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Review

Propranolol Hydrochloride Psychiatric Effectiveness and Oxidative Stress: An Update

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Abstract: In this review, in addition to the potential cardiovascular applications of β-blockers and, more specifically, propranolol, we wanted to list the more recent applications in psychiatry as well as current knowledge on the impact of oxidative stress on propranolol hydrochloride and the oxidative stress that could be limited by the latter. In fact, a number of studies show that this molecule is modified by oxidative stress but is also able to limit it. Mention is also made to studies on the increasingly important problem of eliminating drug waste and its impact on the environment, particularly the marine environment. Given the increase in the consumption of medicines, more rigorous waste management is needed to avoid impacting biodiversity.

Keywords: propranolol hydrochloride; β-blockers; oxidative stress; psychiatric effectiveness; marine environment; ROS scavengers

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1. Introduction

β-blockers were discovered in the 1960s, and since then, this class of drugs has become established in cardiology as in other specialties. New molecules have appeared with specific actions and a better benefit–risk balance. β-blockers are increasingly used not only in cardiology but also in other specialties, such as endocrinology, psychiatry, and neurology. Not all the properties of β-blockers have been fully elucidated, and new indications may emerge [1]. Propranolol is a β-adrenergic receptor antagonist discovered by an English researcher, Sir James Black, to treat the symptoms of angina pectoris. Research soon focused on anxiety. It became clear that β-blockers had a role to play in reducing anxiety, unlike other anxiolytic substances developed in psychiatry, such as benzodiazepines. β-blockers do not carry the same risk of dependence as benzodiazepines, exert several central and peripheral effects, and are, therefore, useful in a variety of conditions [2]. Propranolol is rapidly absorbed after oral administration. Its bioavailability varies according to the dose administered. The area under the curve is multiplied by 2.5 if the dose is doubled. The area under the curve varies according to whether the drug is immediately released or sustained in its release. Propranolol is metabolized by CYP2D6, CYP1A2, and CYP2C19, which are sources of potential drug interactions. CYP cytochromes are a group of enzymes belonging to the cytochrome P450 family. These various enzymes are involved in the metabolism of a large number of drugs, including antidepressants, neuroleptics, and β-blockers, which are of interest here. Renal insufficiency can modify pharmacokinetic parameters, unlike other parameters such as age, gender, and ethnic origin. In the case of renal insufficiency, therapeutic adaptation is necessary [3]. β-blockers can lead to psychiatric disorders or even suicidal behavior; the results must be confirmed [4]. New ideas have emerged that

propranolol could replace benzodiazepines to effectively treat post-traumatic stress disorder (PTSD) without tachyphylaxis as with benzodiazepines. Propranolol is the leading beta-blocker as it is easy to use and requires less monitoring than benzodiazepines. Along with EMDR, propranolol is the best treatment for anxiety disorders. Propranolol acts on stage fright. It is effective in the treatment of post-traumatic stress disorder (PTSD), pending proof of the mechanism of action [5]. For the time being, these extra-cardiological indications remain in the research domain and have not received marketing authorization [5].

In this review, in addition to the various new potential therapeutic applications in psychiatry, we wanted to survey current knowledge on the impact of oxidative stress on propranolol hydrochloride and the oxidative stress that could be limited by it.

2. Results and Discussion

2.1. Role of Propranolol Hydrochloride in Mental Health

A clinical case describes a 44-year-old woman who was a multi-recidivist in road accidents, with 3 out of 5 accidents resulting in post-traumatic stress despite several treatments. Her symptoms reappeared in a sixth accident. Four days after this accident, she received 60 mg of propranolol twice a day, resulting in a reduction in symptoms. On the 11th day after the accident, her clinical scale score fell from 86 to 56. This research is the first to report the efficacy of propranolol in reducing post-traumatic symptoms, particularly its recurrence. Hence, the long-term efficacy of propranolol in preventing post-traumatic stress is a possibility [6]. An activity-dependent labeling system has been registered in mice. Specific mouse models were conditioned to four shocks, followed by immediate or delayed contextual re-exposure. To assess the impact on hippocampal, prefrontal, and amygdala memory, mice were re-exposed with or without propranolol. Propranolol reduced the expression of fear only when it was administered to mice before delayed re-exposure to the context. Propranolol altered functional connectivity between the hippocampal, prefrontal, and amygdala regions. These preclinical in vivo models confirm the efficacy of propranolol in preventing stress recurrence [7]. A total of 3326 senior high-school students, mostly women, took part in the study, with an average age of 22. One-third were considered to suffer from mild anxiety, with a significant positive correlation between β-blocker use and the GAD-7 score. In total, 6.4% of the sample were taking β-blockers. Medical students, particularly men, were more likely to use β-blockers because they were more anxious than other students [8]. In total, 92 psychiatric patients in Okinawa, Japan, were treated with atenolol. Adverse events were systematically recorded. In total, 86% of patients had a positive effect and continued to take atenolol, including 87% with a diagnosis of post-traumatic stress disorder. Overall, 90% of patients had few, transient, or mild adverse effects. Thus, 100% of patients preferred atenolol to propranolol, which they had previously tried [9]. It seems necessary to better identify anxiolytic prescriptions on the basis of better-established clinical evidence. This can help avoid unnecessary and even dangerous prescriptions [10]. B-blockers appear to be effective in the treatment of other disorders, such as specific phobia, panic disorder, and aggression in patients with psychosis, acquired brain damage, or intellectual disability. Robust data from clinical psychiatric research are desirable to establish the efficacy of β-blockers in different forms of anxiety. Randomized, placebo-controlled clinical trials are needed to prove this [11]. For a comparison with benzodiazepines, β-blockers have been used for many years to prevent performance anxiety, such as stage fright. A single dose of propranolol has been used to treat performance anxiety [12]. The brain structures involved are the cortex, limbic system, reticular formation, locus coeruleus, raphe nuclei, and hypothalamus. The neurotransmitters involved are GABA, serotonin, and noradrenaline. Anxiety disorders are thought to be linked to the disruption of the GABAergic and serotoninergic systems. The advantage of β-blockers over benzodiazepines is that they only treat anxiety at the adrenergic level, with no impact on cognition or memory. A person treated with β-blockers retains full powers of concentration, decision making, and memory [5,13].

Why choose propranolol over other β-blockers? Propranolol is an old drug with a proven pharmacovigilance record, which can be titrated gradually. The dose of propranolol can start at 40 mg per day and then be increased in increments every 72 h up to a dose of 160 mg per day [14].

An electrocardiogram is indicated to rule out any cardiac rhythm disorders that contraindicate the prescription of β-blockers. It is a non-cardioselective drug that acts via the competitive antagonism of catecholamines at β-adrenergic receptors, particularly in the heart, vessels, and bronchi. β-adrenergic receptors are, thus, blocked by competitive inhibition, and the somatic symptoms disappear. Propranolol is a highly lipid-soluble molecule. It can, therefore, cross the blood–brain barrier and block noradrenaline receptors involved in memory [15]. The stressful event must be known, and the drug should be taken 12 h before the event. Several forms of anxiety are observed, including worry, panic attacks, anxiety attacks, and post-traumatic stress. Generalized anxiety is a persistent fear that is not related to a specific event or situation. Panic disorder is a form of anxiety that manifests itself in panic attacks. These attacks last between 5 and 30 min. Obsessive-compulsive disorder (OCD) is a form of anxiety characterized by repetitive and persistent thoughts or ideas or repetitive behaviors or rituals, such as washing and rewashing hands, checking that doors close properly, etc. A phobia is an anxiety experienced in a particular situation, such as fear of crowds, fear of insects, fear of lifts, fear of flying, etc. Post-traumatic stress is a form of anxiety that follows a traumatic experience, including aggression, armed conflict, accident, flood, etc. Propranolol has been proven to be efficient in this post-traumatic stress (PTSD) disorder [16].

Benzodiazepines have a rapid effect on anxiety symptoms. They are the first-line treatment in emergency situations, with diazepam at doses ranging from 16 to 30 mg/d being the first choice. The risk of dependence makes it necessary to limit the duration of their prescription. A comparison between propranolol and benzodiazepines showed no statistical differences [17].

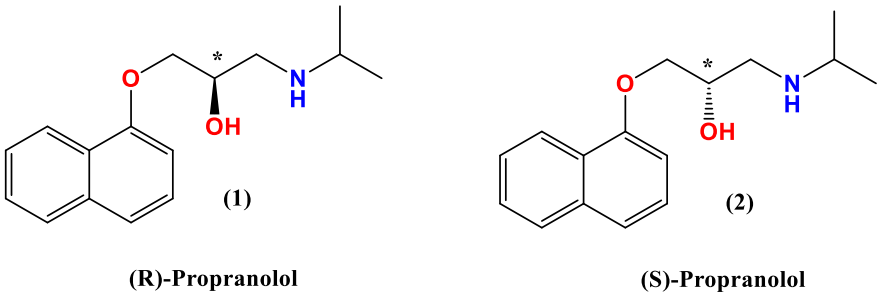
The administration of propranolol shortly after the traumatic event prevents or diminishes the action of noradrenaline, rendering the amygdala inoperative in Takutsubo syndrome [13]. The amygdala is a key human structure involved in the encoding of emotional information, and propranolol is effective at proving emotional encoding via noradrenaline [18,19]. The noradrenergic circuit is involved via the vague nerve [20]. Propranolol has been shown to be effective for the emotional aspects of autism [21], and promising results have been obtained following a recent meta-analysis showing the efficacy of propranolol in reducing emotional disorders [22].

2.2. Antioxidant Activity and Environmental Impact of Propranolol Hydrochloride

As mentioned above, propranolol, a β-adrenoreceptors blocker drug, was traditionally prescribed for the treatment of hypertension, arrhythmia, various palpitations, and cardiovascular manifestations due to hyperthyroidism, migraines, panic attacks, and glaucoma [23]. Given the increasing prevalence of the conditions concerned by treatment with propranolol or other classes of β-blockers, it seemed that the use of propranolol or other β-blockers should increase. Studies were, therefore, carried out to measure the various potential secondary impacts of its use on health and the environment, as well as the impact of oxidative stress. During our bibliographic search on oxidative stress, we used the following search terms in scifinder: "Avlocardyl© AND oxidative stress" or "propranolol AND oxidative stress". Why Avlocardyl? Because it is the original product. It is known by other names in different countries. We did not use the names of all generics in our literature search. Half of the results were patents, and a number of interesting studies, more or less recent, are described in detail here. First, we will look at the impact of oxidative stress, then at the ability of these molecules to act as antioxidants, and finally at the environmental problems associated with taking these drugs. On the one hand, they are found in their initial form in wastewater, and therefore, sometimes in the marine environment when the elimination of excess prescription drugs does not follow the regulatory destruction circuit;

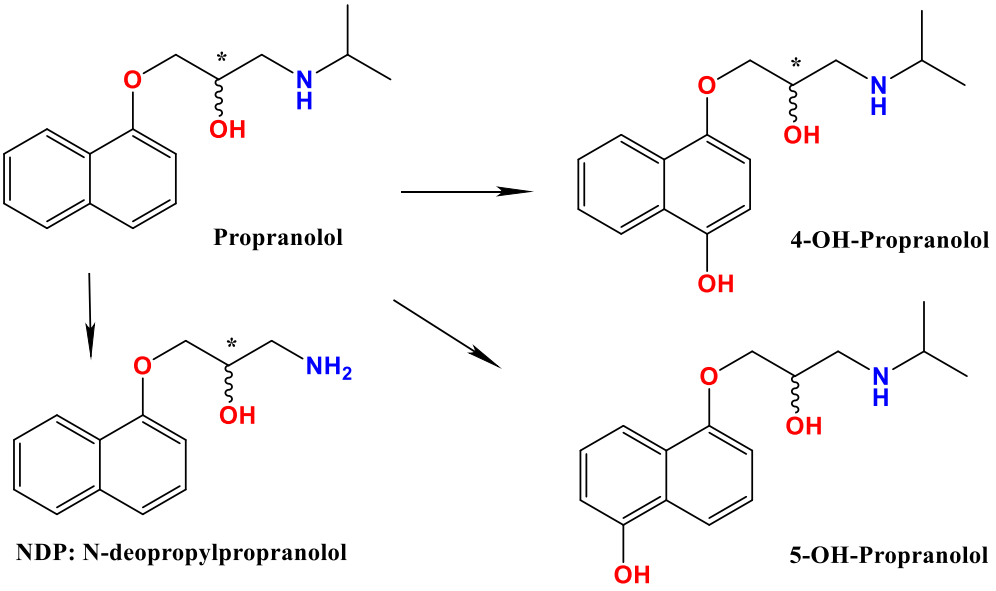
on the other hand, they are also found in the form of various metabolites, which can end up in the same wastewater, this time due to the natural evacuation of body fluids. This concentration in water is a public health problem, and several recent studies have reported toxic effects on marine fauna.

Propranolol has a low bioavailability of around 30% and is eliminated by the liver. It is also known for its antitumoral effects [24,25] and for its inhibitory action on pro-inflammatory cytokines [26–29]. Propranolol is a small molecule with one asymmetric carbon which, unlike many drugs, is marketed in its racemic form (Scheme 1: showing R(1) and S(2)propranolol), although one of the enantiomers S(2) has much greater activity than the other R(1) [30]. As with many drugs, R or S enantiomers whose orientation of certain functions (in this case, the alcohol) differs in space are often responsible for their therapeutic efficacy, as they may or may not fit into the active site.



Scheme 1. The two R and S enantiomers of propranolol.

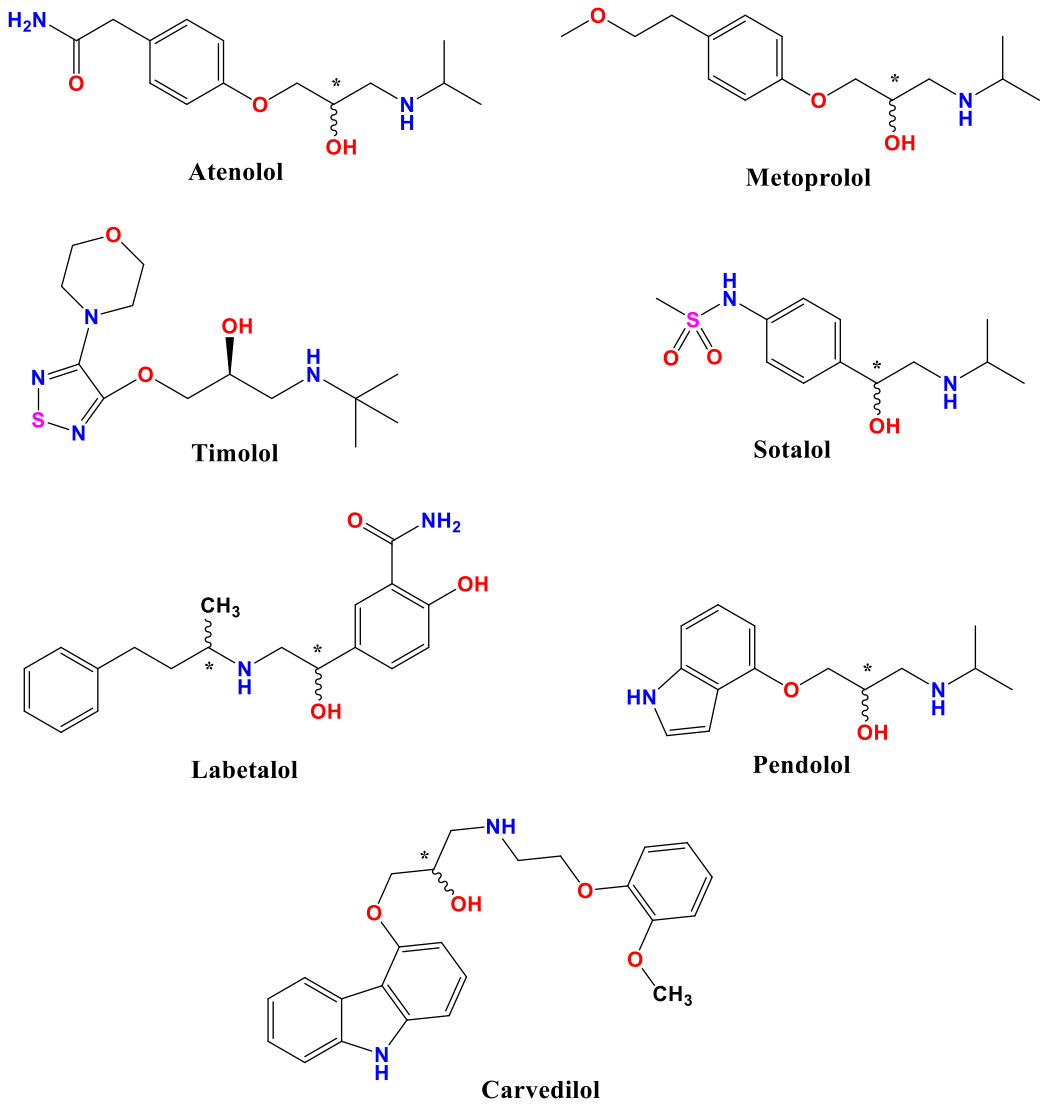
To detect the possible drug pollution of wastewater, it is essential to know the metabolism of drugs and the derivatives produced by the biological transformations they undergo. As propanolol is an old drug, we are well acquainted with its metabolic pathway. In humans, propranolol can be oxidized by cytochrome P450 (CYP) enzymes in a regio- and stereoselective manner. Among the CYP isoenzymes, CYPs 1, 2, and 3 are involved in the metabolism of many human drugs [31]. S. Narimatsu et al. [32]. confirmed that the enantiomers of propranolol can be oxidized by the P450 enzyme (CYP2D6) on the aromatic ring to 4-hydroxyproranolol (4-OH-PL), then to 5-OH-PL and on the linear chain to N-deopropylpropranolol (NDP) by CYP2D6 according to Scheme 2.



Scheme 2. Compounds generated during oxidative metabolism underwent by propranolol.

This hepatic enzyme is the main one involved in drug oxidation [33,34], which, in this case, is propranolol. Other equivalent enzymes are involved in monkeys and marmosets, and the authors have shown that the stereoselectivity of oxidation is similar between humans and monkeys but that the regioselectivity of oxidation is not. Oxidized metabolites and propranolol are substrates of UDP-glucuronosyltransferases and sulfo-transferases [35].

E. Fernandes et al. [36]. showed that the β-blocker family possesses antioxidant activity, which could also be at the origin of their therapeutic activities. Indeed, certain cardiovascular effects are thought to be due to the antioxidant properties of some compounds in this family. They, therefore, tested atenolol, sotalol, timolol, labetalol, metoprolol, pindolol, carvedilol, and the propranolol of interest here (Scheme 3).



Scheme 3. Various structures of β-blockers involved in the literature used and discussed herein.

This study follows another by Mak and Weglicki [37], who were able to demonstrate concentration-dependent membrane anti-peroxidant activity for five β-blockers, including propranolol, which also proved to be the most potent of these. The cardioprotective antioxidant effects of propranolol were subsequently confirmed by other teams, who reported that propranolol was capable of significantly reducing lipid peroxidation products [38]. Propranolol acts at different levels against oxidative stress, whether at the level of enzymes, membrane protection, or cardiovascular cells [39].

Other β-blocker compounds also have antioxidant activities at different levels, such as carvedilol (CVD), which is the most potent at protecting red blood cells from the toxicity of phenazine methosulphate, thus limiting the formation of superoxide radicals [40]. Carvedilol is marketed as a racemic mixture. It has antioxidant properties, although this has not been demonstrated in the treatment of heart failure. This molecule contains both a β-blocker and α-blocker component. Like propranolol, it has a membrane-stabilizing effect. However, its use can lead to alterations in renal function, which are fortunately reversible.

Anxiety disorders are among the most common psychiatric illnesses. Carvedilol, a β-blocker, was studied for hypertension and to assess its efficacy against unpredictable chronic stress in animals. A mouse model was used for 21 days. Between days 15 and 21, mice were treated with carvedilol (5 or 10 mg/kg) or a venlafaxine-like antidepressant, desvenlafaxine (DVS 10 mg/kg). Locomotor tests were performed on day 22. Adrenal demand was observed in stressed animals, which is an effect that was reversed by CVD. The increase in myeloperoxidase (MPO) and interferon-γ (IFN-γ) activity, as well as the stress-induced reduction in interleukin-4 (IL-4), was reversed by β-blocker treatment. Carvedilol has a proven anxiolytic effect and is associated with the regulation of the immuno-inflammatory mechanism [41].

E. Fernandes et al. [36], Therefore, carried out a precise study of the scavenging of ROS and RNS by β-blockers to determine their ranking in terms of potency. The antioxidant capacity of these cardiovascular drugs makes it possible to combine their cardiovascular activities with antioxidant activities, generally taking into account the implementation of an associated dietary protocol or the intake of vitamin-type antioxidants. It turns out that the β-blockers studied, including propranolol, are not capable of scavenging $O_2^{\bullet -}$ but are good scavengers of $HO^{\bullet}$, which enables them to prevent the resulting cardiovascular pathologies. They are also very good scavengers of HOCl, and propranolol and pindolol are good scavengers of $ROO^{\bullet}$ or alkyl radical $R^{\bullet}$, thus limiting the propagation of lipid peroxidase and reducing the formation of oxidized LDL particles. This reduction leads to a reduction in foam cells, as macrophages have far fewer oxidized LDL particles at their disposal, and it is these foam cells that are responsible for the formation of atherosclerotic plaques, which ultimately lead to circulatory problems. Propranolol is also a $^{\bullet}NO$ scavenger, which is interesting because $^{\bullet}NOs$ are involved in central nervous system pathologies [42].

The antioxidant activity of these β-blockers, and propranolol in particular, can also be explained by the molecule's high lipophilicity, which enables it to protect membranes since propranolol is able to accumulate there [43]. The scavenging efficiency of antioxidants depends on the quantity of the reactive species. This is higher in vitro than in vivo [44]. The authors have, therefore, shown that certain β-blockers, including propranolol, are ROS scavengers and, as such, may be useful in preventing the damage caused by oxidative stress, which is often implicated in various pathologies.

In addition to the therapeutic effect of these active substances and their impact on other effects, we increasingly observed the impact of these molecules on nature. Indeed, a large number of the planet's inhabitants live close to the sea and feed off it, and the sea is confronted with numerous more or less controlled discharges of human waste accumulated in various large cities close to the coast. This generates a large amount of accumulated waste that the oceans receive without prevention. This waste is discharged into the sea either through a faulty drug recovery–destruction mechanism or through the elimination of excess drugs or drug metabolites by natural means (biological fluids) [45–48]. This phenomenon is even more pronounced in freshwater environments, where waste can be disseminated by run-off water. Recently, in view of the increasingly frequent effects observed, studies have been carried out on the impact of drugs in the aquatic environment. Propranolol is no exception, as this molecule is not particularly well eliminated in wastewater [49]. It has, therefore, proved essential to study the toxicity of propranolol on aquatic organisms living in environments where human wastewater may be found [50]. Medicines are active molecules, generally at low doses, and their toxicity has been assessed according to the protocols defined for obtaining marketing authorizations, but their toxicity is not

generally assessed in the environment. Population growth will lead to an increase in drug consumption, which is already underway and is already generating definite shortages, so the release of these substances will only increase, hence the need to carry out these studies on the various drugs currently on the market and on any new drugs. This drug acts on human adrenergic receptors, but these have similarities to those of various aquatic and plant species. S.F. Owen and colleagues conducted excellent work in 2021, compiling numerous articles on the aquatic risks of β-blockers and propranolol in particular [51]. The latter is reputed to represent a scientifically proven risk to the environment and the aquatic fauna.

Very recently, propranolol hydrochloride has been shown to be toxic to mitochondrial function in rats [52], and in adult zebrafish, propranolol hydrochloride has been shown to reduce testosterone-type sex hormone levels and increase cholesterol [53,54]. The neurotoxicity of propranolol hydrochloride on zebrafish has been demonstrated; this molecule reduces young neurons, limits neuronal development, and can lead to symptoms of tremor, showing undeniable cerebral damage [55]. These effects are also likely to be present in other aquatic organisms. Like many other drugs, propranolol has many advantages, but given its widespread use, it can also contribute to environmental health risks.

Another study has shown the deleterious impact of propranolol and other xenobiotic substances on the reproduction of sturgeon, which is a fish that is currently overfished and sensitive to pollution. This study by Shaliutina et al. [56]. assessed the effect of propranolol on the spermatozoa of the sterlet Acispenser ruthenus. Sperm mobility decreased linearly with the dose, as did membrane integrity (at 25 μM). At higher concentrations (25–100 μM), oxidative stress was even demonstrated, with an increase in superoxide dismutase activity. This time, it is propranolol that caused oxidative stress in the spermatozoa of this fish, which was, therefore, detrimental to reproduction and the survival of the species. This is even more true if there are synergistic effects with other types of drug waste in the wastewater. Quantities of propranolol are in the order of micrograms per liter and up to 6 micrograms per liter in hospital effluents [57–62]. A very interesting study by B. Duarte et al. [62]. shows that the staple food of marine organisms, diatoms (microalgae essential to the food chain), are essential oxygen-producing agents that are indispensable to marine life because they produce fatty acids essential to the maintenance of various cardiovascular, immune, or inflammatory functions [63]. Essential fatty acids are acquired through the diet, so if diatoms are disrupted in their functioning, the food chain suffers. They worked on Phaeodactylum tricornutum, which is a marine diatom often used for stress studies.

Its genome is known [64], and Phaeodactylum tricornutum reflects the first signs of stress [65]. Phaeodactylum tricornutum is used to test the differential retention and digestive selection of any microalgal component by the mussel Mytilus edulis. Marine bivalves are considered good bio-indicators of chemical pollution, as they have the capacity to filter large volumes of water during respiration and feeding and to bio-accumulate chemicals (biomarkers effective for assessing the toxicity of pharmaceutical residues on marine bivalves). A number of studies have been carried out, notably on responses to oxidative stress [66] and on changes in fatty acid production and membrane unsaturation [67,68]. In this article, B. Duarte et al. [62,68]. sought to assess the impact of propranolol on P. tricornutum. Growth, oxidative stress, and fatty acids were studied to understand the impact of propranolol. Diatom growth rates and cell densities decreased after 48 h of exposure, with a clear dose–response relationship. Potential cellular damage due to oxidative stress was caused by exposure to propranolol at several concentrations, despite the upward trend in peroxidase activities observed for up to 150 μg L^{-1} of propranolol, and changes were only observed from 80 μg L^{-1}. CAT and SOD activities increased, as did lipid peroxidation. The relative abundance of certain fatty acids also differed significantly between treatments.

Based on these results, the authors highlighted a depletion in the oxygenation capacity of diatoms, strongly affected metabolisms, and a possible disturbance in the balance of species since this affects the food chain. Another study by J.P. Shaw and J.W. Readman [69] showed propranolol levels of the order of a few tens of nanograms in British estuaries,

again showing the persistence of certain drugs in water that have not been eliminated by treatment in wastewater treatment plants. Acetaminophen (paracetamol), on the other hand, is found in small quantities because its elimination rate is high depending, of course, on the structure of the drug but also on the methods used in the treatment plants. Adrenergic receptors in invertebrates are poorly documented but could play a role in bivalve larvae such as *Mytilus* species [70] with involvement in the feeding behavior of the gastropod aplysia [71]. Contrary to what we have seen previously, while cytochrome P450 (CYP) and carboxylesterases play an important role in humans and even potentially in vertebrates, this is not the case in invertebrates. In mussels, the activity of cytochrome P450 enzymes does not appear to be important in the management of drug metabolism; it is mainly carboxylesterases and acetylcholinesterases that are active [72]. Studies have been carried out on the marine mussel *Mytilus galloprovincialis* concerning feeding rates, xenobiotic metabolism, and oxidative stress. Lipid peroxidation levels were measured in the gills and digestive glands. The results show that propranolol inhibits the feeding rate at concentrations of 147µg/L, increases liver activity, and may increase metabolism but does not generate oxidative stress in the digestive gland [69], which is reassuring.

3. Conclusions

Although propranolol has a favorable benefit–risk balance and does not appear to pose an immediate threat to the environment or to freshwater and marine pollution, further comparative studies are required. This is a drug that does not present any very serious toxicity, but it is beginning to be found in significant quantities in water because propranolol is poorly eliminated by wastewater treatment plants. The disposal of surplus drugs does not always follow the correct circuit, and they are sometimes thrown away without due care. Other drugs are less concerning because they are easily eliminated or not very soluble in water. Unfortunately, this is not the case for all of them, and very few studies have been carried out on the comparative effect of several drugs and on the possible synergistic effects that could increase their harmful effects on human health or on vertebrate or other organisms that enter the food chain.

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