How to decrease pharmaceuticals in the environment? A review

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Abstract

The global problem of the presence of human and veterinary pharmaceuticals in the environment is under investigation. Despite the increase in the knowledge of its sources, fates and impacts, the assessment of risks and the derived prevention actions are limited to single cases. The predicted increasing trend in the usage of pharmaceuticals forces the various parties involved to think about comprehensive mitigation actions. There are many areas of daily human life and industrial operations where such actions should take place. Thereby, in the presented review, such actions were summarized and divided into the following groups: A. design, synthesis and production of pharmaceuticals, B. prescription, sales and waste handling, C. control of the sources with advanced technologies. As the total amount of proposed actions was found to be quite high, a ranking according to the term of effects was proposed using the pyramid of needs. The advantages of actions taken in the first steps of the pharmaceutical life cycle (acting on the upstream) over end-of-pipe actions and the application of advanced technologies (the downstream option) were discussed, with reference to expert opinions.

Keywords Pharmaceutical residues · Pollution management · Pharmaceutical life cycle · Antibiotic resistance · Advanced treatment technologies

Abbreviations

EDCs	Endocrine Disrupting Chemicals
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organization for Economic Co-operation and Development
WHO	World Health Organization
WWTP	Wastewater Treatment Plant

Introduction

The first reports on the presence of pharmaceuticals in wastewater and natural water were published in 1977–1978 (Hignite and Azarnoff 1977; Cardoso et al. 2014). Since then, knowledge of the sources, fate and ecotoxicology of pharmaceuticals has started to advance. It has been well confirmed that pharmaceuticals are present all over the world in groundwater, surface water, wastewater, soils and biota (aus der Beek et al. 2016; Łukaszewicz et al. 2018; Patel

et al. 2019). In general, many sources and pathways of pharmaceuticals have been identified (aus der Beek et al. 2016; Puckowski et al. 2016). Residential wastewater is often presented as the primary source; thereby, pharmaceuticals can be used as markers of surface and groundwater pollution by domestic wastewater (Tran et al. 2015b). Nevertheless, non-wastewater emission pathways are also important (Bu et al. 2016), for example, aquacultures and wastewaters from livestock. Furthermore, in the case of some groups of pharmaceuticals, pathways other than municipal wastewater may dominate. A good example are antibiotics used in animal treatments. Antibiotics are of particular concern due to bacterial resistance. After several years of monitoring and ecotoxicological studies, pharmaceuticals have graduated to the state of being an emerging problem according to such institutions as the European Commission (Deloitte Sustainability 2018) and HELCOM (International Initiative on Water Quality-IIWQ 2017). The bibliometric analysis of the issue of pharmaceuticals in the environment (Daughton 2016) takes an interest not only in scientific articles and books, but also conference proceedings, TV programs, new media, websites and others. This proves that there is global concern regarding the problem, not only in the field of science.

The problem of environment contamination by pharmaceuticals is complex, not only because of various sources

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and complex fates (Bagnis et al. 2018), but also the numerous medical compounds in use. Of the total number of pharmaceutically active substances—11,926 (<https://www.drugbank.ca/stats>), 713 substances were tested in wastewater and environmental samples (aus der Beek et al. 2016). For 88% of medicines, there are no environmental toxicity data (OECD 2019). It is therefore possible that the so-called Matthew effect is obtained (a psychosocial phenomenon sometimes informally referred to as the “bandwagon effect” or “iceberg effect”)—“decisions that base the selection of target stressors in environmental monitoring surveys on whether they have been identified in prior studies, rather than considering the possibility that additional, but previously unreported, stressors might also play important roles in an exposure scenario” (Daughton 2014). Furthermore, the publicly available data of pharmaceutical consumption are unavailable for most countries, as well as the real environmental concentrations (aus der Beek et al. 2016). Bearing in mind the fact that: A. pharmaceuticals have been known to be present globally for more than forty years and they cause chronic exposure for water organisms, B. there are various sources of each class of pharmaceuticals, C. there is an increasing global trend in the use of pharmaceuticals, D. the presence of pharmaceuticals can induce changes in the environment, E. it is probable that the problem is underestimated due to the “Matthew Effect”—pharmaceuticals are an emerging problem, for which there is no single solution.

The main objective of this review was to present a variety of actions to minimize the problem of the presence of pharmaceuticals in the environment, which should be

implemented for the comprehensive management of the problem, with emphasis on downstream actions. Thereby, despite the pharmaceuticals used in the human medicine, those used for animal (in this for pets) and plants treatment were the subject, despite the general opinion of its minor contribution to environment pollution. Previously published reviews presenting minimalization possibilities for pharmaceuticals (Daughton 2003; Kümmerer 2009; Ebert et al. 2015; Caldwell et al. 2016; OECD 2019; Patel et al. 2019), and micropollutants in general (Schirmer and Schirmer 2008), were also referred. Thanks to this the comprehensive review was carried out. The most effective action, which is not presented here, but is intuitive, is prevention by increasing the wellness, hygiene standards and conditions of humans and animals.

The information presented in this review relates to the life cycle of pharmaceuticals (Fig. 1). The review starts with a presentation of the upstream possibilities: design, synthesis, production, prescription, sales and waste handling. Then, the control of sources (aquaculture, hospital wastewaters, wastewater from livestock, residential and industrial wastewaters, runoff, leaching from landfills, the accidental and intentional introduction of untreated wastewaters) and advanced treatment technologies were highlighted as downstream actions. The reviews focusing on the mentioned areas were cited for readers interested in the details of the proposed solutions.

Fig. 1 Overview of the pharmaceutical life cycle with relation to the possibilities of minimizing their presence in the environment

Design and production of pharmaceuticals

The use of pharmaceuticals will grow for several reasons (OECD 2019): the global trend of an increase in the age and life span of populations, economic growth, intensified livestock practices, climate changes which exacerbate existing diseases (for example, malaria and dengue fever (Cavicchioli et al. 2019)). The global annual growth rate of the pharmaceutical industry is estimated to be 6.5% (United Nations Environment Programme 2019). Thereby, several actions toward reduction should be taken in the design, synthesis and production of pharmaceuticals.

The synthesis of eco-friendly pharmaceuticals is a concept which assumes that pharmaceuticals, after excretion, will easily degrade and be less toxic for aquatic organisms, and this can be done by manipulation of the chemical structure. This improvement should not change the active ingredients during shelf storage and not change the mechanism of action. The trigger for degradation could be a change in the pH or UV. The same concept is proposed for other pollutants with the tenth principle of green chemistry, which is “Design for Degradation.” For example, the re-designing of propranolol (beta-blocker) affects quicker aerobic biodegradation (Rastogi et al. 2015). The concept of “benign-by-design pharmacology” and green chemistry is an area of industry which is attractive from the environmental point of view (Daughton 2003; Kümmerer 2009; Leder et al. 2015).

Furthermore, the design of new active substances should be coupled with two main features: higher bio-availability and higher selectivity of action. The designation of new forms of pharmaceutical application can regulate or accelerate the rate of absorption. Every concept of enhancing the bio-availability and selectivity of pharmaceuticals will be related with the fact that lower doses are used. Another solution is the “smart drug” concept, which aims to produce pharmaceuticals that go into a given receptor.

The new term of Smart Drug Delivery Systems is coupled with innovations in pharmaceutical delivery, such as carbon nanotubes, dendrimers, micelles, liposomes, quantum dots, SPIONS, gold nanoparticles and mesoporous silica nanoparticles (Hossen et al. 2018). All of these can be named nanocarriers and their invention follows the very fresh concept of nanochemistry. The boundaries and opportunities in the field of smart nanoparticles for pharmaceutical delivery are still under investigation (Sercombe et al. 2015). From the other side, the caution in use of nanoparticles should be taken currently, because its impact into environment is still under assessment (Bundschuh et al. 2018). One idea is the well-known solution of the preparation of liposomes, which are highly compatible with cell barriers. Liposomes are spherical colloidal systems consisting of a phospholipid bilayer shell with an aqueous internal core (Li et al. 2018;

Okamoto et al. 2018). They have been known and used as a solution for 50 years, not only in pharmacy, but also in food production, cosmetics and agriculture. Despite their increasing bio-availability, the toxicity of pharmaceuticals can be lower thanks to covering the active substance with a natural barrier. This is used especially in the application of pharmaceuticals for cancer treatment (Soe et al. 2018). Another solution is to use exosomes (Qu et al. 2018; Shyong et al. 2018) or exosome-mimicking liposomes (Lu et al. 2018). Exosomes are naturally occurring elements of cells, which are used, for example, in cancer therapy, as tumors have a high potential for exosome sorption (Bastos et al. 2018). In the case of macromolecules, special dermal and transdermal delivery methods can be used (Münch et al. 2017). Even more innovations have been presented in recent years, and their description is out of the scope of this review (the advised journals are the Advanced Drug Delivery Reviews and the Journal of Controlled Release).

An example of increasing absorption is the production of new salts of active substances, which can easily transfer through skin barriers. Such salts have an ionic liquid character (Wiest et al. 2017; Egorova and Ananikov 2018). For example, diclofenac can be synthesized as a diethylamine salt with high bio-availability (dermal delivery) (Goh and Lane 2014). The strengths and weaknesses of ionic liquids for pharmaceutical application were presented by A. Balk et al. (Balk et al. 2015).

Another idea is the synthesis of prodrugs, which start to be active in-situ, for example, by the fact that some cells have specific enzymes which can release the target pharmaceuticals or change their structure into active forms (Walther et al. 2017). This kind of solution is used in cancer therapy. For example, capecitabine is a precursor of 5-fluorouracil, a popular anticancer agent, whose reactivity is obtained mainly in tumor cells. Chemotherapy agent-unsaturated fatty acid prodrugs are an interesting solution, as such chemicals create nanoparticles similar to liposomes (Sun et al. 2017). A popular reaction which is often used is deacetylation (for example, the release of morphine from heroin in the brain). The presented solutions can be categorized as examples of “click chemistry.”

One action which seems possible to perform is the production of only one enantiomer of a pharmaceutical, which is active (more than 50% of pharmaceuticals in current use are chiral compounds (Ribeiro et al. 2012; Sanganyado et al. 2017)). Such a situation occurs, for example, with some pesticides, such as metachlor (O’Connell et al. 1998). In practice, enantioselective synthesis is often unavailable, and the purification of the enantiomer mixture is hard to perform and time-/energy-consuming. Nevertheless, the number of new pharmaceuticals sold as pure enantiomers increased within the last ten years (FDA data 2017 (Sanganyado et al. 2017)). A review on chiral pharmaceuticals in the environment

(sources, health risks, remediation and more) can be found in (Zhou et al. 2018).

In the case of antibiotics, alternatives can be used, for example, enzymes, peptides, vaccines, antibodies, phage therapies, immune stimulation, prebiotics, probiotics, essential oils and herbal medicines (Czaplewski et al. 2016; Ioannou et al. 2018; Omonijo et al. 2018). The development of alternatives to antibiotics is especially important in this era of antibiotic resistance (World Health Organization 2014; Uppu et al. 2015). One option is the synthesis of bacteria-specific antibiotics.

Furthermore, expiration dates need to be re-evaluated. Most producers deliberately reduce these or use a standard value of one year. Another issue is the environmental sustainability of materials which are used in pharmaceutical packaging (Raju et al. 2016). Such actions would reduce pharmaceutical waste, and in parallel, the cost incurred by patients.

Prescription and sales of pharmaceuticals

The prescription and sales of pharmaceuticals increase each year and will be even greater in the upcoming years (Evaluate Pharma 2017). In the USA, in the last decade, the number of prescriptions increased by 85%, despite the fact that the population increased by 21% (Carr 2017). More than 50% of Americans regularly take prescription pharmaceuticals, often from more than one specialist.

The pharmaceuticals are often wrongly prescribed or chosen when the diagnosis of the pathogen is at a low level. The situation when a patient takes medicines “just in case” is popular, and is caused by both specialist and patient pressure. A good example is the situation when antibiotics are offered for influenza, despite the fact that a viral disease cannot be treated by antibiotics. The use of antibiotics for already antibiotic-resistant bacteria (especially in veterinary medicine) should be eliminated. The WHO estimation is that even 50% of antibiotics are misused (World Health Organization 2014). In Lebanon, about 50% of antibiotics are used without a prescription, thereby without a diagnosis at the same time (Jamhour et al. 2017). Prescribing errors may be numerous in the elderly (Costa-Font and Gemmill Toyama 2011; Mohan et al. 2014). Biosensors and quick tests are already available for fast and reliable pathogen detection (Singh et al. 2014; Nasser et al. 2018). Such tests could be easily available both for specialists and patients.

The abuse of and addiction to pharmaceuticals are more often observed, especially regarding painkillers, psychiatric drugs and sedatives (Costa-Font and Gemmill Toyama 2011; Borgschulte et al. 2018). Furthermore, overdosing on prescription pharmaceuticals can be caused by differences between the established dose and the effective dose. In

extreme cases, the established dose can be even an order of magnitude greater than the active dose. Precise, individual and personalized treatment is needed to reduce overdosing. Pharmaceutical doses should be calculated individually per patient mass, sex, health, age, genetics and sensitivity. Such a solution is already starting around the world (Cree 2013; Cutica et al. 2014; Cenci 2016). Less hazardous active ingredients that are equally fit to cure the disease need to be proposed during prescribing.

Moreover, there is also a trend for self-medication, caused by a lack of trust between patient and doctor, but also a person's educational level, and the development of the country (Jamhour et al. 2017; Smirnova and Owens 2017). Self-medication is mostly connected with pain relief and is unrated (Mehuys et al. 2019). Self-medication with antibiotics has become a significant factor driving antibiotic resistance (Torres et al. 2018). Furthermore, the pressure on doctors from patients can lead to overdoses, also in veterinary medicine (Ekakoro and Okafor 2018).

The control of medical prescriptions is important. Computational systems, which are already in use in several countries, are helpful, but can still have limitations (Alhanout et al. 2017). The control of prescriptions is especially important in the case of older persons, who often take the same active substance supplied by a different specialist. Improvements in the prescription of pharmaceuticals are an essential goal for the current health system (Costa-Font and Gemmill Toyama 2011). More importantly, the prevention of diseases is the best solution for a reduction in pharmaceuticals in the environment. An analysis of demographic structures and the prediction of trends therein would be beneficial for effective long-term strategy building.

The sales of pharmaceuticals can be improved by the following activities:

- The sale of a specific number of pills or mass of active substances, instead of unified bulk packaging. This is especially important for pharmaceuticals with a short expiration date, for example, aspirin. Small-quantity trial and installment dispensing is also a rational option.
- The appropriate packaging—the visibility of the expiration date should be improved, as well as the dosing. Furthermore, information on the necessity of returning expired pharmaceuticals to special places (mostly pharmacies) should be included and highlighted on the information leaflet attached to the packaging. The needs of patients should be taken into account in packaging innovations (Carli Lorenzini et al. 2018). There is a need for the use of pictograms for medicines intended for older people (Ng et al. 2017).
- An electronic and available online system of the history of patient treatment, to avoid the situation where different specialists prescribed the same active substance, but

with different names or forms of application (for example pills and syrup). Furthermore, such a history could avoid the prescription of already tested, but ineffective, pharmaceuticals. This could also improve the search for abuse and addiction, or even combat the illegal re-sale of prescribed pharmaceuticals. Furthermore, prescriptions should have a limited validity.

- A system for the return of unused pharmaceuticals to the pharmacy. A patient whose treatment was shorter than planned has leftover medicines which can be used by other people. Furthermore, this avoids the future use of this pharmaceutical without specialist consultation.
- Improving the medication packaging. The aim of this is to extend the expiration date, for example, by separately packing portions of pills and ensuring better prevention against humidity.
- The unification of pharmaceutical names for those products which contain the same active substance, and for the patient purchasing them without knowledge of the content. A good example is eye drops, as there are several different names on the market with the same active substance.
- Eco-labeling—generally, its use improves consumer choice and awareness, finally improving social welfare (Li 2020). Until today, eco-labeling has not been used by any certification organization. Eco-labeling should be used for the active substance and the packaging material.
- Restrictions in the advertising of pharmaceuticals, especially for painkillers and “lifestyle drugs.” Lifestyle pharmaceuticals are those used for the treatment of non-life-threatening and non-painful disorders, for example, acne, baldness, wrinkles and erectile dysfunction. The other definition is pharmaceuticals used to “satisfy a non-medical or non-health-related goal” (Flower 2004). Most of these are used as self-medication. As examples, sildenafil (Viagra), bupropion (managing nicotine addiction) and methadone (opiate substitute) can be listed. Image and Performance Enhancement Drugs (IPEDs) are a wide range of substances that are taken to alter body image and/or performance (Begley et al. 2017), so their definition is close to “lifestyle drugs.” They are legal, but often illicitly manufactured and sourced. Non-medical use (NMU) pharmaceuticals involve the consumption of prescription or over-the-counter (OTC) pharmaceuticals for non-therapeutic purposes or those other than directed by a healthcare specialist (the best example are opioids) (Hulme et al. 2018).
- Control of internet sales of pharmaceuticals. Often large packages are available at a low price and with unknown purity. IPEDs are mostly purchased online (van de Ven and Koenraadt 2017). Psychiatric pharmaceuticals (for example, amphetamine, lorazepam, diazepam, methyl-

phenidate and lisdexamfetamine, all with a high risk of abuse) are increasingly found online in illegal pharmacies (Monteith and Glenn 2018). NMU pharmaceuticals are found to be primarily sourced through informal exchanges between friends and family (Hulme et al. 2018).

- Control of the black market of pharmaceuticals. Press releases have described that about 25% of pharmaceuticals are sold on the black market (calculations of the World Anti-Doping Agency), with a high percentage of anabolic androgenic steroids (Coopman and Cordonnier 2012; Neves and Caldas 2017). The purchasing of medicines on the black market is often a result of high costs on the legal market. In Africa, even 20% of veterinary pharmaceuticals used come from illegal sources. A report on illegal veterinary pharmaceuticals and ways to avoid them can be found in the literature (Regional Workshop for OIE National Focal Points 2017). In parallel, the sale of counterfeit pharmaceuticals should also be controlled (Almuzaini et al. 2013).

The key to minimizing the use of lifestyle drugs, IPEDs and the black market is to increase awareness in consumers regarding the risks and side effects of self-medication (for example, here for anabolics (Lusetti et al. 2018)). In this concept, the minimalization of pharmaceuticals in the environment is parallel with increasing sensible and safe medication and the reduction in side effects.

The problem which needs to be solved is the high number of leftover medications (it is estimated that even 1/3 of prescribed medications end as waste (OECD 2019)). Here, we can refer to the analysis of Daughton and Ruhoy (Daughton and Ruhoy 2011), in which approaches were presented for preventing the generation of leftover pharmaceuticals.

Source control and advanced treatment technologies

Waste handling by consumers

One of the reasons for the presence of pharmaceuticals in municipal wastewater is improper disposal by flushing down sinks or toilets. Table 1 presents studies of the handling and disposing practices of households for unused and expired pharmaceuticals. The review from 2011 (Tong et al. 2011a) presents more examples and confirms the major observation presented in Table 1 that most unwanted pharmaceuticals end up in the garbage, sink or toilet. The relative importance of this source of pharmaceuticals compared to excretion is unknown (Kotchen et al. 2009). A study from the UK on the distribution of pharmaceuticals, which takes into

Table 1 Household habits in pharmaceutical disposal

Type of survey (year, country)	Main results	References
In-street survey, 1865 respondents from seven sites (2015–2016, China)	75% of the population has unwanted pharmaceuticals at home (182 g per capita); 54% of the population disposes of unwanted pharmaceuticals in the garbage, 4% down the toilet	(Chung and Brooks 2019)
358 university students (2017, USA)	61% of the population has unused pharmaceuticals; disposal by municipal waste (25%), toilet (1%), take-back programs (2%); a large number of students have medicines that need to be disposed of in the near future	(Vatovec et al. 2017)
398 participants (2010, 2011, Ireland)	88% of the respondents have unused pharmaceuticals at home; disposal through household waste (51%), sink (29%), toilet (14%), other	(Vellinga et al. 2014)
1121 participants (2016, Turkey)	41% of the respondents have unused pharmaceuticals at home; disposal practice: take-back program (32%), donation to healthcare facilities (34%), disposal in the garbage/sink/toilet (34%)	(Akici et al. 2018)
452 participants (2008, New Zealand)	Disposal practices: disposal in the garbage/sink/toilet (55%), return to the pharmacy (17%)	(Braund et al. 2009)

account the excretion rate, disposal habits and efficiency of WWTP elimination, supports the statement that the disposal of pharmaceuticals via a sink is an important pathway into the environment (Bound and Voulvoulis 2005). The same opinion has been expressed in the case of selected antibiotics (Al-Maadheed et al. 2019).

In 1996, in the USA, 68% of people disposed of medicines down the toilet (Kuspis and Krenzelok 1996), and from 100 tested pharmacies, only 3% had a special protocol for expired medications (mostly returning to the producer). In 2007, the first federal guidelines were introduced which recommend the disposal of pharmaceuticals in household bins (Glassmeyer et al. 2009). In 2016, the primary route of drug disposal was household trash (25%), while only 1% was disposed of down the toilet (Vatovec et al. 2017). In 2009, only 30 countries had a program for pharmaceutical disposal. Disposal practices differ around the world (Tong et al. 2011b). For example, in Ghana (2014), different disposal strategies were found among inhabitants—burying underground (38%), waste bin (29%), donation to friends (21%), incineration (7%), flushing down the toilet (4%) and, finally, returning to the pharmacy (1%) (Abruquah et al. 2014).

The returning program is of course the best practice. An analysis of pharmaceuticals returned to pharmacies can be found in the literature (Abahussain et al. 2012; Ibrahim et al. 2012). Furthermore, there are several informative campaigns on the disposal of pharmaceuticals and returning them to the pharmacy (for example <http://medsdisposal.eu>, <http://www.medicinewaste.com/campaign>, <http://www.returnmed.com.au>). There are also national programs, like the National Return and Disposal of Unwanted Medicines (NaRUM) Project Audit (Bergen et al. 2013) in Australia and Voluntary Pharmaceutical Take-Back Programs in the Great Lake States (Product Stewardship Institute 2011). These campaigns have an impact on people's habits. Currently, less

young people dispose of pharmaceuticals by flushing down the toilet (Vatovec et al. 2017). Thereby, there is a need for continuous increased awareness regarding the disposal of unused and expired pharmaceuticals. Users are generally willing to participate in such returning programs, even if they should pay the cost of disposal (Kotchen et al. 2009). Medicines returned to the pharmacies are disposed of mostly by incineration, including the packaging, because they are treated as hazardous waste (Kadam et al. 2016).

Surface runoff and stormwater

The pollution of surface runoff by pharmaceuticals is related with various activities: the use of solid sludge from WWTP for soil amendments, the use of reclaimed wastewater for soil irrigation, the use of slurry and liquid manure as fertilizers, and urination and defecation of grazing animals and pets (Li 2014; Bastos et al. 2020). A minor source is the use of antibiotics for the treatment of plant disease.

The use of pharmaceuticals for the treatment of pets is connected with discharge directly into the environment. The estimation (load) of this source has never been presented and is hard to calculate; some may say that this is a minor part of the total mass of pharmaceuticals introduced into the environment. The exact number of pets, especially cats and dogs, which are treated for tumors and cancer is unknown because there is no database nor registration requirement. More pets are treated daily because of the greater care, detection of disease and wealth of the owners. An increase in the sales of over-the-counter medication has been observed (Ramirez et al. 2015). The treatment of pets is often carried out in an experimental way, while the diagnostics of animal diseases is not so advanced as in the case of humans. In most cases, the same medicines are used both for humans and pets. Better control of pet medicines and reporting is needed for an

estimation of the problem and a proposition of an optimal solution.

The antibiotics used for plant disease control are mainly streptomycin, oxytetracycline, gentamicin and oxalinic acid (McManus et al. 2002). They are used mostly to treat fire blight on valuable plants, but also on fruit, vegetables and tobacco plantations. The annual amount used worldwide is unknown. In the USA, less than 0.5% of antibiotics are used for plant treatment. Bacterial diseases of plants are very difficult to manage (McManus and Stockwell 2000). The general possibility of minimizing this pharmaceutical source is to keep the plant in a good condition and minimize the spread of the pathogen. Furthermore, some biological treatment, like beneficial fungi application, can be used for prevention (Robert et al. 2016). For example, fungi from the *Trichoderma* family can produce multiple enzymes, volatile metabolites such as 6-n-pentyl-2H-pyran-2-one, and a number of antibiotics, for example, trichodermin, trichodermol, gliovirin, gliotoxin, viridin, herzianolide, pyrones, peptaibols, ethylene and formic aldehyde (Ghorbanpour et al. 2018). The *Bacillus* species is interesting because of the fact that 8% of the total genome is devoted to the biosynthesis of secondary metabolites which have a broad spectrum of antagonistic activity against plant pathogenic bacteria, fungi and viruses (Fira et al. 2018). *Lactobacillus plantarum* strains were proven to have inhibited pathogen populations on plant surfaces as well (Daranas et al. 2019). Furthermore, plant growth-promoting fungi, plant probiotics and endophytic bacteria can also minimize the use of antibiotics (Hyakumachi 2016).

Stormwater is a cause of concern in urban areas, rather than rural areas. This is due to the fact that urban areas are more polluted by a cocktail of anthropogenic emissions (Markiewicz et al. 2017). Stormwater propagates pollution, also by pharmaceuticals (for example, carbamazepine (Osenbrück et al. 2007) and non-steroidal anti-inflammatory drugs (NSAIDs) (Caban et al. 2015)), to the groundwater used for drinking water. Of course, the presence of pharmaceuticals in stormwater is not caused by their presence in air and natural dust (there is currently no evidence of their presence in these matrices), but by runoff, illegal dumping of wastewater and unsealed systems, and overflow in combined sewer systems (Launay et al. 2016). For example, in New Orleans (U.S.), naproxen (<MDL—145 ng/l), ibuprofen (<MDL—674 ng/L) and triclosan (<MDL—29 ng/L) were found in stormwater canals (Boyd et al. 2004). Domestic markers, such as antibiotics, NSAIDs and trimethoprim, were found in stormwater in China (Yin et al. 2019).

The use of untreated solid sludge from WWTPs in particular causes a significant load of pharmaceuticals (hundreds of kilograms yearly) (Ivanová et al. 2018). Sludge is actually a cocktail of different chemicals with an anthropogenic character, such as microplastics (Pittura et al. 2018),

brominated flame retardants (Demirtepe and Imamoglu 2019), phthalates, chlorinated paraffins, siloxanes, quaternary ammonium compounds, perfluorinated compounds and nanoparticles (Zhang et al. 2017). Sludge can be used treated or untreated, and a regulation limit is specified normally only for the heavy metal content. The disposal of sludge is about 50% of the WWTP operation cost; thereby, it is valuable to use it elsewhere as feedstock (Capodaglio and Callegari 2018). About 40% of the sludge produced in the EU (60 million tons per year) is used for agricultural application. The rest is used for compost production, landfill disposal and energy valorization. What is promising is that there is concern about the increasing production of sludge, and ways to reduce this problem are researched (Zhang et al. 2017).

Treated wastewater can be used as a valuable source of water. Reclaimed water is used mostly for agricultural soil irrigation, landscape irrigation (parks, golf courses), groundwater recharge, industrial use (for example, mining, power sector, manufacturing of paper), seawater intrusion barriers and potable water. The use of reclaimed wastewater for the irrigation of agricultural soil is the option more frequently used because of the general lack of availability of fresh water. Irrigation with treated wastewater has both pros and cons. The main advantages are the recycling of water and nutrients. The negative side is the introduction of contaminants which can inhibit the growth of plants, for example, the increase in sodicity (Erel et al. 2019). The use of reclaimed water contributes to the presence of antibiotic resistant bacteria and genes in the environment (Christou et al. 2017), together with other bacteria and viruses (Pepper and Gerba 2018; Girones et al. 2019). The use of such water also has an impact on the soil fungi community, which is known to perform important functions in a variety of natural processes, and for plant growing (Rangel et al. 2018). On the other hand, there are reports of the absence of negative effects of reclaimed water on the bacteria community, with positive effects on plant vegetation in a long irrigation time (Li et al. 2019a). However, the application of reclaimed water is strictly connected with the presence of pharmaceuticals in soil (Biel-Maeso et al. 2018).

One idea is to prohibit the use of reclaimed water during the winter, when soil organisms have minimal activity. Furthermore, proper safeguards should be established in order to avoid the consequences of the unintended entry of antibiotics into the field of agricultural via irrigation by reclaimed wastewater (Kuppasamy et al. 2018). The perfect solution is to purify the water before irrigation to lower the pharmaceutical content below the risk concentration. It needs to be mentioned that reclaimed water is also used for potable water and bottled water (Zhang et al. 2015; Ellis et al. 2019), and pollutants other than pharmaceuticals can be found in plants growing in irrigated soils (Liao et al. 2018); thereby,

the advanced treatment of reclaimed water would be directly beneficial for human health.

A review of the treatment technology for reclaimed water, with a critical discussion, can be found in the literature (Xu et al. 2016). Generally, such techniques are applicable as: biological nitrification, denitrification, ammonia stripping, ionic exchange, biological phosphorus removal, coagulation, sedimentation and filtering, ultrafiltration, reverse osmosis, electrodialysis, distillation and cooling, ozonation, chlorination, activated carbon adsorption and biochemical treatment, microfiltration, air flotation (Xu et al. 2016). An interesting idea is to use reclaimed water in closed technological systems or as a cooling medium in the power sector (Cherchi et al. 2019).

The control of stormwater pollution can be performed only by knowing the dynamics of stormwater transport (Vezzaro et al. 2014). The traditional technologies of stormwater treatment are mechanical (screens, sieves, separators, filters), physicochemical (flotation, flocculation, sedimentation) and biological (ponds, wetlands, sand filters), and reduction by infiltration, storage and usage. Cheap materials and methods have already been proposed for stormwater treatment from hydrophobic pollutants (Björklund and Li 2015; Soleimani-far et al. 2016), while pharmaceuticals would probably need more advanced technology. The runoff from streets, rich in organics (plasticizers, polycyclic aromatic hydrocarbons, petroleum) and metals (Flanagan et al. 2018, 2019), can be treated by biofilters, such as bioswales. Biofilters are a good solution for nitrogen and phosphorus removal with little effort (Zhou et al. 2016). There are other green infrastructure practices already used around cities (Kazak et al. 2018; Li et al. 2019b). The efficiency of such systems in order to eliminate pharmaceuticals is unknown, but can be related to constructed wetlands. While reed is not the only option for constructed wetlands (more than 150 plants are already used (Kazak et al. 2018), some of them with an attractive appearance), this can be used in the future for the treatment of trace levels of pharmaceuticals from stormwater.

Treatment of waters by advanced techniques

There are several techniques for the reduction in micropollutants from a stream of wastewater. This review does not intend to compare them, but rather to present the options and specialist literature. The advantages and disadvantages of several available techniques (wastewater treatment plants (WWTPs) with activated sludge treatment, WWTPs with coagulation, constructed wetlands, chlorination, membrane bioreactors, micro-, ultra- and nanofiltration, reverse osmosis, ozonation, photocatalysis, advanced oxidation processes (AOPs, for example, photocatalysis, Fenton and photo-Fenton), adsorption and activated powder) have recently been presented by Patel et al. (Patel et al. 2019) according to the

elimination of pharmaceuticals (in terms of efficiency, toxicity of products, cost, technical operation, among others). The current reviews devoted to techniques for the reduction in pharmaceuticals from wastewaters are obtained (Shi et al. 2017; Tiwari et al. 2017; Stadlmair et al. 2018; de Oliveira et al. 2020; Femina Carolin et al. 2020; Shah and Shah 2020). What should be stressed is that there is a need for a standardization of the criteria of evaluation of advanced techniques, because the report lacks important information (Fischer et al. 2019).

Industrial wastewater

Industrial sources include manufacturers of pharmaceuticals and cosmetics who use medications in the content of products. The impact of such sources can be presented by the concentrations of pharmaceuticals found in wastewater and finally, reservoirs. As an example, in one factory in China, the concentrations of oxytetracycline and oxalic acid were as high as 600 mg/L and 9100 mg/L in wastewaters, which were 10^6 higher than the respective concentrations normally found in surface water. 20 km down the river, the concentration of the same antibiotics was 250 µg/L, still higher than the medium concentration found in treated municipal wastewater. More examples can be found in the review (Cardoso et al. 2014), where the reported concentrations of pharmaceuticals were at the levels of µg/L to mg/L. These data undeniably show the need for such wastewater treatment in the place of origin. In the USA, the wastewater from pharmaceutical manufacturing facilities was found to substantially increase the concentration of selected pharmaceuticals in municipal wastewater (Scott et al. 2018). Real case studies proved the effect of industrial discharge on fish, amphibians and the bacteria community (presented in the review (Cardoso et al. 2014)). A probabilistic approach has been proposed to assess the risk of pharmaceutical wastewater discharge (Cardoso et al. 2014).

Pharmaceutical wastewater types are differentiated in terms of chemical composition (Shi et al. 2017). Pharmaceutical manufacturing includes the following categories of actions: fermentation, extraction, chemical synthesis, formulation and packaging. Fermentation and chemical synthesis, in particular, produce hard-to-treat wastewater because of high pH, salinity, the presence of organic solvent and the high load of carbon, organic solvents, heavy metals and ammonia (Zhao et al. 2019). The distribution of pharmaceuticals in pharmaceutical wastewater can be described to be rather stable as the manufacturers mostly focus on single/several products at one time. One characteristic of pharmaceutical wastewater is actually the recommendation to use end-of-pipe technology—the stability of the matrix makes the treatment easy to optimize; the higher concentration of

the pollutant makes the treatment more cost-effective (Man-tovani et al. 2017; Kümmerer 2018). Thereby, industrial wastewater rich in pharmaceuticals should undergo special treatment at the place of origin before discharge into the environment or municipal WWTPs.

One solution is anaerobic treatment in traditional WWTPs, but the elimination of antibiotics should be obtained by advanced techniques (Shi et al. 2017). It was found that the bacteria community in pharmaceutical WWTPs differs from that in traditional WWTPs (Zhao et al. 2019). Generally, the presence of contaminants in high concentrations, especially antibacterial agents, inhibits the activated sludge; thereby, this technology is used less often. Instead, small reactors, often with membranes, are applied (Zhao et al. 2019). The applied technology should also eliminate the other chemicals used in the synthesis, such as heavy metals and organic solvents. The techniques of pharmaceutical wastewater treatment (Fenton, electro-Fenton, ozonation, biodegradation, sonochemical techniques, among others) are presented in the reviews (Tran et al. 2015a; Prabakar et al. 2018; Akhil et al. 2021). An example of a plant for the removal of pharmaceuticals in an industrial district in China can be found in the literature (Ma et al. 2016). A batch mode of treatment is often needed because of the complexity of the matrix of pharmaceutical wastewater.

Presently, the monitoring of industrial wastewater is focused on basic parameters, such as COD, BOD and heavy metal concentrations, as there are no legal limits of pharmaceuticals. In such cases, the impact of the discharge can be measured by biological factors, for example, the differences in biodiversity upstream and downstream of the discharge. Such a solution was used to assess the impact of industrial discharge on fish in France (an endocrine-disrupting effect was observed) (Sanchez et al. 2011). The general rule of prevention and “Best Available Technique” needs to be implemented for the reduction in such point sources of pharmaceuticals in the environment (Cardoso et al. 2014). Regular monitoring will bring an argument for decision-makers to enforce an improvement in the quality of treated wastewater among pharmaceutical manufacturing companies. Furthermore, the introduction of closed water systems into factories can bring even more environmental benefits.

Hospital wastewater

Hospitals (and also old people’s homes, hospices and other health-care facilities) are another source of wastewater with a high content of pharmaceuticals. Most hospitals are connected to public sewage systems. Nevertheless, before entering the public system, this wastewater needs special care because of the high content of pathogens. In the review of Carraro et al. (Carraro et al. 2016), the characteristics of hospital effluents as well as a risk assessment are presented.

Generally, hospital effluents vary in characteristics, because several types of activities can take place in a hospital (routine patient care (laundries and kitchens) and highly specific operations like laboratories, hemodialysis and dental departments or radiotherapy). Chemical, biological and physical/radioactive risks are all connected with hospital discharge. The above-mentioned review presents a comparison of pharmaceutical concentrations in hospital effluents, industrial effluents and domestic wastewater reported in the literature (2010–2014). The highest concentration of almost all target compounds, especially antibiotics, was observed in hospital wastewater (Wang et al. 2018). The contribution of hospital wastewater in the load of pharmaceuticals in municipal wastewater is stated to be significant by some researchers (Santos et al. 2013; Azuma et al. 2019). On the other hand, some authors claim that the volume of hospital wastewater is low and is a minor contribution to municipal wastewater (Kümmerer 2009; Cruz-Morató et al. 2014), or surface water (Xiang et al. 2018). What is indisputable is that there are classes of pharmaceuticals which were detected in higher concentrations in hospital wastewater, like those used only in hospitals (Le Corre et al. 2012) (for example, antipsychotic pharmaceuticals (Reichert et al. 2019)). Furthermore, antibiotic resistance genes can enter the environment together with hospital wastewater (Azuma et al. 2019).

The guidelines for liquid and solid wastes produced by hospitals are different around the world (Carraro et al. 2016). In Europe, there is no specific directive for the management of hospital wastewater. Nevertheless, member states have their own regulations. Generally, the direct disposal of hospital wastewater into surface water should be prohibited. Treatment and disposal into the surface water or pretreatment and disposal into WWTPs is recommended. The WHO recommendation can be found in the book entitled “Safe Management of Wastes from Health-care Activities” (2nd edition, 2014, Geneva) (Yves Chartier et al. 2014).

The waste treatment technology which can be used by health-care facilities is divided into thermal processes, chemical processes, irradiation technologies, biological processes and mechanical processes (Yves Chartier et al. 2014). The choice depends on the current waste characteristics. Several innovative technologies for the removal of pharmaceuticals from hospital wastewater have been presented during the last five years (Table 2). It needs to be mentioned that the vast majority of reports present pilot-scale systems or laboratory-scale tests. The research also lacks a comparison of the efficiency and cost of tested systems, and the reduction in bacteria and viruses in a treated stream was not investigated. In one paper, the simultaneous reduction in antibiotics together with antibiotic resistance genes by advanced technology (membrane bioreactor treatment (MBR), ozonation, granulated activated carbon (GAC) and UV treatment) was presented in a real case study (Paulus

Table 2 Exemplary innovative technologies for the removal of pharmaceuticals from hospital wastewater

Tested technology	Target pharmaceuticals	Effectiveness	References
Ozonation in a pilot-scale Moving Bed Biofilm Reactor (MBBR)	Antibiotics (ciprofloxacin, sulfadiazine, sulfamethizole, sulfamethoxazole, trimethoprim, azithromycin and the sulfadiazine metabolite acetyl-sulfadiazine; beta-blockers (atenolol, metoprolol, propranolol, sotalol); analgesics (diclofenac, ibuprofen, phenazone, tramadol); antidepressants (venlafaxine, carbamazepine); X-ray contrast media (iopromide, iohexol, iopamidol)	90% of pharmaceuticals eliminated	(Tang et al. 2019)
Carbon materials, such as nanotubes (laboratory study)	Carbamazepine (CBZ) Ciprofloxacin (CPX)	High adsorption capacity (242 mg of CBZ per gram of sorbent and 264 mg of CPX per gram of sorbent)	(Álvarez-Torrellas et al. 2017)
Pilot-scale treatment via gas-phase pulsed corona discharge oxidation	Bisoprolol, caffeine, carbamazepine, citalopram, diclofenac, fluoxetine, furosemide, hydrochlorothiazide, ketoprofen, metoprolol, metronidazole, naproxen, propranolol, salbutamol, sotalol, trimetoprim, warfarin	53–100% removal	(Ajo et al. 2018)
Real case—hybrid biofilm and activated sludge system (Hybas™)	Sulfonamides, analgesics, antibiotics, antidepressants/antiepileptics	High diversity of removal (0–100%). The presence of metabolites in the treated wastewater proven	(Escolà Casas et al. 2015)
Batch fluidized bed bioreactor with <i>Trametes versicolor</i> (fungi) pellets	Analgesics, antibiotics, psychiatric pharmaceuticals, metabolites, non-pharmaceutical endocrine disrupting compounds (EDCs; like plasticizers, alkylphenols, bisphenol A)	51 detected pharmaceuticals and EDCs were partially to completely removed. For some compounds, an extended time of treatment was needed	(Cruz-Morató et al. 2014)

et al. 2019). What is promising is that a fungal reactor was capable of removing diclofenac (recalcitrant in municipal WWTPs) (Cruz-Morató et al. 2014).

Finally, advanced technologies should be applied for hospital wastewater, and regulations are highly needed in this area. The advantages of this can be the fact that often the chemical risk of the presence of pharmaceuticals is lowered by the application of advanced processes, together with the biological and radioactive risk of hospital wastewater. For anticancer pharmaceuticals, special care should be taken, as they are highly toxic (Białk-Bielińska et al. 2017). The individual management (collection, treatment) of human excretion from oncological patients was proposed as a solution (Ferrando-Climent et al. 2014).

Wastewater from livestock

Livestock production is connected with a high consumption of pharmaceuticals, mostly antibiotics. Antibiotics are used in India and China as growth promoters, while in the EU such a solution was banned in 2006. The contribution of China to global animal breeding is essential, as well as to the use of antibiotics in such production (Zhi et al. 2018). Nevertheless, all animal breeding is connected with a high concentration of antibiotics in wastewater, because these compounds do not fully metabolize, and the active conjugates are present in feces and urine. The concentrations of antibiotics (tetracyclines, macrolides and others) are reported at the level of a dozen $\mu\text{g/L}$ (Zhi et al. 2018; Gros et al. 2019). Other classes of pharmaceuticals, for example, antihelmintics and NSAIDs, can also be detected in slurry and manure (Łukaszewicz et al. 2016; Gros et al. 2019; Petrie and Camacho-Muñoz 2020). A direct toxic effect from this level of concentration is unlikely, but a change in the bacteria community was observed after a continuous flow of livestock wastewater (Jia et al. 2017). Reviews of the use/fate/environmental effects of veterinary antibiotics are presented in the literature (Kumar et al. 2005; Kuppusamy et al. 2018). The re-inspection of antibiotics shows that each group of antibiotics has different behavior, effects and risk to the agricultural environment (Łukaszewicz et al. 2016).

The treatment of such wastewater depends on its further use or disposal. Agricultural use is the most popular because of the high fertilization potential of this wastewater type (Gros et al. 2019). Anaerobic stabilization is the minimal treatment required before disposal in soil. Currently, more countries are banning the use of antibiotics which are important for human treatment and for livestock use. Existing gaps in the knowledge, recommendations and possible strategies to limit the presence of veterinary antibiotics in the agro-environment are presented in the review by Kuppusamy et al. (Kuppusamy et al. 2018). A review of antibiotic bioremediation has already been published (Kumar et al.

2019). A review of technologies for the elimination of antibiotics and hormones from swine wastewater can be found in the literature (Cheng et al. 2018). The proposed/needed urgent activities recommended by Kuppusamy et al., with the authors' own contribution, are presented in Table 3. The implementation of each of them would prevent the health risk of pharmaceuticals both to wildlife and humans by a potential reduction in the presence of antibiotic resistance.

Aquaculture

Aquaculture is the sector of industry where the production of plants or animals is placed inside water, namely in freshwater aquaculture (63%), estuarine systems (8%) or seawater systems (mariculture) (29%) (Ottinger et al. 2016). The systems are rice fields, ponds (natural or artificial), cages and pens, raceways, tanks and recirculating systems, and each of them employs different ways to deal with waste (Dauda et al. 2018). Aquaculture is a booming industry in the world and China is the largest producer and exporter of aquatic products (Liu et al. 2017).

Several types of pharmaceuticals are used in aquaculture—antibiotics (in predominance), anti-parasitics, hormones and stimulants. Except stimulants injected directly into entrails, the pharmaceuticals are administered with food. This poses a risk of the water environment near the aquaculture. Some of the applied dose is dissolved with the water directly, while the rest is absorbed by fish or shrimps. Not all doses are absorbed inside the ingestion system, and return to the water. Furthermore, there are antibiotics which are not metabolized by fish and eliminated with urine to water. The example is oxytetracycline, which is the most popular antibiotic used in aquaculture (Zhang and Li 2007). Discharge from aquaculture was a primary source of the presence of antibiotics in Bohai Bay, China (Zou et al. 2011). Concentrations of sulfadiazine, amoxicillin, norfloxacin, ofloxacin and erythromycin in a pond of fish and shrimps ranged from 65 to 7722 ng/L . In some Polish rivers, the concentration of fluoroquinolones was as high as 136 ng/L thanks to their use in the aquaculture of rainbow trout (Wagil et al. 2014, 2015). Despite pharmaceutical residues and bacteria resistance, aquaculture has an impact on landscapes, habitat destruction, erosion, diseases of natural organisms and food chain pollution. An overview of the current state and impact, and possibilities in the sustainable management of aquaculture, and future perspectives in relation to the warming effect can be found in the literature (Ottinger et al. 2016).

The low effectiveness of antibiotics used in aquaculture is caused by the fact that the fish which are already infected have no appetite and a significant amount of food with medication goes directly into the water. If a circulated system is used in aquaculture, the exchanged water enters the river without purification. Because of the fact that only a small

Table 3 Proposed actions recommended by Kuppusamy et al. (2018) and us for the minimalization in antibiotics and antibiotic resistance in the environment, focusing on livestock production

Category	Activity
Lowering the use of pharmaceuticals in livestock	<p>The verification of the use of antibiotics, and elimination of those for which resistance is already presented</p> <p>A change in the diet of the human population, lowering the consumption of animal products</p> <p>The identification of alternatives to the use of antibiotics (for example, herbal materials)</p> <p>The development of improved nutritional programs to maintain good animal health and thereby reduce the usage of antibiotics</p> <p>The optimization or control of the use of antibiotics as feed additives</p> <p>The development of standards of limits of antibiotic concentrations in organic fertilizers and plant produce</p> <p>Similarly to the use of pharmaceuticals in human medicine—the improvement in pharmaceutical absorption</p>
The elimination of pharmaceuticals from obtained wastewater	<p>The development of new and/or the improvement in the efficiency of currently existing livestock manure pre-treatment technologies</p> <p>Biological treatment and the containment of antibiotic resistance genes in manure</p> <p>The setting-up of an on-farm methanogenic biogas system which could be a novel and energy-efficient manure management approach on animal farms</p> <p>The development of easily degradable pharmaceuticals</p>
Removal from soils	<p>Rhizosphere growth promoters as support for soil bioremediation</p> <p>Bio-remediation by plants or fungi</p> <p>Soil chemical remediation for places with high pollution</p>
Increase in knowledge and control programs	<p>Extensive studies on the fates (mixed antibiotics, interaction effects with other contaminants) and ecological risks of antibiotics in agro-ecosystems</p> <p>Conducting interdisciplinary research (microbiologists, organic- and geochemists, risk assessment and industry scientists, environmental and agricultural engineers)</p> <p>Monitoring programs and more frequent internal and external controls of animal feed, wastewater and products</p>

dose of applied pharmaceuticals reaches the injured tissue, the mass of medication needs to be enhanced. For example, a typical tetracycline dosage for the whole treatment of fish is 800 mg/kg, six times more than that for terrestrial animals (European Medicine Agency 2014). In China, the dosage of antibiotics reaches 2.5 g of antibiotics per kg of feed (Liu et al. 2017). The duration of the antibiotic treatment depends on the disease and can reach 10 days. Nevertheless, it should be noted that, since 1981, sales of antibiotics used in aquaculture in Europe have declined by 99%, while during the same period, the production of farmed fish increased more than 100-fold (European Medicine Agency 2014). On the other hand, the use of antibiotics in aquaculture in China is increasing, and banned antibiotics are still in use, and detectable in fresh and salt water (Liu et al. 2017).

The use of antibiotics in fish production causes a problem for the environment because of direct contact with water organisms and bacteria resistance to the antibiotics already mentioned (reviewed in (Santos and Ramos 2018)). The emergency increase in bacteria resistance in aquaculture means that alternative environmentally friendly approaches are urgently needed (Pérez-Sánchez et al. 2018). Although the minimalization of fish diseases

is one of the most important tasks, there are ways to reduce the use of antibiotics in aquaculture. A reduction in the amount of fish inside one tank causes less stress for fish and improves their resistance. Guidelines for the responsible use of antibiotics are also available (Serrano 2005). Vaccinations are present, but have limitations, especially in the case of crustacea. Other approaches are the use of bacteriophages, microbiota, phytobiotics, postbiotics, prebiotics, probiotics and synbiotics (reviewed in (Pérez-Sánchez et al. 2018), with specifications of both the advantages and limitations of each approach). The use of probiotics (bacteria from the family of *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and yeast) is in its initial stages in China (Wang et al. 2019).

Holistic regulations in this industry are also urgently needed. In Norway, the use of antibiotics in salmon farms is the lowest around the world, thanks to special regulations (Olaussen 2018). Unfortunately, at the same time, the consumption of chemicals for sea lice treatment has increased several times because of the increase in numbers of this parasite in farming-dense regions, both in naturally and artificially produced salmon stock (a similar problem occurs with Early Mortality Syndrome in shrimps (Sanguanrut et al.

2018)). What is worrying is that the resistance of sea lice to these chemicals starts to be observed both in natural and artificial fish stock (salmon and trout) (Fjørtoft et al. 2017). One solution is the collation of a new aquaculture in a disease-free region, which has been applied in Scotland to manage the sea lice infection of salmon (Murray and Gubbins 2016).

In the case of recirculating aquaculture systems, wastewater can be treated by bioremediation, and traditional and advanced technology before discharge into natural water, similar to other types of wastewaters. The exemplary technologies tested or implemented for aquaculture are presented in Table 4, and more can be found recent reviews (He et al. 2016; Santos and Ramos 2018; Jasmin et al. 2020). A review of the management of pharmaceutical pollution in aquaculture in China, as the region with most intensive aquaculture production, can be found in the literature (He et al. 2016). The other issue is the quality of water which is used in aquaculture, as in some water reservoirs there are pollutants such as endocrine disruptors, which can affect the fish population (Ismail et al. 2017), or pesticides and antibiotics affecting shrimps (Butcherine et al. 2018; Saxena et al. 2018). Thereby, the idea of using closed systems or applying ground water has already been highlighted (Little et al. 2018).

What should be mentioned is that disinfectants and anti-foulants are other chemicals which are applied in aquaculture, and, together with nutrients, are waste which should be dealt with so as not to disturb the surrounding environment (Dauda et al. 2018). Furthermore, by-products and intermediates should be considered during the technology testing step, due to the confirmation of their presence in several studies (Kanakaraju et al. 2018).

Landfills

The leachates of municipal landfills are sources of a cocktail of chemicals, such as new emerging pollutants (a list of some of them can be found in Eggen et al. 2010; Qi et al.

2018)). Medicines disposed of in the garbage and in bins are distributed to landfills mostly in the packaging in which they were supplied. A study performed in the USA showed that the mean concentration of pharmaceuticals in solid municipal waste is 8.1 mg/kg (Musson and Townsend 2009). During this storage, the packaging can become opened, and the active compound, if still present, can leak with rain water to the landfill depth (Musson and Townsend 2009). Exemplary pharmaceuticals and their concentrations are presented in the reports, and their concentration levels are similar to raw and treated municipal wastewater (Clarke et al. 2015; Lu et al. 2016). Pollution of the groundwater caused by landfills has been reported (Samadder et al. 2017; Branchet et al. 2019). The detected concentrations of some pharmaceuticals are so high that they have created a real risk of the quality of groundwater (Peng et al. 2014). What is alarming is that antibiotics and antibiotic resistance genes are also detected in such leachates (Chung et al. 2018; You et al. 2018; Zhao et al. 2018).

There are possibilities for the treatment of such wastewater (as described in Bolyard and Reinhart 2016; Bakraouy et al. 2017)), and in terms of standard regulated parameters they are effective. This exemplary treatment includes mixing with municipal wastewater, recycling, anaerobic and aerobic systems, coagulation/flocculation and sorption on carbon materials (Costa et al. 2019). There are technologies for groundwater treatment by advanced processes (Qi et al. 2018; Li et al. 2019c), but they are expensive and rarely used for pharmaceuticals, or can have low efficiency (Lu et al. 2016). There is an idea to implement treatment by constructed wetlands, but the efficiency of the removal of pharmaceuticals is not total for each compound (Yi et al. 2017). On the one hand, with more restrictive regulations and higher numbers of new landfills with good groundwater protection technology, the leachates from wastewater will be reduced. On the other, the already existing landfills will have more leakage because of the aging of geo-membranes, and such aging increases the risk of the deterioration of

Table 4 The exemplary technologies for the treatment of aquaculture wastewater

Type of aquaculture	Applied technology of treatment	Effect	References
Recirculating aquaculture systems (RAS), 10–20% daily water removal, American eels	UV and UV/H ₂ O ₂	Natural removal of estrogens to the detection limits	(Bennett et al. 2018)
Flow-through System—laboratory scale	ZVI-activated persulfate	Removal of 68% of sulfadimethoxine from filtered and 74% from unfiltered discharge water	(Chokejaroenrat et al. 2019)
Groundwater in a tank with an effective volume and hydraulic retention time of 200 L and 17.7 min, <i>Plecoglossus altivelis</i> fish	Adsorption and photo-degradation on zeolite/TiO ₂ composites	Total decomposition of sulfamonomethoxine	(Nomura et al. 2017)
Through-flow system, laboratory study	Constructed wetland (<i>Phragmites australis</i>)	> 87% removal of antibiotics and other micropollutants	(Gorito et al. 2018)

groundwater quality, and creates a problem for the future (Xu et al. 2018). Thereby, the most effective action is the prevention of the disposal of pharmaceuticals to landfills.

Wastewater treatment plants

The presence of pharmaceuticals in municipal wastewater may be attributed to several factors. First of all, the application of pharmaceuticals via oral, inhalation or epidermal routes and their incomplete metabolism in the human body results in a discharge into household wastewater. The rate of metabolism of pharmaceuticals depends on their type, the method of application and the patient (age, condition, applied dose, etc.), and ranges from 0 to 100%. The metabolism of pharmaceuticals is not equivalent to their degradation. In some cases, the native compound is only converted into polar conjugates to be easily removed by urine. Dermatological medicines are applied in high excess, and the active compound is not totally transmitted through the skin. Therefore, they are flushed into wastewater without a metabolic pathway. Due to the large population, household wastewater can be treated as a dispersive, continuous source. The concentration of a single compound from one house may be below the detection limit. Nevertheless, bearing in mind

that a certain percentage of the population takes medicines every day, human daily life is one of the most important sources of pharmaceuticals in wastewater. Up to 2020, 350 000 chemicals and mixtures of chemicals have been registered for production and use (Wang et al. 2020); thereby, a mixture of pharmaceuticals together with other pollutants is present in the wastewater, with an unrecognized toxic potential (Sigurnjak Bureš et al. 2021).

Generally, lipophilic compounds are more easily eliminated in WWTPs compared to hydrophilic compounds because of the sorption process on activated sludge. Nevertheless, the polar fraction of wastewater should be eliminated as well, as it has a toxic and eco-toxic potential (Hrubik et al. 2016). There are plenty of new technologies for treatment, presented in the literature, focused on pharmaceutical elimination (Patel et al. 2019). Some of them aim to eliminate both antibiotics and antibiotic resistance genes (for example, by membrane bioreactor systems (Le et al. 2018)). What is evident is that most new technologies were tested on the lab scale or pilot scale. The exemplary technologies used for pharmaceutical removal from wastewater streams can be found in the reviews (Ahmed et al. 2015; Jung et al. 2015; Zepon Tarpani and Azapagic 2018; Kümmerer et al.

Table 5 General problems with the implementation of new technologies in wastewater treatment plants (WWTPs), based on (Kümmerer 2009; Zepon Tarpani and Azapagic 2018; Kümmerer et al. 2019), with own comments and impressions

Concern	Needed actions and possible solutions
Effectiveness can differ from compound to compound, and tests are performed for a limited number of pharmaceuticals. While pharmaceuticals can enter the environment in various forms (Kümmerer 2008), they differ regarding polarity and other chemical characteristics; the question is if the new technologies will be effective for each representative. There is no technology which can eliminate all compounds	Before the implementation of new technologies, advanced research needs to be performed, aimed at verifying the co-elimination of organic carbon, trace contaminants of broad chemical characteristics, nutrients, pathogens and genes. The degradation and toxicity of products need to be evaluated. The deconjugation of metabolic products also needs to be evaluated. A sequential treatment can be applied
The presence of degradation products is often not tested; however, some of them can have a higher toxic effect compared to native pharmaceuticals (Majumder et al. 2019)	
The number of new chemicals, not only pharmaceuticals, is increasing; thereby, today's new technologies could be ineffective toward compounds of the future	New technologies need to have a flexibility toward modification and development
The increase in the cost would be significant, as well as the energy cost (together with the increase in greenhouse gases) (Jones et al. 2007). From the technological point of view—a longer retention time will bring a high operational cost with low benefits	WWTPs could have their own power source (for example, bio-gas from fermentation); the reclaimed water and treated sludge can be valuable products on the market. The environmental benefits can be calculated in money terms, and WWTPs can be subsidized more by public money
Resistance genes could be retained on bio-reactors	Currently, no data have been obtained to prove this. There is a need for advanced research. Methods to reduce the propagation of resistance genes in wastewaters have been developed (Pazda et al. 2019)
Low-income countries could have a long time span for the introduction of new technologies	International funding and cooperation is needed in this field. New technologies need to be optimized with regard to operation costs, and ideally—to be self-sufficient
The ecotoxicity potential generated by the treatments themselves being higher than the ecotoxicity potential of the pharmaceuticals being treated	The adaptation of processes to needs, choosing from many available. Green approaches are also available (Azimi and Pendashteh 2016)

2019); thereby, we have not presented all the technologies in this review.

There are general doubts among experts about the use of new technologies for the treatment of wastewaters (Table 5). One of the main concerns is the cost of the implementation of new technologies. A critical analysis of the cost of two advanced systems: 1. sand filters + ozone + granulated activated carbon, and 2. sand filters + membrane filtration + reverse osmosis, is presented in (Jones et al. 2007). This analysis shows that the total cost of a new system is economically and environmentally undesirable, because of the high energy consumption and CO₂ emissions. What was highlighted is that an already existing solution, like the coupling of nitrification + de-nitrification + biological phosphorus removal, can be a great possibility for the removal of endocrine disruptors and pharmaceuticals (with an annotation that the presence of transformation products was not investigated). In summary, the author questioned the use of advanced treatment techniques. A similar point of view was presented in another study (Wenzel et al. 2008). An analysis of the life cycle of advanced wastewater treatment techniques for the removal of pharmaceuticals also shows that often the use of advanced treatment techniques is not recommended, because of the production of the toxicity of the product and the negative impact on climate (Zepon Tarpani and Azapagic 2018). These are general disadvantages of downstream actions—increased cost and the presence of by-products. Nevertheless, the only a slight cost increase is expected, if integrated the removal of micropollutants in a long-term strategy (Eggen et al. 2014). Despite high cost of new technology implementation and operation, in UE several countries are initiate this process (EurEau 2019). For example, the Switzerland has begun in 2016 implementing plan on investing in improvements to cut the release of micropollutants to the aquatic environment from its sewage treatment plants using ozonation process in 100 of 700 existing Swiss WWTPs (Bourgin et al. 2018).

End-of-pipe solutions (namely—the reduction in the concentration of contaminants in the place where they are produced) seem to be encouraged in the case of pharmaceuticals (Kümmerer 2018). Nevertheless, advanced treatment processes are not compatible with sustainable development because they focus on end-of-pipe solutions linked to the abovementioned problems of the presence of transformation products (Leder et al. 2015). Bearing in mind that even if advanced treatment techniques were implemented, some content of pharmaceuticals would finally end up in surface, ground and drinking water, a better solution is to work on the “beginning of the pipe.” The results clearly show the advantage of prevention at the input and integrated emission management compared to the implementation of advanced treatment techniques for micropollutants generally (Kümmerer et al. 2019).

Accidental and intentional introduction of untreated wastewater

The last source, which is immeasurable and has not been estimated so far, is the intentional or accidental introduction of untreated wastewater. The Combined Sewer System Overflow is a source of substantial anthropogenic pollution (Dittmer et al. 2020), such as frequently found pharmaceuticals (Kay et al. 2017). While the overflow frequency is hard to predict, the untreated wastewater in such systems is introduced to the natural water receiver intentionally. Furthermore, accidents and damage to WWTP systems also occur. For example, in August 2019, in Warsaw, the sewage collector of the WWTP malfunctioned, and over 3.6 million m³ of untreated wastewaters was introduced directly into the Vistula River (Stepnowski et al. 2020). In this streams of wastewater, several pharmaceuticals were detected in concentrations of dozen µg/L. Furthermore, there are still undeclared installations and intended leaks in installations. In low-income countries, the lack of wastewater treatment causes as high a concentration of pharmaceuticals in rivers as in untreated wastewater in high-income countries (for example, carbamazepine, selected antibiotics and NSAIDs ranged up to 1900 ng/L in the Ahar River in India (Williams et al. 2019)). Until today, no accidents have been reported in the manufacturing of pharmaceuticals causing a catastrophe in the natural environment. Ways to avoid this source of pollution include primary the investment in the modernization of the sewage system, connecting all houses to sewage systems, and monitoring and connecting the stormwater sewage system to the municipal sewage system. Furthermore, there is need for looking for illegal dumps of wastewater, external controls in pharmaceutical plants, and the improvement in permit systems.

Actions prioritization

The prioritization of actions would be helpful for problem management, but it is hard to perform. Some insights presented in 2006 give an expert analysis of critical points in the management of the pharmaceutical problem (Doerr-MacEwen and Haight 2006). Group of 27 experts from university, government and industry fields were asked in interviews (open-ended and closed-ended questions) for their opinions concerning the effectiveness and feasibility of several actions: advanced treatment, educating medical professionals to reduce prescription rates, pharmaceutical-return programs, requiring all municipalities to have secondary or better WWTPs, separate treatment of hospital wastewater, optimization of existing WWTPs, incentives

for the manufacturing of green pharmaceuticals, and risk assessment regulations. Concerning effectiveness, advanced treatment was the best option (the highest ranking score), but at the same time, the experts had the opinion that this would be hard to implement. The only low score was noted for “incentives for green drug manufacturing.” After several year of research, it seems to be necessary to repeat this prioritization.

Figure 2 summarizes the types of action presented in this review in the form of a pyramid of needs. Exemplary actions were referred to. The pyramid was used in order show which action gives long-term effects with benefits both for humans and the environment (lower-lying boxes). The structure of this pyramid can be adjusted to specific pharmaceuticals. As highlighted, it is possible to work before the pharmaceutical life cycle starts—by increasing the health status/wellness of humans (working in the downstream of health) and the quality of the environment (here, also combating climate change should be added). The actions preventing the diseases, such as healthy lifestyle and early diagnosis, have measurable benefits for society and lower the cost of health-care (Chung et al. 2020; de Boer et al. 2020; Laroche et al. 2020). The cost of actions is hard to determine, as well as the environmental profits, but generally, working in the downstream of the life cycle is connected with higher costs. In previous sections, the actions of mitigation were presented, mostly related to “hard” management. What is lacking, and is intuitive, is the need for education and information. The actions proposed in this review do not guarantee a solution to the problem in a short period, and the effects will not be

easy to observe. Nevertheless, the good example of lowering the phenazone level in the groundwater in Germany, thanks to the preventative action taken, can be a motivation (Reddersen and Heberer 2002). The specific group of pharmaceuticals needed subjective treatment, and the minimalization action needs to be adjusted to current local conditions. The starting point should be modeling of the loads and transport dynamic to estimate the main sources and hotspots of pollution, starting with global scale (Vermeulen et al. 2019), following regions (Björlenius et al. 2018) to specific catchment (Vezzaro et al. 2014).

As was mentioned in introduction, the primary action should be to increase human and animal wellness, as the base of the pyramid of needs presented in Fig. 2. It is highlighted by experts in different fields that working upstream of the pharmaceutical life cycle and the benign-by-design concept are desired in both veterinary and human medicine. Several actions in this stage are connected with benefits for humans, as they increase safety in the use of medication. Advanced treatment technologies, a solution with short-term effects, should be implemented whenever other options are impossible.

Conclusions

In summary, this review presents an impressive number of actions in different fields of pharmaceuticals life cycles. One of the bargaining chips to take action is the argument that the minimalization of the level of pharmaceuticals in the

Fig. 2 Pyramid of needs presenting actions which can be performed to minimize the presence of pharmaceuticals in the environment, with benefits for human wellness

environment will benefit human life. Namely, it will increase the safety of pharmaceutical use, lower the cost of pharmaceuticals, lower the number of interactions between pharmaceuticals and allergy syndromes, increase the efficiency of treatment and lower the level of pharmaceutical residues in food. The logical consequence of the equality for humans and the environment of the effect of actions is connected with mutually inseparable dependencies within the concept of environmental health (Daughton 2003; Daughton and Ruhoy 2011). Working on the upstream of the pharmaceutical life cycle will reduce the impact not only from the native compounds, but also from the metabolites and transformation products created during advanced treatment.

This wide range of actions for the minimalization of pharmaceuticals should be taken in parallel by various players, globally and at different organization levels: scientific institutions, governments, non-governmental organizations, manufacturers, industry and households. Optimistically, after the literature review of 1990–2018, it is visible that there are rising concerns regarding the pharmaceutical contamination of the environment, as well as efforts of remediation (Patel et al. 2019).

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