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EXPERT REVIEWS

Green pharmacy and pharmEcovigilance: prescribing and the planet

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Active pharmaceutical ingredients (APIs) are ubiquitous environmental contaminants, resulting primarily from excretion and bathing and from disposal of leftover drugs by consumers and healthcare facilities. Although prudent disposal of leftover drugs has attracted the most attention for reducing API levels in the aquatic environment, a more effective approach would prevent the generation of leftover drugs in the first place. Many aspects of the practice of medicine and pharmacy can be targeted for reducing environmental contamination by APIs. These same modifications – focused on treating humans and the environment as a single, integral patient – could also have collateral outcomes with improved therapeutic outcomes, and with a reduced incidence of unintended poisonings, drug interactions and drug diversion, and lower consumer costs.

Keywords: APIs • disposal • environmental contamination • evidence-based prescribing • personalized medicine • pharmaceuticals • pollution prevention • sustainability • US EPA • wastewater

The physician–patient relationship often aims to correct, reduce or prevent an undesired health state or to promote or sustain a desired one. This involves a series of iterative steps of assessment, diagnosis, intervention, evaluation, corrective action and management, usually involving a network of entangled feedback loops. The system has many acknowledged flaws, mostly resulting from innumerable, complex and often uncontrollable variables, incomplete or inaccurate science, and from inefficiencies of administration and implementation. Nonetheless, an action is eventually taken or a decision is made and an outcome of some sort eventually emerges. And that's that, or is it?

As tools of the trade, pharmaceuticals are often involved in this loosely choreographed interplay and are frequently expected by the patient (or freely offered by the physician) during a consultation. Whether a prescription for medication is eventually written often becomes an unspoken, *de facto* measure of success for a consultation's outcome. However, questions surrounding the use of medications easily emerge and often relate to whether the selection of a particular medication is rational (evidence-based), appropriate or prudent, or even whether it is based on accurate knowledge of the patient's motivations.

Regardless of why and how medications are employed, concerns regarding their use are traditionally viewed as ending with the patient, whether symptoms improve, persist or deteriorate. But does the pill stop with the patient? Behind the scenes, the patient–physician interplay with pharmaceuticals actually represents only a small portion in the complete lifecycle of a drug. Consider another side of pharmaceuticals, from a perspective rarely considered. Would a physician ever consider indiscriminately prescribing even a vanishingly small amount of a medication – selected at random – to a pregnant mother or infant, or to a patient vulnerable to allergic response? Or surreptitiously administer a medication to someone unaware or without their permission? Would chronic ultra-low doses of a particular active pharmaceutical ingredient (API) ever be prescribed to a patient who may also likely to be receiving multiple other, but unknown, APIs? Or would a prescription-only medication be freely provided to someone lacking a prescription?

Although these scenarios would clearly not occur by choice, this is indeed what can unintentionally result, sometimes because of a single prescription and other times as a result of the collective acts of all prescribers. These scenarios are made possible because the long-accepted roles played by pharmaceuticals in

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the practice of medicine fail to take into account the many other, relatively obscure dimensions of the complete lifecycle of pharmaceuticals, some of which might even conflict with the original treatment intent or, perhaps more expansively, with the aphorism 'Do No Harm'.

The afterlives of drugs: pharmEcovigilance & sustainable use

For a better understanding of the lifecycle of a drug, consider the following aspects of the afterlives of APIs: where they go and what they do after having served their intended purposes. Analogous to the practice of pharmacovigilance, the concept of pharmEcovigilance was introduced by Daughton and Ruhoy to extend the range of concerns regarding adverse impacts of drugs to include the environment [1]. The scope of pharmEcovigilance and sustainable use of pharmaceuticals is outlined in Box 1. In September 2010, the European Parliament adopted amendments to existing pharmacovigilance legislation that serve to extend the realm of conventional pharmacovigilance to encompass environmental concerns (see amendments 3 and 68 on pages 6 and 47) [101].

There are many pathways and processes involving APIs that take place in the environment. These are analogous to those in the body. Almost as soon as a patient begins a course of medication, portions of the API(s) begin a journey into their immediate surroundings and into the ambient natural environment. Portions of the APIs from administered medications are introduced to the environment by way of sewers. Excretion of unmetabolized residues via urine and feces directly introduces measurable quantities of APIs to sewage treatment plants (STPs) or septic systems; also excreted are the numerous metabolites that can be associated with an API, some of which may still be biologically active (norfluoxetine, a major metabolite of fluoxetine, is one of many examples). Adding further complexity to the array of xenobiotics resulting from phase I API metabolism are the reversible conjugates of phase II metabolism (e.g., glucuronides). Various processes in STPs and the ambient environment can hydrolyze conjugates, often resulting in the regeneration of the original, parent API; these processes are part of the environmental lifecycle of APIs, as shown in an illustration [2]. Conjugates in the environment, therefore, can essentially serve as hidden reservoirs of parent APIs.

Less notable but still measurable quantities of systemically absorbed APIs can be excreted via sweat and washed into sewers after bathing. Residues of many APIs in sweat can also be transferred by dermal transfer to the immediate environment, including surrounding surfaces and clothing. The daily activities of any patient treated with pharmaceuticals essentially leave signature trails marked with specific APIs; even physical fingerprints can contain excreted APIs [3]. Comparatively large quantities of those APIs that are applied topically in high-content creams, lotions, gels, shampoos and other vehicles are released during bathing; for those drugs whose primary route of application is external, bathing would be the major route of API entry to the environment. The roles of sweat and of high-content topical medications in the release of APIs to the environment were both examined for the first time by Daughton and Ruhoy [4].

Sewage treatment plants were never designed to efficiently remove exotic xenobiotics such as APIs. Thus, varying portions of APIs, together with their respective byproducts generated by the chemical and biological processes occurring within STPs, are released in the treated sewage that is discharged to streams and to other ambient bodies of water that receive STP discharges. Even for those APIs that can be effectively removed by STPs, the chemical contaminant removal processes that would normally occur (both biological and physicochemical) are sometimes completely circumvented when raw, untreated sewage is discharged without STP treatment; not an uncommon occurrence in certain locales during extreme wet weather events that overwhelm the capacity of an STP, or in certain rural settings where 'straight-piping' (sewer lines discharging directly to water bodies) still exists.

The unceasing introduction of APIs to STPs, resulting from the combined minuscule contributions from a multitude of individuals, can lead to the continual presence of many APIs in the aquatic environment, regardless of the natural rates of removal by way of biodegradation and photolysis. An example of an API with a ubiquitous presence in many natural waters due to this process is the anticonvulsant medication carbamazepine. Analogous to the highly persistent priority chemical pollutants (those regulated worldwide by environmental agencies), which include many of the legacy halogenated pesticides, even APIs that might be readily degradable in the environment can therefore exhibit 'pseudo-persistence' because of their continual replenishment via treated sewage [5].

Many aquatic organisms and vegetation experience continual exposure to multiple APIs; for sessile aquatic organisms, exposure can extend across reproductive generations. Some APIs are bioconcentrated in the tissues of fin- and shellfish [6]. Humans can then be exposed to these residues via their diet. Many municipalities obtain their drinking water from sources that originate at least in part from STP effluents, such as downstream surface waters [7]. Those APIs still present (but now diluted) can survive the subsequent – and more rigorous – treatment processes used for generating finished drinking water (tap water). Indeed, over 60 APIs have been identified to date in finished drinking waters [8], albeit at extremely low individual concentrations (generally less than 10 ng/l). Data linking adverse human health with drinking water originating from sewage have been sparse. One example is a recent study that revealed a possible linkage of breast cancer with exposure to source waters for drinking that originated from treated sewage effluent [9].

Active pharmaceutical ingredients that are not degraded by STPs or discharged in the aqueous effluent can sorb (adhere) to sewage solids, thereby serving to amplify the mass concentrations of APIs by orders of magnitude. Sewage sludge is then usually incinerated, buried in landfills or processed into 'biosolids', which can be applied as an amendment to agricultural land. Agricultural crops or native plants have the ability to take up and sometimes bioconcentrate the API residues from biosolids into their tissues [10]. APIs in biosolids are also subject to leaching and runoff into surface waters [11].

Box 1. PharmEcovigilance and sustainable use of pharmaceuticals: scope of the issue.

Origin of the problem

- Numerous factors lead to leftover drugs, their accumulation and subsequent need for their disposal. Included in this are inefficiencies or imprudence in package design, distribution, marketing, prescribing and dispensing, in addition to a wide spectrum of actions, activities and behaviors of consumers and prescribers alike.
- Leftover, unwanted drugs are stockpiled or disposed by consumers at a wide variety of locations throughout society. Leftovers include not just drugs in opened packaging, but also unused, new medications in factory-sealed packaging; leftovers also include containers and delivery devices (e.g., transdermal patches), where large quantities of active pharmaceuticals ingredients (APIs) can persist in residuals.

Exposure hazards

- Stockpiled leftovers create opportunities for diversion, which exacerbate drug abuse and can lead to accidental and purposeful poisonings of humans and pets; leftovers also increase the incidence of self-medication and attendant adverse drug events.
- Stockpiled leftovers ultimately lead to the need for disposal, although some consumers are known to store leftovers indefinitely (sometimes for many decades); opportunities for drug sharing and inappropriate donations can also be facilitated.

Direct disposal

- Disposal of leftovers is practiced by consumers and healthcare organizations, but the types and quantities of drugs can differ dramatically, as can the controlling regulations. Both consumers and healthcare facilities practice flushing into sewers or discarding into domestic trash or with other medical waste.

Environmental exposure

- Residues of APIs from drugs in sewage can be released to the environment by way of sewage treatment plants (which often do not fully remove APIs) or via discharge of untreated, raw sewage.
- Wildlife can experience continual, low-level exposure to API residues in the ambient environment (especially the aquatic environment) as well as suffer acute-level exposure (e.g., scavengers feeding on animal carcasses containing high residual drug levels, such as from veterinary euthanasia).

Source contributions

- The relative contributions from drug disposal to the presence of APIs in the environment are unknown (both the types and the quantities) compared with the contributions resulting from the intended use of drugs (e.g., residues originating from excretion and bathing). Of the paucity of published data, little supports or refutes claims that drug disposal is a significant contributory source for environmental API residues.

Ecological effects

- The concerns regarding low-level exposure (in the range of µg/l) to APIs surround subtle effects, such as behavioral change (such as predator–prey attraction/avoidance); overt effects are possible, however, from exposure to highly potent APIs (such as synthetic hormones), even at the ng/l level (pM). More profound ecological effects (e.g., mass die-offs) are possible from high-level exposures, such as experienced by scavengers feeding on drug-laced animal carcasses.

Human exposure

- Human exposure to APIs from the ambient environment can occur from drinking water derived from effluent-dominated source waters and from foods such as fish that have bioconcentrated APIs from chronic low-level exposure (in the ng/l range).

Pollution control

- Various programs exist in certain countries to collect leftover drugs from the public and dispose of them in an environmentally prudent manner (generally by incineration or landfilling as hazardous waste) [54]. These programs often entail returns to pharmacies, an option currently not acceptable in the closed-loop pharmaceutical distribution system in the USA. The USA does not yet have a cohesive nationwide collection program but is investigating various options, including mail-backs [54,124]. Drug collections are end-of-pipe solutions that focus on disposition of generated waste rather than preventative management approaches that target the generation of waste at its source.

Disposal guidance

- Current guidance in the USA issued by the White House Office of National Drug Control Policy recommends disposal of most drugs to trash, with a few select drugs that are acutely hazardous still needing to be flushed into sewers [103]. The Controlled Substances Act has proved to be a major limitation in implementing efficient collection programs [114]. Disposal guidance faces the challenge of balancing the need to protect human health and safety (e.g., unintended poisonings from drugs disposed imprudently) versus protecting the environment.

Donation and reuse

- Donations among countries are discouraged (such as during humanitarian operations); see international guidance developed by the WHO [125]. Drug reuse is allowed under certain situations (e.g., donation to free clinics of free samples by physicians), as permitted by state and local agencies [105].

Data from [55,105].

Box 1. PharmEcovigilance and sustainable use of pharmaceuticals: scope of the issue.

Pollution prevention and sustainability

- In contrast with end-of-pipe pollution control (which focuses on the handling of drug waste), a wide spectrum of approaches under a pharmEcovigilance program can be designed, which would minimize the generation of leftover drugs, thereby reducing the need for disposal in the first place. Prescribers and dispensers can play major roles in pharmEcovigilance [1,48].

Data from [55,105].

Specially treated STP aqueous effluent can also be used for land irrigation or for reinjection into ground water, which can sometimes serve as a drinking water source. A related issue involves APIs in graywater (wastewater from all domestic sources other than toilets). With increasing pressure to conserve by reusing graywaters (e.g., on-site irrigation), the presence of APIs could pose an impediment to reuse.

Significant quantities of dispensed medications often remain unused and unwanted as a result of patient noncompliance and nonadherence, a problem long recognized as having great significance in the practice of medicine and one that has innumerable, complex causes [102]. These leftover drugs are often flushed down drains or discarded into household trash or garbage. The disposal of unused medications into sewers holds the potential to cause large episodic, transient spikes in API concentrations entering STPs. For those APIs that would otherwise be extensively metabolized and poorly excreted if used as directed, these elevated levels of unaltered APIs released to sewers by disposal may pose additional risks [4].

Medications disposed in trash may end up in landfills, where they are subject to ingestion by domestic animals and wild scavengers. They may also be reclaimed by people who handle trash or who 'glean' trash for recoverable items. API prevalence in landfills might be expected to increase as a result of current disposal guidance in the USA, which discourages disposal to sewers [103]; it is also important to note that drug disposal practices vary greatly among countries. However, little is known regarding the extent, frequency or magnitude of API disposal to landfills or the eventual fate of APIs in landfills. Among the first comprehensive investigations of drug wastes in landfills (and, to date, the only hand-sorting inventory of municipal solid waste for drugs) was conducted by Musson [104], who quantified the amounts of APIs in a landfill. Medications in trash can also follow a route ending with eventual incineration.

Discarding of leftover medications to trash can result in diversion by those for whom the medications were never intended. When imprudently discarded in trash, leftover medications can contribute to unintended poisonings for inquisitive toddlers and pets. This is a particular concern for those medications that can be lethal in a single dose. The literature on single-dose lethality as it pertains to drug disposal was reviewed for the first time by Daughton and Ruhoy [4]. Leftover, unwanted medications stockpiled in the home (perhaps even accumulated while awaiting disposal in bulk) also contribute to inappropriate self-medication and diversion, resulting in abusive use and unintended and purposeful poisonings. This problem has grown to such magnitude in the USA that it has captured the attention of the White House (through the Office of National Drug Control Policy), resulting in the nation's first drug disposal guidance for the consumer (originally issued in February 2007) [103], in a variety of Congressional hearings and various legislative bills at the state and federal levels [105], and in the first national take-back event for unwanted medications in September 2010 [106].

Medications can also remain unused even when a patient's compliance is perfect. One example is a result of continuing innovation in the development of delivery devices, especially transdermal delivery devices. Certain transdermal delivery devices result in significant quantities of residual medication that remain inaccessible and unusable [4]. Transdermal patches, a delivery format currently used for many highly potent APIs, are a notable example. The majority of the API often remains in transdermal patches after dermal application for the prescribed period. These devices sometimes contain the mass equivalent of API that would normally be excreted from thousands of oral doses. A used device often ends up being flushed into sewers, which is sometimes recommended [107], or disposed in trash. But when disposed of in trash (or set aside even momentarily), used patches pose significant hazards for unintended poisonings in children, sometimes with fatal outcomes [4]. As delivery device innovations and complexity advance, and more medications are dispensed via this route, the concern about escalating wastage and disposal of medications increases. This type of problem is exacerbated by the inevitable changes in treatment by the physician, in which case the patient must either discard or store the unused portions of the discontinued medication.

Further contributing to the quantity and diversity of APIs that will enter the environment is polypharmacy. In addition to added inputs from excretion are the greater quantities of medications leftover unused and then disposed. The incidence of leftover medications becomes a factor that serves to amplify its own magnitude. Leftover medications tend to result in yet more leftovers, a self-reinforcing cycle. The greater the accumulation, the harder it is for patients to keep track of them, leading to ever-greater difficulty in maintaining compliance (a problem further exacerbated by the greater probability of adverse events from drug–drug interactions). Leftover medications may become an ever-escalating problem as the incidence of polypharmacy grows. At one time driven primarily by the aging population, polypharmacy is also becoming more prevalent in younger populations, as the incidence escalates for chronic diseases, especially obesity and diabetes ('diabesity'). Polypharmacy therefore poses dual risks, for the patient (from over-medication and drug–drug interactions), and for the environment.

The potential for environmental impact is not limited to the API itself. Also of concern are the so-called inert ingredients (excipients) used in formulating a medication. These chemicals include preservatives such as parabens (para-hydroxybenzoic acid esters). Packaging and drug delivery devices constitute waste in their own right and have a set of concerns distinct from APIs. Increasing sophistication in the design of delivery devices (especially the incorporation of electronics) will add to the problems faced by disposal. Packaging can also dictate what route of disposal a consumer might select (e.g., individual doses packaged in blister packs are not conducive to flushing but containers of bulk pills are), and it can increase the quantities of medications that are eventually disposed (e.g., drugs in large bulk-size containers often face expiration before they can be completely consumed). More consideration devoted to packaging can also serve to reduce the quantities of drugs being disposed (e.g., drug-dispensing containers designed for improving patient compliance) [105].

Many of the same processes and scenarios already described for human pharmaceuticals also pertain to veterinary and agricultural medications. One significant difference exists, however, and in some instances has resulted in profound environmental consequences. After certain veterinary procedures, the level of an API remaining in an animal carcass is sufficient for an acute, lethal dose in certain wildlife scavengers. Two prime examples have been the use of pentobarbital in animal euthanasia and the use of certain nonsteroidal anti-inflammatory drugs (NSAIDs) for treating inflammation in domestic animals such as cattle. Carcasses of pentobarbital-euthanized animals when disposed improperly have led to the deaths of numerous raptors, especially eagles [108]. Diclofenac used for cattle in parts of Asia has led to an ongoing ecological catastrophe with the massive die-offs of various vulture species [12]. The latter example is important in that it demonstrates that adverse effects from exposure of nontarget species to a given API cannot necessarily be anticipated based on experience with human therapy.

With this very cursory, thumbnail sketch of the varied fates of APIs once prescribed to a patient, we can see a complex network of ordinarily obscured secondary actions resulting from the intended uses of medications; flowchart illustrations of this network are available [2,13]. It becomes evident that by treating patients with medications, the environment is experiencing collateral exposure to APIs. Along with prescribing for a patient comes unintended prescribing for the surrounding environment, as well as unintended prescribing for the general, nonpatient human population. Although the levels of individual APIs in various environmental compartments might be extraordinarily low (e.g., in the µg/l or nM range), the numbers of different APIs simultaneously involved in inadvertent exposures to nontarget organisms can be considerable. For example, while a single selective serotonin reuptake inhibitor (SSRI) might be prescribed for a patient, the end result may be the exposure of aquatic organisms (on a continual basis) to low levels of all six SSRIs commonly used in the USA, simply as a result of the combined prescribing from numerous physicians. SSRIs are known to have the potential for subtle but profound effects on many aquatic organisms [14,15].

Healthcare facilities use and dispose of significant quantities and varieties of pharmaceuticals. A major difference from consumer use, however, is that the types and quantities of drugs can differ dramatically; examples include antineoplastics, anesthetics and diagnostics such as contrast agents. Another difference with healthcare facilities is the regulations that specify waste handling and disposal. Portions of drug waste from healthcare facilities, for example, are inherently hazardous, and complex regulations have evolved to govern their safe handling and disposal. Handling of this waste often strays from regulatory requirements simply because of insufficient staff training or time. With regard to minimizing drug waste in healthcare facilities, several questions are germane for those who order, stock, dispense and prescribe. Does the facility measure or track the medications that become waste after dispensing, both used and unused? Is worker exposure to hazardous waste effectively prevented? Is the replacement cost known for these wasted drugs? The US Environmental Protection Agency (EPA) is developing guidance for the handling of leftover drugs in healthcare facilities [109].

This background reveals a hidden world for the after effects of prescribing and the afterlives of drugs and their APIs. While the toxicological ramifications for the continuing actions of APIs released to the environment are gradually coming to light, a conceptual framework for minimizing the release of APIs to the environment has begun to take shape. This framework treats the individual and the environment as a single patient. Under the concepts of the green pharmacy [16] and the holistic assessment system termed pharmEcovigilance [1], numerous approaches can be used to not only reduce or minimize the entry of APIs to the environment, but to simultaneously improve the efficiency and effectiveness of healthcare. Significantly, by taking actions to minimize the entry of APIs to the environment, healthcare can possibly benefit at the same time, with outcomes such as lower costs for the consumer, improved therapeutic outcomes and reduced incidence of unintended poisonings and drug diversion.

APIs as environmental contaminants: toxicological unknowns

Discussions regarding the potential for adverse biological effects from the presence of API residues in the environment or in drinking water inevitably become speculative or hypothetical when considering several of the major challenges and unknowns facing toxicology today. Included are questions surrounding: low-dose effects, the potential for biological effects (especially in nontarget organisms) from APIs at levels far below therapeutic levels, and often at levels below traditional no-observed-effects-thresholds; interactive effects, resulting from simultaneous (or sequential) exposure to multiple APIs, including additivity (from APIs sharing the same mechanism of action) and synergism or potentiation; exposure timing, during critical windows of vulnerability, which can range from particular developmental lifecycle stages to particular periods of a daily biorhythm (chronobiology); and exposure duration, chronic exposure sustained during a lifetime or even over multiple generations. Also important to note is that exposure to chemical stressors encompasses all chemicals, not

just APIs. These unknowns are greatly magnified when other chemicals are factored into exposure scenarios. These include not just anthropogenic/synthetic compounds, but also naturally occurring xenobiotics, especially those present in foods (e.g., toxicants produced by plants and microorganisms). Adding yet further complexity is simultaneous exposure to countless other, nonchemical, stressors.

The importance of filling these gaps in toxicology becomes clear when considering the basics of what is known regarding the occurrence of APIs in the environment; in ambient waters, drinking water and the tissues of fish and plants. API occurrence in these compartments clearly poses concerns regarding exposure for nontarget biota, organisms for which APIs were generally never designed or intended. Analogous concerns pertain to human exposure, not just via drinking water, but also via the diet in the form of contaminated biota, especially fish and plants. As mentioned earlier, the concerns surrounding human exposure focus on those for whom exposure should be avoided, as well as for those who are exposed without their knowledge. The concerns regarding human exposure have recently been summarized [8].

The universe of APIs

The published literature addressing the many facets of APIs in the environment has grown exponentially over the last 10 years and now totals in the thousands of articles [17]. Much of the earlier work focused on identifying and measuring APIs in various environmental compartments and in studying the removal of APIs by STPs. Only more recently have efforts begun to focus on nontarget organism exposure and biological effects [14]. Despite this considerable body of work, comparatively few of the APIs in current use have been evaluated. For some perspective, an examination of the US FDA's Orange Book reveals that roughly 1450 or so small-molecule, molecularly distinct APIs are FDA approved for use in the USA. These comprise roughly 800 with dosage forms for oral use, 400 for parenteral use and 250 for topical use; experimental APIs, which total over 3200, can also enter the environment. This core group of 1000 or so small-molecule APIs is formulated into over 21,000 drugs products with different strengths, dosage forms, multi-API combinations and excipients [18]. These numbers serve as a useful backdrop when examining what is known about APIs in the environment. Although a large armamentarium of APIs is available, an inevitable question is how many are truly needed. For example, the WHO's list of essential medications comprises only approximately 350 APIs, only a portion of which are small-molecular synthetic organics [110].

API environmental occurrence & fate

The maximum API levels known to occur in the aquatic environment tend to be in the parts per billion-range (µg/l, which is roughly the nM range for conventional small-molecule APIs). The numbers of APIs to which aquatic organisms are known to have been exposed simultaneously are roughly a dozen [6]; Kolpin *et al.* reported the simultaneous presence of multiple APIs in the first large-scale monitoring of streams in the USA [19]. This means that if many APIs are present and share the same mechanism of action (MOA), then the dose is effectively summed accordingly (known as dose additivity). For APIs known to occur in the environment, examples of drug classes whose individual APIs share the same MOA include estrogens, SSRI antidepressants, NSAIDs, specific classes of antibiotics (e.g., sulfa drugs) and statin lipid-lowering agents.

Over 60 APIs in total have been reported in samples of finished drinking water worldwide, but only a couple of dozen come from reports with substantive data [8]. Note that it is only because of the advancements in analytical chemistry over the last two decades that the routine detection of contaminants at the part per trillion levels and below has been made possible. The maximum concentrations in finished drinking water tend to fall within the part per trillion range (ng/l, or roughly the pM range for conventional small-molecule APIs). For the APIs that have been targeted for measurement in certain samples of finished drinking water, no study has yet identified more than a dozen present together in any given sample [8], regardless of the number of APIs targeted for analysis. APIs reported most frequently in finished drinking water include: carbamazepine, phenytoin, meprobamate, clofibric acid, gemfibrozil, iopromide, iopamidol, ibuprofen and sulfamethoxazole. The six APIs consistently reported to have the highest concentrations are: ibuprofen, triclosan, carbamazepine, phenazone, clofibric acid and acetaminophen. Only one API (ibuprofen) and its methyl ester metabolite are reported as having exceeded a concentration of 1 part per billion (1 µg/l) in finished drinking water [8].

Monitoring studies are much less common for fish having APIs concentrated in various tissues; this is largely because of the difficulty in analysis of trace levels in these difficult matrices. The first compilation of the published fish-tissue data is available from Daughton and Brooks [6]. Even when multiple APIs are targeted in fish monitoring, the number present at the same time in any one fish total fewer than half a dozen; for example, diphenhydramine, diltiazem, carbamazepine and norfluoxetine have been reported simultaneously in the same wild fish by Ramirez *et al.* [20]. The concentrations across tissues vary by many orders of magnitude as a function of the species and specific tissue, with bile often serving to concentrate the most (commonly in the mg/kg range) and the brain the least (µg/kg and lower).

Native plants and agricultural crops are known to actively remove a wide variety of APIs from soil, with residues detectable in the roots, stems and leaves. This can be a common occurrence when sewage biosolids or treated sewage effluent are applied to arable land. Tissue levels can range above the µg/kg range and are influenced by the concentration of the API in the soil [10,21–24]; for example, the application of biosolids to land can introduce more APIs than treated sewage effluent. Other terrestrial organisms, such as worms, can also bioconcentrate APIs applied to land [25].

The exposure scenario posing the most uncertainty regarding toxicology is long-term exposure to multiple APIs, with some having different MOAs and with each being present at

an ultra-low level (e.g., ng/l). As originally proposed, the outcomes that might be expected in the aquatic environment are usually expected to be subtle [15], such as alteration of behavior, rather than more obvious effects end points such as growth or survival. One example is a reduction in activity or alteration in behavior of aquatic organisms when exposed to trace levels of APIs such as SSRIs or NSAIDs [26,27]; alterations in avoidance or attraction can change predation and reproductive behaviors, thereby effecting change in ecological community structure. The exposure levels at which these types of effects can be measured can be up to six orders of magnitude lower than the existing no-observed-effects-thresholds for conventional end points. For highly potent APIs, profound effects can occur at low ng/l levels; the adverse effect of ethynylestradiol on fish populations is one example [28].

Compared with aquatic exposure, many more uncertainties surround the potential for outcomes from human exposure. Given the sparse research performed on ultra-low-dose studies, and the complexity introduced by mixed-mode (nonmonotonic) dose–response curves (which effectively prevent extrapolations to lower doses), it might seem unlikely at first, but not improbable, that adverse or even benign effects could occur in humans [8]. But as noted earlier, the additional unknowns regarding sensitive subpopulations, including those individuals whose exposure to certain APIs would ordinarily be forbidden or avoided, make this a controversial subject. Another aspect of exposure to APIs key to this discussion is that regardless of the number of APIs to which nontarget organisms and humans are exposed, these chemical stressors only represent a small fraction of the total number of other chemical stressors that are also present. These chemicals include toxicants that are naturally occurring as well as anthropogenic or synthetic. The significance of chemical exposure can truly be assessed only by understanding its complete context, in terms of the 4Ts: 'Toxicant, Totality, Tolerance, Trajectory' (see illustration in [29]).

An alternative perspective on low-level exposure asks whether it should be surprising that effects at the sub-pM level are possible, given that a concentration of 1 pM equates to 10^{10} molecules per liter or 10^{7} per ml. After all, biological effects have been noted for whole-body doses of certain APIs at the ng or even pg level [8]. With this very brief background regarding the toxicological significance of APIs in the environment, many believe it prudent to invoke the precautionary principle [30–32].

Prescribing & sustainability

With the growing emphasis on sustainability, existing processes and activities are increasingly scrutinized with respect to their so-called 'ecological footprints' – the demands placed on natural resources versus their capacity, and the potential for resulting impacts and consequences. Although many of the aspects of the healthcare industry, including facility design and the handling of general medical wastes, have been examined with respect to various sustainability criteria, one aspect has escaped with little notice (up until the last couple of years), namely, the network of processes governing the use of medications and API lifecycles.

When a prescription is written, the focus understandably defaults to the patient's immediate health status and the anticipated treatment outcomes. Rarely considered are the longer-term ramifications involving the entire scope of the medication's interconnections with the environment at large. Additional questions that could be asked include: what might be the eventual impacts of the excreted residues or the leftovers? Or even the packaging?

Leftover medications pose a wide array of vulnerabilities and risks. They encourage diversion, with its attendant problems with fueling drug abuse, facilitating self-medication or promoting unintended exposure; for example, accidental ingestion (perhaps resulting from confusing medications with similar names or appearance) or even the handling of teratogens (such as tamoxifen, methotrexate or finasteride) pose extreme risks for pregnant women. Leftovers are involved with unintentional poisonings, especially for children. They can also contribute to serious problems when donated to charitable or humanitarian causes [105]. The disposal of leftovers has direct ramifications for environmental impacts, such as the potential for disruption of aquatic biota. Disposal also entails hidden energy costs (fuel required for transportation or incineration) and creation of additional potential pollutants (such as unidentified products of incomplete combustion or from environmental transformations). Leftovers represent the loss of potentially recyclable resources (when disposed or destroyed), as well as monetary losses for patients. Intangible impacts include: the consequences from the opportunities lost due to premature cessation of therapy; potential consequences from failure to sufficiently explore alternative treatments (exercise, nutrition, behavioral or lifestyle modification); and time wasted from prescribing and dispensing of drugs never used. Medications prescribed imprudently or unnecessarily contribute APIs and bioactive metabolites to the environment by way of excretion and bathing. Essentially, leftover medications can be indirect measures of inefficiencies and weaknesses in the administration of healthcare, as summarized in Table 1.

The imprudent use of drugs is reflected in the studies of the WHO, which maintains that half of all medications worldwide are incorrectly prescribed, dispensed or sold [33,111]. This is reflected in the WHO's list of essential medications, which represents but a small fraction of all APIs available [110].

The spectrum of consequences from the accumulation of unused drugs is bewildering. But only recently have efforts begun to consider the environmental ramifications of drugs prior to prescribing or dispensing. Sweden, for example, has implemented a form of 'ecolabeling', which is being used to compare APIs in terms of various environmental attributes, such as persistence, bioaccumulation and toxicity [34]. These impacts might seem relatively unimportant compared with achieving the desired treatment outcomes. A significant irony emerges, however, upon closer assessment of the causes for leftover drugs. Since many emanate from suboptimal aspects of the prescribing process itself, the very same actions required to minimize drug wastage also hold great potential for improving healthcare outcomes. By factoring in the potential for environmental consequences – treating the

Table 1. Accumulation and imprudent disposal of leftover medications: measures of failure in healthcare.

Measure and adverse outcome	Examples
Leftover drugs can serve to indicate	
• Therapeutic outcome never achieved • Mismatch of medication with desired therapeutic outcome • Wastage of healthcare resources • Imprudent consumer behavior • Purchasing and inventory practices have not been optimized • Unit dose dispensing not widely implemented	• Patient noncompliance • Ineffective, nonefficacious, adverse drug events • Money spent on unneeded drugs; time lost for prescribers and dispensers • Hoarding or stockpiling of drugs for anticipated future use, self-medication, sharing or consolidation and storage of unwanted drugs for future disposal • Multiple dosage forms and strengths for same API used by different units of healthcare facility; lack of inventory rotation (to avoid expiration) or poor inventory control [126] • Avoids accumulation of large quantities of a drug regimen that a patient cannot complete
Accumulation of drugs can promote	
• Sharing with others and diversion by others • Unintended poisonings in humans and pets by unsecured stockpiling; single-dose lethality • Donations of drugs that are inappropriate or unwelcomed	• Drug abuse, unintended poisoning from self-medication, fatal medication errors, suicide • Infants, toddlers, the elderly and pets can all inadvertently ingest leftover drugs imprudently stored • Charitable causes, especially humanitarian operations, often receive tons of unwanted drugs that then require disposal
Disposal of leftover drugs	
• Maximizes the entry of APIs to the environment by avoiding ADME processes that otherwise might have reduced their amounts upon excretion • Wastes healthcare facility resources from costs associated with segregation of leftover drugs and their disposal • Can add to existing levels of APIs already involved with low-level chronic exposure of aquatic organisms and humans • Can lead to diversion when disposed in landfills • Can lead to acute wildlife poisonings	• APIs that would ordinarily be extensively metabolized (minimally excreted unchanged) are freely discharged to the environment via disposal by trash or sewers; disposal also increases the need to landfill or incinerate hazardous wastes • Drug disposal as hazardous waste is a complex and costly process; imprudent disposal can incur infractions with many regulations, such as the RCRA • Drugs disposed in sewers contribute to the ambient levels of APIs already present from excretion and bathing • Those who glean through curbside trash or landfills can reclaim discarded drugs • APIs discarded unsecured in trash can be ingested by wildlife scavengers

ADME: Absorption, distribution, metabolism and excretion/elimination; API: Active pharmaceutical ingredient; RCRA: Resource Conservation and Recovery Act (USA). Data from [55].

environment as a direct extension of the patient – the treatment, management and ultimately the health of the patient may also benefit. The following section will explore some of the many factors contributing to drug wastage from the administration of healthcare and the ways in which wastage could possibly be reduced or minimized.

Reducing the entry of active pharmaceutical ingredients into the environment

Despite the lack of knowledge regarding the ramifications of APIs as contaminants in the natural environment, possible modifications to the broad spectrum of actions, activities, behaviors and customs surrounding the physician and patient hold potential for reducing the introduction of APIs to the environment. These span the gamut from initial drug design and manufacturing, to prescribing and dispensing, and ultimately to usage and disposal. While the consensus opinion has been that API levels in the ambient environment can only be reduced by prudent disposal, evidence instead points to a potentially more important role for the patient–physician relationship in how drugs are prescribed and used [105]. There are countless points along the pathway in the prescriber–patient continuum that influence the types and quantities of medications that are dispensed and eventually consumed. Some increase the potential for (or actively promote) the entry of APIs to the environment. Others reduce the potential. Many of these have been discussed in the literature for decades – patient noncompliance/nonadherence being just one example – but have rarely been identified as viable means for reducing the incidence of APIs in the environment.

Summarized in **Box 2** are some of the numerous facets of the physician–patient–drug relationship that influence the overall usage of medications (which can increase the release of APIs

to the environment via excretion) or whether they accumulate unused (leading to the need for disposal, sometimes into sewers). Most of these facets are under the direct control of the healthcare provider or patient. There is no intent to discuss these in detail, but rather to give a thumbnail sketch, with the objective of making clear that for the practice of healthcare there are numerous actions, activities, behaviors and customs that can be modified to reduce the entry of APIs into the environment; a more detailed presentation of many of these factors is available [105]. Given that protection of the environment may not be a prime concern for healthcare practitioners, it is important to keep in mind that the very same efforts required for environmental protection can invariably also bring collateral benefits for improving the overall quality of healthcare by making it more efficient, efficacious and cost effective (Table 1).

How prescribing can transform prescription drugs into over-the-counter

A brief aside provides some interesting perspectives regarding the responsibilities of the prescriber, whose role can involve both prescription-only and over-the-counter (OTC) drugs. Although a large portion of drug waste comprises OTC medications and drugs obtained from the gray and black markets, the prescriber is often viewed as having little control over patient behavior with respect to whether these medications are purchased without a prescription or ever used by the patient. Although this is not necessarily true, the primary focus of this article is on prescription-only drugs. It should be noted, however, that the prescribing of OTC drugs might possibly increase in the USA due to changes regarding the reimbursement of medical expenses, as implemented through the Patient Protection and Affordable Care Act and the Healthcare and Education Reconciliation Act of 2010 [112].

Prescription-only medicines are also referred to in the USA as 'legend' drugs and include both noncontrolled and controlled substances; at one time, the labels for these drugs were required to carry what was called the federal legend: 'Caution! Federal law prohibits dispensing without a prescription', but which has generally been simplified to 'Rx only'. Prescription-only drugs are defined in 503(b)(1)[21 USC §353] of the Federal Food Drug and Cosmetic Act and are those for which adequate directions for self-administration by consumers cannot be accommodated on a label [113]. Instead, only a licensed prescriber can provide the necessary directions, prior to a prescription being filled; this usually entails a doctor, nurse practitioner, physician's assistant, dentist or veterinarian. Whether a drug is designated as prescription-only in the USA is determined by standards set by the United States Pharmacopeia and as regulated by the FDA.

Given this context (being that the essential difference between prescription-only and OTC drugs is whether self-administration is safe), an important irony results from the way in which prescription-only medications are actually prescribed. Conspiring to enhance the likelihood of the accumulation of unused, leftover drugs is lack of attention by the prescriber regarding the effectiveness or appropriateness of medications prescribed and the prescribing of excessive quantities (or any of many other actions). Leftovers, in turn, are subject to diversion, often resulting in their use by others for self-medication. Therefore, in the final analysis, by failing to exert sufficient oversight in the practice of prescribing, and by not devoting attention to the complete lifecycle of drugs, prescription-only medications can be essentially transformed into OTC medications, certainly an outcome never intended by the Federal Food Drug and Cosmetic Act or by prescribers.

Perspective on the future

The objective of this article has not been to argue for an overwrought focus on the potential for environmental impacts when prescribing and dispensing. However, by using the environment as an additional factor to consider when prescribing, it is possible that a wide spectrum of positive outcomes for healthcare might naturally follow. The extent to which drugs become waste, coupled with the extent to which they are imprudently used, are intertwined with both the effectiveness and efficiency of the practice and administration of healthcare. The focus to date in the USA regarding the entry of APIs into the ambient environment (including surface and groundwaters, land and everyday surroundings) has been on the unknown risks for nontarget organisms (such as fish) as well as for humans (such as from unwelcomed exposure via drinking water). Measures for reducing API residues in the environment have centered on developing ways to collect unwanted, leftover drugs from consumers. This is evident from Congressional hearings and the issuance of guidance from the White House Office of National Drug Control policy on the topic of drug disposal [105]. However, even if disposal of leftover drugs by consumers to sewers and trash were completely eliminated, it is unknown whether this would measurably reduce the overall occurrence of APIs in the environment [105]. By shifting the focus away from ways to more prudently handle and dispose of drug waste and instead redirecting it toward preventing the accumulation of leftover drugs to begin with, numerous collateral benefits could accrue for healthcare.

Leftover drugs are an overt symptom of numerous inefficiencies and imprudence in the conduct and administration of healthcare. They can be a direct measure of wasted healthcare resources. By designing or implementing any number of a wide spectrum of possible approaches for more prudent prescribing (ranging from the evidence-based selection of optimal APIs to lower doses or shorter treatment regimens) and more prudent use (tracking and ensuring patient compliance), potential collateral benefits include improved therapeutic outcomes and reductions in medication cost, drug diversion and accidental poisonings. Treating the environment and the patient as an integral whole, by applying the concepts of green pharmacy and pharmEcovigilance, could strengthen healthcare as a sustainable enterprise and improve its overall efficiency and efficacy.

The practice of medicine as a source of environmental contamination by APIs has received surprisingly little attention in the medical literature. More effort would be useful in facilitating change in the administration of healthcare. The first articles in medical journals on APIs as environmental contaminants did not appear until the early 2000s [5,35]; the Institute of Medicine's

Box 2. Factors influencing the consumption of medications (which affects active pharmaceutical ingredient excretion) and whether they accumulate unused (leading to the need for disposal).

Promotionals by manufacturers

Wide spectrum of services and items supplied gratis by pharmaceutical manufacturers. Ready availability of free medications (samples). Short trials can minimize wastage, but can also lead to wastage by the patient. Samples can lead to accumulation of expired drugs by physician. Detailing can promote over-prescribing. Sampling and medical journal advertising can promote prescribing of less efficacious and more costly drugs, sometimes unnecessarily. Extensive resources are available [127–129].

Increase exacerbated by:

- Detailing (sales calls to physicians)
- Sampling (sales calls and virtual; can encourage patient to accept unwanted medications they have no intention of using; creates drug waste at point of care due to expiration)
- Educational meetings and events for physicians (can create real and perceived conflicts of interest and biases in prescribing)
- Continuing medical education linked to marketing (can distract from evidence-based prescribing)
- DTC advertising (can increase patients' expectations for prescriptions and also lead to nonadherence if expectations are not met)

Counteracting promotionals

Counter-promotion involves programs and interventions designed to balance promotionals by educating health professionals in how to critically asssess drug promotion and to critically interact with sales representatives and interpret promotional information. Extensive resources are available [127–129].

Reduction facilitated via:

- Educational counter-detailing ('academic-detailing'; counter approach to balance drug representative detailing and sampling)
- Ethics codes restricting or banning promotionals
- Physician education
- Consumer education
- Abuse and addiction prevention
- Evidence-based prescribing
- E-vouchers (avoids expiration of drugs at point of care; allows patient to not feel obliged to accept samples they do not want)
- Restrictive formularies
- Pay for performance (incentivize prudent prescribing by incorporating in pay-for-performance programs)
- Point-of-care dispensing (but this can also increase consumption)

Prescribing

Optimal, prudent and efficacious prescribing can be complicated and time-consuming. Medicine is often practiced according to generic algorithms and protocols. Optimal treatment, however, can require approaches that are customized for each patient, as the range of genetic and epigenetic variables concerning ADME (such as polymorphisms) can be extremely broad. Responders and nonresponders for a particular API are often not distinguished. In the absence of personalized, evidence-based medicine, there is a greater likelihood for prescribing less efficacious APIs in doses higher, and for longer durations, than needed or justified.

ADME: Absorption, distribution, metabolism and excretion/elimination; API: Acute pharmaceutical ingredient; CSA: Controlled Substances Act; DTC: Direct to consumer; LTCF: Long-term care facility; OTC: Over the counter; Rx: Prescription; TDDS: Transdermal delivery system.
Most of these factors are covered in more detail in [105].
Data from [56].

Box 2. Factors influencing the consumption of medications (which affects active pharmaceutical ingredient excretion) and whether they accumulate unused (leading to the need for disposal).

Prescribing (cont.)

Increase exacerbated by:

- Drugs prescribed based on patient expectations and requests
- Drugs prescribed based on prescriber anticipation of patient's expectations
- Drugs prescribed as 'prn' (use as needed)
- Extra-label (off-label) prescribing; new uses for existing drugs; new target age groups
- Changes in treatment (therapy switches)
- Drugs with complicated or confusing instructions
- Drugs prescribed to treat side effects (e.g., exacerbating polypharmacy)
- Insufficient physician knowledge (e.g., imprudent prescribing, non-evidence-based)
- Over-prescribing
- Patient hand-offs (causing represcribing in hospitals for medications the patient already possesses)
- Providing free samples to patients with no intention of using them
- Prescribing pharmacists (point-of-care prescribing)
- Increased need for future prescribing as a result of current under- or over-prescribing
- Asynchronous repeat prescribing (misalignment) and inequivalence
- Facilitation of abuse from unnecessary prescribing
- Physician underestimation of the cost of expensive drugs
- Inability to take back controlled substances that patients wish to voluntarily surrender (a result of the impediments imposed by the CSA)

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Prescribing (cont.)

Reduction facilitated by:

- Rational, evidence-based prescribing; more attention to meaningful measures such as number needed to treat
- E-vouchers (eliminate many problems from free samples)
- Small-quantity trials
- Drug Utilization Review; concordance; brown-bag reviews; focus on minimizing polypharmacy
- Patient empowerment and patient–physician shared decision-making
- Prior to prescribing, check with prescription drug monitoring programs to reduce polypharmacy and avert drug abuse
- Physician profiling against accepted norms (outside review of prescribing practices by insurers and others)
- Benchmarking individual prescriber's habits and behaviors against those of the profession as a whole
- Restricting insurance reimbursement for OTC drugs only when prescribed (2010 Patient Protection and Affordable Care Act) [112]
- Lifestyle modification (prescribing diet, nutrition, exercise, sleep hygiene)
- Pharmacogenomics (improved selection of optimal API, dose, dosage form, timing [e.g., chronobiology] and dosing duration/regimen) may allow lower doses for shorter durations, better avoidance of drug–food and drug–drug interactions; API prescribed only to responders, avoiding nonresponders
- Improving dose effectiveness by matching schedule with diurnal rhythms
- Enantiopure drugs (dose reduced by eliminating nontherapeutic enantiomers [optical isomers] present in racemic drugs)
- Using pharmacokinetic profiles to select APIs that are extensively metabolized (thereby reducing contributions from excretion) or to avoid nonresponders

Dispensing

Dosage form, strength, quantity, design of packaging and delivery devices, wording/legibility of labeling, refill schedules and errors incurred in dispensing can all affect patient compliance or adherence, as well as the degree to which inaccessible residuals remain unused (e.g., in delivery devices).

Increase exacerbated by:

- Free/low-cost medications
- Stat dispensing for extended and mandated quantities (insurance requirements for 30–90-day supplies) especially for initial trial (may reduce dispensing costs at the expense of increasing leftovers)
- Automatic refill schedules (especially problematic upon patient's death)
- Mail-order dispensing (lost or damaged shipments)
- Expanded behind-the-counter availability of previously Rx-only drugs
- Nonstandardized or hard-to-read prescription medication labels; inaccurate label translations into foreign languages; patient illiteracy
- Automated dispensing machines for public use [130]
- Dispensing physicians (point-of-care dispensing)
- Multiple dosage forms and strengths of the same API stocked in the same healthcare facility
- Partial administration (primarily in surgeries) promotes leftover residuals [126]

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Dispensing (cont.)

Reduction facilitated via:

- Installment dispensing
- Small-quantity trials (but may also escalate dispensing costs and interfere with ease of access for patients)
- 15-day limitation of initial prescriptions for certain drugs [131,132]
- Unit-dose dispensing
- Medication reuse/recycling (e.g., within LTCFs)
- Eco-labeling (specifying proper disposal)
- Pharmacist counseling

Administration

Residuals in partially used devices (e.g., cessation of intravenous drips mid-stream) and stocking of same drug in multiple package quantities or dose strengths can be a major contributor to healthcare facility drug waste [126]. Leftovers resulting from a closed distribution loop can often be returned to stocks for redispensing.

Increase exacerbated by:

- Medications dispensed in healthcare facilities that patients are required to leave behind upon discharge (often necessitating repurchase with a new prescription)
- Unused medications left over in surgery rooms cannot be reused
- Unknowns surrounding duration of drug regimen (when to stop therapy)
- Dose form modification (e.g., tablet splitting or crushing)
- Over-application of high-content topical drugs (unnecessarily high doses or excessive dermal coverage)
- Used delivery devices usually contain high-content residuals (e.g., TDDS)

Consumer involvement/behavior

A broad spectrum of consumer behavior other than failure to comply with directions can influence the extent to which medications are purchased in excess or consumed insufficiently. These behaviors are often driven by unreasonable expectations (resulting from DTC advertising or lack of understanding), efforts to economize (e.g., purchase of excessive quantities) or the desire to anticipate possible future needs (hoarding for self-medication).

The incidence of leftover medications becomes a factor that serves to amplify its own magnitude. Leftovers tend to attract more leftovers. The more they accumulate, the harder it becomes for the patient to keep track of them, leading to ever-greater difficulty in maintaining compliance. Leftovers become an ever-escalating problem as the incidence of polypharmacy expands.

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Consumer involvement/behavior (cont.)

Increase facilitated by:

- Purchase of excessive quantities of OTC drugs, fostered by perceived economy of scale (losses due to expiration in bulk containers)
- Failure to complete regimen before expiration
- Filling prescriptions with no intent to ever use them (to conceal noncompliance from physician); especially problematic for repeat prescriptions
- Self-medication (often diverted from, or provided by, friends); exacerbated by storage of excess stocks in home
- Cost-sharing with insurance provider can both increase and reduce noncompliance
- Internet patient forums (can promote sharing of misinformation)
- Responding to direct-to-consumer advertising
- Rx-to-OTC switches (can increase purchasing, especially for discounted bulk containers)
- Internet and gray-market availability (Rx-only medications purchased without a prescription)
- Expectations for receiving prescriptions (followed by nonadherence if desired results are not achieved)
- Aging population (exacerbates polypharmacy)
- Paradoxically, drug-collection programs may encourage consumers to discard medications that are still useful, followed by need to repurchase replacements
- Doctor shopping and hospital shopping (primarily via emergency services)
- Abandoned, lost, misplaced or forgotten drugs; includes drugs left behind at home when patients are admitted for long-term care
- Patient's urge to stockpile and hoard medications for possible future use (increases incidence of expiration); particularly pertinent to antibiotics and narcotics
- Marketing of human drugs for pets

Nonadherence/noncompliance

Patient noncompliance and nonadherence are major factors in failure to consume full courses of medications. Their causes are innumerable and complex, ranging from conscious decisions to subconscious behavior or simple inability to follow directions. The reasons for noncompliance can vary widely among drugs and among patients. Noncompliance has proved extremely refractory to easy solutions. Noncompliance has been referred to as 'America's other drug problem' [133], as well as the 'sixth vital sign' [57].

Most, but not all, forms of noncompliance can lead to drug leftovers and the consequent need for disposal. A common form of noncompliance that does not directly lead to leftover drugs is failure to fill a prescription.

Countless published articles discuss the causes and possible solutions for noncompliance [58,59,102,134]. Pound *et al.* innumerate over 200 factors involved with noncompliance [60].

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Nonadherence/noncompliance (cont.)

Increase exacerbated by:

- Poor perception of disease severity (e.g., symptoms no longer perceived; imagined improvement); diminished incentive to continue therapy (e.g., perceived lack of benefit that is not obvious)
- Ineffectiveness, both real and perceived; frustration with lack of rapid desired outcomes
- Long-term maintenance therapy
- Refusal of dispensed medication (e.g., in LTCFs)
- Cost of medication discourages immediate use and encourages hoarding
- Sensory aversion (unpleasant taste/odor, texture or appearance)
- Deliberate under-dosing (splitting, cutting or skipping doses)
- Adverse drug reactions; drug–drug interactions (made worse by polypharmacy) ; drug–nutrient interactions
- Difficulty in opening containers (e.g., child-resistant closures)
- Drugs with complicated labels or delivery systems that are too difficult, uncomfortable or confusing to use
- Complicated treatment regimes or dosing schedules (e.g., resulting from polypharmacy or asynchronous dispensing)
- Patient confusion (e.g., illiteracy, mistranslated labels, complicated/nonstandardized labels)
- Inherent aversion of the patient toward use of drugs
- Fear of becoming addicted to nonaddictive drugs or of the possibility of long-term adverse effects
- Patient's distrust of doctors, believing that the prescribed drug is unnecessary
- Patient's belief that the mere act of taking a drug verifies that the patient is indeed ill
- Abandoned or lost drugs
- Inaccessible, irretrievable liquid residues remaining in used vials, syringes, dispensers and other containers
- Disease state (including dementia, depression)
- Fear or anticipation of adverse reactions (nocebo effect)
- Inappropriate and unusable charitable contributions
- Drug sharing, loaning and borrowing for nonmedical use
- Self-medication
- Death of patient (leftover medications and continuing auto-refills from mailorder)

Reduction facilitated via:

- Wide array of devices and other technologies can sometimes improve compliance, including design of packaging
- Devices such as TDDS may increase compliance, but also lead to the disposal of large quantities of residual API that remains in device
- Educate patients that behaviors leading to leftover drugs are not in their self-interest with regard to favorable therapeutic outcomes or because of risks to others
- Drug Utilization Review; brown-bag reviews
- Vouchers allow patient to decide not to accept free samples they do not want
- Long-acting formulations that avoid confusion caused by more frequent dosing regimens

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Box 2. Factors influencing the consumption of medications (which affects active pharmaceutical ingredient excretion) and whether they accumulate unused (leading to the need for disposal).

Medication collection programs

Collection programs for unwanted, leftover drugs range from take-back collection events to mail-backs [124]. Design of an effective nationwide approach in the USA has not yet proved possible for a number of reasons, but especially because of restrictions imposed by the CSA.

Possible paradoxical roles in increasing the incidence of unused drugs:

- Unwanted drug-collection programs are intended to reduce the quantities of leftover drugs stored in the home. Paradoxically, collection programs may not be without liabilities. They may also serve to increase temporary storage, depending on the motivations and behaviors of the consumer.
- Some consumers, for example, might be encouraged to store their unwanted drugs until the stockpiled quantity is sufficiently large that it warrants transport to a disposal location. Formal collection programs might unwittingly encourage the replacement of these medications with new stocks and thereby generate yet more waste, perpetuating the cycle of excessive, repeated purchase and disposal. By facilitating easy ('cost-free') disposal of drugs with formal take-back programs, consumers may be inadvertently encouraged to not hesitate in purchasing additional, large replacement quantities (to achieve false economies of lower unit-dose pricing), only to again find themselves unable to fully consume them before expiration. Disposal is then followed by a repeating cycle of repurchasing new supplies.
- At least one report of a new drug diversion scheme has emerged that capitalizes on the mere existence of drug-collection programs, by diverting drugs from sham medicine collections, which were designed to appear genuine [135].

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Roundtable on Environmental Health Sciences, Research and Medicine first examined the topic in 2004 from the perspective of drinking water [36]. The medical literature has, however, been attuned to some of the human health issues (primarily poisoning risks) surrounding drug waste, household storage and disposal for at least 50 years [37,38].

Effective solutions will require a concerted transdisciplinary, holistic approach, involving a wide spectrum of professions that have never before had reason to communicate or collaborate outside the conventional boundaries of traditional healthcare; from prescribers and dispensers to insurers, environmental scientists and legislators. In the USA, a nationwide solution will require collaborations across agencies, including the EPA, FDA, Department of Justice and the Drug Enforcement Administration, and the CDC.

Activities and actions spanning a remarkable range of possibilities are feasible in the near term for directly and indirectly reducing the use of drugs and the accumulation of leftover drugs. Some of these are inevitable, as they are driven by consumer demands. Others would need to be initiated by a proactive healthcare community. Indeed, recognition that interventions involving drugs are not necessarily optimal is increasingly evident from the published literature. The *Archives of Internal Medicine* began publishing a series of articles in 2010 on the topic 'Less is more' [39]. An excellent example of how reduced intervention with drugs can improve patient health is the evidence-based use of antibiotics, where imprudent use accelerates selection for antibiotic resistance [40] and can promote overgrowth of pathogens, such as *Clostridium difficile* or *Candida* spp. Less appreciated, however, is that antibiotic usage has additional potential for patient harm by disrupting the assemblage of indigenous bacteria in the gut, with some patients experiencing permanent loss of certain species [41]; disruption of microbial community composition of the gut can, in turn, alter the immune system and the regulation of inflammation [42].

The immediate need the USA is facing in the disposal of consumer-generated drug waste (as well as a portion of healthcare drug waste) is the reworking of certain regulations, especially the Controlled Substances Act, which has posed major limitations for drug-collection programs. The Drug Enforcement Administration is already engaged in trying to find solutions for modifying the Controlled Substances Act [43]. Progress in the regulatory arena will probably now be accelerated by the Congressional passage of the Safe Drug Disposal Act of 2010 [114,115].

Regardless of whether the disposal process can be streamlined in the near term, the most pressing need with respect to healthcare is the design of prescribing and dispensing practices that result in more prudent, critical, optimal drug usage and in ways to better counsel patients in compliance and adherence. Although advances in technology for improving patient compliance will undoubtedly continue, the major force behind pollution prevention will occur from modification of the actions, activities, behaviors and customs on the part of those involved with prescribing and dispensing. Since this would – at least initially – entail additional time and resources, leveraging might be achieved with new approaches for getting the patient to better understand the issues at hand.

Enhanced patient involvement in controlling the destiny of their individual healthcare has been demanding more attention. Many feel that by increasing the transparency of medical care, a better-informed patient can be more proactive in ensuring their own compliance; participatory medicine also becomes more effective. One emerging example that will lead to increased transparency is the recent accessibility of healthcare records to patients. The OpenNotes project [44,116], as one example, allows patients to explore the records maintained by their general practitioner. Having access to their records may make patients feel more responsible for their healthcare. The FDA has been striving to expand accessibility of drug approval data to the public. In particular, the FDA is attempting to integrate all clinical trials data – premarket and postmarket – as part of its transparency initiative [117].

Increasingly, consumers will have ready access to an astonishing spectrum of comparative data regarding drug effectiveness and safety, including results from comparative effectiveness research [45,118]. This could at least serve to discourage patient requests for drugs that have a high probability of being ineffective. A new open-access online journal for the rapid publication of negative, neutral, partial and inconclusive clinical trial results could also improve consumer and prescriber understanding. Launched in response to the ever-increasing regulatory demands to publish all trial results, the *Journal of Drug Assessment* plans to offer peer-reviewed publications of this type of research [119].

Technologies allowing the patient to monitor their own health status might also encourage the titration of drug doses to the lowest optimal levels. Noninvasive continuous monitors for several different parameters or chemicals might help patients see the effects in near real-time of alterations to diet, exercise, stress and other factors that can improve health and thereby reduce the need for pharmaceutical interventions. Progress has been made, for example, in developing an infrared monitor that would noninvasively and instantly assess systemic glucose levels [46].

Another way to enhance patients' participation in their healthcare also holds potential for enhancing the understanding of drug effectiveness by prescribers: by enlisting the public to track and report on the types and quantities of their medications that go unused. Data on how and why medications go unused are currently obtainable only by way of time-consuming and expensive public surveys or inventories, usually during collection events for unwanted drugs or during inventories of households [47]. A much easier approach for mining such data would be to create a publicly accessible Internet database in which individuals could log the types and quantities of their leftover drugs, together with other data that might be useful to healthcare researchers, such as the causes for the wastage; this was first proposed by Daughton [105]. With access to such data, prescribers could become better informed as to which drugs are being over-prescribed and not utilized. Although quality assurance issues abound, such a database could hold great potential for providing insights on many of the issues involving the relationships and inefficiencies within the manufacturer–physician–patient chain. Such data could be used in formulating better ways to select appropriate medications and to prescribe and dispense medications in optimal dosages, dosage forms and quantities. An additional benefit would derive from the mere act of patients being able to enter the types and quantities of their leftover medications into a publicly accessible database, thereby allowing comparison of their personal pharmaceutical wastage with that of others. This could possibly alter their behavior and attitude toward future purchases of medications by making them more aware of over-purchase, unnecessary purchase and wastage. The use of feedback and comparison of usage among peers (e.g., via social networking sites) has been shown to be effective, for example, in reducing household energy usage [120].

For the physician, several developments have the potential to aid in the effort to reduce the incidence of APIs as environmental contaminants, by minimizing both the need for disposal and overall drug usage (thereby reducing the entry of APIs to sewers via excretion); many of these are captured in **Box 2**. One of particularly noteworthiness is the coupling of personalized medicine with a shift away from the current physician–patient paradigm, which is focused on medications, and toward one that emphasizes achieving desired outcomes. This approach essentially sells a service or desired outcome, rather than the drug itself; in other disciplines, this is known as 'material flow management service' [17,48]. An interesting example of this approach has been recently proposed by Kesselheim and Outterson, with the ultimate objective of reducing the incidence of antibiotic resistance (conserving effectiveness) [49]. The curative power of antibiotics can be viewed as a resource for protecting society at large. This means that a balance must be maintained between protecting the patient without jeopardizing public health. The outcome that would be 'sold' in this example comprises two parts: the physician selling a cure for an infection and the antibiotic manufacturer ensuring that the rate of drug use keeps resistance from spreading (maintaining therapeutic effectiveness society-wide); note, however, that this example might require compensating the manufacturer to restrict sales to lower, but sustainable, levels.

Much has been written regarding personalized medicine, most notably as embodied in the application of pharmacogenomics. But rarely discussed is the possibility of making use of pharmacogenomics to tailor medications to individual patients with the intention of lowering excretion of bioactive residues. By evaluating absorption, distribution, metabolism and excretion/elimination characteristics specific to the individual patient, various attributes of pharmacokinetics could be used to avoid prescribing specific APIs to those who are poor responders or to reduce the dose for those who are poor metabolizers [48]. Within a given therapeutic class, there may be APIs with more favorable metabolic profiles that result in less excretion. With careful consideration of pharmacokinetics, an API within a given therapeutic class could be selected on the basis of its reduced excretion; this approach would be especially useful for APIs in those classes showing little difference in effectiveness.

In addition to personalized dosing, numerous other approaches are available for reducing the dose of APIs. These range from sophisticated delivery techniques to the emerging possibility of

nanomedicine, which holds the potential for more precise targeting of the desired receptor. Advancements in nanomedicine, however, have been delayed in part by the same problem faced by other commercial applications of nanomaterials, the inability to chemically and structurally characterize nanoparticles for regulatory clearance [50]. The fate and possible effects of nanomaterials in the environment is largely unknown.

Numerous nondrug interventions also hold potential in reducing the drug-centric practice of medicine. As examples, nutrigenomics, probiotics and endogenous bacteria modulate a wide array of genes, including those involved in the immune system. As the evidence continues to mount that these factors (largely implemented via diet) play biochemical and physiological roles of clinical importance, they will have to be factored into personalized treatment or used to replace conventional pharmacologic therapy. Modulation of gene expression (and epigenetics) often intersects among the biological activities of nutrients, bacteria and APIs [51] and can have multigenerational ramifications.

Drug consumption could also possibly be reduced by incorporating evidence-based practice with advancement and broader acceptance of computerized clinical decision support systems to assess initial and sustained dosing, dose monitoring and adjustment, and duration of treatment (to ensure that treatment is stopped at the earliest efficacious time). Many resources on evidence-based practice are available, but acceptance has been slow in the medical community; two examples are the Cochrane Collaboration [121] and the Agency for Healthcare Research and Quality [122]. Comparative effectiveness research, despite the controversies surrounding the perception for abuse in allocation of patient care, holds great potential for better targeting drug use [52]. As the available information and data regarding drug management and therapy outcomes continue to escalate distilling it for clinical application will prove ever more daunting. This highlights the need for rapid advancement in health informatics and expert systems.

Finally, consumer education regarding prudent drug consumption may benefit from more effective use of traditional approaches for altering behavior. Even though 'social marketing' (social change campaigns) was developed in the 1970s [53], it has rarely been applied to the therapeutic use of consumer drugs. A recent example of social marketing for pharmaceuticals, however, is the PharmaNet program, which is operated at various pharmacies in the USA [123].

Expert commentary & five-year view

Leftover, unused medications can be viewed not just as chemical waste (with attendant risks associated with unintended exposures for humans and animals) but also as measures of poorly invested healthcare resources and as opportunities lost for achieving intended therapeutic outcomes. Leftover medications represent the nexus of numerous nonoptimized facets of the healthcare system and patients' complex relationships with drugs. The current narrow focus on developing better means of disposing of unwanted drugs may be detracting from the more important objective of reducing the occurrence of leftover medications in the first place. An overwrought focus on design of more prudent approaches for disposal is an inefficient way to tackle the overall problem of APIs as environment contaminants and fails to capitalize on opportunities that would lead to collateral improvements in healthcare systems. Numerous facets of the complex chain of actions, activities, behaviors and customs involved in all aspects of the lifecycle of medications contribute to leftovers. Significantly, redesign of key places in this lifecycle holds great potential for not only reducing the incidence of leftovers, but also for improving the quality and cost–effectiveness of healthcare. These collateral benefits may become a major driving force behind the need for comprehensive environmental stewardship programs directed at pharmaceutical use. A large portion of the efforts to address the issue of drug waste is perhaps better directed at solutions for minimizing the generation of waste at the outset rather than on how to handle it once generated; focusing on upstream pollution prevention and stewardship practices rather than downstream mitigation measures. The ultimate objective to strive for should be to eliminate the need for avoidable disposal altogether.

At the same time, previously unrecognized benefits from minimizing the need for disposing of drugs could be achieved. For example, of the numerous facets of medical care that could be modified to reduce the incidence of drug accumulation and subsequent need for disposal, many would entail changes in dosage regimes, generally resulting in consumption of reduced quantities over the course of treatment. Lower overall dosing (e.g., guided by evidence-based prescribing and personalized prescribing) would necessarily result in lower excretion. Although excretion is a major source for most APIs in the environment, it has not previously been considered as a variable that could be controlled. The control and optimization of drug selection and usage holds great potential for reducing overall entry of APIs into the environment, as it can reduce the need for disposal while also minimize the residues released to sewers by excretion and bathing. By treating the patient and the environment as an integral whole, a more sustainable healthcare system could emerge, one with a greatly reduced ecological footprint and maximal benefits for the patient.

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Key issues

- Active pharmaceutical ingredients (APIs) become widespread contaminants in the environment when excreted (in urine, feces and sweat), during bathing (from topical drugs and sweat), and when unwanted leftover drugs or used devices (such as transdermal patches) are flushed down toilets or discarded into trash.
- The continual entry of APIs to surface waters from treated and raw sewage poses risks for aquatic organisms, even at exposure levels ranging from ng to µg/l of water (pM–nM levels).
- Major unanswered questions for environmental toxicology surround chronic, low-level simultaneous exposure to multiple APIs – exposures that can persist across generations for some aquatic organisms.
- Certain APIs and their bioactive metabolites (e.g., serotonin reuptake inhibitors) are known to concentrate in the tissues of fish and shellfish.
- Municipal drinking water derived from surface waters that originate at least in part from treated or raw sewage can contain multiple APIs, each present at levels in the ng/l range.
- Although one of the sources of APIs in the environment – disposal of leftover drugs into sewers – has received considerable attention by the public, water utilities, Congress and news media, it is unknown how important disposal might be as an overall contributor of APIs to the environment.
- Leftover medications can be a direct measure of the inefficiencies in the healthcare system, representing lost opportunities to treat and wasted healthcare resources.
- By establishing a focus on environmental impacts of medication use and disposal, alterations to the practice of healthcare (such as changes to prescribing and dispensing practices) hold potential for significant collateral benefits, including: improved therapeutic outcomes and reductions in medication cost, drug diversion and unintended poisonings.

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