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Published in:
Environmental Toxicology and Chemistry

DOI:
10.1002/etc.5563

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Environmental Toxicology and Chemistry—Volume 00, Number 00—pp. 1–11, 2023
Received: 17 August 2022 | Revised: 23 September 2022 | Accepted: 13 January 2023

Critical Review

Broadening the Perspective on Reducing Pharmaceutical Residues in the Environment

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Abstract: The present study reviews options for reducing harm from pharmaceuticals that are known to cause adverse impacts by their presence in the environment. It reviews recent global and European Union policy development, which could go further in recognizing and addressing the issue in a global context. It considers green chemistry, which can help clean up production processes but holds only long-term promise for creating "green" alternatives. It explores the potential of health promotion and disease prevention, which can contribute significantly to a reduction of the disease burden and thus the need for medicines, both for infectious and for noncommunicable disease. Eco-directed sustainable prescribing practices are reviewed, which have been adopted successfully to reduce the use of harmful pharmaceuticals. We note recent developments in medicines optimization and precision medicine, which hold promise for improving patient outcomes, saving costs, and reducing pharmaceutical use, through individually tailored prescribing whereby the patient codecides their therapy. Waste prevention through reuse or redistribution is beginning to find public support and "take-back" waste disposal schemes set up via extended producer responsibility systems have achieved high returns. Finally, the paper summarizes preferred advanced wastewater technologies, including innovative low-cost, low-energy options. In summary, although end-of-pipe options have a role to play, particularly for highly concentrated wastewaters, solutions further up the medicinal chain and disease prevention interventions, informed by a broad view of health and health care, are needed to pursue a much greater potential reduction of pharmaceuticals in the environment than can be achieved by end-of-pipe solutions alone. *Environ Toxicol Chem* 2023;00:1–11. © 2023 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

Keywords: Contaminants of emerging concern; Emerging pollutants; Pharmaceuticals; Water quality

INTRODUCTION

The present study reviews intervention options if a pharmaceutical compound is found to pose an unacceptable environmental risk. Broad intervention categories suggested by Boxall et al. (2012) were substitution of problematic active pharmaceutical ingredients (APIs) with alternative, "greener" compounds; improved drug delivery to allow for smaller doses to suffice; reduced wastage; changes to prescribing practices; and improved wastewater treatment, reflecting a primary focus on ecotoxicological impacts. Boxall and colleagues posed the challenge of quantifying the potential effectiveness of these measures to optimize a mitigation strategy.

In reviewing this challenge a decade later, the present study does not offer quantification but poses that it is important to broaden the discussion in several ways (Textbox 1). First, earlier stages in a drug's "life span" should be included—captured as the "medicinal product chain," recognizing that medicines are authorized for market access, produced, and distributed before they are prescribed and consumed (Grinten et al., 2016). Second, a wider range of impacts from pharmaceuticals should be considered, for example, emissions of solvents, harmful intermediates, or CO_2 during production; nonecotoxicological impacts associated with the consumption phase (e.g., carbon emissions associated with asthma inhalers or packaging waste); secondary pollution during advanced

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Published online 17 January 2023 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/etc.5563

TEXTBOX 1: Priority research questions

1) How can the issue of PiE be integrated in a wider discussion on public and ecological health, in particular in the planetary health context?
2) What synergies can be found between improving public health, providing value-based health and care, and reducing PiE, acknowledging the global societal complexities of these issues?
3) What further drivers can be put in place, in a range of global contexts, to aid the integration of the transformative changes that are achievable through cleaner environments and health promotion into strategies on PiE?

wastewater treatment; and the contribution to the development and spread of antimicrobial resistance (AMR), which is a serious public health concern. Third, we expand the suggestion of changes to prescribing practices by considering preventative approaches to ensuring population health. Only by acknowledging this broader agenda is it possible to identify priorities and synergies connecting public health and ecological health within their global contexts. Clearly, these topics cannot be fully explored within this short paper; nevertheless, we hope to illuminate some of the societal complexities in which the issue of pharmaceutical pollution is embedded, drawing on examples from around the world.

Although some interventions aim to reduce the environmental burden from pharmaceuticals generally, others can be targeted at specific drugs that have been identified as problematic. In the present study, we do not advocate one approach over another but rather acknowledge the interplay of impacts, opportunities, and considerations. In doing so, we draw on the *planetary health* concept to acknowledge the need for a collective transdisciplinary knowledge that amalgamates social, economic, and environmental strategies to prevent and reduce the environmental impacts of pharmaceuticals (Whitmee et al., 2015).

RECENT GLOBAL AND EUROPEAN UNION POLICY DEVELOPMENT

In 2015, environmentally persistent pharmaceutical pollutants were first identified as an emerging policy issue at the fourth meeting of the International Conference on Chemicals Management for the Strategic Approach to International Chemicals Management (2015) because of potential adverse effects associated with exposure on human health and the environment. In 2020, the United Nations' *Assessment Report on Issues of Concern* (United Nations Environment Programme, 2020) recommended expanding the scope of this designation to pharmaceuticals in the environment (PiE) to include pharmaceutical pollutants that accumulate as a result of continuous use and release or cause effects difficult to reverse, such as AMR. In the same year, the World Health Organization (WHO) adopted a points-to-consider document (WHO, 2020) on environmental aspects of manufacturing for the prevention of AMR to address waste and wastewater management from pharmaceutical production. It followed a decision of its executive board (WHO, 2019) that technical input should be provided to good manufacturing practices (GMP) guidance, which is otherwise mostly concerned with quality control, on waste and wastewater management from the manufacture of critically important antimicrobials.

However, the global regulatory framework on PiE remains overall weak. According to Wilkinson et al. (2022), at a quarter of 1000+ sites monitored across the world, concentrations of at least one API were above levels considered safe for aquatic organisms or of concern in terms of selection for AMR, highlighting the global geographical range of pharmaceutical pollution. An Organisation for Economic Co-operation and Development report (OECD, 2019) concluded that current policy approaches developed to manage pharmaceutical residues in OECD countries were inadequate for the protection of water quality and freshwater ecosystems and recommended a policy mix of source-directed, use-orientated, and end-of-pipe measures, with the necessary economic and regulatory drivers. Much of manufacturing, however, especially of generic drugs, occurs outside of OECD countries; and of the countries above the 90th percentile in terms of total concentrations of API in water environments in the Wilkinson et al. (2022) study, three were in Asia, six in Africa, three in South America, one in North America (Costa Rica), and just one in Europe (Spain). The responsibility for addressing manufacturing emissions lies not only with the industry and regulators in the countries of production but also with actors in the countries importing the drugs produced. There is, however, a need for careful consideration of the appropriateness of proposed solutions to the countries where they are to be implemented. For example, tighter environmental regulation may be ineffective where the necessary monitoring and enforcement cannot be put in place, changes to prescribing regimes will not help where self-medication is prevalent and where universal health care is lacking, and advanced wastewater treatment may not be the right focus where basic wastewater treatment is not in place. Global policy development must seek to expand rather than reduce access to appropriate medication, while taking account of the need to protect local environments and safeguard the efficacy of antibiotics.

In recent policy development in the European Union (EU), the increasing recognition of pharmaceutical pollution as a concern has led to the development of a strategic approach to PiE (henceforth *the Strategic Approach*), adopted by the European Commission (2019). This approach outlines six areas of action: increasing awareness and promoting prudent use, supporting the development of greener drugs and green manufacturing, improving environmental risk assessment (ERA), reducing wastage and improving waste management, expanding environmental monitoring, and filling other knowledge gaps. However,

both the European Parliament (2020) and a civil society group (Health Care Without Harm, 2019) have raised concerns about the soft nature of the Strategic Approach, while the Council, which represents member states, stressed "the importance to accelerate concrete and ambitious actions to reduce the risk from pharmaceuticals and their residues to the environment" (Council of the European Union, 2019).

Following the adoption of a new pharmaceutical strategy in 2020 (European Commission, 2020), the European Commission embarked on a comprehensive revision of the EU regulatory framework on medicines for human use. This provides a unique opportunity to improve environmental aspects of this legislation, in particular in relation to ERAs and pharmaceutical supply chains. Pharmaceutical companies must submit ERAs to the European Medicines Agency during the marketing authorization process to evaluate and limit potential adverse environmental effects. However, this does not apply to drugs that entered the EU market before 2006, which means that ecotoxicity data are missing for many medicinal products currently used in the EU. Environmental risks are also not criteria in the benefit–risk assessment for human medicines, which means that marketing authorizations cannot be refused based on environmental risks. As a result, member states tend not to dedicate appropriate resources to the evaluation of ERAs, and pharmaceutical companies often do not prioritize ERAs in the marketing authorization process (Caneva et al., 2014). Another limitation is that ERAs have a limited scope as AMR, combination effects, and risks from production are not considered, although the current guidance does not require testing of metabolites. Finally, underlying study reports produced by the industry to inform ERAs are not publicly available, and their categorization by product rather than compound in public assessment reports, makes environmental information on APIs difficult to research.

More change could be expected as a result of developments in water policy. In 2015, the European Commission included three pharmaceuticals on the (surface water) Watch List, a list of potential water pollutants for monitoring to determine whether they pose risk to surface water. Further pharmaceutical compounds were added in 2018, 2020, and 2022; and the European Commission has recently proposed adding several pharmaceuticals to the Priority Substances List (Directorate-General for Environment, 2022). If adopted, this would encourage member states to take measures to reduce the presence of these pharmaceuticals in surface waters and set the first EU–wide environmental quality standards for pharmaceuticals in surface water. Although this would only apply to a small number of compounds, it would provide an important testing ground for compound-specific measures, targeted at drugs for which risks have been identified. The prospect of such limits has already been discussed by the water industry to undertake more research on effluent concentrations (Gardner et al., 2012; Stichting Toegepast Onderzoek Waterbeheer, 2017, p. 1).

Finally, controls on pharmaceutical supply chains could be improved from the EU. The relatively high capacity for strong regulation in the EU could be used to improve environmental management in other parts of the world, for example, via GMP guidance. The Strategic Approach also considers procurement policies to encourage greener design and manufacturing and the spread of AMR from manufacturing in non-EU countries. This is much needed as the current lack of transparency in pharmaceutical supply chains makes it difficult to trace the origin of APIs and their discharge during production.

HEALTH PROMOTION

The Royal Pharmaceutical Society's Sustainability Policy states "the most environmentally friendly medicine is the one that is not required and not prescribed" (2021). Strategies are needed to prioritize disease prevention over disease treatment. The COVID-19 pandemic focused unprecedented attention on the prevention of infectious diseases through social and behavioral change. Measures such as handwashing and good food handling can also prevent gastrointestinal diseases, improved water quality and sanitation reduce water-borne diseases, and promotion of condom use lowers risk of sexually transmitted infections. These are nonpharmacological approaches that can help reduce the need for anti-infective drugs, which are considered to have high environmental risk (Cooper et al., 2008), while of course also avoiding impacts associated with production (e.g., energy) and consumption (e.g., packaging waste). Globally, seven of the 10 leading causes of mortality in 2019 were noncommunicable diseases (NCDs; e.g., cancer, cardiovascular diseases, diabetes, chronic respiratory diseases, mental health conditions; WHO, 2021). Medicines used to manage NCDs can also pose high environmental risks (Cooper et al., 2008; Li et al., 2019). The WHO's Global Action Plan for the Prevention and Control of NCDs targets a 25% relative reduction in the risk of premature mortality from NCDs, via prevention programs that target modifiable risk factors (WHO, 2013)—such as physical inactivity, unhealthy diets, smoking, and excessive alcohol use—through an integrated approach guided by the principles of multistakeholder collaboration, coordination, and effective communication (Arena et al., 2015). Many NCD prevention programs have been implemented in both higher- and lower-income countries. These have often focused on nonpharmacological and patient-centered approaches, which had health and economic impacts (Bertram et al., 2018). Examples include community health worker models (Jeet et al., 2017); health promotion in communities, workplaces, and schools (Arora et al., 2011); and educational programs (Bay et al., 2017). Improving access to early prevention and care is vital in preventing NCDs; an integrated and comprehensive NCD prevention in India targeted individual-, family-, and community-level risk factors by improving early diagnosis, monitoring, and access to universal health care (Srivastava & Bachani, 2011). In Finland, a regional community-based NCD prevention program targeting primarily people's diet and lifestyle behaviors was expanded nationally because of its positive effects on reducing cardiovascular disease (specifically, ischemic heart disease)–related mortality (Pekka et al., 2006). In Scotland, a nature-based social

prescribing program, the Green Health Partnership, has been recognized as an innovative approach to improving human and planetary health by connecting people with nature- and community-based organizations (McHale et al., 2020; Robinson & Breed, 2019). Although all social prescribing can reduce the need for pharmaceuticals, nature-based prescribing in particular illustrates the relevance of a planetary health approach.

Environmental risk factors also contribute to the development of communicable diseases and NCDs. Air pollution is associated with illnesses such respiratory diseases, cancer, and diabetes (Manisalidis et al., 2020; Whitmee et al., 2015). Climate change contributes to increased prevalence of vector-borne diseases, water-borne diseases, and mental health conditions (Haines et al., 2006). Many societal risk factors are similarly important. Addressing these wider societal issues globally has huge potential for improving human health and reducing pharmaceutical use.

GREEN CHEMISTRY

In recent years, advances have been made by pharmaceutical companies to reduce manufacturing impacts by applying the 12 principles of green chemistry (Anastas & Eghbali, 2010). Such practices have greatly reduced energy consumption, CO_2 production, waste products, and toxic by-products (Mishra et al., 2021; Sharma et al., 2020). Still, residual APIs may cause environmental issues following excretion by the patient, either as the parent pharmaceutical or as the metabolite. The Strategic Approach supports the development of "greener" drugs, and incentives could be provided to focus on alternatives to replace drugs with identified risks. A useful first step is to fund research to determine what specifically it is, in terms of aspects of their chemical makeup, that makes drugs "green" so that these features can be designed into the start of the drug discovery process. Moreover, in any green chemistry approach, criteria for "greenness" and "harmlessness" would need to be defined—including whether these concepts are limited to compound characteristics or also include production and consumption impacts. The Strategic Approach proposes "pharmaceuticals that degrade more readily, to harmless substances, in waste water treatment plants and the environment" (European Commission, 2019); but a fuller understanding of the biodegradation mechanisms and environmental transport pathways is required to enable the comparison, as are ecotoxicity, dosage, and manufacturing emissions. This will be investigated through a Horizon-funded project (European Commission, 2022).

Drug development takes 10–15 years and has a large attrition rate because many potential drugs drop out during the extensive safety and toxicity studies, regardless of pharmacological efficacy. A drug is an organic molecule with different functional groups, each with a specific "task" in treating a disease. Even small changes to the molecule, which would be required to produce a benign breakdown product, can affect all the functional groups and render the molecule no longer pharmacologically active or even toxic. To design a drug that is pharmacologically active, has few side effects, and rapidly degrades to a benign product is therefore not straightforward. Rastogi et al. (2015) proposed redesigning existing pharmaceuticals by making small changes to the molecular structure of active compounds to improve degradability, while retaining therapeutic potency. Despite the promise held by such studies, the molecules would be different and would need to undergo the same lengthy efficacy and safety testing procedures as a newly designed drug.

Finally, even if new drug alternatives are developed that are "greener" than existing ones, interventions are needed to ensure that these are used in preference to existing ones. At the moment, in most countries, no such incentives or guidelines are in place.

CHANGING PRESCRIBING PRACTICE

A welcome and notable development over the past decade is that interest in the environmental effects of pharmaceuticals—and preparedness to change policy and practice—among health-care professionals appears to have grown. This may be due to increasing awareness of the issue of PiE specifically but also of the health–environment nexus more generally, the latter connected to developing insights on environmental AMR, acknowledgment of human–nature relationships as a root cause of zoonoses (WHO, 2021, p. 26), and nature's restorative effect on human health. During the Climate Change Conference (COP 26) in Glasgow, more than 50 countries recognized the need for a more sustainable and climate-smart health-care system (WHO, 2021). In this section, we describe the important role of health-care workers in addressing the environmental impact of pharmaceutical prescribing through eco-directed sustainable prescribing, medicine optimization, and precision medicine.

Eco-directed sustainable prescribing

The term *eco-directed sustainable prescribing (EDSP)* commonly refers to prescribing pharmaceuticals with less environmental impact based on data from ERAs (Daughton, 2014). It holds particular promise for addressing specific problematic compounds and can be used in tandem with "green chemistry." However, EDSP requires integrating data on environmental profiles of pharmaceuticals—possibly with consideration of a wider range of environmental impacts than ecotoxicological risk alone—in rational prescribing guidelines and medicine formularies that consider environmental effects of pharmaceuticals. Moreover, because EDSP promotes changes in prescribing practices, its implementation requires addressing the behavioral and systemic challenges of prescribers (e.g., physicians, pharmacists) in implementing "new" and "environmentally informed" clinical guidelines (Wang et al., 2020).

An evidence synthesis on EDSP programs suggests that different models have been implemented at varying scales, in which seven behavior change interventions were used in

various combinations to change prescribing behaviors of prescribers (e.g., doctors, pharmacists; Alejandre et al., 2022). These behavior change interventions include training and education, enablement strategies (e.g., peer support), persuasion through new clinical guidelines, incentivization (e.g., monetary, reward, recognition), and environmental restructuring (e.g., provision of new tools to support selection of medicines). For example, the implementation of the Stockholm Region's Wise List in Sweden (Gustafsson et al., 2011) provided prescribers with continuous medical education and feedback on prescribing patterns, pocket-sized guidelines and an e-prescription tool indicating which medicines have the safest environmental profiles across a list of alternatives for different medical conditions, a comprehensive communication strategy, and economic incentives for prescribers. Another targeted ecopharmacovigilance intervention, in rural China, utilized a combination of educational, enablement, incentivization, and environmental restructuring strategies to reduce ofloxacin in the water environment (Wang et al., 2019). Similar interventions were used in a pilot study to encourage the prescribing of naproxen over diclofenac in The Netherlands (Afdeling Strategie en Beleid, 2017; Alejandre et al., 2022). These examples have indicated a high level of acceptance of EDSP among patients and prescribers. The availability of robust, comparable data on environmental effects of the various interventions, however, remains a serious monitoring and research challenge. Changing prescribing practices also requires investigating patient safety and potential adverse effects of environmentally friendly pharmaceuticals (Grinten et al., 2017). Moreover, addressing the barriers of clinicians and hospital staff (Singleton et al., 2022) and the leadership of health-care organizations (Singleton et al., 2014) in promoting sustainable clinical practices in the context of the health-care system where EDSP would be implemented is crucial.

Medicine optimization

In countries without universal health care, providing universal health-care coverage, characterized by safe, effective, and affordable medicines at the point of care, is a crucial step for improved medicine use. Medicine optimization is another lever for improving medicine use that could contribute to reduced consumption and wastage of pharmaceuticals and the wider sustainability goal of the health-care sector by making sure that the right patient gets the right medicine at the right time and that the patient is engaged in decision-making for their treatment plan (Picton & Wright, 2013). Key to medicine optimization is the assurance that prescribed medicines are clinically effective and cost-effective, improve outcomes for the patient, and help patients take medicines correctly and safely and avoid taking unnecessary ones (National Institute for Health and Care Excellence [NICE], 2016). In the United Kingdom, NICE (2016) developed a quality standard for medicine optimization where these key elements are present. Similar national medicine policies implemented in Thailand, China, and Australia also integrated medicine optimization in their guidelines by highlighting rational use of medicines with a focus on judiciousness, appropriateness, safety, efficacy, and quality (Yoongthong et al., 2012).

Medicine optimization is a useful tool to manage challenges in prescribing medicines for treating communicable diseases and NCDs. For example, concerns on AMR highlight the need to use antimicrobials cautiously, with minimal, appropriate prescribing, ensuring adherence to guidelines, patient and prescriber education, and tools for medicine selection. Other interventions to reduce inappropriate use of antimicrobials for communicable diseases include closer involvement of both patients and pharmacists in decisions on therapy. Similarly, inappropriate prescribing, patient adherence, and medicine inaccessibility are also some of the many challenges in the treatment of NCDs (Hogerzeil et al., 2013; Nakajima et al., 2021; Zidan et al., 2018).

Precision medicine

Each human is genetically unique, yet health care has a "one-size-fits-all" approach for most prescribing interventions where a particular medicine is used to treat all patients suffering from a specific condition. This leads to only a percentage of patients responding to the medicine, many more not responding, and some developing adverse events caused by various factors such as age, sex, genetic variations, and ethnicity. The Human Genome Project is set to revolutionize health care in the 21st century with the advent of precision medicine (Collins & Mansoura, 2001). Genetics can determine how risk factors for a disease affect each person and how well the same medicine works in different people. Medicines interact with the body in numerous ways, depending on both how they are administered and where in the body they act. When a medicine is taken, the body needs to absorb it and transport it to the intended target. A person's DNA can affect the multiple steps in this process, ultimately influencing how someone responds to a medicine. Examples of such interactions include drug receptor response, medicine uptake, and metabolism. The future of medicine development and prescribing will see more "precision medicine" and "precision dosing" whereby, using pharmacogenomics, a medicine is prescribed to an individual based on their personal risk of a disease or predicted response (Hockings et al., 2020), allowing therapy to be optimized through correlating gene expression with pharmacokinetics and pharmacodynamics. Patient testing enables prescribers to select the most suitable medicine and dose of a medicine for a patient, optimizing response and clinical outcomes while reducing adverse drug reactions (De Villiers, 2021). Various tools in precision medicine have the potential to eliminate the trial-and-error aspect of prescribing. Techniques such as omics and pharmaco-omics (e.g., genomics, transcriptomics, epigenetics, proteomics, microbiomics, and metabolomics); "big data" obtained from medical records, tests, sensors, and smart devices as well as from the various omics, artificial intelligence, and machine learning which can convert big data into diagnostic and therapeutic interventions; along with better understanding of environmental,

social, and behavioral factors will all contribute to precision medicine and dosing along with a new approach to public health and preventative health care, changing the way in which medicines are used, reducing waste and environmental harm, and ultimately improving population health and clinical outcomes (Naithani et al., 2021).

ADDRESSING PHARMACEUTICAL WASTAGE

Other than through medicine optimization and precision medicine, medicine wastage could also be reduced through improved research and manufacturing processes, reviewing "use-by" dates, reducing pack sizes, and reusing returned, unused medicines. An OECD report (OECD, 2022) recommended development of targeted life-cycle approaches toward source-directed, user-oriented, and waste management measures to reduce pharmaceutical wastage, including local and national assessments into redistribution of returned, unused, and close-to-expiry medicines and development of marketplaces and redistribution platforms to better match supply and demand. At the individual pharmacy level, targeting the dispensing stage through reducing stocks of medications on shelves was found to be an effective, feasible, and easily implemented intervention to reduce medication waste (Bekker et al., 2018).

At present, medicine reuse is prohibited across most of Europe. However, a recent UK study indicated that people could embrace this, with the right interventions (Alhamad & Donyai, 2020). Approximately 20%–25% of medicines returned for disposal to community pharmacies in the United Kingdom are potentially eligible for reuse (Mackridge & Marriott, 2007). Concerns over the resale and redispensing of unused medicines include quality assurance and ethical and legal considerations, but although risks must be recognized, workable solutions could be found. A review of "use-by" dates by the Shelf Life Extension Program undertaken by the US Food and Drug Administration to determine the actual shelf life of stockpiled military medications found that, based on stability data, 88% of expiry dates could be extended by an average of 66 months (Lyon et al., 2006). Stability is dependent on the actual drug ingredients, presence of preservatives, temperature fluctuations, light, humidity, and other conditions. Innovative work in the United Kingdom's "Reuse of Medicines Through Informatics, Networks and Digital Sensors" project combines sensor technology with the internet of things to indicate the "reusability" (based on quality indicators and safety checks) of unopened medicines (Lam et al., 2021). Successful schemes have been launched in The Netherlands, the United States, and Greece (GIVMED, 2022; OECD, 2022). In The Netherlands, PharmaSwap is an online sharing marketplace where pharmacists share supply and demand information on medications in stock, enabling licensed pharmacists to sell close-to-expiry medicines to other pharmacies (Pharma Swap, 2022). Two start-ups in the United States, Sirum and Prescription Promise, and a similar scheme in Greece, GIVMED, run collection schemes where patients and pharmacies donate unused medicines for redistribution to low-income patients, people in need, or socially vulnerable people (GIVMED, 2022; OECD, 2022). For such schemes to become widespread and socially acceptable, interventions with prescribers, pharmacists, and the general public are necessary, as are adequate resources for their implementation.

WASTE AND WASTEWATER MANAGEMENT SOLUTIONS

It is inevitable that some pharmaceutical wastage will occur, either via solid waste (e.g., unwanted or expired medicines disposed of in bins) or via wastewater (e.g., disposal of liquid medicines but also washed-off residue of topically applied medicine and excretion via urine and feces). This section reviews good practice for waste and wastewater management.

Appropriate disposal

Pharmacy disposal schemes and associated awareness campaigns prevent significant amounts of unwanted or expired pharmaceuticals from entering waste streams through inappropriate disposal of both solid and liquid medication. In France, it was estimated that households disposed of 17 600 t of unused or expired medicine in 2018, equivalent to 260 g per capita (OECD, 2022). Disposal and take-back schemes are commonly run through on-site pharmacy receptacles, one-day collection events, or mail-back envelopes (OECD, 2022) and generally either supported voluntarily by pharmacies, funded publicly, or paid for through extended producer responsibility (EPR). In Australia, the Return Unwanted Medicines (RUM) project (established in 1998) is a nationally run pharmacy disposal scheme offering free and convenient disposal of medicines via community pharmacies, which has collected >11.9 million kg of medicines to date and is funded by the Department of Health and supported by pharmaceutical wholesalers (RUM, 2022; Singleton et al., 2014). In The Netherlands and Finland, many pharmacies voluntarily provide collection schemes used by an estimated 54% of population and returning an estimated 60%–80% of unused medicines, respectively (OECD, 2022). In particular, EPR schemes have been shown to be an effective approach to organize separate collection and environmentally sound treatment. Countries with high collection ratios (France, Sweden, Portugal, and Spain) have an EPR system in place with full and harmonized national coverage and with collection points at pharmacies (OECD, 2022). Overall, it is generally observed that the public and pharmacists are receptive to actions on appropriate medicine disposal, but again consistent messaging, convenient and accessible processes, sufficient resources, and increased engagement between patients and health-care professionals are needed to facilitate optimum outcomes. Interventions to foster appropriate disposal can be specifically targeted toward drugs classified by therapeutic group; administrative route, such as inhalers, insulin pens, or liquid pharmacotherapy for methadone doses (RUM, 2022); or pharmaceuticals with an adverse risk profile. In Taiwan, antibiotics, hormones,

cytostatics, and immunosuppressants are collected separately (Department of Health, Taipei City Government, 2022).

Global differences in waste collection and disposal affect the implementation and uptake of appropriate disposal schemes. In particular, low- and middle-income countries may lack the infrastructure and regulation to underpin these interventions, whereas the concept of and regulation for correctly separating waste have become commonplace in high-income countries (noPILLS in Waters, 2015; OECD, 2022). Globally, some countries do not encourage pharmacy take-back schemes, or pharmacies may refuse to accept unused medicines because there may be no legislation in place (e.g., in Israel, Turkey, and Chile) or because household waste is considered the correct disposal route (e.g., in Germany and some US states; OECD, 2022). Countries may also face challenges in rural and dispersed populations, where accessibility and inconvenience may affect participation, as observed in Lithuania, Poland, the United States, and the United Kingdom (OECD, 2022; Tong et al., 2011). Mail-in and mobile collection schemes may provide a suitable alternative. On the individual level, barriers such as stigma, education, and social class were also found to affect people returning medicines; and many schemes have highlighted the confusion and misunderstandings among people about the need for and purpose of returning medicines and safe disposal (noPILLS in Waters, 2015; OECD, 2022; Tong et al., 2011). This reinforces the continued need to educate the public and prescribers not just on preferred behavior changes but also on the rationale behind these. Information campaigns such as the European #Medsdisposal, Germany's "No pharmaceuticals down the toilet or sink!," New Zealand's "Disposal of Unwanted Medicines Properly," and Australia's RUM Project are proactive steps which can reduce misinformation and increase effectiveness of take-back schemes (OECD, 2022; RUM, 2022).

Interception of urine

Urine interception, deployed at the patient level or hospital scale, may be used to capture and separate waste from patients on particular medicines such as cytostatic drugs and X-ray contrast media (noPILLS in Waters, 2015; Stenuick, 2021; Strehl et al., 2019). At the hospital level, this can be achieved via specific toilets or urine bags, with the latter generally also considered a low-cost intervention that can be easily implemented in routine hospital and at-home patient treatments (OECD, 2022; Strehl et al., 2019). In Germany, hospital and at-home urine bag trials resulted in reduced concentrations of targeted X-ray contrast agents in effluents, achieving an estimated 270 kg/year reduction of contrast agents entering the receiving surface water (Strehl et al., 2019). Although the implementation of such measures may reduce quantities of targeted compounds in wastewater, research is needed to understand source apportionment and evidence catchment-wide impact, including final disposal methods especially for urine bags (solid waste or dedicated incineration; Stenuick, 2021; Strehl et al., 2019).

Segregation of contaminated effluents

The use of source segregation and separate treatment of specific wastewater streams at a location level, in particular hospitals, have become more commonplace over the past decade. Targeting a wider selection of pollutants than urine interception, separating out relatively small flows of highly contaminated effluent allows for the targeted application of costly and energy-intensive advanced treatment technologies. Within hospitals, treatment can be applied to the whole facility, specialized wards, or laboratory units (Verlicchi, 2020), either by on-site dedicated smaller treatment works or separate sewer lines into dedicated treatment at existing wastewater-treatment plants (WWTPs). Pilot and full-scale applications have been reported in The Netherlands, Belgium, Denmark, Germany, Spain, Israel, Thailand, Vietnam, and China (Chonova et al., 2018; Stenuick, 2021; Verlicchi, 2020). These generally deployed advanced treatment technologies, although nature-based solutions with constructed wetlands for effluent polishing have also been reported (Verlicchi, 2020). The results indicated that segregation and separate treatment of hospital wastewater was beneficial to overall final effluent quality discharged into surface water, including emission of specific pharmaceuticals and antibiotic-resistant gene load (Chonova et al., 2018; Laquaz et al., 2018; noPills in Waters, 2015). In addition, for significant pharmaceutical point sources, separation of gray and wastewater lines may be of benefit, particularly in hospitals where large quantities of water (up to 50%) are consumed for laundry (Verlicchi, 2020). Site-specific research (composite sampling, flow characterization, drug mass balance, catchment assessment) on source attribution is needed for such interventions because separate treatment may not have a significant impact on total pharmaceutical loads leaving municipal WWTPs. A set of criteria to support decision-making for point-source treatment could include AMR and ecotoxicity risks, costs, efficiency, energy consumption, legal compliance, life-cycle analysis, and expected operation and management of the treatment system (noPILLS in Waters, 2015; Stenuick, 2021; Verlicchi, 2020).

Advanced treatment technologies

Whether at hospital scale or at municipal WWTPs, effluent quality has been improved through advanced treatment techniques such as chlorination, advanced oxidation processes, ultraviolet light irradiation, ultra- and nano-filtration, reverse osmosis, and activated carbon adsorption (Hübner et al., 2015; Moreira et al., 2016). However, some treatments have been shown to produce toxic by-products. Studies on the effectiveness of such techniques for removing pharmaceuticals from effluents show that this is compound- and dosage-specific for both the mainly favored oxidation and adsorption processes, but generally, both address a broad range of investigated APIs (noPILLS in Waters, 2015). Most technologies are, however, energy-intensive; and the quantification of the potential of these techniques to reduce environmental harm is now

primarily a management question, whereby cost and life-cycle carbon impacts must be weighed against environmental benefit. According to current Swiss water legislation (Swiss Federal Council, 2021) and Germany's trace substance strategy (Fraunhofer Institute for Systems and Innovation Research ISI, 2017), not all but selected WWTPs should be upgraded with such technologies.

Alternative and sustainable wastewater treatment solutions

Considering the net-zero carbon goals of the water industry, alternative, more sustainable solutions have been investigated such as low-cost materials for adsorptive treatment or nature-based solutions with wetlands/stabilization ponds for final effluent polishing (Escolà Casas & Matamoros, 2020; Zietzschmann, 2020). Adsorption, in particular biosorption, is a low-tech and robust wastewater treatment technique that uses sorbent materials (e.g., activated carbon, biochar, chitosan, algae, and food waste materials) to bind compounds with varying chemical properties and remove them from the aqueous phase (Zietzschmann, 2020). Carbonaceous adsorbents are the most commonly deployed; but their effectiveness toward pharmaceuticals can be affected by competition with dissolved organic matter, and removal depends on the sorbent material and its specificity toward the targeted compounds (Zietzschmann, 2020). This can, however, be optimized, for example, through textural and surface chemistry modifications to add reactive functional groups and heteroatoms (i.e., oxygen, nitrogen), to increase adsorbent quality and capacity for broad ranges of micropollutants (Pap et al., 2021). Full-scale applicability must consider maintenance and development costs, optimization for broad-range and continuous removal of pharmaceuticals (including reuse or reactivation of spent adsorbent), and incorporation into WWTPs. Constructed wetlands are another sustainable, low-cost treatment option for effective removal of pharmaceuticals, via sorption, biodegradation, phytoremediation, and photodegradation mechanisms (Escolà Casas & Matamoros, 2020). These have been deployed in a variety of settings, including final-effluent polishing for WWTPs, hospitals, and agricultural and aquaculture wastewaters; they offer additional benefits including support of biodiversity and ecosystem services (Escolà Casas & Matamoros, 2020) and may provide a viable option for implementation in wastewater infrastructure in low- and middle-income countries.

Global context of wastewater management

It is estimated that globally 70%, 38%, 28%, and 8% of produced wastewater is treated in high-income, upper-middle-income, lower-middle-income, and low-income countries, respectively (Jones et al., 2021). The management and treatment of wastewater are challenging issues with a complex mixture of social, economic, political, geographic, environmental, and hydrological factors, which vary greatly in the global context (Jones et al., 2021). Improvements to wastewater management through centralized or segregated treatment may not be feasible because of lack of regulation, management, enforcement, or economic and political drivers for change. This is likely to be a continuing challenge, disproportionately affecting low-income countries, because raw or poorly treated wastewater is directly released into surface water (Verlicchi, 2020; Wilkinson et al., 2022), even though widespread, but intermittent, direct release occurs in many high-income countries as a result of combined sewer overflows (Quaranta et al., 2022). It is evident that there is increasing global interest in the management and treatment of wastewater for pharmaceuticals, but continued research is needed to better understand the risk posed by highly contaminated wastewater to the environment and the benefits of point-source and decentralized treatment. This will require economic and government buy-in to support new construction of or changes in sewer networks, further complicated by aging infrastructure, growing populations, and climate change effects. These issues highlight the complexities of addressing pharmaceutical effluent treatment in the context of competing priorities, including multiple environmental crises. Although technological end-of-pipe segregation and treatment systems are available, they must not be seen as the panacea option for intervention but instead be considered—and evaluated—in the context of decision-making and intervention along the whole medicinal product chain as well as disease prevention and nonpharmacological treatments.

CONCLUSION AND PRIORITIES FOR FURTHER RESEARCH

The present study sought to explore what can be done if a drug is known to be particularly problematic in the environment. In summary, possible approaches can be hierarchized as follows.

At the most profound level, societal and environmental risk factors contribute significantly to a wide range of diseases, including those that require some of the most toxic pharmacological treatments. Addressing these risk factors will help prevent disease and hence reduce the demand for pharmaceuticals. Facilitating healthier lives through environmental or societal changes should be the primary approach to reducing pharmaceutical consumption, overall. Such changes are not easy to achieve, but their pursuit is critical and fits with a planetary health approach.

Interventions for risk reduction at the community and individual levels can include health promotion, which contributes to reduced levels of illness and therefore reduced pharmaceutical use. Where appropriate, nonpharmacological options can be considered as part of a person-centered approach, whereby the individual codecides their treatment plan together with community partners and health-care teams. This constitutes a more proactive approach to health, whereby the point where an individual becomes a patient becomes blurred.

If medicines are required, then EDSP tools can guide prescribers toward the least harmful medicine that is therapeutically appropriate; where none are currently available, research

is required to identify alternatives from existing medicines or by developing greener, sustainable medicines—whereby definitions of *green* and *sustainable* need to be agreed.

Through medicines optimization and precision prescribing, patient outcomes can be improved while reducing pharmaceutical consumption and waste. Process and system changes in health care may be needed to facilitate these, while the importance of universal health care and access to medicines cannot be underestimated as a prerequisite for such improvements.

Harmful pharmaceutical residues can be intercepted before reaching the water environment via urine separation, targeted application of advanced wastewater treatment by segregating contaminated effluents, or whole-effluent treatment at WWTPs, for which site-specific source and pathway analysis of the compounds to be targeted is required. The less targeted the application, the less efficient the intervention in terms of financial and environmental cost. Novel alternatives, such as low-cost natural sorbent materials or nature-based solutions, are well worth considering.

Perhaps the most important recommendation for future research is to consider what further policy drivers can be put in place to speed up the implementation of these interventions, in particular how the more transformative changes achievable through cleaner environments and health promotion can be integrated into a strategy on PiE (Textbox 1). Surface water quality targets, such as those discussed in the EU, can unintentionally focus attention in the first instance on end-of-pipe solutions because a quantitative evaluation of their effectiveness is currently the easiest to pursue. In combination with growing environmental awareness in the health sector, however, they have also led to increased stakeholder cooperation and novel partnerships that have put in place interventions further up the medicinal chain, with financial, public health, and environmental benefits, although a limitation remains that such targets may cause attention to be limited to the regulated compounds only. From a planetary health perspective, a broader perspective on human health and the environment, in which health promotion could play a significant role along with eco-directed prescribing and waste and wastewater management, offers the greatest potential to address the root causes of ill health and minimize pharmaceutical use.

Author Contributions Statement—**K. Helwig, L. Niemi, J.-Y. Stenuick, J. C. Alejandre, S. Pfleger**: Conceptualization; Writing—original draft; Writing—review & editing. **J. Roberts, J. Harrower**: Writing—original draft; Writing—review & editing. **I. Nafo, O. Pahl**: Conceptualization; writing—review & editing.

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