reduced overall health care costs (Roebuck et al., 2011).

This paper focuses primarily on just one of these factors (dosage strength and frequency), as it plays a central role in directly impacting many of the other variables; analogous evaluations could be conducted for each of the other variables in Table 4, most of which also pose opportunities for reducing API excretion. The inter-connectivity of these factors is shown in the following exemplary general scenarios, which are also captured in Fig. 1.

Examples of APIs that have already been identified in the environment (excluding samples influenced by discharges from drug manufacturers) and whose ambient levels could be lowered by reduced doses are presented in Table 5 and Supplementary Table S1. The latter table includes the literature references that document each API's identification in representative environmental monitoring studies. It also includes an indication of whether each API has been among the top 200 most-frequently prescribed generic or branded drugs in the U.S.; note that this ranking does not include APIs from sales of OTC medications.

7.1. Example scenarios for drug dose promoting bystander impacts

The following general scenarios are pertinent to Fig. 1. A dose that proves excessive for a patient (which may include the on-label dose) will initially lead to the excretion of APIs (and bioactive metabolites and reversible conjugates) in excess of what would have resulted from a lower, optimal dose. A higher-than-needed dose might also lead to ADRs sufficient to force non-compliant behavior and eventual cessation of therapy (with resultant accumulation of leftover medications); in particular, "first-dose" ADRs are problematic for some drugs, such as anti-hypertensives (Cohen, 2001a), leading to abrupt non-compliance and showing the importance of initiating certain treatments with low doses. An unnecessarily high dose might also create ADRs that are mistaken for independent comorbidities that mislead into treatment with an additional API (leading to polypharmacy); in particular, the initiation of a drug therapy may induce anxiety, whose symptoms could be mistaken for comorbidities. An unnecessarily high dose of a maintenance medication could also lead a patient to self-adjust to lower doses (e.g., via pill splitting/crushing or less-frequent administration); while this might eventually guide the patient to a proper dose, it will also lead to the accumulation of unused medications.

Non-compliance may prompt the physician to switch therapy to another API (even though many ADRs derive from dose rather than the API itself). Nonetheless, compliance may then improve with fewer side effects — but new ADRs are also possible (caused by the API or by genotoxic impurities). Either way, a therapy switch leads to the accumulation of leftovers from the failed medication, which represents wasted cost for the patient and a failure to have achieved the therapeutic goal. Finally, non-compliant behavior resulting from excessive dose may breed distrust in conventional medicine and lead to experimentation with unapproved, imprudent alternative treatments, some of which might include unapproved drugs (such as those accessible via certain Internet pharmacies).

7.2. Some caveats regarding dose

In the published literature, discussion of "low" dose is sometimes confused by two different meanings. One involves the lowest on-label dose. The other involves an off-label dose below the on-label range. Other adjectives are often used in attempts to provide a subjective sense of "low," including: lower, very low, ultra-low, micro-dose, and sub-therapeutic. This all adds to confusion when searching the published literature for pertinent references.

Although the dose for many drugs can be reduced while retaining therapeutic efficacy, situations occur where dose reduction is not a

Table 4
Major variables involving dose and its administration that can be optimized to reduce excretion as well as the incidence of ADRs and leftovers.

Variable involved	Example	Problem exacerbated
Administration of dose		
Route	Enteral, parenteral, topical	Dictates route of release of API to environment (excretion and bathing); APIs in topical preparations are highly concentrated and often over applied
Dosage strength[a]	Quantity (e.g., mass) of API per dose	Key consideration in optimizing efficacy, ADRs, and patient compliance
Dose form (includes API and formulation ingredients)	Capsules, tablets, lotions, aerosols, delivery device, and specific forms such as sustained/extended release, etc.	Influences adherence and dictates dosage
Dose purity	Racemate versus enantiopure	Racemic APIs with higher enantiomeric eudismic ratios result in excretion of unnecessary, non-therapeutic enantiomers (distomers); one advantage to chiral switches
Dosage regimen (dosing frequency or interval)	Number of doses and their timing throughout a day; must accommodate duration of action	Defined daily dose (DDD) is an average collective measure; PRN can promote leftovers; complex regimens degrade patient compliance
Duration (course of treatment)	Long-term, continual maintenance versus shorter term	Excessive duration poses over-treatment risks to patients and contributes to non-compliance, especially when treatment endpoints are not obvious to patient; long-term treatment can require periodic dose adjustments
Titration (rate of escalation from a lower dose)	"First-dose" phenomena (e.g., blood-pressure medications); doubling of dose versus smaller steps	May lead to non-compliance
Timing/schedule	Chronobiology (diurnal rhythms) can affect efficacy and excretion (Ravi Sankar et al., 2010)	Incorrect timing may increase excretion or reduce effectiveness (thereby necessitating increased dose); circadian rhythms often control the biosynthesis of many proteins that serve as drug receptors
Regimen complexity	Complex, non-uniform, episodic dosing; asynchronous dosing; combination therapy; polypharmacy	Drug–drug interactions (often made worse by pleiotropic APIs); patient confusion leads to non-compliance/adherence
Pharmacokinetic profile	Determines extent of excretion of parent API and reversible conjugates (e.g., glucuronides)	Within a therapeutic class, some APIs are more extensively excreted than others; long-acting versus short-acting can increase compliance; conjugates can later be hydrolyzed back to the parent API
Organoleptic properties	Taste and odor	Can cause non-compliance, especially in children and super-tasters
Dispensing of medication that promotes the generation of leftover medications		
Total amount prescribed or quantity dispensed (quantity limit)	Number of doses dispensed (e.g., 30-day or 90-day stat supply)	Therapy failure and changes in treatment lead to leftover medications; excessive quantities increase potential for leftovers; small-quantity trial prescriptions can reduce leftovers
Refill schedule	Number of refills allowed	Patients sometimes feel obligated to refill — even when medication is no longer needed or desired
Automatic refills	Refills on predetermined schedule	Patients sometimes fail to stop automatic refills even when no longer needed; mail-order refills may continue when patient dies
Patient-specific intrinsic and extrinsic attributes		
Individual, personal variation in pharmacokinetics (PK) or pharmacodynamics (PD)	Genetic polymorphisms (e.g., leading to slow versus fast metabolism; responders versus non-responders)	Can lead to either increased, reduced, or otherwise unnecessary excretion of bioactive chemicals depending on the API; the advent of companion diagnostics for small-molecule APIs will greatly assist in more targeted treatments
Compliance/adherence[b]	Failure to consume full regimens; causes span a wide spectrum — from purposeful decisions to subconscious behavior	Patient adherence/compliance is an extremely complex topic and is one of the major factors leading to leftover drugs; affected by the design of the dosing regimen and its complexity, frequency and severity of ADRs, and innumerable other factors (Daughton, 2010a)
Polypharmacy	Excessive number of distinct APIs used for multiple conditions; can result from multiple monotherapy or combination therapy; may result from failure of multiple prescribers to coordinate	Excessive "pill burden" promotes non-compliance and leftovers; prescriber/patient medication reviews can reduce incidence of polypharmacy; for APIs sharing the common MOA (and therefore have additive effects), doses can often be reduced accordingly
Diet/nutrition, fasting status	Including alcohol (Fagerberg et al., 2012) and tobacco consumption	Drug-nutrient interactions affect PK/PD, impairing effectiveness or causing ADRs — all leading to non-compliance (Laviano and Fanelli, 2012)
Health status	Renal, hepatic, and cardiopulmonary dysfunction	Impaired function can profoundly affect excretion
Gender, age, race, ethnicity, body fat/weight	Major variables affecting the PK/PD of dose	Children (Ekins-Daukes et al., 2003) and the elderly (Shah, 2004) in particular may be unusual in processing APIs and require lower doses

Most of these factors have been discussed in Daughton (2010a) and Daughton and Ruhoy (2011) and in the references cited therein.
[a] Dosage (API quantity and frequency of administration) is the focus of this paper.
[b] Patient non-compliance is sometimes used in a more general sense to also include non-adherence, as they both can lead to the generation of unused, leftover doses, regardless of the motivating behavior.

prudent or viable strategy. The on-label dose is clearly prudent in situations where life is threatened or for conditions where the incidence of the endpoint is so infrequent (e.g., seizures) that experimenting with upward or downward titration is not possible. Low dose may be imprudent where an immediate therapeutic response is required (acute pain, acute asthma, severe infections by indicated pathogens). Examples include the off-label low-dose administration of antibiotics for infections, especially in children. This is the primary off-label use of drugs in children, a population needing special considerations regarding dosages (Ekins-Daukes et al., 2003). Note, however, that the

Table 5
Examples of common APIs having evidence for lower, effective (off-label) doses and with evidence of also occurring in the environment.[a]

Acebutolol	Ezetimibe	Omeprazole
Amitriptyline	Famotidine	Ondansetron
Amlodipine	Felodipine	Penbutolol
Atenolol	Fexofenadine	Pravastatin
Atorvastatin	Fluoxetine	Propranolol
Bisoprolol	Flurazepam	Ramipril
Bupropion	Furosemide	Ranitidine
Captopril	Hydrochlorothiazide	Sertraline
Celecoxib	Ibuprofen	Sildenafil
Cerivastatin[b]	Imipramine	Simvastatin
Chlorthalidone	Lisinopril	Spironolactone
Cimetidine	Losartan	Sumatriptan
Colchicine	Lovastatin	Torsemide
Diclofenac	Metoprolol	Trazodone
Doxepin	Misoprostol	Triamterene
Enalapril	Nefazodone[b]	Venlafaxine
Estrogens (conjugated)	Nizatidine	Verapamil
Ethacrynic acid	Nortriptyline	Zolpidem

[a]Generic names arranged in alphabetical order for 53 commonly prescribed APIs (and one discontinued). Many of these APIs have been identified in environmental monitoring surveys of treated and untreated sewage and of ambient waters or sediments (see Supplementary Table S1). Shaded cells indicate that API is not commonly reported in environmental monitoring surveys or has never been targeted for monitoring.
[b]Cerivastatin was withdrawn from the market in 2001; nefazodone brand-name sales were partly discontinued beginning in 2003.

doses of certain antibiotics that would be sub-therapeutic for infections may have bona-fide uses for other indications; one example is the use of low-dose tetracyclines for modulating over-expression of inflammatory matrix metalloproteinases (e.g., use of 20-mg doses of doxycycline for reducing collagenase activity in gingival disease).

Certain APIs have relatively flat dose–response curves. While this might seem to justify lower doses, the duration of action must also be considered. One example is the angiotensin-converting enzyme (ACE) inhibitors. If a lower but just as effective dose is selected, the shorter duration of action can lead to adverse fluctuations in blood pressure for hypertensive patients (Taddei et al., 2011).

In certain critical situations, higher than normal "loading" doses may be prudent at the initiation of therapy to rapidly increase plasma levels. In some situations, doses higher than the on-label dose may be more efficacious. One example is statin maintenance treatment for coronary artery disease (Mark et al., 2008; Rosen et al., 2010); another example is with antiepileptic medications prescribed for seizure control.

Even when standard doses (or even supraphysiological doses) are called for at the outset of treatment, subsequent downward titration may be prudent for long-term treatment. In fact, success with downward titration might eventually reveal that a drug is no longer needed (Therapeutics Initiative, 1995).

For substantial numbers of medications, sufficient evidence can usually be obtained to justify lower doses — at least for the initiation of therapy. Obvious general indications include any chronic or mild condition not requiring an immediate intervention. One example — which attracts substantial over-prescribing — is mild-to-moderate depression, where prudent prescribing may involve initiation at low doses and followed, if needed, by titration in either direction (de Jong and Raz, 2011). Another example is the neuroprotective use of statins (such as simvastatin) in reducing the risk of stroke (García-Bonilla et al., 2012); caution is required in striving for the necessary, effective higher doses, as such aggressive use can overcorrect targeted LDL (low-density lipoprotein) levels — where levels too low can increase other risk factors.

Some medications have subjective dosing instructions. These require more attention by the prescriber in describing prudent use to the patient. A general example comprises the high-content topicals, where proper, controlled application requires diligence and attention; over-application by hand (when an integral delivery device is lacking) is common and often unavoidable by the patient. High-content topicals using those APIs having limited enteral or parenteral approved uses may be responsible for a disproportionate share of release to the environment via bathing and can result in substantial inter-dermal transfer to others and to the immediate, made environment — especially surfaces (Daughton and Ruhoy, 2009).

Methods are sometimes available for predicting proper doses based on the patient's personal pharmacokinetics. One example of personalized dosing (for risperidone) bases the dose calculation on two time points for plasma concentrations (Uchida et al., 2012).

In some situations where the dose needs to be increased, alternative approaches might achieve better outcomes. For example, drugs with the same mode of action but different mechanisms of action can sometimes be co-administered — each at a low dose but with additive effects (Dimmitt and Stampfer, 2009). Clinical studies involving five classes of blood-pressure medications show that combining low doses (one-half the standard dose) of drugs from two or three different classes yielded only moderately reduced efficacy but disproportionately lower incidence or severity of ADRs compared with a single drug at a conventional dose (Law et al., 2003). Alternatively, low dose (or sometimes elimination of dose) combined with alterations to lifestyle and other behaviors (e.g., adoption of healthful nutrition and exercise, or avoidance of risky behaviors such as smoking or alcohol consumption) is often an effective and more sustainable treatment approach — albeit usually more challenging for the patient.

Finally, some medications are available in approved (on-label) dosage ranges that span 20-fold and more, such as for anti-hypertensives (Cohen, 2001a). For these, selecting the lowest on-label dose is clearly one strategy requiring no justification for the majority of indications. For those medications having broad, approved dose ranges, success with the lowest on-label dose could indicate the potential for excursions to yet lower, off-label doses. For drugs with notoriously poor patient compliance because of ADRs (e.g., anti-hypertensives) or drugs that are costly for the patient, such a strategy might be welcomed by the patient.

The prudence of low-dose off-label prescribing for non-severe conditions is partly substantiated by the incidence of over-the-counter (OTC) switches. Drugs that were once available only by prescription and at comparatively high doses that spanned narrow ranges (purportedly justified by manufacturer claims that lower doses would be ineffective) later become available OTC but at lower doses (Cohen, 2003). Also of possible relevance is that compared with the U.S., the approved dose range is often lower in the EU and invariably lower in Japan (Malinowski et al., 2008).

8. The role of lower-dose prescribing

Many physicians are not aware of the advantages sometimes afforded by lower-dose prescribing. By highlighting that unnecessary API contamination of the environment occurs as a consequence of non-optimal prescribing, the role of lower-dose prescribing might gain more traction. Lower-dose prescribing could be advantageous for many, including:

patients (lower costs resulting from lower doses; fewer side effects; improved therapeutic efficacy), "bystanders" (reducing morbidity and mortality from accidental poisonings in non-users, and inadvertent exposure to hazardous drugs excreted via sweat from chemotherapy patients), municipal infrastructure (reduced costs associated with the need to dispose of excess leftovers), physicians (improved patient relations and communication, and trust and respect from the patient), and the environment (reduced API burdens).

Campaigns for more attention to dose reduction began to achieve momentum in the 1980s–1990s (e.g., Therapeutics Initiative, 1995). Since then, widespread evidence has evolved to show that the therapeutic effectiveness of off-label, low doses often matches — and sometimes exceeds — that of on-label drug doses. This evidence has grown sufficiently that some have called for revisiting the dosing guidelines for many medications and creating a ready and authoritative source that prescribers can access for emerging evidence regarding effective low-dose therapies not covered in traditional resources such as the PDR (Cohen, 2001a; Dimmitt, 2011). More direct approaches would be to encourage clinical trials to evaluate the lower end of the dose–response curve and to compile data mined from the published literature into a centralized database.

In the ongoing compilation of pharmacovigilance and post-market (Phase 4) efficacy data, recommended doses for many drugs are often readjusted — more often downward than upward. For example, an evaluation of the 71% (354) of the new molecular entities approved by the FDA from 1980 to 1999 revealed that 21% later experienced on-label dose changes. Among the 73 that were changed, 79% were adjusted downward; the dominate category (27%) comprised neuropharmacologic drugs (Cross et al., 2001). Similarly, a study of DDD for the period 1982–2000, reported 115 instances of adjustments, with 61% downward compared with 39% upward (Heerdink et al., 2002).

One obvious driver for the need to initiate treatment at lower doses involves drugs having very narrow therapeutic ranges — where therapeutic effects and toxicity are closely positioned on the dose–response curve. Another driver to remain at the lower end of the dosage range is when the dose–response curve flattens — where efficacy gains fall precipitously and ADRs rise with incrementally increased dose. Complicating this, however, is that medications are often manufactured in a limited (and sometimes restrictive) range of doses. The need for a lower, non-standard dose may necessitate other strategies such as pharmacy compounding, dose-form modification, or dose skipping; each has disadvantages. Even so, low-dosages pose many potential advantages. Two important potential benefits frequently overlooked are: (i) the empowering of patients by encouraging self-titration to the lowest effective doses (this, in turn, can promote better compliance and ultimately achieve therapeutic goals more reliably), and (ii) permitting the prescriber to ethically administer doses sufficiently low that a portion of the drug's action may derive from the placebo response (McCormack et al., 2011).

8.1. Barriers to low-dose prescribing

The traditional linear, monotonic dose–response curve forces the conviction that lower doses are increasingly and proportionately less effective. With growing interest in the toxicological aspects of the lower end of the dose–response curve, such as for studies of exposure to trace levels of environmental or occupational toxicants (e.g., carcinogens), low-dose action is emerging as a complex and possibly significant toxicological process. This is compounded when considered within the larger context of mixture toxicity and the fact that seemingly paradoxical non-monotonic (and multi-phasic) dose–response at low levels is attracting more scrutiny and debate (e.g., Daughton, 2010b; Rhomberg and Goodman, 2012; Vandenberg et al., 2012). APIs are no different than other xenobiotic chemicals in the sense that the potential for biological activity at diminishingly low exposure levels is a largely unexplored area of toxicological science.

8.2. Examples of drugs with evidence supporting therapeutic efficacy for low-dose, lower-dose, fractional dose, or sub-therapeutic dose

Much has been published on the efficacy and advantages of low-dose treatment — including the fact that "less can be more." Many specific examples of commonly used drugs with evidence supporting lower doses are presented in a number of general overviews: Cohen (2000; see Table 2, therein), Cohen (2001a; see Table 1, therein), Cohen (2001b), Dimmitt and Stampfer (2009), and McCormack et al. (2011; see Table 1, therein). From these published examples, 53 APIs have been compiled in Table 5. Effective doses are commonly one-half to one-quarter (and sometimes lower) of the on-label low dose.

Table 5 also indicates whether environmental monitoring data have been published — showing whether the API is reported to occur as a contaminant in the environment. For these 53 APIs amenable to lower dosing, environmental monitoring data for 38 (72%) indicate their occurrence as environmental contaminants. This shows that lower doses of these particular 38 APIs could help reduce their levels in the environment. The supporting references are available in Supplementary Table S1. In Table S1, it is apparent that of these 38 APIs only six have not originated from the combined top 200 generic and branded drugs prescribed in the U.S. (2010–2011).

The shaded cells in Tables 5 and S1 indicate that minimal evidence exists for 15 of these APIs being reported in environmental monitoring surveys. The lack of environmental data can result from either the absence of data (never targeted in monitoring) or from data of absence (targeted by monitoring but never detected). The latter could occur, for example, if an API were extensively metabolized, with little parent API or conjugate being excreted [celecoxib is one example (Paulson et al., 2000)], or if the analytical methodology was insufficient (e.g., levels too low for detection; or conjugates, if present, are not purposefully hydrolyzed prior to analysis). In contrast, certain APIs with little evidence for environmental occurrence may simply represent an absence of data; one example (Table 5) is ezetimibe, which is extensively excreted as a reversible conjugate (Patrick et al., 2002).

Also note that the absence of an API in the environment does not rule out the potential for environmental consequences because excreted metabolites or transformation products (such as disinfection by-products) may possess biological activity of their own. For example, APIs (or their metabolites) that contain the dimethylamine (DMA) moiety can serve as precursors to N-nitrosodimethylamine (NDMA), a carcinogen that can be formed during water disinfection with chlorine. For example, of the common APIs compiled in Table 5, five with DMA moieties (ranitidine, nizatidine, amitriptyline, sumatriptan, and venlafaxine) have been shown to form NDMA (Shen and Andrews, 2011).

Certain drug classes have attracted abundant attention with regard to the potential therapeutic importance of lower dose. A major example comprises the selective serotonin reuptake inhibitor (SSRI) antidepressants. A survey of the literature on the use of SSRIs by general practitioners and psychiatrists for the treatment of mild-to-moderate depression points to a controversy regarding dose (de Jong and Raz, 2011). SSRIs are frequently prescribed at initial or maintenance doses below the lowest on-label dose — often at purported sub-therapeutic doses. Evidence often shows little added therapeutic effect from SSRIs compared with a placebo in mild-to-moderate depression, while both treatments offer significant benefit compared with no treatment. In this situation, low-dose treatment might be serving as an ethical implementation of surreptitious placebo treatment — so-called "convenient placebos" (de Jong and Raz, 2011) — while at the same time also serving to avoid ADRs from the use of conventional doses.

9. The future

The argument can be made that adjustment of dose to the lowest that meets the individual patient's requirements for optimal balance of efficacy and ADRs is an obligation fundamental to the practice of

sound and ethical medicine. Without access to current low-dose data, sub-optimal treatment of the patient and the environment is unavoidable — and harm to both is more difficult to avoid. To accomplish this, greatly improved promulgation to clinicians of data from emerging low-dose efficacy studies will be required (Cohen, 2001b).

Perhaps the most pressing challenge faced by truly informed, evidence-based medicine is gaining access to currently inaccessible clinical trial data — especially data from individual patients. The extent, quality, and usefulness of the unpublished data generated from public and private clinical trials are unknown but potentially very significant; progress has been made by journals and by the U.S. FDA in requiring more timely publication of clinical trial data (e.g., via ClinicalTrials.gov). Those striving to distill and synthesize what might be revealed by these data have only recently had success in gaining access to comprehensive and often voluminous data files (e.g., see commentaries by: Grens, 2012; Lehman and Loder, 2012). These data could have significant influence on what was previously known not just about efficacy but also perhaps dose. As one example, consider a recently published re-analysis of previously published 42 meta-analyses that had involved efficacy studies of nine drugs from six drug classes. After incorporating previously unpublished trial data retained by the FDA, efficacy was revealed to be lower for 46% of the cases and higher for 46% (remaining unchanged for only 7%) (Hart et al., 2012).

Access to unpublished data poses enormous challenges. And even if successful, an efficient mechanism would then be needed to promulgate the findings to practicing clinicians. One possible approach for improving prescribers' selection of optimal dose would be the use of academic detailing (Benjamin et al., 2011; Stowell et al., 2009). The initial focus could begin with those most frequently prescribed drugs (or those prescribed representing the largest mass of API) and also having sufficient evidence supporting lower doses. This group would be further selected on those drugs whose APIs are known to widely occur in the environment (e.g., see: Verlicchi et al., 2012), together with those drugs having insufficient evidence supporting prescribed indications. A cursory examination of the classes of APIs commonly identified in the environment shows them to closely — but not surprisingly — overlap with the ones that tend to be collected as leftover waste in consumer take-backs. In one study of take-backs, for example, two-thirds of the consumer-returned medications comprised CNS agents (23%), cardiovascular agents (15%), psychotherapeutic agents (15%), anti-infectives (7%), and gastrointestinal agents (6%) (Kaye et al., 2010).

In addition to reducing dose directly, other options could eventually become routinely available to the prescriber for indirectly facilitating reduced dose. These would capitalize on various aspects of pharmacokinetics — especially improving absorption of the API or retarding metabolism or excretion (thereby increasing elimination half-life) — by way of designed interactions with co-administered drugs or dietary measures that impact metabolism. One of possibly many examples is shown in a recent clinical trial of an existing macrolide drug (sirolimus — or rapamycin) under evaluation for a new purpose (cancer treatment). Doses of rapamycin could be reduced to 28% and lower when co-administered with another active agent known to inhibit metabolism (Cohen et al., 2012) — in this case an antifungal drug (ketoconazole) or grapefruit juice (which contains CYP-inhibitory furanocoumarins and polyphenols). Of course, many other approaches exist for effectively lowering dose, but most are not under the control of the prescriber. Examples include drugs designed or formulated to enhance absorption, or delivery devices designed for improved targeting or more efficient delivery.

Not to be overlooked in this discussion of dose reduction for reducing environmental API loadings is a parallel approach that would focus on APIs having little potential for entry to the environment intact or as bioactive metabolites. Some APIs, for example, are extensively metabolized and also do not undergo excretion as reversible conjugates that can later undergo hydrolysis (deconjugation). One example of an API with such pharmacokinetics — and which has not been routinely detected in environmental monitoring (Table 5) — is celecoxib (Paulson et al., 2000). APIs possessing excretion profiles that are inherently protective of the environment could be noted as having little potential to impact the environment as a result of intended use.

In the final analysis, the prescriber's concept of the "patient" actually extends to our immediate made environment, the natural environment, and other "bystanders." Any prescribed treatment can have unanticipated, collateral impacts that are far reaching and which may incur impacts and costs beyond those commonly considered. Attention to reducing these collateral impacts from non-optimized prescribing — especially via the use of lower, optimized dosing — could have reciprocal benefits for therapeutic outcomes and reduced costs for patients and society. Monetary costs in the form of waste avoidance is a consideration gaining traction in the medical community (Brody, 2010) and one for which optimal, reduced dose could certainly play a key role.

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Appendix A. Supplementary data

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Supplementary Table S1. Examples of common APIs having evidence for lower, effective (off-label) doses - and cross-references for those APIs with evidence of also occurring in the environment. [1]

acebutolol - (Andreozzi et al., 2003; Jacquet et al., 2012; Lahti, 2012; Varga et al., 2011; Vieno et al., 2007; Vieno et al., 2006)	**ezetimibe** *(#95&136)* [absence of data; data of absence] (Chapman et al., 2011) (Fick et al., 2011) [trace levels]	**omeprazole** [#10] - (Gracia-Lor et al., 2011; Komori et al., 2012; Pérez-Carrera et al., 2010; Rosal et al., 2010; Verlicchi et al., 2012) [detected even though it is extensively metabolized]
amitriptyline [#53][2] - (Baker and Kasprzyk-Hordern, 2011; Batt et al., 2008; Bisceglia et al., 2010; Chari and Halden, 2012; Komori et al., 2012; Lajeunesse et al., 2008; Soulier et al., 2011; Unceta et al., 2010; Verlicchi et al., 2012)	**famotidine** [#106] [mixed findings] [data of absence or trace levels] (Gros et al., 2012; López-Serna et al., 2012b; Martínez Bueno et al., 2012; Prieto-Rodriguez et al., 2012; Rodríguez-Rodríguez et al., 2012; Valcárcel et al., 2012; Varga et al., 2011; Verlicchi et al., 2012); [positive reports] (da Silva et al., 2011; Dolar et al., 2012; Matsuo et al., 2011; Rosal et al., 2010)	**ondansetron** [#105] [absence of data]
amlodipine [#6] - (Chari and Halden, 2012); [data of absence] (Al-Odaini et al., 2012; Al-Odaini et al., 2011; Fick et al., 2010; Jensen et al., 2012) [trace levels]	**felodipine** [#185] [data of absence] (Fick et al., 2011) [partitions to sewage sludge: (Møskeland, 2006; Sundstøl Eriksen et al., 2009)]	**penbutolol** [absence of data]
atenolol [#14] - (Al-Odaini et al., 2011; Batt et al., 2008; Daneshvar et al., 2010; Ferrari et al., 2011; Fick et al., 2011; Gros et al., 2012; López-Serna et al., 2012a; MacLeod and Wong, 2010; Radjenovic et al., 2009; Rosal et al., 2010; Salgado et al., 2012; Varga et al., 2011; Verlicchi et al., 2012; Vieno et al., 2006)	**fexofenadine** [#190] - (Fick et al., 2011; Fick et al., 2010; Kosonen and Kronberg, 2009)	**pravastatin** [#36] - (Gracia-Lor et al., 2011; Gros et al., 2012; Miao and Metcalfe, 2003; Radjenovic et al., 2009; Valcárcel et al., 2012)
atorvastatin *(#5)* - (Conley et al., 2008; Ferrari et al., 2011; Gros et al., 2012; Komori et al., 2012; Lee et al., 2009; Tarcomnicu et al., 2011)	**fluoxetine** [#25] - (Baker and Kasprzyk-Hordern, 2011; Batt et al., 2008; Conley et al., 2008; Fick et al., 2011; Gros et al., 2012; Schultz et al., 2010; Tarcomnicu et al., 2011; Unceta et al., 2010; Verlicchi et al., 2012)	**propranolol** [#109] - (Batt et al., 2008; Ferrari et al., 2011; Gros et al., 2012; Lahti and Oikari, 2012; López-Serna et al., 2012a; MacLeod and Wong, 2010; Radjenovic et al., 2009; Rosal et al., 2010)
bisoprolol [#145] - (Fick et al., 2011; Lahti and Oikari, 2012; Ramil et al., 2010)	**flurazepam** [absence of data; data of absence] (van der Aa et al., 2011) [occurs as the metabolite N-desalkylflurazepam: (Hogenboom et al., 2009)]	**ramipril** [#79] [data of absence] (Paxéus, 2011; Salgado et al., 2011; Salgado et al., 2010; Varga et al., 2011) [trace levels]
bupropion [#163] - (Ferrer and Thurman, 2012; Fick et al., 2011; Metcalfe et al., 2010; Schultz and Furlong, 2008; Schultz et al., 2010)	**furosemide** [#12] - (Al-Odaini et al., 2011; Batt et al., 2008; Ferrari et al., 2011; Gros et al., 2012; López-Serna et al., 2012a; Rosal et al., 2010)	**ranitidine** [#42] - (Batt et al., 2008; Fick et al., 2011; Pedrouzo et al., 2011; Radjenovic et al., 2009; Rosal et al., 2010; Valcárcel et al., 2011b; Varga et al., 2011; Verlicchi et al., 2012)
captopril - [mixed findings] (Khan and Ongerth, 2005; Khan, 2002; Khan and Ongerth, 2004; Salgado et al., 2012)	**hydrochlorothiazide** [#9] - (Batt et al., 2008; López-Serna et al., 2012a; Radjenovic et al., 2009; Rosal et al., 2010; Verlicchi et al., 2012)	**sertraline** [#15] - (Chari and Halden, 2012; Fick et al., 2011; Schultz et al., 2010)

celecoxib *(#74)* [absence of data] (MacLeod and Wong, 2010) [trace levels] [3]	**ibuprofen** [#21] - (Fick et al., 2011; Gracia-Lor et al., 2011; Gros et al., 2012; Pedrouzo et al., 2011; Rosal et al., 2010; Verlicchi et al., 2012)	**sildenafil** *(#89)* - (Baker and Kasprzyk-Hordern, 2011; Nieto et al., 2010)
cerivastatin (withdrawn from market in 2001)	**imipramine** (melipramine) [data of absence] (Nakada et al., 2007; Rabiet et al., 2006; Soulier et al., 2011; Togola and Budzinski, 2008; Unceta et al., 2010; Vystavna et al., 2012)	**simvastatin** [#3] (also a metabolite of atorvastatin) - [mixed findings] [data of absence or trace levels] (Al-Odaini et al., 2011; Gracia-Lor et al., 2012; Komori et al., 2012; Martín et al., 2011; Valcárcel et al., 2011a); [positive reports] (Ottmar et al., 2012; Sousa et al., 2011; Wille, 2011)
chlorthalidone (chlortalidone) - (Terzic and Ahel, 2011) [retention in sediments]	**lisinopril** [#2&24] - (Tarcomnicu et al., 2011; Varga et al., 2011)	**spironolactone** [#67] [absence of data; data of absence] (Pérez-Carrera et al., 2010) [identified in waters receiving manufacturer discharges: (Sanchez et al., 2011)]
cimetidine - (Batt et al., 2008; Gros et al., 2012; Varga et al., 2011; Verlicchi et al., 2012)	**losartan** [#90&141] - (Gros et al., 2012; Tarcomnicu et al., 2011)	**sumatriptan** [#107] [absence of data]
colchicine [#160] [absence of data]	**lovastatin** [#38] - (Al-Odaini et al., 2011; Conley et al., 2008; Martín et al., 2011)	**torsemide** (torasemide) - [mixed findings] (Gros et al., 2012; Terzic and Ahel, 2011; Unceta et al., 2010)
diclofenac [#97] - (Al-Odaini et al., 2011; Fick et al., 2011; Gracia-Lor et al., 2011; Gros et al., 2012; MacLeod and Wong, 2010; Rosal et al., 2010; Unceta et al., 2010; Verlicchi et al., 2012)	**metoprolol** [#13&16] - (Al-Odaini et al., 2011; Batt et al., 2008; Bisceglia et al., 2010; Daneshvar et al., 2010; Fick et al., 2011; Gros et al., 2012; López-Serna et al., 2012a; MacLeod and Wong, 2010; Radjenovic et al., 2009; Rosal et al., 2010; Varga et al., 2011; Verlicchi et al., 2012)	**trazodone** [#37] - (Gros et al., 2012; Himmelsbach et al., 2006)
doxepin - (Hummel et al., 2006; Wick et al., 2009)	**misoprostol** [absence of data]	**triamterene** [#39] - (Batt et al., 2008; Chari and Halden, 2012; Emery et al., 2010)
enalapril [#55] - (Gracia-Lor et al., 2011; López-Serna et al., 2012a; Salgado et al., 2012; Tarcomnicu et al., 2011)	**nefazodone** (brand-name sales partly discontinued beginning in 2003) [absence of data; data of absence] (Breitholtz et al., 2012); (Fick et al., 2011) [first report]	**venlafaxine** [#100&164] - (Baker and Kasprzyk-Hordern, 2011; Fick et al., 2011; Gracia-Lor et al., 2011; Gracia-Lor et al., 2012; Himmelsbach et al., 2006; Lajeunesse et al., 2008; Metcalfe et al., 2010; Rúa-Gómez and Püttmann, 2012; Schultz et al., 2010; Tarcomnicu et al., 2011)
estrogens (conjugated) - (Verlicchi et al., 2012)	**nizatidine** [absence of data]; (Varga et al., 2011) [first report]	**verapamil** [#99] - (Batt et al., 2008; Chari and Halden, 2012; Fick et al., 2011)
ethacrynic (etacrynic) **acid** [absence of data]	**nortriptyline** [#161] - (Baker and Kasprzyk-Hordern, 2011; Lajeunesse et al., 2008)	**zolpidem** [#17] - (Fick et al., 2011; Terzic and Ahel, 2011; Woldegiorgis et al., 2007)

[1] Generic API names arranged in alphabetical order (in columns) for 53 commonly prescribed APIs that are amenable to lower doses; compiled from: (Cohen, 2000; see Table 2, therein), (Cohen, 2001a; see Table 1, therein), (Cohen, 2001b), (Dimmitt and Stampfer, 2009), and (McCormack et

al., 2011; see Table 1, therein). Many of these APIs (unshaded cells) have been identified (representative references cited in footnotes) in environmental monitoring surveys of treated and untreated sewage, or of ambient waters or sediments; data from waters receiving wastewaters discharged from pharmaceutical manufacturers were excluded. All data were mined from the published literature using the comprehensive bibliographic database compiled by Daughton and Scuderi (2012).

[2] Numbers in square brackets (for relevant APIs) indicate ranking of an API among the top 200 most-frequently prescribed generic drugs in 2010 (Drug Topics, 2011); number in italicized parentheses indicates ranking of API among the combined top 200 most-frequently prescribed generic and branded drugs in 2011 (Bartholow, 2012). Lack of number indicates API is not among the most-frequently prescribed; note that this ranking does not include APIs from sales of OTC medications.

[3] Shaded cells denote APIs that are not commonly reported in monitoring surveys of treated and untreated sewage, or of ambient waters/sediments. This can reflect either data of absence (negative data) or absence of data (API not yet targeted in monitoring surveys); data of absence can occur if drug is not commonly prescribed (such as not being among the top 200 most-prescribed generic drugs) or if the API is extensively metabolized and little is excreted as reversible conjugates [celecoxib being one example (Paulson et al., 2000)] or conjugates are not hydrolyzed prior to analysis.

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