LEADING ARTICLE

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The Afterlife of Drugs and the Role of PharmEcovigilance

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Abstract

The prescribing and usage of medications (for both humans and domestic animals) have ramifications extending far beyond the traditional objectives of conventional medical care. The healthcare industry has an environmental footprint that includes the active pharmaceutical ingredients (APIs) from medications, residues of which can establish themselves as environmental pollutants. This occurs by a variety of routes, but primarily from excretion, bathing and disposal. Many parallels exist between healthcare and the protection and remediation of the environment, spanning the stages from symptomology and diagnosis to treatment. The critical role played by pharmacovigilance in healthcare has a counterpart with the ecological environment. The term ecopharmacovigilance has been used with respect to the unforeseen consequences APIs can have once they enter the environment. We propose that conventional pharmacovigilance could be expanded to encompass environmental concerns – a concept we term pharmEcovigilance – as a way to unify the parallel but interconnected needs for protecting both human and ecological health.

To convey the scope of a pharmEcovigilance programme, we provide an overview of the occurrence of APIs as environmental pollutants, their ramifications for human health and the environment and some of the ways in which their impact could be reduced or minimized. The major areas discussed include: (i) the routes by which APIs become contaminants in the environment; (ii) the hazards of leftover drugs as a result of stockpiling and from disposal to sewage, which can also eventually contribute to the contamination of drinking water; (iii) why drugs accumulate unused; and (iv) the benefits for humans and the environment that could accrue from reducing the accumulation of leftover drugs and the subsequent introduction of APIs into the environment.

A broad spectrum of actions could be taken by prescribers (including veterinarians) and the healthcare industry at large (including manufacturers and insurers) to reduce the release or introduction of APIs to the environment. Most significantly, however, a major reason to consider implementing a pharmEcovigilance programme – beyond reducing the environmental footprint of healthcare – is the previously unforeseen collateral benefit in making further progress in optimizing the delivery, effectiveness, outcomes and cost of healthcare, as well as improving safety for humans, pets and wildlife.

For this reason, the relationships that healthcare professionals and patients have with medications might also include consideration of pharmEcovigilance. Like any profession that deals with chemicals, perhaps a major challenge to be faced is how to ensure the sustainability (and minimize the life cycle exposure hazards) of a chemical-based, chemical-centric society in the most cost-effective and safest manner. Given that the medical community is a major source of numerous 'exotic' chemical pollutants in the environment (with thousands of chemically distinct APIs in current use), albeit at very low levels, an imperative could be created for designing and implementing approaches for reducing and controlling this source of pollution. With reduced wastage of medications, in part driven by appropriate or rational prescribing and dispensing, the ecological footprint of medicine could be greatly reduced, with concomitant improvements in many aspects of healthcare.

During medical training, student doctors learn the importance of evaluating an individual patient before deciding which medication to choose for treatment or whether to prescribe a drug at all. The pharmacological education in most medical schools emphasizes the negative health consequences for the patient from inappropriate or inadvertent exposure to prescribed pharmaceuticals, and physicians are trained to investigate potential adverse effects or inappropriate consumption by their patients. But the reality is that another type of human exposure to medication ingredients may be occurring routinely, albeit at extremely small doses. Unbeknownst to most physicians, all who prescribe play a large, however unintentional, role in the exposure of the public to the active ingredients in medications because these bioactive chemicals are continually introduced or released to the environment as a result of their intended and purposeful use. The most significant exposures occur for aquatic organisms (because the concentrations are higher than exist in drinking water and because they are exposed for longer durations – sometimes on a continual basis). However, it is currently unknown to what extent humans are exposed to these trace residues that are recycled from the environment in drinking water. Nor do we know the potential for additive, synergistic, antagonistic or unexpected effects from simultaneous trace exposure to multiple ingredients. While a broad spectrum of pollution prevention and stewardship approaches exists for minimizing the subsequent exposures of the public and the environment, these approaches are just beginning to be considered. Many of these approaches fall under the purview of physician responsibility with regard to prescribing and treatment management practices; others reside within the purview of those who oversee or influence dispensing, insurance companies being one example. Physicians have a variety of opportunities to play a major role in this public health dilemma. Note that in this article, the term 'physician' is often used in a very broad, general context to include other professions that can prescribe (although often to more limited extents), including veterinarians, dentists, nurse practitioners, physician assistants and pharmacists.

In this article we discuss the occurrence of active pharmaceutical ingredients (APIs) as environmental pollutants, their ramifications for human health and the environment and some of the ways in which their impact could be reduced or minimized. The major areas discussed include: (i) the routes by which APIs become contaminants in the environment; (ii) the hazards of leftover drugs as a result of stockpiling and from disposal to sewage, which can also eventually contribute to the contamination of drinking water; (iii) why drugs accumulate unused; and (iv) the benefits for humans and the environment that could accrue from reducing the accumulation of leftover drugs and the subsequent introduction of APIs to the environment. We also introduce the concept of pharmEcovigilance as a way to unify the

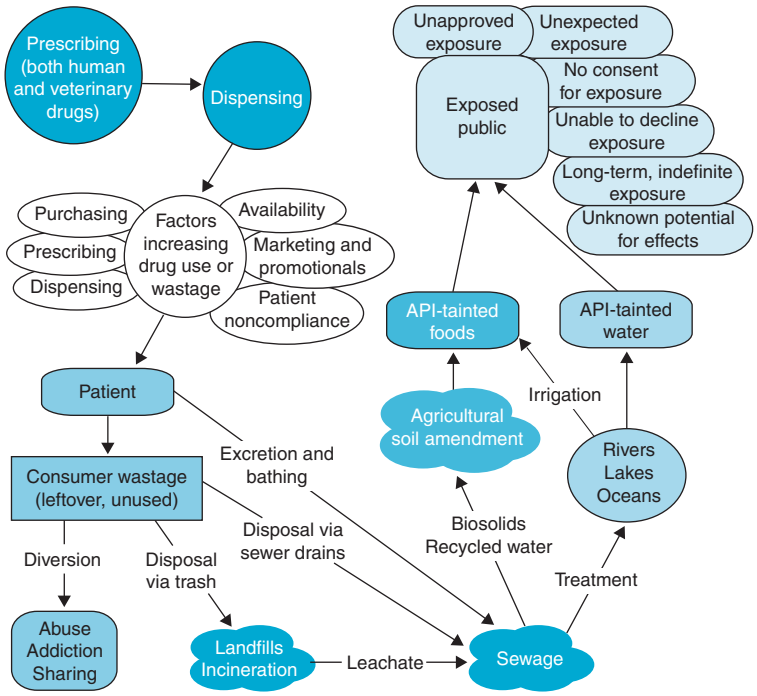

Fig. 1. Unanticipated exposure to active pharmaceutical ingredient (API) residues from the environment.

parallel but interrelated needs for protecting both human and ecological health.

1. The Life Cycle of a Drug

Humans impart unique chemical signatures on the environment in the form of minute residues of pharmaceuticals that we excrete, wash from our bodies or discard to sewage or trash. While the minuscule contributions from each individual may be insignificant by themselves, the collective contributions from all individuals can reach measurable levels in surface and ground waters and on land receiving treated sewage. After release to the environment, the life cycle of APIs continues with biological exposures for the environment and humans (see figure 1). Some of the unique aspects and consequences of this extended life are summarized in table I and table II, respectively.

APIs occur in the ambient environment at concentrations that not long ago were considered infinitesimally low (especially when compared with common therapeutic doses, which are often in the mg/kg range). Concentrations in water or foods generally range from parts-per-billion (ppb) [µg/L or µg/kg] to sub-parts-per-trillion (ppt) [sub-ng/L or ng/kg, or picomolar] and lower. That APIs are widespread environmental pollutants has been well established in an ever-growing body of published literature (see literature database[8] maintained by the US Environment Protection Agency [EPA]).[9,10] Worth noting, however, is that while there are thousands of distinct APIs in commercial use, all of which are capable of eliciting a broad spectrum of unique biological effects, chemists have sought to identify only a small fraction of them in environmental samples. So the true extent and magnitude of contamination of the environment by APIs has been only partly delineated.

The APIs in medications that are prescribed and dispensed enter the environment by two major routes. First, excess medications find their way into the environment when consumers dispose of unwanted leftover stocks, especially into sewers (e.g. flushing down toilets or grinding in garbage dispos-

Table I. Consequences of active pharmaceutical ingredients (APIs) in the environment

Consequence	Example
Contamination of the environment	Continual, low-level exposure of aquatic organisms to APIs excreted or washed from the skin, or disposed via sewage
Acute risks for wildlife	Acute poisoning can occur (especially raptors and scavengers) when medicated or euthanized animal carcasses are improperly disposed (e.g. extirpation of vultures in Asia from scavenging the carcasses of cattle that have been treated with diclofenac[1])
Widespread, unintended exposure of the general public to 'recycled' APIs	The routine use of medications poses unknown risks for the general public by long-term ingestion of drinking water and foods tainted with minute residues of APIs recycled from the environment
Diversion of unused, unwanted drugs; exacerbated need for disposal	Leftover medications accumulate at a wide spectrum of locations,[2] eventually leading to the need for disposal and increased likelihood of diversion and accidental poisonings
Contamination of drinking water	Can lead to consumer distrust in municipal water supplies and catalyse public rejection of water recycling programmes; could also elicit the nocebo effect[3]
Disposal poses some unique environmental hazards	Disposal of unwanted medications to sewers can result in transient concentrations much higher than those resulting from ongoing excretion
Development of resistance to antibacterials	Minute concentrations of antibacterial residues in the environment from excretion are probably too low to promote bacterial resistance. But episodic, transiently high concentrations from disposal might have an effect within sewer lines; the higher levels in sewage sludge could also possibly promote resistance

als). Second, APIs enter the environment as a result of their intended use – as a result of excretion of APIs not fully metabolized and as a result of washing away topically applied medications during bathing. Worth noting are several additional aspects to these routes that are rarely ever discussed. First, while disposal primarily concerns leftover unused medications, partially used medications (especially delivery systems or devices) also serve as a source of APIs during disposal, as the remaining residuals can represent a significant portion of the amount present in new, unused devices. Transdermal and transmucosal devices are two examples; after 3 days of use, for example, fentanyl patches are reported to retain 28–84% of their original fentanyl content, more than sufficient for a lethal oral dose.[11] Second, while most unmetabolized, parent APIs are excreted via faeces and urine, measurable quantities can also be excreted via sweat and can then be introduced to sewers during bathing (or can be transferred to other surfaces during bodily contact); this route of excretion has been investigated primarily for drugs of abuse (e.g. Barnes et al.[12]), such as for use in abuse monitoring by 'sweat patch' testing, but the route is also known to pertain to therapeutic pharmaceuticals (e.g. Høiby et al.[13]). While the concentrations of APIs in the aqueous environment are generally very low,[14,15] usually less than 1 μg/L, it is not known what the relative contributions are from excretion versus disposal.[16]

Many APIs are not fully removed by sewage treatment plants[15] and are then discharged with the treated sewage effluent into waterways. The release of untreated raw sewage by straightpiping or by overflow events, a growing problem in certain municipalities, serves to maximize the release of APIs to waterways. Iodinated x-ray contrast media (which are used in very large quantities) and carbamazepine are examples of APIs that resist removal in sewage treatment plants. Even for those APIs that have relatively short half-lives in the environment (those that are rapidly degraded by natural means such as biodegradation), their continual replenishment via sewage leads to their constant presence – a phenomenon termed 'pseudopersistence'.[17] Alternatively, APIs released into septic systems can leach into the groundwater (roughly one-quarter of the US population is served by on-site septic systems).[18] Contaminated surface and ground waters often serve as supplies for drinking water. APIs can therefore be unintentionally 'recycled' back to humans in drinking water, providing ongoing, minute doses;[19] this aspect of APIs as pollutants garnered attention from US Senate[20] and House of Representatives[21] sub-

committees during 2008 hearings on pharmaceuticals in water.

During sewage treatment, many APIs will associate with the sewage sludge, resulting in concentrations much higher than in the treated waters.[22] The API-contaminated sludge is often used (together with treated wastewater) to amend (and irrigate) agricultural croplands. Agricultural food crops can sometimes absorb the APIs,[23] posing the possibility of serving as a subsequent source for unintentional exposure for humans.

Reducing the initial introduction of pharmaceuticals into the environment, and thereby diminishing the significance of the weaknesses in the treatment process, is an important, but complicated, focus of pollution prevention and source control. Leftover, unwanted medications can also accumulate in a bewildering number of locations[2] (also see illustration in Daughton[19]), far beyond the ubiquitous household medicine cabinet, from where they are often disposed into toilets and trash.[16] Physicians are very aware of many of the causes for leftover drugs that are not fully consumed and therefore accumulate. Patient non-compliance and alterations in treatment regimens are two of the major reasons (figure 1).[2,24]

Examining the life cycle of a medication perhaps reveals the most important aspect of why we should care about trace levels of pharmaceuticals in the environment. To date, the focus of environmental scientists has tended to dwell on establishing the extent of environmental contamination by APIs and on studying the means for source control (waste and drinking water treatment) and the potential for aquatic effects. The actual origins of the problem have garnered significantly less scientific scrutiny, attention being focused instead on designing stewardship approaches for dealing with unwanted, leftover medications. In the US, the first federal guidance for consumer disposal of unused drugs was issued in February 2007 by the White House Office of National Drug Control Policy.[25] The US EPA has summarized the prudent disposal alternatives available in the US and is evaluating new alternatives.[26]

The proper disposal of drugs is important for reducing the unnecessary entry of drugs into the environment (such as by flushing or disposal to trash), but even more so for reducing the very real problem of human morbidity and mortality due to diversion of drugs from accumulated stockpiles awaiting disposal and consequent poisonings. Even partially used medications can pose serious hazards. Used fentanyl patches are one example, where poisonings occur from their intentional reuse[7] and from ingestion, such as by children.[6] This is the major reason that prompt and prudent disposal of leftover, unwanted drugs and partially used medications is so critical.

Beyond the proper disposal of unwanted drugs, the ultimate focus with regard to pollution prevention should address the way in which drugs are

Table II. Medical and environmental consequences of accumulated, leftover medications

Consequence	Example
Wasted healthcare resources	Leftover, unused drugs range from inexpensive over-the-counter bulk drugs to costly prescription medications; leftover drugs can be indication that they were unneeded or ineffective
Lost opportunities to treat	Unused medications can mean the patient imprudently terminated therapy prematurely, for any number of reasons (e.g. Bosworth et al.,[4] O'Donohue and Levensky[5])
Risky self-medication	Diverted medications can be used by others attempting to self-medicate
Unintentional poisonings	Access to leftover medications (or partially used medical devices such as transdermal patches) by children (e.g. Teske et al.[6]), other adults, pets or wildlife through accidental spillage or imprudent disposal into the trash
Facilitates diversion	Access by those for whom the medication was not intended promotes abuse and sustains addiction; even used medicated patches (e.g. fentanyl) can be abused (e.g. Flannagan et al.[7])
Imprudent disposal contaminates the environment	Disposal to sewage leads to continual introduction of APIs to surface or ground waters, as well as to land (via sewage sludge); disposal to trash promotes accumulation in landfills

APIs = active pharmaceutical ingredients.

prescribed and dispensed. The concept of the 'green pharmacy' (which serves as a guide for continual improvement) would comprise a comprehensive, holistic programme whose objective would be to ensure that the types and quantities of medications used in the practice of medicine (and in self-medication) would optimize the health of society as balanced against the well-being of the environment; indeed, the need for balancing human and ecological health is noted by an EU directive: "An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (associated with) undesirable effects on the environment."[27] An efficient and widely implemented approach to a green pharmacy would strive to avoid the generation of leftover medications, resulting in minimal waste requiring disposal. Humans and domestic animals would ideally receive exactly the treatment they needed, with minimal, well targeted doses that also minimized adverse effects. APIs would be designed for extensive metabolism or environmental transformation to less active products, and excreted residues would have minimal impact on the environment (e.g. minimal potential to persist, bioconcentrate or impart adverse effects on non-target organisms).

Many suggestions have been made[28,29] regarding the concept of the green pharmacy. Approaches to minimize environmental impact using green chemistry (e.g. "benign by design") have been recently published by Kummerer[30] and Khetan and Collins.[31] Additional factors may play roles (such as patient compliance and direct-to-consumer advertising, which is practiced only in the US and New Zealand), which would also require attention. The end result of a 'greener' healthcare system would not just be a cleaner environment, but also more efficient usage of healthcare resources, reduced healthcare costs, improved healthcare outcomes and reduced incidence of purposeful abuse and accidental poisonings from diversion of stockpiled drugs. The health of humans and the environment is indeed intertwined, and there is a need for their mutual care and attention.

2. The Roles of Pharmacovigilance and PharmEcovigilance

The medical, pharmaceutical, pharmacy and regulatory communities have long tracked the incidence of adverse effects of medications once they are in routine use. Formal programmes are established for postmarketing surveillance, referred to as pharmacovigilance.

Since the public at large can be exposed to APIs unknowingly, APIs clearly have a more complex life cycle – one where an expansion of the traditional role and scope of pharmacovigilance might benefit all. We have recently coined the term pharmEcovigilance,[32] which considers the more wide-ranging implications of medication usage – adverse consequences for both humans and the environment. Just as most medications have the potential for adverse or unintended effects on patients, they also have the potential for adverse effects on the environment and pose at least a perceived risk for the unsuspecting public (see table I). The many unknowns involved with whatever risks might exist from exposure of humans or the environment to 'recycled' APIs contribute to the debate surrounding the precautionary principle, and specifically its impact on risk assessment with respect to pollution by APIs. This topic of risks and the precautionary principle has been recently discussed by Enick and Moore.[33] The concept of pharmEcovigilance incorporates the many actions that physicians (among others, such as insurance companies, pharmacists, other prescribers, veterinarians, manufacturers and consumers) can take to reduce the introduction or release of APIs into the environment, as well as to lessen diversion. Since a major objective of pharmEcovigilance and its role in a green pharmacy would be to improve the overall quality of healthcare, we believe that the precautionary principle does not need to be invoked in order to justify such a programme.

Attention to the importance of adverse drug reactions (ADRs) was largely fostered by Meyler's famous work *Side Effects of Drugs*, first published in 1951 and now in its 15th edition.[34] The WHO has played a central role in ADR reporting. Approaches leading to the formalization of pharmacovigilance

began in the 1970s, with adoption of a resolution by the World Health Assembly to explore the feasibility of an international system for monitoring ADRs, which led to the WHO's Programme on International Drug Monitoring and the WHO Uppsala Monitoring Centre, which maintains the international database of ADRs. A widely accepted definition of pharmacovigilance comes from the WHO: "… science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem."[35]

Awareness and practice of many of the aspects of pharmacovigilance (especially that medicinal products could cause undesired effects) had existed for hundreds of years, being first formally discussed in the 1700s. The term 'pharmacovigilance' was coined in France, and the concept was first formally used in the French open literature during 1974–6[36-39] largely prompted by the 1961 thalidomide-phocomelia affair, which catalysed expanded monitoring of ADRs (e.g. Hurwitz and Wade[40]). This, in turn, led to the formation of the French Association of Regional Centers PharmacoVigilance (Centres Régionaux de PharmacoVigilance). The term pharmacovigilance entered the English literature in the 1980s (e.g. Moore et al.[41]). An historical perspective is provided by van Grootheest.[42] With a look to the future, the US FDA has launched an effort (the Sentinel Initiative) to develop a national computer network capable of mining postmarketing surveillance databases for drug safety problems (the Sentinel System).[43]

Only in the last 2 years has a realization emerged for the analogous need to pay attention to APIs that enter the environment as pollutants. This has prompted the coining of a number of expressions that deal with the interactions (and possible adverse effects) of API residues with the environment and the possible stewardship approaches for lessening these impacts. These terms first appeared in the open literature in 2006–7 and include: environmental pharmacology,[44] ecopharmacology,[45] ecopharmacovigilance[46] and pharmacoenvironmentology.[44,47]

Integrating all of these terms and approaches under one conceptual framework could be a significant step forward in fostering a stronger understanding of the intimate link between human and ecological health. In this article, we propose a framework termed 'pharmEcovigilance' (figure 2), which would merge traditional pharmacovigilance with ecopharmacovigilance – encompassing the many dimensions of both ecological and human health. PharmEcovigilance would emphasize the fact that human and ecological health are intimately connected, and that actions designed to protect one could afford improvements to the other. PharmEcovigilance would seek to optimize the effectiveness and overall safety of the life cycle of medications, which includes design, manufacturing, sales/distribution, prescribing/dispensing and usage. This could be accomplished largely by: emphasizing the imperative to prescribe only the most effective medications in efficacious minimal doses individualized for each patient; dispensing in quantities and for durations that ensure patient compliance (full consumption); and minimizing/eliminating the generation of leftover medications – so the need for disposal is actively avoided. The major objectives of

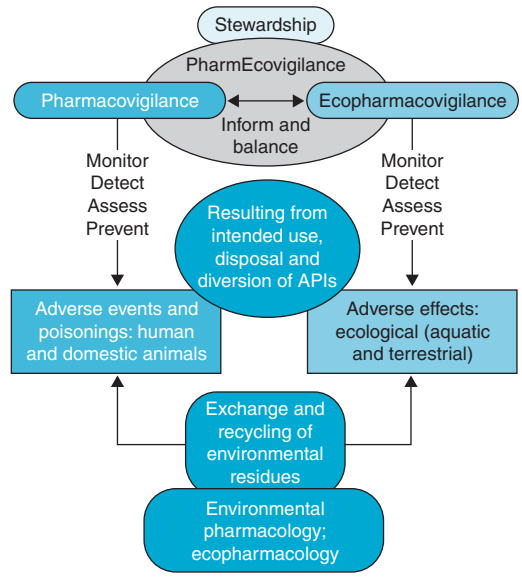

Fig. 2. Role of pharmEcovigilance in minimizing human and ecological impacts of active pharmaceutical ingredients (APIs).

pharmEcovigilance would be to: minimize impacts on the environment from APIs as pollutants; minimize exposure of humans via consumption of APIs 'recycled' from the environment (e.g. as trace residues in drinking waters and foods); and minimize the hazards posed to safety and health from diversion or scavenging of unused medications by humans, pets and wildlife from homes, trash and other locations.[2]

That APIs are ubiquitous in the environment makes obvious the connection that should exist between the practice of medicine and the study and protection of the environment. The two are intimately tied but little recognized as such. The two share many commonalities and connections. Just consider the processes of data collection, epidemiology, diagnosis, mitigation/treatment, prognosis, determination of vulnerability and pollution/disease prevention. Each of these plays a critical role in both healthcare and in environmental protection – in the ecology of health and in the health of ecology. Improvements in one can leverage unintended improvements in the other.

3. Potential Consequences of Ecological Exposure to Active Pharmaceutical Ingredients (APIs)

Two types of ecological exposures to APIs occur. The first is a general, primary route that results in long-term, low-level exposures of the aquatic environment to the on-going release of APIs via sewage and trash. The second results in acute poisonings made possible by unique, unforeseen circumstances, such as improper disposal of highly medicated animal carcasses (see example in table I) or of unsecured medications in trash (see figure 1).

For the aquatic environment, major unknowns include the consequences of long-term (sometimes transgenerational) exposure to very low levels of multiple pharmaceutical residues. This exposure sometimes involves receptors that differ from those in humans, and mechanisms of action can change as the exposure levels are reduced (known as mixed-mode dose response). The potential for adverse or off-target effects can increase when multiple APIs with the same mechanism of action occur together. Two examples are selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, and efflux pump inhibitors,[48] such as reserpine; simultaneous exposure to multiple APIs among a particular class can result in concentration (or dose) addition, effectively serving to increase the actual dose or level of exposure. The behavioural responses in fin- and shell-fish from exposure to SSRIs at ppb (μg/L) levels are one example.[48]

More pronounced effects can occur when very potent APIs are released in sewage.[49] A prime example occurs with ethinylestradiol, prescribed for oral contraception, to which fish are sensitive at the ppt (ng/L) level; a recent experiment in a Canadian test lake has shown the complete collapse of a fish population after 1 year of exposure at 5 ppt.[50] Some APIs can act as indirect toxicants. A prime example is those APIs that can inhibit efflux pumps (verapamil is an example), which serve as a first line of defence against toxic substances for many aquatic organisms. Inhibition of efflux pumps can greatly increase intracellular exposure to levels of chemical toxicants that an organism could ordinarily sustain.[51]

4. Concerns Regarding Human Exposure to APIs from the Environment

The single most significant aspect of benefit-risk assessment that is usually ignored in prescribing medications is that consideration is given only to the benefits that accrue to those who are willing to assume the risks (such as adverse effects). An unknown portion of risk, however, focuses on those who are not seeking any benefits and must often assume the risks unknowingly or begrudgingly as a result of surreptitious exposure. No matter how much the benefits might outweigh the risks for the consenting population, unknown risks (or at least perceived risks) also can accrue to those who are unaware and to vulnerable populations, such as fetuses and older adult populations.

Exposure for humans to environmental residues of APIs, compared with aquatic exposure, is probably lower because unintended ambient residues

occur in drinking water at greatly reduced levels; but foods grown on sewage- or manure-amended land may contain substantially higher concentrations.[23] Another major difference is that ecological exposure is considered adverse only when the effects are expressed at the level of an entire population (e.g. failure of reproductive sustainability). For humans, in contrast, any type of effect on an individual could be considered adverse if the exposure were unwarranted and not welcome. Even psychological effects (e.g. from the nocebo phenomenon) could result if a consumer became overly concerned by the presence of minute residues of APIs in their drinking water.[3]

Additional unknowns arise regarding human exposure. These are summarized in table III. Some of the currently unanswerable questions include how one assesses the significance of exposure due to: (i) long-term exposures to APIs designed for short-term use; (ii) exposure routes that differ from the approved clinical routes (e.g. ingestion of APIs that are approved for dermal use only); (iii) simultaneous exposure to low levels of multiple APIs, especially those that are contraindicated (this could be particularly problematic for APIs present below purported no-effects levels but which share common modes of action, making the effective dose the sum of the individual doses); and (iv) unintended, unexpected exposure of certain sub-populations to APIs that should be actively avoided (e.g. drugs contraindicated during pregnancy; chemotherapeutics or antipsychotics for healthy people)?

While no adverse effects from human exposure to minute levels of APIs in drinking water have been documented,[19] concern persists nonetheless, prima-

Table III. Significance of exposure of the general public to ambient active pharmaceutical ingredients (APIs) via recycling in drinking water and food

Exposure factor	Significance
Dosage is uncontrolled	APIs in drinking water and foods occur at arbitrary, unpredictable concentrations, generally less than 10 ng/L;[19] exposure can occur on a long-term, indefinite basis
Route of exposure may not be approved or studied	Exposure routes may differ from approved routes of administration (e.g. ingestion of APIs approved only for topical use)
API may not be approved for the exposed person	Many APIs are not approved for certain populations (e.g. infants, pregnant women, elderly, immune-compromised, particular sex, etc.) who should actively avoid exposure. One example is drugs contraindicated during pregnancy[a]
Exposure is unanticipated by the exposed person	Exposure via drinking water and foods, no matter how low the level, is an event not expected or recognized as normal by the public
Dose is not consented to by the exposed person	Exposure via API-contaminated drinking water and foods occurs without the knowledge of the consumer
Exposed person has no opportunity to refuse the dose	Even if the consumer knew that drinking water and foods were routinely contaminated, alternatives may not be available
Exposure duration can be long-term and indefinite	With the continual release of APIs via sewage, ambient environmental residues can persist, and trace contamination of drinking water and foods will sustain. Unlike long-term maintenance drugs, certain medications are intended for use over much shorter periods of time
Simultaneous exposure	Exposure to low levels of multiple APIs could be particularly problematic for APIs that are contraindicated (resulting in adverse interactions) or that share common modes of action (yielding a larger, combined dose)
Potential effects are unknown and not being monitored for	Human effects are unknown for doses that amount to at most micrograms per day. The possibility of subtle effects (e.g. behavioural or learning disorders, or delayed-onset effects) has never been examined. Another unexplored issue is that of allergic or autoimmune responses
Nocebo effect can be provoked	The nocebo effect entails an adverse response from exposure (or even anticipated exposure) to substances at non-hazardous levels. Unwarranted perceived risk and the nocebo effect can jeopardize the implementation of water recycling programmes[3]

a This concern has been codified in the Faroes statement on Human health effects of developmental exposure to environmental toxicants,[52] which emphasizes that beyond the traditional view of toxicity – where the "dose makes the poison" – exists a second dimension, where the "timing makes the poison".

Table IV. Actions to reduce active pharmaceutical ingredients (APIs) in the environment and protect human health and safety

Pollution reduction action	Example or benefit
Reduce patient non-compliance	Implement approaches for gauging the magnitude and extent of patient non-compliance and for its reduction.[2] Non-compliance can lead to disposal of leftovers, bypassing the extensive metabolism that can occur for some APIs
Rational or appropriate prescribing[55,56]	Follow evidence-based prescribing, especially for antibacterials (e.g. see the Cochrane Collaboration[57]); be alert to off-label uses, especially for children. Evaluate unapproved new uses purported to be effective for approved drugs.[58] Inform patients of the NNT of a prospective medication. Consider the classification system developed in Sweden for assessing the potential for impact of an API on the environment[59]
Prescribe medications with optically pure APIs	Chiral drugs cut by at least half the quantity of API needed for therapeutic doses (depending on how many therapeutically active optical isomers compose a racemic drug); for example, salbutamol (albuterol) is a racemic drug having two optical isomers, only one of which is therapeutically active[28]
Personalized medicine (sometimes called 'efficacy pharmacogenetics')	Genetic testing could avoid certain unnecessary, inappropriate prescribing; could allow for a reduction in drug dosage by concentrating on those patients who should prove to be responders (by identifying poor or exceptional metabolizers)
Trial prescriptions	90-day courses of medications often lead to leftovers, especially for drugs where patient non-compliance is high
Evaluate need for samples	Samples often go unused by patients due to a lack of understanding of the need or dosing, or fear of adverse drug reactions
Consider prescribing placebos	Placebos are widely used[60]
Increase vigilance for doctor shopping	Prevents multiple prescriptions for the same medications, or different medications containing the same API
Ensure patients understand hidden dangers in over-consuming OTC drugs	Some drugs (e.g. paracetamol [acetaminophen]) are inadvertently over-consumed because they occur in a variety of OTC (as well as prescription) drugs that are often taken together
Increase vigilance for polypharmacy	Eliminating certain unneeded medications could eliminate the need for others, while also reducing adverse effects
Ramifications of the US FDA Amendments Act	The FDA amendments of 2007[61] could result in reduced medication usage because of provisions that: (i) expand vigilance via postmarketing studies and clinical trials, (ii) expand posting of clinical trials and adverse reactions for all drugs, (iii) restrict DTCA, (iv) require REMS for certain drugs
Provide prudent hygiene instructions to patients	Fingers or hands used to apply concentrated topical hormone preparations (e.g. testosterone and estrogens) but not properly washed can then transfer the API by direct contact to other surfaces or people
Provide clear usage instructions	For example, drugs designed for topical use are often over-applied, leading to increased loadings to sewage by bathing
Ensure patients understand prudent disposal practices for unwanted drugs	The ONDCP issued the first US federal guidance for consumer disposal of unused drugs in February 2007.[25] [a] Collection programmes are another alternative[26,65]
Ensure patients understand prudent disposal practices for used medical devices, especially patches	Used medical patches (especially narcotics such as fentanyl) pose a major health risk for those who will reuse them or accidentally come into contact with them. Current ONDCP guidance[25] recommends flushing but this can contaminate the environment. Better disposal options might become available in the future with the development of take-back programmes
Donate unwanted physician samples to charity	Physician samples can be donated to charitable institutions by licensed practitioners if the samples meet certain criteria set forth in CFR Title 21.[66] Some states have legislation allowing closed drug-delivery systems to return certain high-cost items (e.g. cancer drugs) to approved pharmacies for redispensing to indigent patients. Note, however, that charitable contributions during humanitarian relief efforts can pose significant problems, especially for disposal of un-useable or unneeded donations[67]
Prescribe exercise, nutrition and good sleep hygiene	Writing actual scripts for good sleep hygiene and appropriate exercise and nutrition personalized for the patient can sometimes preclude the need for medication

Continued next page

Table IV. Contd

a A variety of state legislation has been proposed or passed since 2006 addressing various aspects of drug reuse (such as allowing or encouraging donation of unused pharmaceutical drugs) or disposal. As of February 2008, the National Conference of State Legislatures[62] reported that 11 more states were considering legislation addressing some aspect of reuse or recycling of pharmaceuticals. New York State A00840 ("An Act to amend the environmental conservation law, in relation to the management and disposal of drugs")[63] would prohibit "the disposal of drugs as solid waste in a landfill; requires drug manufacturers to establish drug collection programs to accept unused or expired drugs from consumers; requires consumers to return drugs to such a drug collection program; all drugs collected by a manufacturer shall be disposed of in an environmentally sound manner." Note, however, that some non-federal laws can run crosswise of federal law, as discussed by McKee.[64]

CFR = Code of Federal Regulations; **DTCA** = direct-to-consumer advertising; **NNT** = number needed to treat; **ONDCP** = Office of National Drug Control Policy; **OTC** = over-the-counter; **REMS** = risk evaluation mitigation strategies.

rily because of the difficulty in ruling out the possibility of effects, especially those that might be subtle (behavioural or learning impairment) or delayed in onset, especially with regard to fetal exposure.[53,54] Certain APIs have the potential to elicit effects at concentrations similar to those found in the environment. One example is ethynylestradiol[50] and another is morphine, which can achieve analgesia in rats at extremely low doses; the simultaneous administration to rats of morphine 0.1 μg/kg coupled with naltrexone 1 pg/kg (an opioid receptor antagonist) can achieve the same level of analgesia as with morphine alone at the conventional dosage of about 1–10 mg/kg – a dosage about six orders of magnitude higher.[28]

5. Role of the Physician and Other Prescribers

Some of the many pharmEcovigilance actions that could be implemented by the medical community are summarized in table IV. A wide spectrum of pharmEcovigilance programmes could be designed to reduce the occurrence and accumulation of leftover drugs, thereby reducing the need for disposal, reducing the risks of drug diversion, improving patient outcomes and conserving healthcare resources. Some approaches are particularly attractive because they can be implemented within a physician's office simply with improved vigilance.

It is clear that a large, diverse array of data can be mined from tracking the leftover, unused, unwanted drugs from patients.[2,24] These data can then be used to design a variety of measures to reduce drug wastage. Time considerations aside, by collecting drug wastage data from patients, a wide spectrum of weaknesses and liabilities associated with the administration of healthcare could possibly be quickly revealed and perhaps actions devised for improvement.

Such information collected by physicians could help to identify those patients who are non-compliant with their treatment regimens. Non-compliance continues to be a major public health concern, and any measure to improve compliance holds the potential to also improve therapeutic outcomes.[4,5] In addition, the information would help to discover trends in pharmaceuticals most commonly discarded by patients. Armed with these data, physicians could further evaluate the choice of treatment for a particular patient. Another opportunity in the course of regular medical practice is in those scenarios where a chosen medication is either discontinued or changed by the physician. At these management junctures, the physician could question the patient regarding quantities of original drugs remaining and further instruct the patient on proper methods of disposal.

Medical management has increasingly emphasized the importance of proper nutrition and lifestyle choices as part of disease treatment and preventative care. Reducing the introduction of pharmaceuticals into the environment, and thereby minimizing the exposure and potential risks to human health, is another important reason why this trend should continue. Certainly, pharmaceuticals have the potential to alleviate symptoms, cure disease and improve the overall quality of life for many patients. However, it would be prudent if healthcare professionals would continue to try to prevent disease and improve wellness by coaching, teaching and encouraging healthy

lifestyles. This may perhaps reduce reliance on medications, avoiding the effects of long-term administration of prescribed drugs and reducing our negative impact on our environment and ecological habitat. This, in turn, might abate the concern for human exposure to 'recycled' pharmaceutical residues.

6. Conclusion

The impacts of medical practice have been shown to extend far beyond humans in their immediate roles as patients. For this reason, the relationships that healthcare professionals and patients have with medications might also include consideration of pharmEcovigilance. Like any profession that deals with chemicals, perhaps a major challenge to be faced is how to ensure the sustainability (and minimize the life cycle exposure hazards) of a chemical-based, chemical-centric society in the most cost-effective and safest manner. Given that the medical community is a major source of numerous 'exotic' chemical pollutants in the environment (with thousands of chemically distinct APIs in current use), albeit at very low levels, an imperative could be created for designing and implementing approaches for reducing and controlling this source of pollution. With reduced wastage of medications, in part driven by appropriate or rational prescribing and dispensing,[55,56] the ecological footprint of medicine could be greatly reduced, with concomitant improvements in many aspects of healthcare. The collateral benefits from reduced wastage would include continual progress toward the optimization of delivery, effectiveness and cost of healthcare, as well as improved safety for humans, pets and wildlife, resulting from reduced diversion and scavenging of leftover medications.

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