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Antipsychotics as environmental pollutants: An underrated threat?

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ABSTRACT

The heterogeneous class of what we nowadays call antipsychotics was born almost 70 years ago with the serendipitous discovery of chlorpromazine. Their utilization is constantly growing because they are used to treat a diverse group of diseases and patients across all age groups: schizophrenia, bipolar disease, depression, autism, attention deficit hyperactivity disorder, behavioural and psychological symptoms in dementia, among others. They possess a complex pharmacological profile, acting on multiple receptors: dopaminergic, serotoninergic, histaminergic, adrenergic, and cholinergic, leading scientists to call them "agents with rich pharmacology" or "dirty drugs". Serotonin, dopamine, acetylcholine, noradrenaline, histamine and their respective receptors are evolutionary ancient compounds, and as such, are found in many different living beings in the environment.

Antipsychotics, do not disappear once excreted by patient's urine or faeces and are transported to wastewater treatment plants. But as these plant´s technology is not designed to eliminate drugs and their metabolites, a variable proportion of the administered dose ends up in the environment, where they have been found in almost every matrix: municipal wastewater, hospital sewage, rivers, lakes, sea and even drinking water.

We believe that reported concentrations found in the environment might be high enough to exert significant effect to aquatic wildlife. Besides, recent studies suggest antipsychotics, among others, are very likely bioaccumulating through the web food. Crucially, psychotropics may provoke behavioural changes affecting populations' dynamics at lower concentrations.

We believe that so far, antipsychotics have not received the attention they deserve with regards to drug pollution, and that their role as environmental pollutants has been underrated.

KEYWORDS

Antipsychotics, pharmaceuticals in the environment, drug pollution, environmental risk assessment

1. Introduction

Most of health care professionals probably remember the ADME scheme learnt in University times while studying pharmacy, nursing or medicine (Figure 1). Drugs were administered through different routes, absorbed, distributed within the organism, metabolized and then excreted outside. And that's it. In this anthropocentric figure, once excreted, little attention was paid to drugs and metabolites.

-Insert figure 1-

Of course, drugs do not disappear once excreted outside our bodies. In fact, they can provoke important environmental damage, an issue which has been widely studied by environmentalists, chemists and biologists. For example, between 2000 and 2003, an unusual increase in the mortality of specimens of a vulture species was observed in Pakistan, dramatically decreasing the population and placing it on the list of endangered animals. The cause of death was surprising: the non-steroidal anti-inflammatory drug diclofenac. It was proven that the vultures, feeding on the carcasses of cattle previously treated with this drug, died from acute kidney failure. This was the first documented case of an ecological disaster due to drug contamination (Oaks et al., 2004). Another well-known example is the feminization of fishes produced by ethinylestradiol which has the potential to wipe-out complete fish populations (Kidd et al., 2007). Drug pollution is a key element of the concept of "One Health", which recognises the interconnection of interconnection between people, drugs, animals, plants, and their shared environment (Destoumieux-Garzón et al., 2018; Orive & Lertxundi, 2020).

Despite generally neglected or ignored by healthcare professionals, concern about potential deleterious effects of drugs in the environment is growing fast (European Commission, 2019). In fact, pharmaceuticals are probably the most relevant group of substances among

contaminants of emerging concern. Drug pollution is a complicated and diffuse problem, and as such, has been catalogued as a 'wicked problem' by the Dutch authorities (DUTCH TASK FORCE, 2019). But any feasible solution will need the participation of all involved stakeholders. Eco-sustainable or green prescribing was already proposed by Christian Daughton, former director of the American Environmental Agency (Daughton 2014). Nevertheless, in order to make any impact, increasing awareness in healthcare professionals is going to be absolutely necessary. Issues considering drug pollution must be included in schools of Pharmacy and Medicine worldwide (Lertxundi et al., 2020a).

We believe drug pollution may have a major impact on our daily practice in a way we, as healthcare professionals, are just starting to glimpse. Some patients may start feeling guilty about taking certain psychotropic drugs, when they hear about the consequences of their excreta in the environment. Patient's reluctance increasing towards certain drugs could even have a negative impact on drug adherence (Lertxundi et al., 2020c).

In this paper, we will focus on the potential role of antipsychotics as environmental pollutants. We believe this therapeutic class has, undeservedly, received less attention than other psychiatric drugs like antidepressants and anxiolytics from researchers devoted to the consequences of medicines in the environment. For example, the Dutch Government specifically mentions antidepressants among psychotropics, but does not tell anything about antipsychotics in their interesting "Chain approach to reduce pharmaceuticals residuals in water"(DUTCH TASK FORCE, 2019). The article of Ford & Herrera: "'Prescribing' psychotropic medication to our rivers and estuaries", does not mention this therapeutic class at all (Ford & Herrera, 2019). Even papers reviewing the presence of "psychiatric drugs" in the environment omit antipsychotics (Calisto & Esteves, 2009). The objective is to incorporate our perspective as healthcare professionals and academics, focusing on the complex pharmacology of this therapeutic group, reviewing their maximum concentrations in the most relevant

environmental matrices and collecting relevant ecotoxicological studies, in order to increase awareness about their environmental deleterious effects.

2. Antipsychotics: "Dirty" drugs, or agents with rich pharmacology?

The introduction of chlorpromazine in France in 1952 has traditionally been considered as the starting point of psychopharmacology (Medrano 2015). The "tranquilization" effects of this phenothiazine drug were serendipitously discovered by a French Navy anaesthesiologist, Henri Laborit, which had already been trying chlorpromazine's predecessor, promethazine, as a sedative. He communicated his findings to colleague psychiatrists working in Paris, encouraging them to try the new product in patients. In January 1952, it was administered to a patient with psychotic mania, obtaining a marked improvement (Shen, 1999).

The unprecedented clinical success of chlorpromazine encouraged the search for other similar drugs. Modifications introduced in the prototypical chemical structure generated an important amount of phenotiazinic "*me-toos*".

Chlorpromazine has been used in a range of doses in very different conditions, both psychiatric and somatic, showing remarkable versatility. This characteristic is well reflected in chlorpromazine´s trademark in France (Largactil®: large action). Later, the arrival of clozapine led to the emerging concept of "atypical" antipsychotic drugs. These are far less likely to cause extrapyramidal side effects than first generation drugs, but are known to cause weight gain, metabolic problems, and sexual side effects, among others.

Whether you consider these pharmaceuticals "dirty" drugs (Medrano 2015) or "magic shotguns with enriched pharmacology" (Roth et al., 2004), the truth is that the heterogeneous drug class we call antipsychotics (King & Voruganti 2002) are anything but selective substances acting on a unique receptor. A quick look to any of the abundant tables detailing their relative receptor affinity reveals their complex pharmacological profile: they can bound to multiple dopaminergic, serotoninergic, histaminergic, adrenergic and cholinergic receptors.

Nowadays, antipsychotic utilization, (especially atypicals) is on the rise (Hálfdánarson et al.,

2017), because they are used to treat a plethora of different diseases and patients across all age groups: schizophrenia, bipolar disease, depression, autism, attention deficit hyperactivity disorder, behavioural and psychological symptoms in dementia, etc. (Birnbaum et al., 2013, Rhee et al., 2018, Kuroda et al., 2019).

Besides, some phenotiazinic antipsychotics are also used in the increasing number of companion animals. In concrete, to treat canine and feline behaviour management (Hammerle et al., 2015).

Almost 70 years after its discovery, chlorpromazine's properties continue to marvel. A French team from Sainte-Anne hospital, Paris, precisely one of the first places ever to administer an antipsychotic to a patient, will test the hypothesis that chlorpromazine could not only decrease the unfavourable evolution of COVID-19, but also reduce the contagiousness of SARS-CoV-2 (Plaze et al., 2020).

Chlorpromazine kills virus? Yes. And many more things.

3. Bacteria have acetylcholine, plants serotonin

Normally, healthcare professionals working in the field psychiatry don't pay much attention to the phylogenetic origins of dopamine or serotonin, even if they are present in every conversation about antipsychotic psychopharmacology. But the truth is that these substances are not something that appeared in humans for the first time, neither even in mammals. In fact, biogenic monoamines are found in embryos of both vertebrates and invertebrates, including amphibians, fish, insects and echinoderms (Bauknecht & Jekely 2017, Turlejski 1996). These substances are so evolutionarily ancient that they are even found in organisms outside the animal kingdom. For example, acetylcholine is present in fungi and bacteria (Horiuchi et al., 2003) and serotonin in plants (Mukherjee 2018).

It seems biogenic amines first started regulating intracellular cell activity, then acting like hormones (Csaba 2015). Later in evolution, they incorporated neurotransmitter function by acting on specific receptors in the nervous system. So, it shouldn´t be a surprise to discover that serotonin, dopamine, acetylcholine, noradrenaline, histamine and their respective receptors are widely found in many different living beings. Think about the novel tank test, which is used as a sensitive and efficient behavioural assay in basic psychopharmacology studies, which does not longer use mammals (rodents), but fish. The use of zebrafish (*Danio rerio*) is becoming increasingly popular, because anxiety-like behaviour can be bi-directionally modulated by drugs affecting the GABA, monoaminergic, cholinergic, glutamatergic and opioid systems (Stewart et al., 2011).

Anyway, reviewing phylogenetic trees of all these receptors is out of the scope of this review. Of course, these drugs were developed with humans in mind, and may not interact in the same way with other receptors present in other living beings (Osuna-Luque et al., 2018). Besides, we have to keep in mind that, despite their pivotal physiologic role, the evolution of the some of these receptors has not been completely resolved to date (Pedersen et al., 2018).

4. 'Prescribing' psychotropic medication to our environment. Drug pollution with antipsychotics

Drugs, including antipsychotics, don't disappear once excreted by patient's urine or faeces, but they are transported to wastewater treatment plants. But as these plant´s technology is not designed to eliminate drugs and their metabolites, a variable proportion of the administered dose ends up in the environment. Besides, this is what is happening on the best scenarios, as globally, it is likely that over 80% of the world's wastewater is released to the environment without adequate treatment (UNESCO, 2017).

Increasing preoccupation about the deleterious consequences of pharmaceuticals in the environment has driven the European Union to publish a Strategic Approach (European Commission 2019). Along with other drug groups such as antibiotics, psychiatric drugs have received particular attention because of their widespread use and their potential impacts on many living beings due to their effects on phylogenetically highly conserved neuroendocrine systems (Ford & Herrera, 2019). In fact, the chain approach proposed by the Dutch authorities incorporates a specific "psychotropic task force" with the aim of reducing psychotropic drugs in water (DUTCH TASK FORCE, 2019).

But even antipsychotics have the potential to pose an important threat to the environment (Reichert et al., 2019), so far, antidepressants have received preferential attention among drugs acting on the central nervous system.

A study carried out in 16 countries worldwide analysed the trends in antipsychotic from 2005 to 2014. They showed that the overall prevalence of antipsychotic use increased in 10 of the 16 studied countries, and that atypical antipsychotic use increased in all populations. The pattern and prevalence varied markedly between countries. The overall prevalence use was highest for Taiwan (78.2/1000 persons) and lowest in Colombia (3.2/1000 persons). In 2014, the drug used most frequently by most countries across all age groups was quetiapine, followed by risperidone and olanzapine (Hálfdánarson et al., 2017).

Notwithstanding, literature showing the presence of antipsychotics in the environment is abundant. To find out the highest ever concentrations of antipsychotics measured in different environmental matrices, we used two sources of information: The first one is the Pharmaceutical Database published by the German Environment Agency – Umweltbundesamt (UBA, 2019). The second one is a review published by Cristian Daughton (Daughton & Scudery, 2016). As both sources identify the original reference, this was analysed for confirmation. Nevertheless, despite all the efforts made to capture all relevant data, some published data

may be still missing, considering the very large body of published literature and inconsistencies in classification of pharmaceuticals. Antipsychotics included were those pertaining to the N05A group of the ATC classification system, excluding lithium (ATC classification). In the UBA database, antipsychotics were sometimes classified as “psychiatric medication”, “neuroleptics” or as “antipsychotic drug”. In the case of aripiprazole, it is incorrectly classified as an “antiepileptic drugs”. So a manual search was need to extract all relevant data.

As can be seen in the following table, (table 1), antipsychotics have been found in almost every environmental matrix: municipal wastewater, hospital sewage, rivers, lakes, sea and even drinking water. Even considering antipsychotics have been used since 1952 and the exponential growth in research in the field of drug pollution since the late 1990s, the first report of the presence of an antipsychotic in the environment did not come until 2007, in Japan (Nakada et al., 2007). The highest ever concentration for any antipsychotic in the environment was 8.24 mg/l, for clozapine, measured in a psychiatric hospital´s wastewater in Germany (Bähr, 2009). Since progressive dilution occurs across different matrices highest concentrations are found in hospital sewage. The majority of the cited studies were conducted in Europe.

-Insert table 1-

4.1 About laboratory tools and the method used to measure drug concentrations in environmental matrices

Complex analytical methods need to be employed for quantification of the low concentration of pharmaceuticals (down to ng/L) in water, i.e: High-Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS). Cross-comparison between different datasets obtained via various methodologies can result problematic, complicating accurate and reliable interpretations of existing data. Key issues include different sample collection protocols, analytical techniques and statistical/quantitative interpretations and use of quality-control

samples throughout collection and analysis. Approaches employing the use of a miniaturised sampling and shipping with a validated direct-injection HPLC-MS/MS may help. For example, in the study carried out by Wilkinson et al, one laboratory in the UK analysed the samples taken from all over the world making them extremely comparable (Wilkinson et al., 2019).

5. Environmental risk assessment of antipsychotics

As detailed in the previous section, significant amounts of atypical and typical antipsychotics have been detected in rivers, lakes, sea water and even drinking water. For active pharmaceutical ingredients, the potential environmental risk is calculated from the ratio between the predicted environmental concentration (PEC) of the substance in the aquatic environment based on a conservative emission scenario (or even better, measured concentration) and the predicted no effect concentration (PNEC), a concentration below which no toxic effects are expected. This ratio is known as the risk coefficient. However, it should be noticed that interaction between antipsychotics (including metabolites) and biotic and abiotic factors like radiation may lead to formation of potentially more toxic intermediates in the environment, which complicates precise risk assessments (Trawiński & Skibiński, 2017).

The main three attributes of pharmaceuticals that determine their environmental risk are persistence, the potential to bioaccumulate and toxicity (PBT). Some drugs rapidly disappear in the environment, while others are resistant to degradation. For example, the benzodiazepine oxacepam persists without biodegradation in the bottom of lakes for decades (Klaminder et al., 2015). Still, one critical factor has to be considered. Aquatic organisms may accumulate water-borne chemicals. Besides, antipsychotics may concentrate even more as they move from one trophic level to the next. The third attribute relates to the substance's inherent toxicity profile.

Apart from, PBT properties, volume of consumption is of enormous importance to determine the environmental risk of an active ingredient. So the increase in antipsychotic use over the last decades needs also to be taken into account.

5.1. Ecotoxicity

Assuming this knowledge, one interesting question arises. Are reported antipsychotic concentrations in the environment high enough to exert significant effect to aquatic wildlife? The recently study published work by Reichert et al (Reichert et al., 2019) showed that risperidone, clozapine and chlorpromazine concentrations on hospital wastewater were well above PNEC. The risk coefficient was >600 for all of them. However, environmental risk assessment is not conducted with hospital wastewater but with surface water, where the concentrations are much lower. Besides, environmental risk assessment is not conducted with hospital wastewater but with surface water, where the concentrations of pharmaceuticals (including antipsychotics) are much lower. PNEC values used by Reichert et al were obtained from the work published by Orias & Perrodin. These authors, reviewed the ecotoxicity of hospital effluents (Orias & Perrodin, 2013) without performing any testing of toxic effects of drugs, but using older PNEC related to acute aquatic toxicity classification instead (Sanderson et al., 2003). But data required in proper ERAs of pharmaceuticals (long-term tests needed for all three trophic levels, i.e. fish, daphnia, algae) cannot be replaced by acute toxicity or modelling data.

Although vastly diluted, pharmaceuticals may invoke widespread environmental impacts as they are designed to trigger major biological effects at extremely low concentrations. Crucially, psychotropic may provoke behavioural changes affecting populations' dynamics at lower concentrations than PNEC, and this indirect effects are still not considered in the ERA of these drugs, as stated in the EMA guideline draft: *"Behaviour is an example of an ecotoxicological endpoint not yet established as a reliable and standardised endpoint. It may however be very*

relevant for neuroactive substances and when standardised guidelines become available, be taken up in a tailored risk assessment scheme for neuro-active substances" (ERA Draft, 2019).

Even more worryingly, a study with risperidone in zebrafish showed that some of these behavioural changes were seen during the entire life of the animal and passed to subsequent generations. In concrete, zebrafish exposed to risperidone during embryonic and larval stages presented impaired anti-predatory behaviour during adulthood. So, even short exposures to environmentally relevant concentrations, at crucial stages of development, can persist throughout the whole life of the fish, including its offspring (Kalichak et al., 2019).

Antipsychotics are administered to patients, are excreted reaching wastewater treatment plants, and are subsequently incorporated into the aquatic environmental matrices. Later, they can be bioconcentrated and bioaccumulated through the food web. In table 2, the PBT score for each drug obtained from the Swedish environmental classification of pharmaceuticals (The Swedish classification) can be consulted. Drugs in this classification receive a score ranging from 0 to 3 points for each of the three aforementioned characteristics (persistence, bioaccumulation, toxicity). PBT global score is then obtained. Information for many drugs is lacking. A study published by scientists from the University of Umeå, Sweden, predicted which water concentrations would elevate the plasma concentration in exposed fish to a level equal to the human therapeutic plasma concentration (CEC), Table 2. For some antipsychotic drugs (risperidone, haloperidol, clozapine) concentrations found in rivers are capable of producing very elevated concentrations in fish's plasma (Fick et al., 2011).

-Insert table 2-

Nowadays, it´s mandatory for the marketing authorization holders to send a dossier including an environmental risk assessment (ERA) to the European Medicines Agency (EMA) for the marketing authorization of o a new human medicine. This ERA is based on the expected use of the product and the physicochemical, ecotoxicological, and fate properties of its active

substance (degradation, persistence). However, this ERA only became mandatory in 2005, so environmental risk assessments for older drugs may not exist. Besides, even if an important environmental risk is expected with a certain drug, in any event this impact should constitute a criterion for refusal of a marketing authorization. So far, the EMA doesn't publish complete ERAs, and finding information about the environmental consequences for a certain active substance is challenging, as the ERA dossier should be updated if there is an anticipated increase in the environmental exposure, e.g. a new indication which results in an increase in the extent of the use.

As can be consulted in table 2, according to available ERAs, an environmental risk is not expected for antipsychotics except for asenapine. This drug was shown to be not ready biodegradable and the aerobic and anareobic transformation study in aquatic sediment systems (OECD 308) demonstrated significant binding (> 10 % after or at 14 days) of asenapine to the sediment. In addition, endocrine disrupting effects were also observed for asenapine in mammals and reproductive effects on aquatic species could not be excluded. The EMA was of opinion that the applicant should conduct further studies and a search for potential endocrine disrupting effects.

Nevertheless, the majority of antipsychotics lack a proper environmental risk assessment. Potential consequences of antipsychotics in different organisms was obtained from the WikiPharma database (WIKIPHARMA).

5.2 Bioaccumulation

Besides, caution is needed when comparing environmental concentrations with in-vitro toxicity tests, since drugs can bioaccumulate. Information about available evidence of bioconcentration or bioaccumulation and measured ecotoxicological effects is also detailed. In this sense, recent studies suggest drugs are very likely bioaccumulating through the web food. For example, Platypus´s and trouts were bioaccumulating 66 of the 80 measured drugs of

different therapeutic classes including antipsychotics in Australian waters through their insectivorous diet. Strikingly, the researchers estimated that in the case of antidepressants they were taking as much as half of daily human dose (Richmond et al., 2018). For example, clozapine, who has a 3 point score (the highest) for bioaccumulation in the FASS classification, was shown to bioconcentrate in 2 fresh water fishes, in tissues relevant to pharmacological targets in mammals (brain) (Nallani et al., 2016). In another study carried out in a Czech Republic´s river, levomepromazine and haloperidol were found in brown trout´s tissues. The organs with highest presence of these pharmaceuticals were the liver and kidney. As these compounds were not found in grab water, bioaccumulation through the food-web seems the best explanation. (Grabicova et al., 2017).

A recent work studied the presence of 94 pharmaceuticals pertaining to 23 different drug classes in blood plasma of wild European fish. Three of the four drugs that showed a moderate or a high risk of inducing toxic effects on fish were antipsychotics: i.e: risperidone, flupentixol and haloperidol (Ceverny et al., 2020). Another study carried out in Croatia has also shown that haloperidol, among many other pharmaceuticals, is bioaccumulating in wildfish (Malev et al., 2020). On the contrary, a review of the pharmaceutical exposome in aquatic fauna (fish and invertebrates) showed that so far, published literature has mainly focused to antibiotics and antidepressants (Miller et al., 2018).

The structure of the ERAs sent to healthcare authorities by the marketing authorization holders is now being reviewed to include aspects of bioconcentration/bioaccumulation and all designated indications for the product in drugs which can be used for more than one indication for the calculation of the expected environmental concentrations (ERA draft 2019).

Apart from acting on neurotransmitter´s receptors, several antipsychotics, especially phenothiazines, possess antimicrobial activity (Nehme et al., 2018). A study published in Nature in 2018 tested >1000 marketed drugs (representing all human therapeutic classes)

against 40 representative gut bacterial strains. Among the drugs that inhibited the growth of at least one strain, antipsychotics were overrepresented (Maier et al., 2018). In fact, some phenothiazines have been suggested for the treatment of antibiotic resistant bacterial strains (Amaral et al., 2004). Nevertheless, whether this activity has an impact on ecosystem balance, apparition of resistant strains, or alteration of the gut microbiome remains to be elucidated. It seems that some of the antimicrobial activity occurs at concentrations in the mg/l range.

Besides, many antipsychotics, especially fluphenazine, inhibit cultured protozoan Toxoplasma gondii parasites (with concentrations in the mcg/l range), a finding that supports the potential role of this unicellular organism in the pathogeny of schizophrenia (Flegr, 2015). In addition, this first-generation antipsychotic has also shown activity against the Leishmania parasite (Neville et al., 2015). Chlorpromazine also has antimalarial properties, since it shows activity against the Plasmodium protozoan (Amaral et al., 2004). This should not be a surprise, since already in 1891, Paul Ehrlich observed the antimalarial effects of methylene-blue, a phenothiazine derivative (Shen 1999). Moreover, phenothiazines, and chlorpromazine in particular has also shown to inhibit the formation of disease-causing prionic isoforms at the mg/l range (Korth et al., 2001).

Moreover, chlorpromazine has shown antiviral activity against a wide arrange of virus: flu, HIV, virus JC, herpes virus etc (Amaral et al., 2004). Interestingly, independent studies revealed that chlorpromazine is an anti-MERS-CoV and an anti-SARS-CoV-1 drug. Based on these findings, a French team will test the hypothesis that chlorpromazine could decrease not only the unfavourable evolution of COVID-19, but also reduce the contagiousness of SARS-CoV-2. It seems antiviral activity depends on the inhibition of clathrin-mediated endocytosis (Plaze et al., 2020).

6. Possible solutions

Possible interventions to improve antipsychotic drug pollution could be implemented across the complex pharmaceutical life cycle. Healthcare professionals ought to be encouraged to use these drugs more rationally, not only to improve patient´s health, but to indirectly help ecosystems (DUTCH TASK FORCE 2019, Lertxundi et al., 2020b). Initiatives like the Swedish "wise list" (*Kloka Listan*), in which a multifaceted approach incorporates environmental aspects to recommend drugs in ambulatory care, should be further explored (Gustafsson et al., 2011).

Besides, source-directed measures should be complemented with complementary end of pipe measures. For example, proper disposal of unused drugs (Bungau et al., 2018) especially in countries with poorly functioning waste management schemes is going to be essential (Paut Kusturica et al., 2017). The development and implementation of sustainable advanced wastewater treatment techniques (de Oliveira et al., 2020) is also going to be important (Ginghina et al., 2020).

7. Conclusions and future outlook

Since the birth of antipsychotics almost 70 years ago, they have shown to be anything but selective drugs acting on a concrete therapeutic target. Extensive research shows that, as occurs with any other drugs, a variable proportion of the administered dose will end up in the environment. In fact, antipsychotics residues have been found in almost every environmental matrix, including tap water. Apart from their effects on the central nervous systems of humans and many living beings, they can kill bacteria, protozoans, viruses and even inhibit the formation of disease-causing prionic isoforms. Still much research is needed to clarify what is the precise ecotoxicological impact of these drugs with "rich pharmacology". We believe that so far, antipsychotics have not received the attention they deserve with regards to drug pollution. As a consequence, we should not underestimate the role of antipsychotics as environmental pollutants. So far, the problem of pharmaceuticals in the environment has been

largely ignored by healthcare professionals. But to effectively fight drug pollution, all involved stakeholders in the complex life cycle of drugs have to be considered. Promoting the rational use of drugs as a source control measure, and incorporating one health's philosophy in our daily practice in psychiatry is going to be essential to fight antipsychotic pollution.

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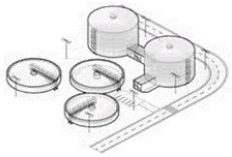
Figure 1. What happens to excreted drugs and metabolites?

Table 1. Maximum reported concentrations of antipsychotics in environmental matrices (mcg/l)



Drug	Location	Sewage hospital	WWTP influent (untreated)	WWTP effluent (treated)	River	Sea/ Ocean	Drinking Water	Groundwater	Citation
Amisulpride	Saronikus gulf, Greece					5.5			Alygizakis et al., 2016
	Switzerland				47				Moschet et al., 2015
	Germany		1.3					0.07	Bollman et al., 2016
Aripiprazole	New York State, USA		22	[illegible]					Subedi & Kannan 2015
	Suffolk County, NY, USA	2							Oliverira TS et al., 2015
Benperidole	Baden-Württtemberg, Germany	0.7		53			0.74	0.28	Bähr 2009
Chlorpromazine	Beijing, China		[illegible]99						Yuan et al., 2013
	Madrid, Spain				0.002				Fernández et al., 2010
	Santa Maria, Brazil	0.							Reichert et al., 2019
Clozapine	Baden-Württtemberg, Germany	8240		1080			18.7		Bähr 2009
	Saxony, Germany		350						Gurke et al., 2015
	Umgeni River, Durban, South Africa				8890				Matongo et al., 2015
Cyamemazine	Porto, Portugal	0.8 (treated)							Logarinho et al., 2016
Flupentix	Uppsala, Sweden		72	40					Fick et al., 2011
Fluphenazine	Madrid, Spain				45				Fernández et al., 2010
	Uppsala, Sweden		130	14					Fick et al., 2011
Haloperidol	Baden-Württtemberg,	1330		39			1.092		Bähr 2009

Drug	Location	Sewage hospital	WWTP influent (untreated)	WWTP effluent (treated)	River	Sea/ Ocean	Drinking Water	Groundwater	Citation
	Germany								
	Brazil				40				Caldas et al., 2016
	Jannsen Pharmaceuticals, Belgium			2690					Loos et al., 2013
	Uppsala, Sweden		69	39					Fick et al., 2011
	Tone river basin, Japan				45				Nakada et al., 2007
	Pacific Ocean, USA					5.6			Nödler et al., 2014
	Gottingem, Germany							0.0258	Reh et al., 2013
Levomepromazine	Stockholm, Sweden		0.041	0.003				0.31	Breitholtz et al. 2012
Melperone	Baden-Württtemberg, Germany	1910		102			0.73		Bähr 2009
	Saxony, Germany		73						Gurke et al., 2015
	Schwerte, Germany			390					Keysers et al., 2013
Olanzapine	Baden-Württtemberg, Germany	127400		73					Bähr 2009
	Coimbra, Portugal		15,3						Santos et al., 2013
Paliperidone	Santorini, Greece		11.8	6.6					Borova et al., 2014
Perazine	Baden-Württtemberg, Germany	1948000		99					Bähr 2009
Quetiapine	Saxony, Germany		11.1						Gurke et al., 2015
	New York State, USA			29.3				0.89	Subedi & Kannan 2015
	Beijing, China	4.9							Yuan et al., 2013
Risperidone	Baden-Württtemberg, Germany	1014000							Bähr 2009
	USA (DWTP-12)						0.0029		Benotti et al., 2009
	Kenya				50				K'oreje et al., 2016

Drug	Location	Sewage hospital	WWTP influent (untreated)	WWTP effluent (treated)	River	Sea/ Ocean	Drinking Water	Groundwater	Citation
	Lede, Belgium		364	15.4					Vergeynst et al., 2015
	Southern California, USA					1.4			Vidal-Dorsch et al., 2012
Ziprasidone	Beijing, China	0.004	0.004						Yuan et al., 2013
Zuclopenthixol	Baden-Württemberg, Germany	930		11					Bähr 2009

WWTP: Wastewater treatment plant

Pharmaceuticals can be metabolized in organisms or transformed in the environment that can result in less activity, different activity or high or lower toxicity. Metabolites were not considered in this study.

Table 2. Environmentally classified antipsychotics

Drug	CEC (Fick etal 2010)*	ERA (year†)	PBT (P;B;T)	Evidence of bioconcentration/ bioaccumulation	Measured ecotoxicological effects
Amisulpride	-	-	4 (3;0;1)		
Aripiprazole	1024	Not considered to be of concern. (2004)	6 (3;0;3)		• Stress response, zebrafish (Barcellos et al., 2016) • Alter touch response and pharyngeal pumping in wild-type nematodes (*Caenorhabditis elegans*) (Osuna-Luque et al., 2018) • Cardiotoxicity (Lee et al., 2013)
Asenapine	-	Environmental impacts need further evaluation and additional studies (2010)	-		
Cariprazine	-	Not expected to pose a risk to the environment (2017)	-		
Chlorpromazine	36		-	Caddisfly larvae, riparian spiders (Richmond et al., 2018)	• Lethal anostracan crustacean (Nałęcz-Jawecki & Persoone, 2006) • Stress, *Daphnia magna* crustacean (Oliveira L et al., 2015) Very toxic, aquatic plant (Kaza et al., 2007)
Clozapine	321428	-	9 (3;3;3)	Fish tissues (Nallani et al., 2016)	• Intestinal motility, fish (De Alvarenga et al., 2017) • Song control system, zebra finches (Cornil et al., 2008) • Cardiotoxicity (Lee et al., 2013 • Decreased survival, fathead minnow (Overtruf et al., 2012) • Inhibition of locomotor activity, zebrafish (Boehmler et al., 2007)
Chlorprothixene	27	-	-	Caddisfly larvae, riparian spiders (Richmond et al., 2018)	
Flupentixol	3.9	-	-	Caddisfly larvae, riparian spiders (Richmond et al., 2018) Wildlife fish (Ceverny et al., 2020)	

Drug	CEC (Fick etal 2010)*	ERA (year†)	PBT (P;B;T)	Evidence of bioconcentration/ bioaccumulation	Measured ecotoxicological effects
Fluphenazine	-	-	6 (3;0;3)	Caddisfly larvae, riparian spiders (Richmond et al., 2018)	
Haloperidol	6.5	-	8 (3;3;2)	Caddisfly larvae, riparian spiders (Richmond et al., 2018) Fish tissues (Grabricova et al., 2017) Wildlife fish (Ceverny et al., 2020, Ma ev et al 2020)	• Feeding inhibition in crustaceans (Furuhagen et al., 2014) • Decreased time spent at dark, zebrafish (Magno et al., 2015) • Decreased swimming activity, zebrafish (Huang et al., 2019) • Decrease on acetylcholinesterase activity, zebrafish (Seibt et al., 2009)
Levomepromazine	7.7	-	9 (3;3;3)	Fish tissues (Gra ricova et al., 2017)	
Loxapine	-	Not expected to pose a risk to the environment (2013)	-		
Lurasidone	-	Is not a PBT substance and is not expected to pose a risk to the environment (2014)	-		
Olanzapine	3634	Does not present a significant risk to the environment (2008‡)	2 (0;0;2)		Cardiotoxicity (Lee et al., 2013
Paliperidone	-	No impact to the environment is expected (2007)	4 (3;0;1) (Mankes et al., 2013)		
Perphenazine	9.9	-	3 (-3-)	Caddisfly larvae, riparian spiders	

Drug	CEC (Fick etal 2010)*	ERA (year†)	PBT (P;B;T)	Evidence of bioconcentration/ bioaccumulation	Measured ecotoxicological effects
				(Richmond et al., 2018)	
Quetiapine	290938	-	5 (3;0;2)		Cardiotoxicity (Lee et al., 2013
Risperidone	129	-	5 (3;0;2)	Caddisfly larvae, riparian spiders (Richmond et al., 2018) Wildlife fish (Ceverny et al., 2020)	• Impaired initial development and egg- hatching (Kalichak etal., 2016) • Stress response, zebrafish (Kalichak et al., 2017, Idalencio et al., 2015). Transgenerational impaired anti-predatory behaviour in zebrafish (Kalichak et al., 2019) • Alter touch response and pharyngeal pumping in wild-type nematodes (*Caenorhabditis elegans*), with transgenerational effects (Osuna-Luque et al, 2018). • Attraction, zebrafish (Abreu et al., 2016)
Sertindole	-	-	0 (-;0;-)		
Ziprasidone	110	-			• Survival and reproduction crustaceans *Daphnia magna* and *Ceriodaphnia dubia* (Constantine & Huggett 2010) • Cardiotoxicity (Lee et al., 2013)
Zuchlopentixole	-	-	-		

PBT: Persistent, bioaccumulation, toxic

*The predicted water concentrations (ng/L) that would elevate the plasma concentration in exposed fish to a level equal to the human therapeutic plasma concentration.

† Year of the publication of the European Public Assessment Report. European Medicines Agency.

‡ Refers to the long acting injectable presentation. Oral olanzapine was marketed in 1996, so no ERA is available.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Antipsychotics are increasingly used to treat a wide range of diseases.
- They possess a complex pharmacological profile, acting on multiple receptors.
- Environmental concentrations might exert significant effect to wildlife.
- Studies show they are bioaccumulating through the food web.
- Their potential role as environmental pollutants has been underrated.

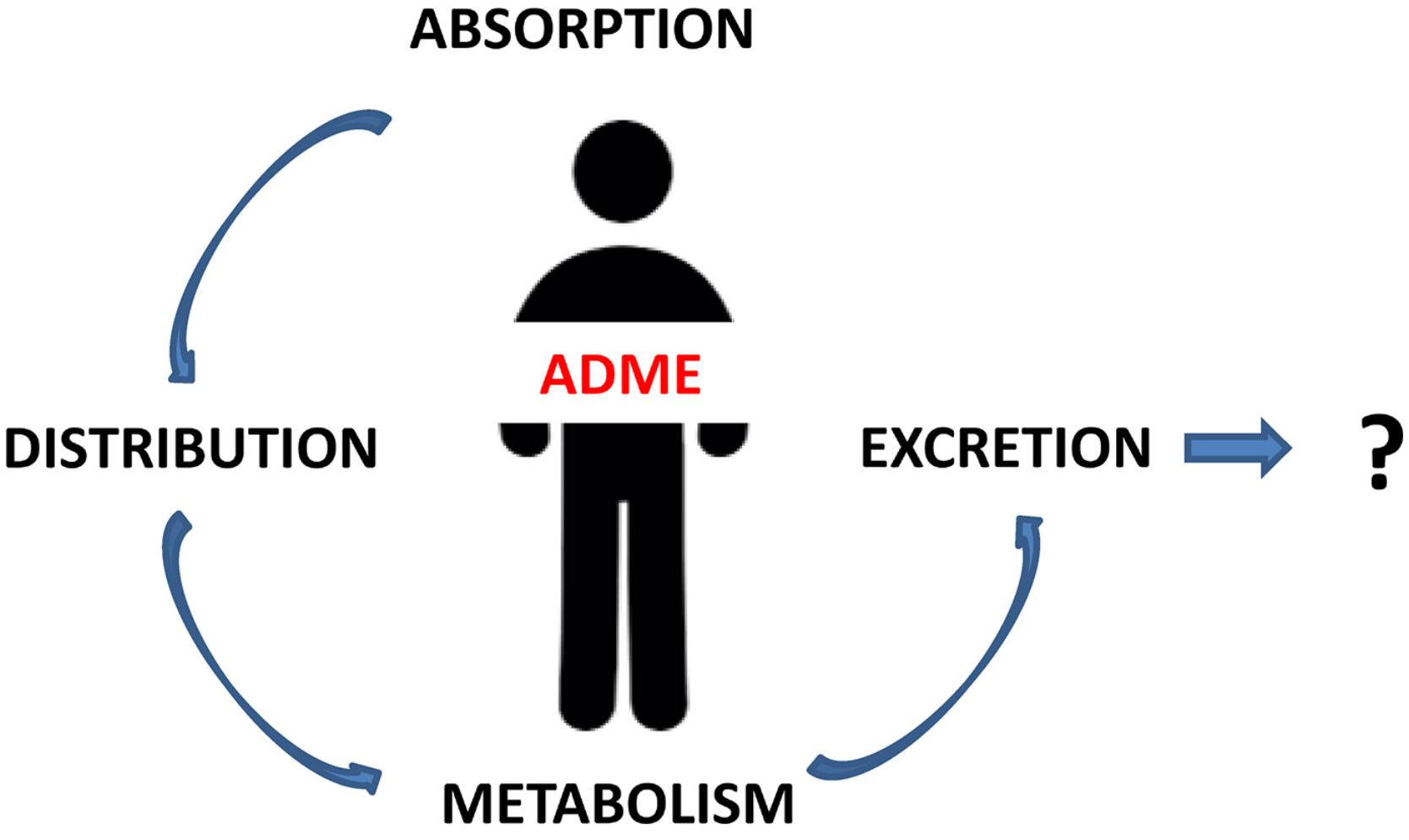


Figure 1