Editorial

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# Medical therapeutics with an ecological concern

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An elderly patient presents herself for a medical appointment. Since the patient has a number of different diagnoses, the patient receives a prescription including more than ten different pharmacological compounds. Later that day and in the following days, multiple small molecules enter the sewage system, appearing at a later stage in wastewater treatment systems, and after a significant reduction in the number of molecules has taken place, some will nevertheless appear in a nearby river and later at an ocean. Some molecules are likely to be ingested by different types of fish or otherwise impact other living beings. Some of the molecules mentioned above could, once again, be absorbed by a human being, after drinking or eating.

Pharmacology textbooks have, for a long time, described the general cycle of drugs in the human body, and it is well known that drugs will, in general, be biotransformed, excreted, or both.

It is true that there are examples of drugs that are similar to endogenous molecules and that are not expected to leave any significant "footprint" outside the human body in which they are used (however, other drugs included under the label "naturally occurring substances" may do so). Other drugs are also likely to be destroyed before or when reaching the environment ("readily biodegradable" drugs).

Many drugs, however, will appear in the urine or in the feces after their administration, either unchanged or changed by the human body. Therefore, drugs and derived products are expected to reach and even perhaps to accumulate, in variable degrees, in the environment.

Studies of wastewater, wastewater treatment plants, and river waters have shown the presence of drugs or derived products of different types. Neuropsychiatric drugs are among the molecules found in this context,[1] as are antibiotics.[2,3] Antibiotic resistance genes have been shown to exist in sludge wastewater treatment plants,[4] in hospital effluent, and in treatment plants influent samples.[3] Illicit drugs have been shown to be present in drinking water in different countries.[5] Multiple examples of anticancer drugs were described in wastewater and natural environments.[6] Estrogen (an example of an "endocrine active substance") has been shown to be present in wastewater,[7] and reproductive disruption was described in fish, in this context.[8] A similar or related situation exists regarding thyroid hormones[9] and in respect with other multiple substances.[10-12] A possible (non-target) impact of commonly used drugs on photosynthesis in phytoplankton is currently under study.[13] The presence of drugs in sewage water has been identified at least since the decade of 1970,[14] and it presently spans many parts of the world.

This may be seen as a case of speciesism,[15] since drugs are taken, in medical or veterinary contexts, with an interest in human beings and little or no attention to the impact on the remaining biosphere. However, since humans share many biological mechanisms with many other animals, drugs of medical or veterinary use may lead to consequences in nonhuman animals.[8,16]

The increase in the global human population, the increase in average life span, the rise in importance of chronic medical conditions, and the continuous appearance of new drugs in the market, all contribute to make the contamination of the environment by drugs a progressive phenomenon, of which we are probably not more than witnessing the beginning.

As yet, we do not have a complete global perspective of the environmental impact of all molecules under current therapeutic use, let alone that of drugs not synthetized yet. The environmental impact is likely to translate into an impact on future generations, both humans and nonhumans—and these must be taken into account in the present moment.

How detrimental can this situation be? The answer to this question is not clear at the present stage, but some aspects may be pointed out. Many drugs act under a concentration/response basis, meaning that higher concentrations elicit a larger response. Many drugs are very selective for their target molecules or structures and therefore may lead to effects in relatively low concentrations. Many drugs will act both on human and on nonhuman target molecules, given their similarities. A considerable number of drugs, on the other hand, have teratogenic potential.

For the time being, it may be unlikely that a "steady state" (inputs of drug molecules in the environment similar to the amount of molecules by any means no longer present in the environment) exists or can be reached—this is one of the reasons why we must turn to every aspect of the problem.

Among other angles, we may consider taking a new look at medical therapeutics. The care of patients is the traditional focus of medicine, and drug therapy is currently an integral and major component of clinical practice. The use of drugs has achieved impressive results in the clinical setting. Antibiotics hold a particularly important role and cure patients on a daily basis. Molecules used to treat neoplastic diseases, cardiovascular

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disease, and brain diseases, among others, are also of great importance and often achieve a marked degree of usefulness, as shown in controlled clinical trials.

When caring for patients, medical doctors pay attention to clinical outcomes—curing a disease, preventing clinical conditions, and improving symptoms and the quality of life of patients. At the present stage, the accumulation of tons of drugs or of molecules derived from them in the environment gets relatively little, if any, attention, when treating any individual patient. Hopefully, the awareness of the environmental impact of the use of drugs in the medical setting will increase in the near future, and this will impact medical therapeutics itself.

A thoughtful medical prescription of drugs, with avoidance of any unnecessary use of drugs, taking into account the medical needs and clinical indications of each patient, is advisable. The use of the smaller possible number of drugs for the shorter period of time possible; the use of drugs with definite favorable effects in patients, especially drugs with a favorable impact on mortality; the avoidance of the use of drugs with uncertain effects; and the adequate disposition of unused drugs are principles to be followed.

A drug does not make an impact on the environment if it was not prescribed and is not taken by anyone. Ecological reasons should be taken into consideration, alongside clinical considerations, in every medical prescription.

Medical guidelines should be fully revised taking into consideration these latter reasons, namely analyzing in detail the time span of drug administration for each clinical situation. Drugs with similar effects but more limited impact on the environment should be preferred. It is clearly important to involve patients in all decisions, since an ecological awareness, from the part of patients, may be important.

Hopefully, the future will bring therapeutic options which will make a decoupling between therapeutic effect and ecological consequence possible, by substituting some of the drugs presently in use by new and readily biodegradable molecules.

The European Medicines Agency has released a directive on environmental risk assessment of medicinal products.[17] The text states that the outcome of the environment risk assessment "should not constitute a criterion for refusal of a marketing authorization"[17] (op. cit., page 7). Some drugs were labeled "persistent, bioaccumulative, and toxic chemicals" or "very persistent and very bioaccumulative,"[17] and for these drugs, it has been recognized that "it is not possible to predict the environmental fate of these substances or the kind of adverse effects that could occur over long periods of time"[17] (op. cit., page 50).

From an ecological and long-term perspective, many medications may end up being considered as potentially inappropriate. International cooperation in regulating medical drug pollution of planet Earth is clearly necessary. Even if we accept the primacy of the interest of the human species, it is of our own interest to limit the use of drugs in a reasonable way.

It can be argued that the release of many tons of drugs into the environment each passing year can be seen as a potentially inadequate situation. Apart from other possible measures, one can adapt the strategy laid out by Russell and Burch, concerning animal experimentation,[18] in this case regarding the impact on the environment of medical drug use (Table 1): replacement, the substitution of a drug by a nondrug alternative (as would be the case of promoting diet and physical exercise to treat obesity); reduction, in the quantity of drugs used to attain a given clinical outcome; and refinement, the use of drugs with a more favorable ecological profile. To these, further topics may be added: refrainment, from using drugs with uncertain effects and research, possibly a major tool to overcome this problem. Hopefully, these suggestions will lead to better therapeutics, both for patients and for the environment—perhaps helping to open the new era of ecotherapeutics (medical therapeutics with an ecological concern).

**Table 1**

**Suggested principles of medical therapeutics with an ecological concern.**

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|---|---|
| Replacement | substitution of a drug by a nondrug alternative |
| Refrainment | avoidance of the use of drugs with uncertain effects |
| Reduction | in the quantity of drugs used to attain a given clinical outcome, including in the duration of treatment |
| Refinement | use of drugs with a more favorable ecological profile |
| Research | regarding the environmental impact of drugs used in medical therapeutics |

Adaptation and increment of the "replacement, reduction, and refinement" concept, developed by Russell and Burch, concerning animal experimentation (for reference see text).

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