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ΣΧΟΛΗ ΧΗΜΙΚΩΝ ΜΗΧΑΝΙΚΩΝ ΚΑΙ ΜΗΧΑΝΙΚΩΝ ΠΕΡΙΒΑΛΛΟΝΤΟΣ

Μεταπτυχιακό Πρόγραμμα Σπουδών: Διαχείριση νερού και υγρών αποβλήτων

Photochemical treatment methods for the degradation of antidepressants in aqueous matrices

Φωτοχημικές μέθοδοι επεξεργασίας για τη διάσπαση αντικαταθλιπτικών ουσιών σε υδατικές μήτρες

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Abstract

During the last decades, human population growth and progress have increased the pharmaceutical contamination of the environment. Active pharmaceutical ingredients are stable in water matrices and are not fully degraded by standard treatment processes. The existence of pharmaceutical drugs and pharmaceutically active metabolites in the environment has been considered one of the emerging concerns in environmental sciences. These substances are referred to as contaminants of emerging concern (CECs), as they appear to have consequences on aquatic organisms.

Many articles have been published regarding the presence of pharmaceuticals in the environment until now. A group of pharmaceuticals with an increasing presence in the environment is antidepressants.

The present diploma thesis attempts to review the presence and impact of antidepressant pharmaceuticals in environmental matrices and non-target organisms, as well as different methods to remove them based on UV radiation. The literature used, consisted of scientific papers published in the last decade. This project was focused on the degradation methods, mostly the Advanced Oxidation Processes based on UV radiation. Lastly, an effort to evaluate the efficiency of these processes was made.

Keywords

Antidepressants, Occurrence of antidepressants, UV based Advanced Oxidation Processes

ABBREVIATIONS

AOPs	Advanced oxidation processes
APIs	Active Pharmaceutical Ingredients
CECs	Contaminants of Emerging Concern
COD	Chemical Oxygen Demand
EfOM	Effluent Organic Matter
MAOIs	Monoamine Oxidase Inhibitors
PPCPs	Pharmaceuticals and Personal Care Products
SNRIs	Serotonin – Norepinephrine Reuptake Inhibitors
SSNRIs	Selective Serotonin – Norepinephrine Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antideprassants
TOC	Total Organic Carbon
TUAs	Tetracyclic and Unicyclic Antidepressants
WWTP	Waste Water Treatment Plant
FLX	Fluoxetine
FVX	Fluvoxamine
STR	Sertraline
PRX	Paroxetine
NFLX	Norfluoxetine
DUL	Duloxetine
CTP	Citalopram
VFX	Venlafaxine
AMT	Amitriptyline
NTL	Nortriptyline
DPM	Desipramine
IMI	Imipramine
MDD	Major Depressive Disorder
TPs	Transformation Products
BDNF	Brain-Derived Neurotrophic Factor
HPA	Hypothalamuspituitary-Adrenal
SERT	Serotonin Transporter
NET	Norepinephrine
UV	Ultra Violet
LEDs	UV-light emitting diodes
VUV	Vacuum UV
DOC	Dissolved Organic Carbon
NOM	Natural organic matter
DOM	Dissolved Organic Mater
MP lamps	Medium Pressure lamps
LP lamps	Low Pressure lamps

1. Pharmaceutical substances in the environment

The history of pharmaceutical sciences is an impressive success story. The products of pharmaceutical industries are present everywhere in everyday life. Pharmaceuticals are chemicals that are used because of their more or less specific biological activity. They help to pursue the modern way of living and contribute to our health and high standard of living. For a long time, the production of chemicals and pharmaceuticals, as well as their usage and application, caused heavy pollution of the environment and serious health effects. During the second half of the twentieth century, tremendous progress was made to prevent the pollution of the environment and to reduce the impact of such pollution on health (Kümmerer et al., 2010). Now, proper and effective treatment and prevention of air, water, and soil emissions are in place in developed countries and are making their way worldwide.

In the 1990s, it was found that the amount of waste generated was 50–100 kg for the synthesis of 1 kg of an active pharmaceutical compound. This insight triggered activities within the pharmaceutical industries to reduce waste generation by various measures, such as using different and more appropriate (i.e., "greener") solvents and developing new synthesis routes to avoid intensive waste. However, since the end of the past century, it has been learned that the pharmaceutical industries' products, i.e., medicinal drugs, present a new type of environmental pollution and possible health risks for the consumer. It is expected that the consumption of pharmaceuticals will increase in the future because of higher standards of living and because more people are living longer and using more drugs as they age (Kümmerer et al., 2010).

Because of the ever-increasing sensitivity of analytical instruments, pharmaceuticals have been found (as have other micropollutants, such as disinfectants, pesticides, flame retardants, de-icing fluids, and others) present in the environment in low concentrations (ng L^{-1} to µg L^{-1}). If the pharmaceuticals, their metabolites, and Transformation Products (TPs) are not eliminated during sewage treatment or sorbed in soil, they may enter the aquatic environment and eventually enter drinking water supplies. Pharmaceutical residues from human use have been a topic for several years now. Because of their biological activity, there is concern about their presence in the aquatic environment and drinking water: Are there negative effects caused by these compounds on humans and/or environmental organisms? (Kümmerer et al., 2010).

1.1 Pharmaceuticals as emerging contaminants

Pharmaceuticals constitute a fundamental component of modern medicine and confer significant societal benefits (Kümmerer et al., 2010).They are a large and diverse group of organic compounds used in very high quantities worldwide (Bound and Voulvoulis, 2005; Radjenovic et al., 2007). Nowadays, and in the European Union, more than 3000 active substances are on the market (Redshaw et al., 2008). The first reports referring to the incomplete removal of some pharmaceuticals by wastewater treatment plants (WWTP) and their discharge into the environment were published in the 1960s and 1970s (Stumm-Zollinger and Fair, 1965; Hignite and Azarnoff, 1977).

Despite these first findings indicating pharmaceuticals as a potential group of environmental contaminants, this issue did not attract significant attention until the 1990s, when it was discovered that some compounds have the ability to interfere with ecosystems in concentrations as low as a few nanograms per liter (Halling-Sørensen et al., 1998). It was also during that decade that the first optimized analytical methods for quantifying pharmaceuticals in environmental samples were developed, allowing the determination of very small quantities in aquatic matrices. Since then, due to the large amounts of pharmaceuticals produced and their increasing use and diversity (Bound and Voulvoulis, 2005, their existence in the environment has been considered one of the emerging concerns in environmental sciences (Heberer, 2002; Carlsson et al., 2006).

In addition, and taking into consideration that pharmaceuticals do not occur in the environment individually but as complex mixtures, several investigations showed that the toxicity of pharmaceuticals to non-target organisms might occur at environmentally relevant concentrations due to combined and synergistic effects (Theodore et al.,2007; Schnell et al., 2009). They can enter the water from discharge of domestic wastewater, industrial wastewater, commercial industries, and surface application of manure, as well as through the WWTPs effluents and land application of sludge (Kinney et al., 2006; Loganathan et al., 2009), as result of the inadequacy of removal treatment methods. Once in the environment, the concentration of pharmaceuticals may be attenuated by dilution, absorption, and microbial biodegradation. However, some are resistant to conventional wastewater treatment and can be present in waters at high concentrations.

Pharmaceuticals are used to have some biological or physiological effect on humans or animals. Among their specific characteristics, these compounds can pass through cellular membranes and are relatively persistent in order not to be inactivated before having the desired therapeutic effect (Sanderson et al., 2003; Radjenovic et al., 2007). In the particular case of nervous system-related pharmaceuticals, and in addition to the referred intrinsic properties, these have great relevance to the regulation of behavior, having the aptitude to affect the central nervous system and disrupt neuroendocrine signaling directly. The alteration of the reproduction patterns in non-target aquatic

organisms (Brooks et al., 2003b; van der Ven et al., 2006) is one good example that illustrates the possible adverse effects in test organisms, thus reflecting the action mode of this particular group of pharmaceuticals. Several studies have demonstrated that these compounds can affect physiological systems at very low concentrations (Schultz and Furlong, 2008; Calisto and Esteves, 2009).

Usually, a pharmaceutical, such as a pill or a liquid, consists of one or several active pharmaceutical ingredients (APIs), excipients, and additives, as well as inorganic salts or other organic chemicals, such as sugars, scents, pigments, and dyes. They are often of minor importance to the environment. Some medicines, however, may contain endocrine-disrupting chemical excipients and additives. From a chemical point of view, APIs cover a wide range of so-called small molecules (with molecular weights that typically range from 200 to 500 Da) with different physicochemical and biological properties. Even small changes in the chemical structure of an API may have a significant impact on its environmental fate. Many pharmaceuticals undergo a structural change in the bodies of humans and animals before excretion, resulting in metabolites. This change is rarely complete, i.e., typically, a certain share of the parent compound (the API) is excreted together with the metabolites. After their excretion and introduction into the environment, both parent compounds and metabolites can undergo structural changes by various biotic and abiotic processes. Pharmaceuticals can be incompletely transformed by organisms in the environment, such as bacteria and fungi, and by light and other abiotic chemical processes. Structural transformations may also result from technological processes, such as effluent treatment by oxidation, hydrolysis, and photolysis. The resulting molecules are called transformation products. Such structural changes result in new chemical entities with new properties (Kümmerer, 2010).

During the last decades, industry development and population growth increased anthropogenic contaminant emissions into the environment (Starling et al., 2019). Simultaneously, the improvement of analytical techniques allowed the identification of these contaminants in various environmental media and foods (Starling et al., 2019; Wilkinson et al., 2017). Consequently, the presence of contaminants of emerging concern (CECs) (a variety of newly identified anthropogenic-source contaminants) such as microplastics (MPs), pharmaceuticals and personal care products (PPCPs), bisphenol A (BPA), phthalates, alkylphenols, and perfluoroalkyl and polyfluoroalkyl substances (PFASs) in different media and food could be detected and became a topic of public concern (Wilkinson et al., 2017; Gogoi et al., 2018).

1.2 Pharmaceuticals' presence and fate in the environment

Emerging contaminants have received interest from regulatory organisms worldwide due to their detection in different water bodies. Human pharmaceuticals are included in the list of emerging contaminants by UNESCO. Their detection and elimination were incorporated in the 2030 Agenda for Sustainable Development Goal Targets. Recently, several researchers have detected psychiatric pharmaceuticals in different countries at high and low concentrations (in the orders of magnitude from ng L^{-1} to mg L^{-1}respectively) (Castillo-Zacharias et al.,2021).

Because conventional processes used in WWTPs are not designed to remove micropollutants, these can persist in the treated wastewater effluent. As a result, many of these micropollutants can be present in aquatic environments, including surface waters, thus threatening the ecosystem and human health. The occurrence of micropollutants in the aquatic environment is associated with various adverse effects, including short- and long-term toxicity and antibiotic resistance in microorganisms. Pharmaceuticals are frequently detected in aquatic environments, originating from hospitals, drug stores, and convenience stores; some drugs are available without a prescription (e.g., acetaminophen, ibuprofen, naproxen, and aspirin) (Castillo-Zacharias et al.,2021).

Figure 1. Origin, fate, and sources of antidepressant drugs in urban and non-urban waters (Castillo-Zacarías et al., 2021).

Although these pharmaceuticals are produced for human and animal healthcare, they are not completely metabolized in the body. Humans and animals excrete both residual pharmaceuticals and their metabolites into wastewater. Waste from the manufacturing process and expired drugs can also be sources of pharmaceuticals. Physicochemical properties and bioavailability can affect the presence of micropollutants in natural waters. The generation and elimination of micropollutants are based on physicochemical properties, environmental factors, transport and retention, transformation, and accumulation. The volatility, water solubility, stability of the chemical structure, and particulate distribution characteristics are additional factors that determine whether micropollutants remain dissolved in water (Castillo-Zacarías et al., 2021).

2. Antidepressant pharmaceuticals

Mental health has been a major concern in the 21st century. In fact, mental health-related disorders are the non-fatal disorders with the greatest impact globally, accounting for more than 7% of the global burden of disease and one-third of the burden of disease in Europe (Antunes et al., 2018). Major depressive disorder (MDD) is a primary public health concern with significant impairment in psychological, occupational, and social functioning. The prevalence rates for depression are estimated to be around 3.2% in patients without comorbid physical illnesses and 9.3% to 23.0% in patients with chronic conditions. It is the fourth cause of disability around the world and is estimated to be the second leading cause of disability by 2020 (Kessler et al., 2013). It affects around 300 million individuals regardless of gender, ethnicity, geographical location, and socioeconomic status, contributing to the overall global burden of disease. The economic impact is also severe: it is estimated that a loss of 16 trillion US$ caused by mental disorders is faced by the global economy when considering the productivity losses throughout the course of lives and the early onset of mental health disorders (Patel et al., 2018).

Major depressive disorder (MDD) is characterized by a depressed mood most of the time for at least two weeks and/ or loss of interest or pleasure in most activities. In addition, depression is characterized by disturbances in sleep and appetite, as well as deficits in cognition and energy. According to a 2007 report by the Centers for Disease Control and Prevention, antidepressant drugs were the most commonly prescribed medications in the USA at the time of the survey. The wisdom of such widespread use of antidepressants is debated. However, it is clear that American physicians have been increasingly inclined to use antidepressants to treat various conditions and that patients have been increasingly receptive to their use. The primary indication for antidepressant agents is the treatment of MDD. Some of the growth in antidepressant use may be related to the broad application of these agents for conditions other than major depression. For example, antidepressants have received Food and Drug Administration (FDA) approvals for the treatment of panic disorder,

generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). In addition, antidepressants are commonly used to treat pain disorders such as neuropathic pain and the pain associated with fibromyalgia. Some antidepressants are used to treat the premenstrual dysphoric disorder (PMDD), mitigate the vasomotor symptoms of menopause, and treat stress urinary incontinence (Katzung et al., 2018).

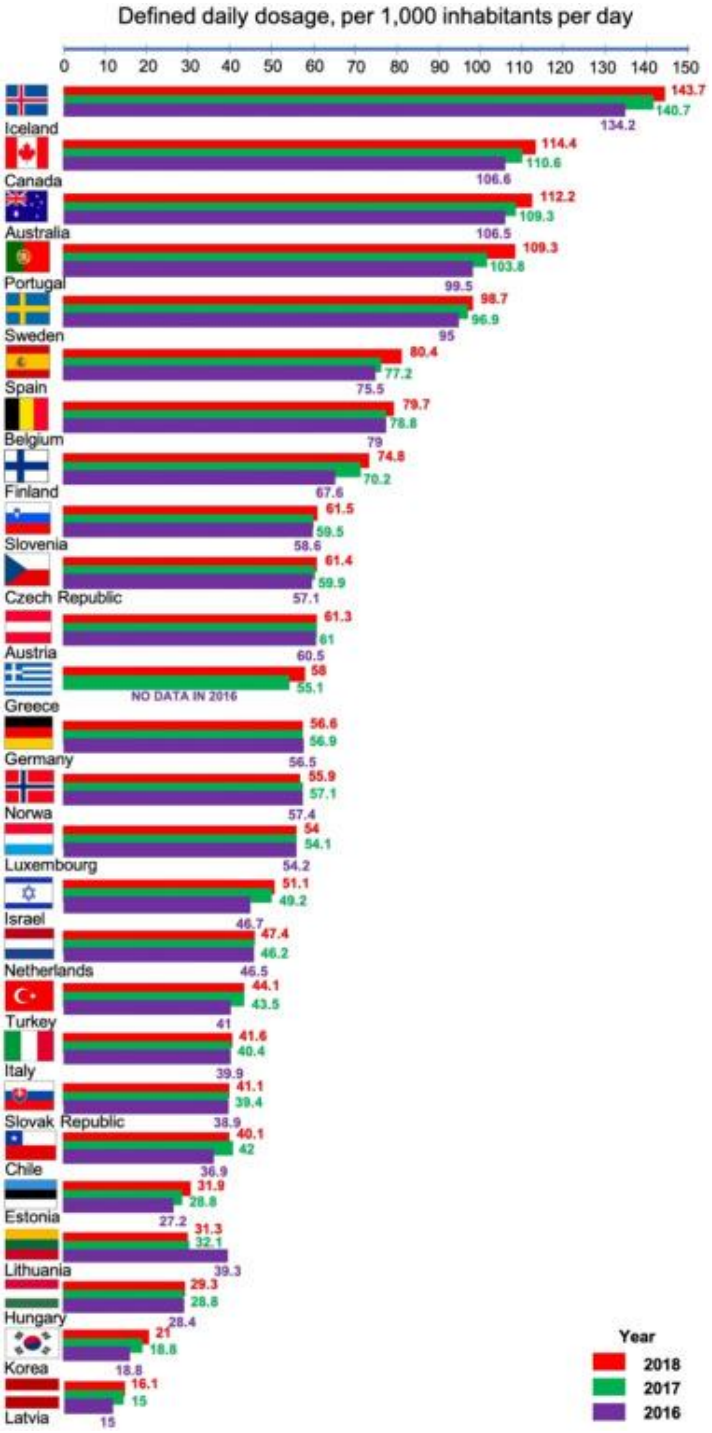


Figure 2. Antidepressant consumption in the Organization for Economic Co-operation and Development member countries (Castillo-Zacarías et al., 2021).

2.1 The pathophysiology of major depression

Two hypotheses have been developed for the understanding of the pathophysiology of depression; the first is the idea that a deficit in function or amount of monoamines (the monoamine hypothesis) is central to the biology of depression, and the second is that neurotrophic and endocrine factors play a significant role (the neurotrophic hypothesis). The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT), norepinephrine (NE), and dopamine (DA). It has been known for many years that reserpine treatment, which is known to deplete monoamines, is associated with depression in a subset of patients. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine, which causes a depletion of presynaptic stores of NE, 5-HT, and DA, induced a syndrome resembling depression. All available antidepressants appear to have significant effects on the monoamine system. All classes of antidepressants appear to enhance the synaptic availability of 5-HT, norepinephrine, or dopamine (Katzung et al., 2018).

In the neurotrophic hypothesis, depression is associated with the loss of neurotrophic support, and effective antidepressant therapies increase neurogenesis and synaptic connectivity in cortical areas such as the hippocampus. The nerve growth factor BDNF (brain-derived neurotrophic factor) is thought to influence neuronal survival and growth by activating the tyrosine kinase receptor B in both neurons and glia. Human studies seem to support animal data on the role of neurotrophic factors in stress states. Depression appears to be associated with a drop in BDNF levels in the cerebrospinal fluid and serum, as well as with a decrease in tyrosine kinase receptor B activity. Conversely, administration of antidepressants increases BDNF levels in clinical trials and may be associated with an increase in hippocampus volume in some patients (Katzung et al., 2018).

The monoamine hypothesis and neurotrophic hypothesis are, at best, incomplete. Many studies have not found an alteration in function or levels of monoamines in depressed patients. In addition, some candidate antidepressant agents under study do not act directly on the monoamine system. Thus, monoamine function appears to be an important but not exclusive factor in the pathophysiology of depression. Much evidence supports the neurotrophic hypothesis of depression, but not all evidence is consistent with this concept. Animal studies in BDNF knockout mice do not always have the expected results that would be expected with a deficiency of BDNF. In addition, some animal studies have found an increase in BDNF levels after some types of social stress (Katzung et al., 2018).

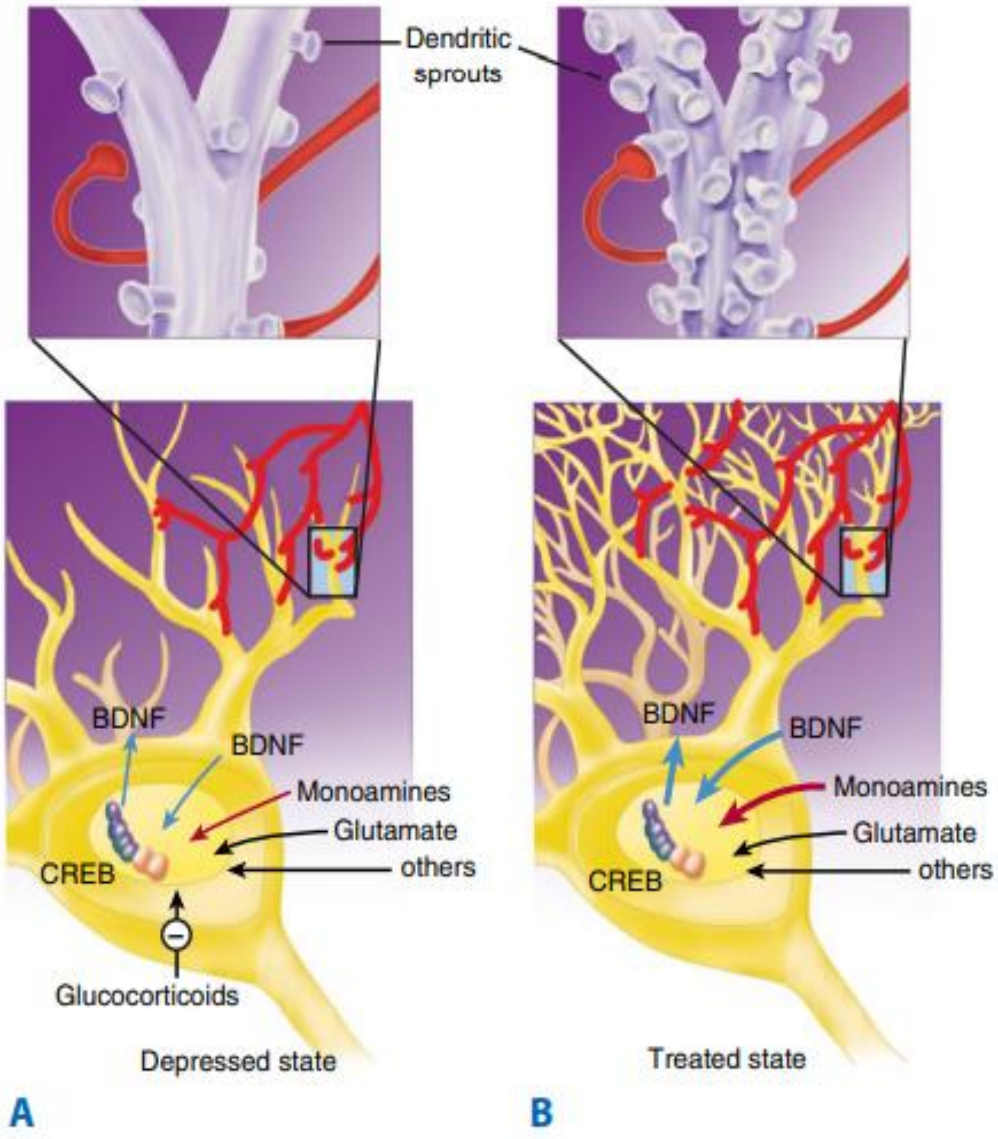


Figure 3. The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor (BDNF) and hormones appear to play a significant role in the development of major depression (Katzung et al., 2018).

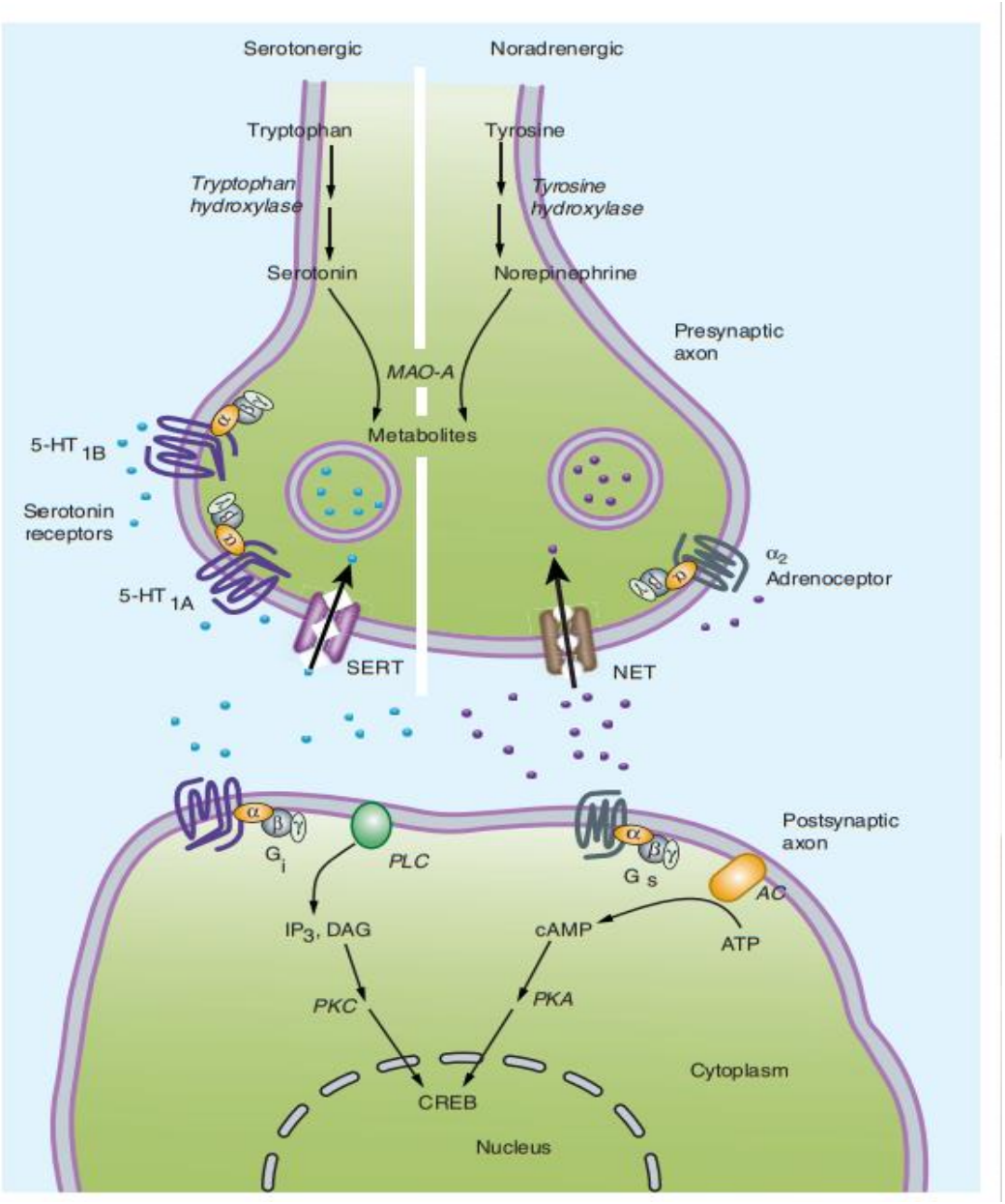


Figure 4. The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; IP 3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter (Katzung et al., 2018).

Various hormonal abnormalities, such as altered levels of cortisol, growth hormone (GH), or thyroid hormones, indicate the existence of endocrine disturbances, especially dysfunctions in the hypothalamus-pituitary-adrenal (HPA) axis and/or the regulation of thyroid function. The significance of these HPA abnormalities is unclear, but they are thought to indicate a dysregulation

of the stress hormone axis. More severe types of depression, such as psychotic depression, are more commonly associated with HPA abnormalities than milder forms of major depression. It is well known that both exogenous glucocorticoids and endogenous elevation of cortisol are associated with mood symptoms and cognitive deficits similar to those seen in MDD. The several pathophysiologic hypotheses just described are not mutually exclusive. It is evident that the monoamine, neuroendocrine, and neurotrophic systems are interrelated in important ways (Katzung et al., 2018).

2.2 Antidepressant subgroups

The currently available antidepressants make up a remarkable variety of chemical types, which are distinguished by their structure and molecular targets. The most commonly used medications, often referred to as second-generation antidepressants, are the selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs), which have greater efficacy and safety compared to most older drugs (i.e., first-generation antidepressants).

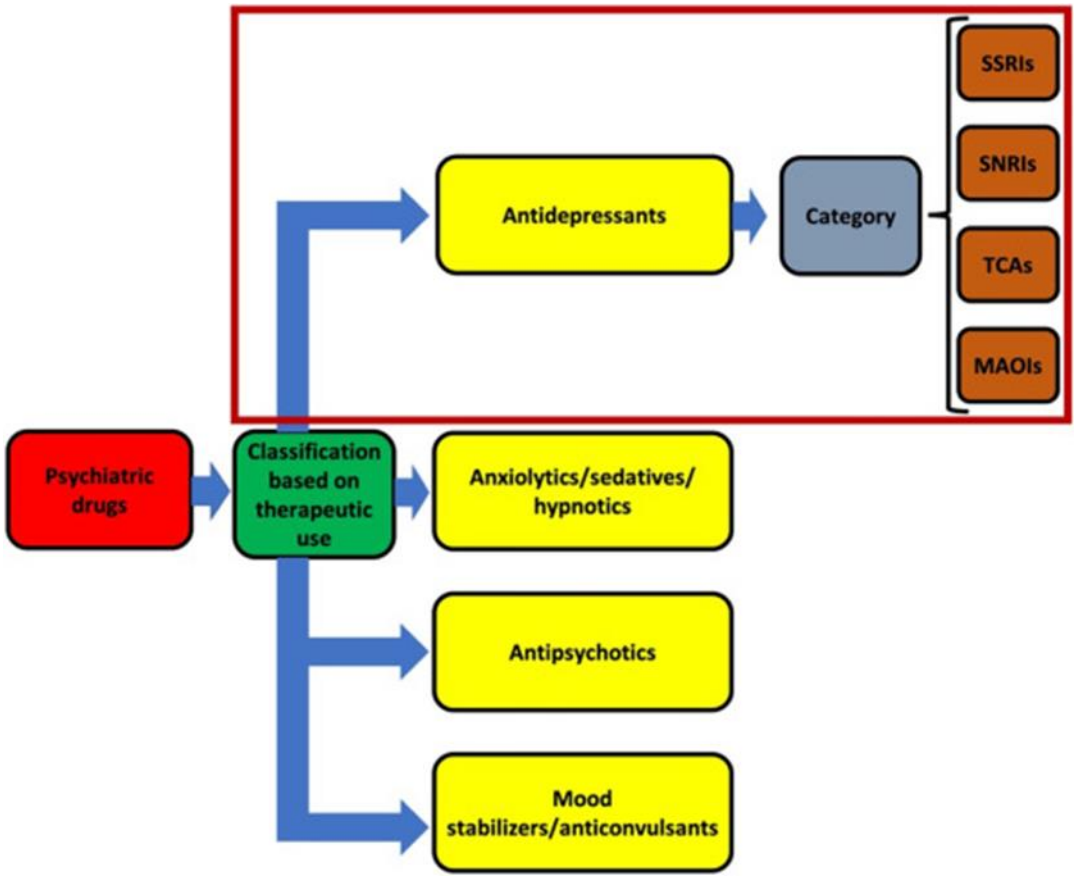
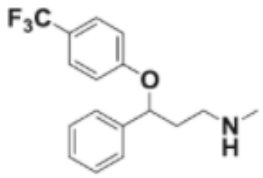
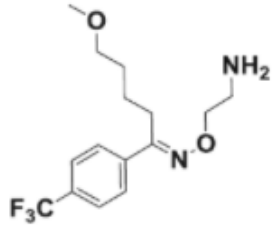
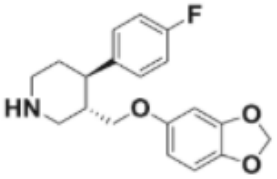
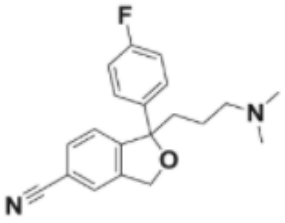
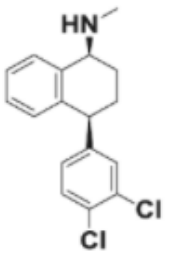
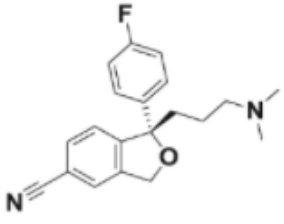


Figure 5. Classification of psychiatric drugs with special insight on antidepressants (Castillo-Zacarías et al., 2021).

2.2.1 Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) represent a chemically diverse class of agents that have as their primary action the inhibition of the serotonin transporter (SERT), which mediates the reuptake of serotonin into the presynaptic terminal. Thus, treatment with an SSRI initially blocks reuptake and results in enhanced and prolonged serotonergic neurotransmission. SSRIs used clinically are relatively selective (10-fold or more) for inhibition of SERT relative to norepinephrine (NET). They are the most common antidepressants in clinical use. In addition to their use in major depression, SSRIs have indications in GAD, PTSD, OCD, panic disorder, PMDD, and bulimia. Fluoxetine, sertraline, citalopram, paroxetine, fluvoxamine, and escitalopram are the SSRIs available for use (Table 1). As with all antidepressants, SSRIs are highly lipophilic. The popularity of SSRIs stems mainly from their ease of use, safety in overdose, relative tolerability, cost (all except escitalopram are generically available), and the broad spectrum of uses (Katzung et al., 2018).

Table 1. Name and chemical structure of SSRIs (Katzung et al., 2018).

 Fluoxetine (Prozac)	 Fluvoxamine (Luvox)
 Paroxetine (Paxil)	 Citalopram (Celexa)
 Sertraline (Zoloft)	 Escitalopram (Lexapro)

2.2.2 Serotonin-Norepinephrine Reuptake Inhibitors

Two classes of antidepressants act as combined serotonin and norepinephrine reuptake inhibitors: tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and TCAs.

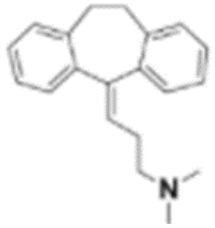
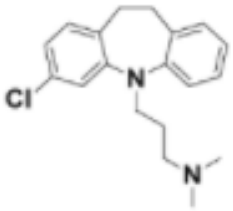
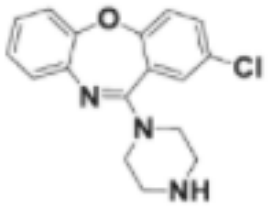
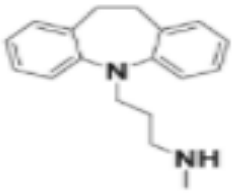
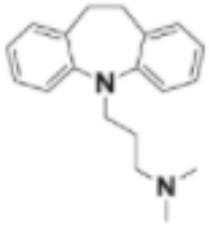
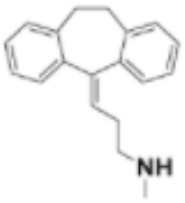
A. Tricyclic antidepressants (TCAs)

The TCAs were the dominant class of antidepressants until the introduction of SSRIs in the 1980s and 1990s. Nine TCAs are available in the USA (some of them are given in Table 2), and they all have an iminodibenzyl (tricyclic) core. The chemical differences between the TCAs are relatively subtle. Currently, the TCAs are used primarily in treating depression that is unresponsive to more commonly used antidepressants such as SSRIs or SNRIs. Their loss of popularity stems mainly from relatively poorer tolerability compared with newer agents, the difficulty of use, and lethality in overdose. Other uses for TCAs include treating pain conditions, enuresis, and insomnia. Available TCAs are amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine (Katzung et al., 2018).

B. Selective serotonin-norepinephrine reuptake inhibitors

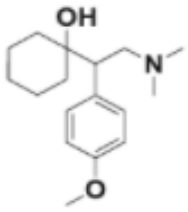
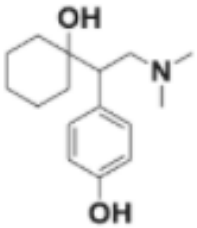
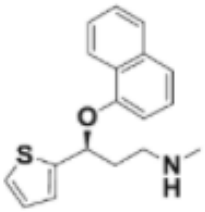
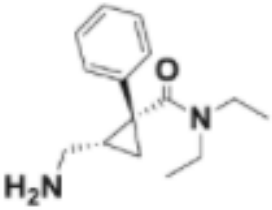
Many older TCAs block both SERT and NET, but at a high side effect burden. Four medications with a non-tricyclic structure that inhibit the reuptake of both 5-HT and norepinephrine have been approved for use in the U.S. for the treatment of depression and anxiety disorders (see Table 3); venlafaxine and its demethylated metabolite, desvenlafaxine; duloxetine; and milnacipran (approved only for fibromyalgia pain in the U.S.). SNRIs are also used to treat generalized anxiety, stress urinary incontinence, and vasomotor symptoms of menopause.

Table 2. Name and chemical structure of some TCAs (Katzung et al., 2018).

 Amitriptyline	 Clomipramine
 Amoxapine	 Desipramine
 Imipramine	 Nortriptyline

As do the TCAs, all SNRIs bind the serotonin (SERT) and norepinephrine (NET) transporters. However, unlike the TCAs, SNRIs do not have much affinity for other receptors. Venlafaxine and desvenlafaxine are bicyclic compounds, whereas duloxetine is a three-ring structure unrelated to the TCAs.

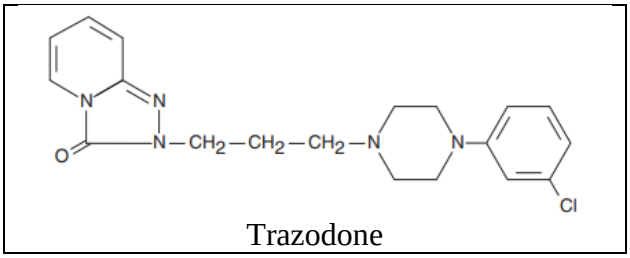
Table 3. Name and chemical structure of SNRIs (Katzung et al., 2018).

 Venlafaxine (Effexor)	 Desvenlafaxine (Pristiq)
 Duloxetine (Cymbalta)	 Milnacipran (Savella)

2.2.3 Serotonin Receptor Antagonists

Several antagonists of the 5-HT_2 family of receptors are effective antidepressants, although most agents of this class affect other receptor classes as well. Two antidepressants are thought to act primarily as antagonists at the 5-HT_2 receptor: trazodone and nefazodone. Trazodone (Table 4) was among the most commonly prescribed antidepressants until the SSRIs supplanted it in the late 1980s. The most common use of trazodone in current practice is an unlabeled hypnotic since it is highly sedating. Nefazodone is chemically related to trazodone. Nefazodone is no longer commonly prescribed due to its implication in hepatotoxicity cases (Katzung et al., 2018).

Table 4. Chemical structure of trazodone (Katzung et al., 2018).

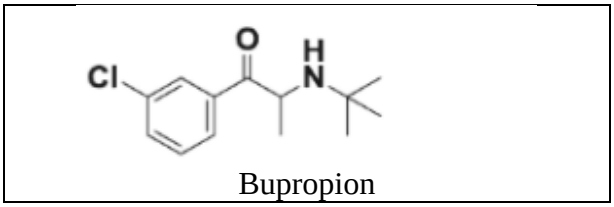


Trazodone

2.2.4 Tetracyclic and Unicyclic Antidepressants

Several antidepressants do not fit neatly into the other classes. Among these are bupropion, mirtazapine, amoxapine, and maprotiline. Bupropion has a unicyclic aminoketone structure, as seen in Table 5. Mirtazapine, amoxapine, and maprotiline have tetracyclic structures. Amoxapine and maprotiline share structural similarities and side effects comparable to the TCAs. As a result, these tetracyclics are not commonly prescribed in current practice. Their primary use is in MDD that is unresponsive to other agents (Katzung et al., 2018).

Table 5. Chemical structure of bupropion (Katzung et al., 2018).



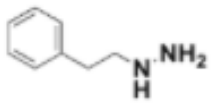
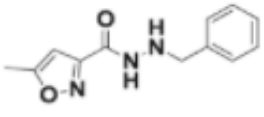
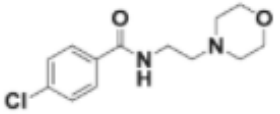
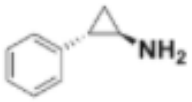
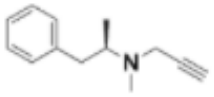
Bupropion

2.2.5 Monoamine Oxidase Inhibitors

Arguably the first modern class of antidepressants, monoamine oxidase inhibitors (MAOIs), was introduced in the 1950s but is now rarely used in clinical practice because of toxicity and potentially lethal food and drug interactions. Their primary use now is in treating depression

unresponsive to other antidepressants. Current MAOIs include the hydrazine derivatives phenelzine and isocarboxazid and the non-hydrazines tranylcypromine, selegiline, and moclobemide (Table 6).

Table 6. Name and structure of some MAOIs (Katzung et al., 2018).

 Phenelzine	 Isocarboxazid	 Moclobemide
 Tranylcypromine	 Selegiline	

2.3 Antidepressant presence in the environment

Like other groups of pharmaceuticals, psychiatric drugs are not completely metabolized by the human body and are excreted as the unchanged parent compound or metabolites. Even if pharmaceuticals are adequately metabolized, their metabolites may continue to be biologically active and, in some cases, be easily transformed to the parent compound under environmental conditions due to bacterial action. Antidepressant drugs have been observed in many urban and natural water bodies around the globe (Aus der Beek et al., 2016).

Table 7 presents the studies reporting the presence of SSRI antidepressants. These studies highlight the importance of monitoring these drugs and paying close attention to areas with increasing populations and inadequate wastewater treatment systems. It is important to remark that natural water reservoirs can receive water containing these antidepressant drugs leading to their acute and chronic exposure in the aquatic native life and humans (Grabicová et al., 2020).

Not surprisingly, antidepressants are among the many pharmaceuticals detected at measurable concentrations in the environment. The highest reported concentration of sertraline, one of the most commonly prescribed antidepressants worldwide, is 0.0084 μg/L (Vasskog et al., 2006) in raw sewage in Norway and 0.006 μg/L in Canada (Lajeunesse et al., 2008). Fluoxetine is another antidepressant commonly detected in wastewater. Kolpin et al. (2002) estimated the concentration of fluoxetine at 0.012 μg/L in a stream in the United States in one of the first large-scale studies of pharmaceutical contamination in North America.

In recent years, venlafaxine and citalopram (SSRIs) have surpassed fluoxetine as antidepressants occurring at the highest environmental concentrations. Lajeunesse et al. (2008) measured venlafaxine concentrations from Canadian treatment plants up to 0.213 μg/L in raw sewage, to 0.214 μg/L in the effluent, and up to 0.045 μg/L in streams flowing into the St. Lawrence River.

Similar high concentrations were measured by Schultz and Furlong (2008) in wastewater effluent in Minnesota and downstream from treatment plants in Texas.

Table 7. Detection frequency and geographic distribution of SSRIs in wastewater influent sewage, effluent, freshwater and saltwater (Mole et al., 2019).

Influent detection (ng/L)						**Geographic distribution**			
Compound	Times Studied	Times Detected	Ratio	Min	Max	Asia-Pacific	Europe	North America	South America
Citalopram	27	26	(26/27)	ND	17100	3	19	5	–
Desmethyl citalopram	6	4	(4/6)	ND	209	1	3	2	–
Desmethyl fluvoxamine	1	1	(1/1)	ND	12	–	–	1	–
Escitalopram	1	1	(1/1)	ND	32228	–	1	–	–
Fluoxetine	38	34	(34/38)	ND	3465	6	22	10	–
Fluvoxamine	4	3	(3/4)	ND	435	2	–	2	–
Norfluoxetine	12	11	(11/12)	ND	10400	–	8	4	–
Norsertraline	10	8	(8/10)	ND	386	2	2	6	–
Paroxetine	19	15	(15/19)	ND	39732	2	11	6	–
Sertraline	22	19	(19/22)	<0.13	997	5	11	6	–
Effluent detection (ng/L)						**Geographic distribution**			
Compound	Times Studied	Times Detected	Ratio	Min	Max	Asia-Pacific	Europe	North America	South America
Citalopram	42	42	(42/42)	ND	9200	5	28	9	–
Desmethyl fluvoxamine	1	1	(1/1)	ND	9.3	–	–	1	–
Desmethyl citalopram	7	5	(5/7)	ND	425.7	1	4	2	–
Didesmethyl citalopram	1	1	(1/1)	0.9	20	–	1	–	–
Fluoxetine	70	57	(57/70)	ND	2700	7	36	27	–
Fluvoxamine	5	3	(3/5)	ND	3.9	2	1	2	–
Norfluoxetine	21	18	(18/21)	ND	9810	–	12	9	–
Norsertraline	11	9	(9/11)	ND	423	2	3	6	–
Paroxetine	26	20	(20/26)	ND	740	3	12	11	–
Sertraline	30	22	(22/30)	ND	1930	6	13	11	–

Freshwater detection (ng/L)						**Geographic distribution**			
Compound	Times Studied	Times Detected	Ratio	Min	Max	Asia-Pacific	Europe	North America	South America
Citalopram	31	30	(30/31)	ND	426.6	–	19	11	1
Desmethyl citalopram	3	2	(2/3)	ND	2.41	–	1	1	–
Fluoxetine	44	25	(25/44)	ND	330	2	15	26	1
Fluvoxamine	1	0	(0/1)	ND	ND	–	–	1	–
Norfluoxetine	11	3	(3/11)	ND	80.5	–	5	6	–
Norsertraline	1	0	(0/1)	ND	ND	–	1	–	–
Paroxetine	14	7	(7/14)	ND	40	–	8	6	–
Sertraline	20	13	(13/20)	ND	75	1	10	8	1
Saltwater detection (ng/L)						**Geographic distribution**			
Compound	Times Studied	Times Detected	Ratio	Min	Max	Asia-Pacific	Europe	North America	South America
Citalopram	2	2	(2/2)	0.9	5.4	–	2	–	–
Fluoxetine	4	2	(2/4)	ND	36	1	3	–	–
Norfluoxetine	1	0	(0/1)	ND	ND	–	1	–	–
Paroxetine	1	0	(0/1)	ND	ND	–	1	–	–
Sertraline	1	0	(0/1)	ND	ND	–	1	–	–

2.4 Toxicity of psychiatric drugs for non-target organisms

Like other pharmacological groups, psychiatric pharmaceuticals occur in the environment in the range of ng L^{-1}–µg L^{-1} (Bound et al., 2006). Although these concentrations are below the levels predicted to cause harm to humans, as well as to cause acute or even chronic toxicity to non-target organisms, it is pertinent to take into account that these compounds do not occur isolated but as complex mixtures. In this context, and due to having an intrinsic biological activity that would affect nervous and endocrine systems, psychiatric pharmaceuticals are one of the most significant groups concerning the evaluation of ecotoxicological effects in terrestrial and aquatic non-target organisms (van der Ven et al., 2006). Pharmaceutical compounds are designed to interact with biological systems to produce beneficial effects in humans and other animals (Boxall et al., 2003). Because such substances are not completely metabolized within the treated organisms, they are excreted and can enter and adversely affect the environment and other organisms (Küster and Adler, 2014). Medicinal products, such as antidepressants, antimycotics, antibiotics, and estrogens, can have ecotoxicological impacts on non-target organisms and pose environmental risks even at low concentrations (Ginebreda et al., 2010).

Antidepressants are the most commonly prescribed medication for major depressive disorders and represent a class of pharmaceuticals that can pose an elevated level of risk to aquatic organisms (Brodin et al., 2014). The presence of antidepressants in waters can produce adverse effects on exposed aquatic fauna (Schultz et al., 2010). Studies have demonstrated that fish experimentally exposed to minute concentrations of antidepressants can become more aggressive and less cautious, and some have shown a loss of ability to camouflage (Scott and Sloman, 2004). The widely used antidepressant oxazepam has been reported to alter the behavior and feeding rate of *Perca fluvialitis* (Brodin et al., 2014) at concentrations lower than that considered a health risk to humans. Exposure to the antidepressant fluoxetine resulted in decreased feeding in fish species, including goldfish (Carassius auratus) and hybrid striped bass (Morone saxatilis) (Gaworecki and Klaine, 2008; Mennigen et al., 2010). In addition to impacts on fish behaviour and physiology, these drugs can affect other aquatic fauna, especially macroinvertebrates (Ford and Fong, 2014). Aquatic macroinvertebrates play important roles in the ecology of water bodies, occupying a broad range of ecological niches and exhibiting an array of behaviors, the modifications of which can lead to significant changes in trophic relationships (Shaliutina-Kolešová, et al. 2019). Research has suggested that trace amounts of fluoxetine endanger freshwater mussels, a species that plays a key role in the ecology of streams and rivers. The presence of fluoxetine in water can reduce mussel embryo production and the number of offspring and, hence, decrease their numbers (Ford and Fong, 2014).

2.4.1 Invertebrates

Invertebrates can bioaccumulate pollutants in their tissues. Also, it is known that high levels of contamination can reduce the immune system's responsiveness (Matozzo et al., 2013, Torre et al., 2013). For these reasons, invertebrates are suitable organisms for biomonitoring coastal water quality. Their ability to develop consistent responses makes these organisms excellent sentinel organisms, and they are therefore employed in a large number of bio-monitoring programs.

De Castro-Català et al. (2017) studied low dose effects (100 ng/L) of the SSRI fluoxetine on the behavior of the freshwater invertebrate Gammarus pulex and found an increase in swimming velocity. Previous studies have also detected altered swimming behavior in amphipods at very low concentrations (1–100 ng/L) and in cladocerans found that fluoxetine significantly altered camouflage efficiencies on uniform and sandy backgrounds at the lowest concentration but not at 100 ng/L. Hatchlings exposed to 1 ng/L of fluoxetine exhibited a decrease in uniform camouflage efficiency dependent on the duration of exposure. They also showed a significant increase in the frequency of sand digging behaviors which might make them highly visible to natural predators. This means that environmentally realistic concentrations of fluoxetine significantly impair the cryptic performances of newly hatched cuttlefish and may ultimately reduce their chances of survival. Hazelton et al. (2014) came to a similar conclusion after studying the effects of fluoxetine at concentrations of 0, 0.5, 2.5, and 22.3 μg/L on the behavior of the adult freshwater mussel Lampsilis fasciola over a 67-day experiment. Statistically significant increases in movement, decreased times to movement, an increased likelihood of diurnal movement, and increased rates of lure display were observed in mussels treated with fluoxetine at less than 22.3 μg/L compared to the untreated control. Such changes are likely to increase the susceptibility to predation, and may also alter sediment nutrient cycling, as mussels are important in maintaining sediment stability and structure as well as in providing habitat for other macroinvertebrates and in-sediment nutrient dynamics and oxygenation through bioturbation (Vaughn and Hakenkamp, 2001). In two freshwater snails, exposure to venlafaxine and citalopram was reported to cause significant foot detachment from the substrate, Leptoxis carinata, and Stagnicola elodes. This was caused by venlafaxine at a concentration of 313 pg/L in L. carinata and 31.3 ng/L in S. elodes, and by citalopram at a concentration of 405 pg/L in L. carinata and 4.05 μg/L in S. elodes (Fong and Hoy, 2012). Foot detachment from the substrate is a sub-lethal effect that could result in transport to unfavorable habitats and which would be difficult to detect in nature (Fong and Ford, 2014).

However, it is not only behavior that has been found to be influenced by low concentrations of antidepressants. Péry et al. (2008) reported the effects of fluoxetine on the life cycle of Daphnia magna, Hyalella azteca, and the snail Potamopyrgus antipodarum exposed to fluoxetine spiked water.

The newborn length was impacted by fluoxetine. For P. antiporadum, a significant decrease in reproduction was found at a 10 μg/L concentration. The exposure of H. azteca to fluoxetine significantly affected growth (the NOEC was established to be 33 μg/L). Also, Brooks et al. (2003) found a decrease in reproduction in Ceriodaphnia dubia after exposure to fluoxetine, with a NOEC of 56 μg/L and a LOEC of 112 μg/L. In contrast, Fong and Ford (2014), revealed that external applications of serotonin induced spawning in bivalves. Fong et al. (1998) found that spawning in male zebra mussels (Dretssena polymorpha) was induced by the SSRIs fluvoxamine (1 nM) and fluoxetine (50 nM). Lazzara et al. (2012) exposed zebra mussels to environmentally relevant concentrations of fluoxetine (20 and 200 ng/L).

Histological analyses of female and male gonads showed a concentration-dependent decrease in oocyte and spermatozoan density in fluoxetine-treated groups compared to the control, suggesting the ability of fluoxetine to induce spawning at concentrations as low as 20 ng/L. In addition, their experiment showed that the short-term exposure of zebra mussels to fluoxetine at a concentration of 200 ng/L led to a significant increase in esterified estradiol. This impact on zebra mussels and other species with external spawning can be detrimental since spawning has to be highly synchronized because of the brief viability of gametes in water (Newell et al., 1982; Ram et al., 1996; Juhel et al., 2003). Chen et al. (2015) investigated the effect of fluoxetine on cellular detoxification and defense system in bivalves. The adult Asian clam (Corbicula fluminea) was exposed to 0.5, 5, and 50 μg/L of fluoxetine resulting in a decrease in superoxide dismutase and glutathione reductase activity and an increase in catalase, glutathione peroxidase and glutathione-S-transferase activity which suggest oxidative stress. Regarding the overview of data given above, even in environmentally relevant concentrations, antidepressants can significantly influence both behavior and development of invertebrates. Even if not all tested concentrations are related to those found in the environment, it is always a good approach to study the concentration-dependent answer of the organism, which often helps to understand the mechanism of toxicity.

2.4.2 Vertebrates

A. Fish

Pollution is a significant threat to populations of wild fish. Habitats under chronic exposure to pollutants often suffer reduced species richness and loss of community integrity (Fazio et al., 2012, Aliko et al., 2018). Fish are susceptible to anthropogenic impacts and, for this reason, some can be employed as bio-monitors in the evaluation of the ecological status of aquatic environments (Fazio et al., 2014; Chromcova et al., 2015; Alomar et al., 2017; Sehonova et al., 2017b; Plhalova et al., in press). Consequently, fishes in contaminated areas are often exposed to much higher concentrations

or to chemical forms different from those that are typically in the environment. In response to stressors, a fish undergoes a series of biochemical and physiological changes in an attempt to compensate for the challenges imposed upon it and thereby cope with the stress. The effect of antidepressants on fish is of great importance as fish are at the top of the food chain in aquatic environments. Moreover, fish serotonin transporters have a high affinity to the selective serotonin reuptake inhibitors (SSRIs) used in human therapy (Gould et al., 2007).

Lepage et al. (2005) studied the role of citalopram in shaping dominant-subordinate relationships and aggression in rainbow trout in a one-week feeding experiment. In fish exhibiting dominant behavior, citalopram treatment for 7 days at a concentration of 100 μg per 1 kg of fish body mass resulted in a significant reduction in the number of attacks performed against intruders. Such fish also performed significantly lower numbers of attacks than fish that exhibited dominant behavior but were fed control feed. Holmberg et al. (2011) studied the effect of waterborne citalopram on aggressive and sexual behavior in rainbow trout and guppies. Rainbow trout fry and adult male guppies were exposed to waterborne citalopram for 3–7 days, the concentrations of citalopram ranging from environmentally relevant to high (1, 10, 100 μg/L). Under these conditions, citalopram did not appear to cause significant effects on aggression in rainbow trout fry or sexual behavior in male guppies. The authors explained the results by the relatively low uptake of citalopram from water to fish. However, we believe it is also the length of the experiment that should be considered. Was the trial long enough to observe some changes? Another SSRI, fluoxetine, was found to significantly impact mating behavior, such as nest building and defensive behavior, in male fathead minnow (Pimephales promelas) at a concentration as low as 1 μg/L. Males were also found to display aggression, isolation, and repetitive behaviors at higher concentrations (Weinberger and Klaper, 2014). In the Gulf toadfish, Opsanus beta, fluoxetine treatment increased the number of aggressive behaviors in dominant individuals (McDonald et al., 2011). Parrott and Metcalfe (2017) exposed fathead minnows (P. promelas) over their full life cycle to environmentally relevant concentrations of the SNRI venlafaxine in order to study the effect on survival, development, and reproduction. According to their results, such exposure at environmentally relevant concentrations (0.88 and 8.8 μg/L) caused no adverse effects in fathead minnows.

In contrast, other authors have described various biological effects in fish exposed to venlafaxine. Schultz et al. (2011) observed reduced survival in adult male fathead minnows (P. promelas) exposed to 0.3 and 1.1 μg/L of venlafaxine for a period of 21 days. In our opinion, the difference in observations of Parrott and Metcalfe (2017) and Schultz et al. (2011) can be explained by trial design. In the case of Parrott and Metcalfe (2017), fish were exposed over their full life cycle. Hence, these organisms could have adapted to the exposure to venlafaxine, which was not possible

in the case of Schultz et al. (2011). Galus et al. (2013) exposed adult zebrafish for 6 weeks to venlafaxine at a concentration of 10 µg/L, resulting in significantly reduced embryo production.

Also, behavior has been found to be affected by venlafaxine. Escape responses were slowed in larval fathead minnows exposed to 5 µg/L venlafaxine over a period of 12 days (Painter et al., 2009). Time to capture prey was increased in hybrid striped bass (Morone saxatilis × Morone chrysops) exposed to 50, 250, and 500 µg/L of venlafaxine for a period of 6 days (Bisesi et al., 2014). A disturbed circadian rhythm with decreased locomotion during the day was seen in adult mosquitofish (Gambusia holbrooki) exposed to 100 µg/L venlafaxine for 7 days (Melvin, 2017).

Sehonova et al. (2017a) studied the effects of the tricyclic antidepressant amitriptyline, nortriptyline, and clomipramine at concentrations of 10, 100, and 500 µg/L on early-life stages of common carp (Cyprinus carpio) for a period of 30 days. Long-term exposure resulted in a significant increase in mortality, developmental retardation, morphological anomalies, and pathological changes in the brain, heart. In addition, changes in antioxidant enzyme activity and an increase in lipid peroxidation were observed, even at the lowest tested concentrations.

Antidepressants have been proven to influence fish in various ways. Effects on behavior, such as shaping of dominant–subordinate relationships in the case of clomipramin, or changes in sexual behavior after exposure to fluoxetine have been observed. Tricyclic antidepressants can even influence the survival or development of fish in early-life stages.

B. Amphibians

Only very little is known about the effects of antidepressant residues on amphibians. Ten Eyck and Regen (2014) studied the influence of the SSRI fluoxetine on the establishment of dominant/subordinate and territorial (calling)/non-territorial (non-calling) relationships in males of the frog Eleutherodactylus coqui. Fluoxetine at a concentration of 10 mg/kg mass injected into adult males every day for a period of 20 days resulted in changes in male territorial and social behavior. Foster et al. (2010) studied the effects of chronic exposure to fluoxetine on Rana pipiens larvae. Tadpoles were exposed to fluoxetine at concentrations of 0.029 and 0.29 µg/L from stages 21 and 22 through completion of metamorphosis resulting in delayed development compared with the control. SSRIs have also been examined for their potential to disrupt the hypothalamus-pituitary-thyroid axis in amphibians. In particular, SSRIs were able to alter metamorphosis in amphibians, which is dependent on thyroid hormone (Kollros, 1961). In addition, Conners et al. (2009) studied whether low environmentally relevant concentrations of fluoxetine and sertraline could impair growth and development in tadpoles of the African clawed frog. The concentrations were 0.1, 1, and 10 µg/L of both chemicals. They reported that after exposure to sertraline, Xenopus laevis required less time to

complete metamorphosis and that its body mass was decreased. Based on the little data available, further research is necessary to consider the effect of antidepressant residues on amphibians. However, it is already possible to claim that antidepressants can potentially disrupt social behavior and the development of amphibians.

3. Advanced oxidation processes based on UV radiation

Persistent contaminants remain in WWTP effluents since conventional physical and biological wastewater treatment can only partially remove these substances (Lim, 2008; Zhang et al., 2008; Luo et al., 2014). The application of advanced oxidation processes (AOPs) provides an improved removal efficiency of these compounds due to the production of oxidation radicals. UV-based AOPs involve processes based on UV-irradiation (mostly UVC) and its combination with different radical promoters. Photochemical technologies provide both contaminant degradation and disinfection as well. UV wavelengths applied are usually 200-300nm and >200 mJ/cm^2 and therefore exceed UV-dose requirements for 4-log inactivation of most pathogens, including UV-resistant organisms (e.g., adenovirus) (EPA, 2006). UV-irradiation sources usually consist of either low-(LP) or medium-pressure (MP) mercury lamps with mono- or polychromatic emission spectra, respectively. Recently, sunlight has been explored as another source of irradiation, as well as UV-light emitting diodes (LEDs) with specific wavelength distributions (Song et al., 2016). The advantages of LEDs are the elimination of mercury, unique peak emission wavelengths, compact size, flexible application design, and a short start-up phase.

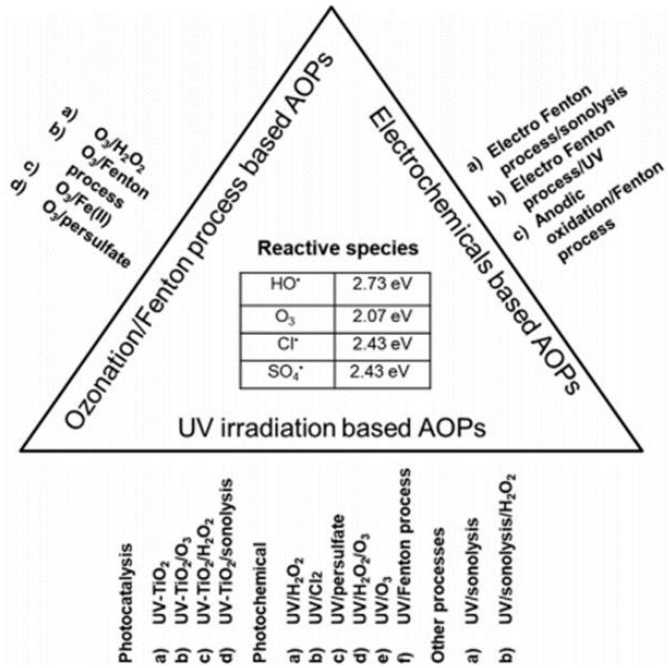


Figure 6. Integrated AOPs. (Tufail et al., 2020)

3.1 UV photolysis

In direct UV photolysis, UV irradiation excites photolabile moieties present in contaminants and oxidizes them, while indirect UV photolysis uses different oxidants, such as hydrogen peroxide, to generate radical species that contribute to the contaminant's degradation. The removal efficiency depends on various factors such as turbidity of the matrix, type and intensity of UV lamps, molar absorption coefficient, as well as the functional groups present in target compounds.

In UV direct photolysis, the contaminant absorbs the radiation and undergoes degradation through the electronic excitation of atoms present in the structure. UV irradiation transforms the compounds' chemical structure. When the compounds are strong absorbers of UV radiation, direct photolysis is the primary degradation pathway during the treatment, but ineffective degradation occurs when the applied UV irradiation does not possess enough energy. Additional degradation pathway is triggered by the photosensitization processes from NOM or photolysis of water constituents, referred to as indirect photolysis. The long-lived (triplet) excited states of water organic constituents can induce chemical transformation of the organic pollutants either through direct energy transfer or by generating reactive species that further react with the pollutant. The typically low concentrations of pollutants in the contaminated water and, in general, the low light absorption in various matrices limit the applications of UV photolysis compared to the hydroxyl radical-driven technologies. Sometimes, a contaminant can be treated by both direct and indirect photolysis, and the optimization of the treatment process is driven by economic considerations (Parsons et al., 2004).

3.2 UVC/H_2O_2

The combination of UVC irradiation and H_2O_2 leads to the photolytic cleavage of H_2O_2 into two ·OH.

$$H_2O_2 + h\nu \rightarrow \cdot OH + \cdot OH \qquad (1)$$

These radicals may combine to either form hydrogen peroxide or react with other chemical species present in the system. UVC/H_2O_2 enhanced overall reaction kinetics due to direct and indirect photolysis by forming hydroxyl radicals. Applied H_2O_2 doses are mainly set based on economic aspects. However, higher concentrations also result in the scavenging of ·OH with H_2O_2 and affect the efficiency of the reaction.

$$\cdot OH + H_2O_2 \rightarrow \cdot HO_2 + H_2O \qquad (2)$$

$$\cdot HO_2 + H_2O_2 \rightarrow \cdot OH + H_2O + O_2 \qquad (3)$$

$$\cdot HO_2 + \cdot HO_2 \rightarrow H_2O_2 + O_2 \qquad (4)$$

Inorganic carbon species, such as bicarbonate and carbonate ions, are also scavengers of the hydroxyl radicals (Weeks and Rabani, 1966) and, therefore, are expected to affect the rate of OH-mediated reactions of organic compounds. UVC/H_2O_2 for contaminants removal has been examined at the lab-scale (Wols and Hofman-Caris, 2012; Wols et al., 2013; Keen et al., 2016) for matrices such as ultrapure water or landfill leachate (Xiao et al., 2016; Ghazi et al., 2014). First, full-scale applications are already established for potable water reuse (Audenaert et al., 2011) and surface water treatment applications (Kruithof et al., 2007), as well as some textile, paper and pulp, and olive oil industries. Moreover, commercial-scale UV/H_2O_2 systems are now available for contaminated water treatment. UV/H_2O_2 is not established for advanced wastewater treatment mainly because of low UV-transmittance and high scavenging capacity of secondary or tertiary treated wastewater effluents but is used in some potable reuse treatment plants employing integrated membrane systems (ultrafiltration/ reverse osmosis) (Drewes and Khan, 2015). Due to the high demand for oxidants and energy, optimizing the conditions of chemical oxidation is essential for economic feasibility.

3.2.1 Other oxidants

Besides hydroxyl radicals, sulfate radicals ($SO_4\cdot^-$) have been identified as efficient, potent, and more selective organic contaminant oxidants activated by UVC radiation. The consumption of $SO_4\cdot^-$ by NOM is lower than that of HO·, so sulfate radicals are reported to be more efficient in natural water matrices. Persulfate ion (PS, $S_2O_8^{2-}$) is the most common oxidant used for the generation of $SO4\cdot^-$, together with peroxymonosulfate and peroxydisulfate. However, more selective reactivity of sulfate radicals results in a higher sensitivity to water matrix changes and DOM composition than UVC/H_2O_2 (Ahn et al., 2017).

Peracetic acid (PAA) is an organic peroxy acid that also can be used in advanced oxidation processes when irradiated by UVC, producing highly reactive free radicals that degrade organic contaminants (Cai et al., 2017, Caretti and Lubello, 2003). UVC/PAA has unique advantages over UV/H2O2 in that it produces multiple different radicals in the form of acetyloxyl radicals, methyl radicals, peroxyl radicals and acetylperoxyl radicals. Though these radicals are generally less reactive than hydroxyl radicals, they offer new reaction mechanisms and pathways.

3.3 UV/catalyst

The electronic structure of most semiconductors comprises the highest occupied band full of electrons called the valance band (VB), and the lowest unoccupied band called the conduction band (CB). These bands are separated by a region that is largely devoid of energy levels, and the difference in energy between the two bands is called the bandgap energy, E_{bg}. Photocatalysis for contaminant degradation involves photo-excitation of an electron from the valance band to the conduction band

on the surface of the catalyst by UV irradiation, resulting in the generation of an electron (e^-) in the conduction band and hole (h^+) in the valance band. The electron in the conduction band reacts with oxygen in the reaction mixture to produce $O_2^{\cdot-}$ that reacts with OH^- to produce hydroxyl radicals. (Bamba et al., 2008; Martínez et al., 2013; Alvarez et al., 2016; Zhao et al., 2018; Dong et al., 2019). Either electron-hole pair or hydroxyl radicals react with the compounds and oxidize them. The degradation by photocatalysis depends on the type of lamp, the nature of the catalyst, and the contaminant. For decades, TiO_2 has been used as a photocatalyst due to the strong photocatalytic activity, large surface area, and comparatively lower cost.

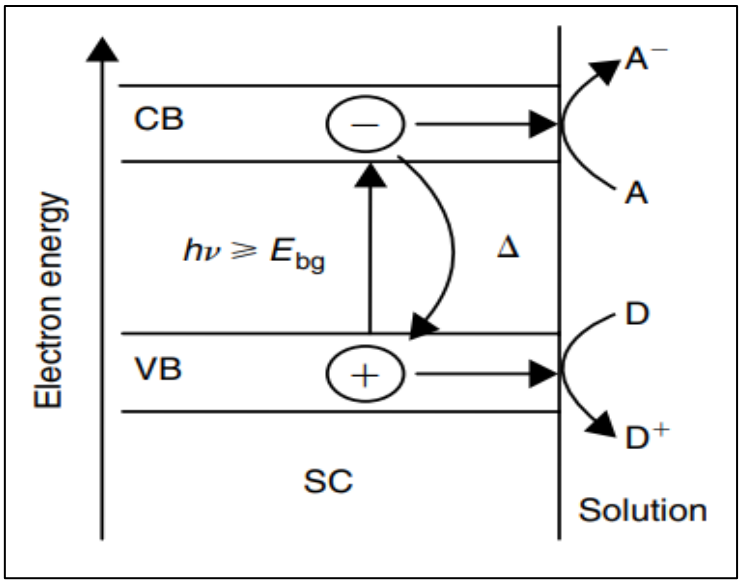


Figure 7. Schematic illustration of the energetics of semiconductor photocatalysis (Parsons et al., 2004).

However, fast electron-hole pair recombination results in low radical concentration, leading to poor contaminant degradation. Other catalysts like ZnO, WO3, and WS2 can be used in photocatalysis and show a lower recombination rate of electron-hole pairs (Wang et al., 2018a). In addition to removing organic pollutants, semiconductor photocatalyst has been used to sensitize the photoconversion of toxic inorganic substrates to harmless or less toxic ones and destroy biological material, like bacteria, viruses, and mold. The efficiency of the reaction is affected by the UV light energy conversion efficiency, the aquatic matrix, the reactor, the contaminant type, the electron-hole recombination, as well as the form and dispersion of the catalyst.

3.4 UVC/Cl_2

The UVC/chlorine process is an emerging AOP alternative to the UVC/H_2O_2 process. UVC photolysis of free chlorine (HOCl/OCl^-) is known to produce $^{\bullet}OH$ and reactive chlorine species, such as $^{\bullet}Cl$, $^{\bullet}ClO$, and $Cl_2^{\bullet-}$. $^{\bullet}OH$ is non-selective and reacts with various contaminants, whereas $^{\bullet}Cl$ is a selective oxidant that can be more reactive to compounds containing an aromatic ring and electron-rich moieties (Zihao Wu et al., 2016, Fang et al., 2014). Also, $^{\bullet}Cl$ reacts with chloride to produce $Cl_2^{\bullet-}$ (5) and both $^{\bullet}OH$ and $^{\bullet}Cl$ react with HOCl/OCl^- to produce $^{\bullet}ClO$ (5)-(9).

$$^{\bullet}Cl + Cl^- \leftrightarrow Cl_2^{\bullet-} \qquad (5)$$

$$HOCl + {}^{\bullet}OH \rightarrow {}^{\bullet}ClO + H_2O \qquad (6)$$

$$HOCl + {}^{\bullet}Cl \rightarrow {}^{\bullet}ClO + Cl^- + H^+ \qquad (7)$$

$$OCl^- + {}^{\bullet}OH \rightarrow {}^{\bullet}ClO + OH^- \qquad (8)$$

$$OCl^- + {}^{\bullet}Cl \rightarrow {}^{\bullet}ClO + Cl^- \qquad (9)$$

However, regarding hypochlorite, pH dependency of HOCl/OCl speciation needs to be considered since it significantly influences the molar absorption coefficient. UVC/Cl_2 is favorable for aquatic matrices with lower pH values, such as reverse osmosis permeate (Watts et al., 2007). Research has mainly been conducted on lab-scale systems for the degradation of organic indicator compounds (Jin et al., 2011; Sichel et al., 2011; Fang et al., 2014; Wang et al., 2016). A first full-scale application for indirect potable reuse recently started operation at the Los Angeles Terminal Island Water Reclamation Plant (Xylem, 2015). However, Cl· based reactions involve the formation of oxidative chlorine species (e.g., $^{\bullet}ClO$, $OCl^{\bullet-}$), which might be oxidized by OH· to chlorate, perchlorate, and halogenated by-products.

4. AOPS in antidepressant degradation

Advanced oxidation processes (AOPs) have been widely used in water and wastewater treatment to remove organic and inorganic contaminants and improve industrial wastewater biodegradability. The following tables summarize the different AOPs used in the degradation of antidepressants.

4.1 UVC irradiation

Table 8 summarizes the various studies on the degradation of antidepressants using direct UVC photolysis.

Table 8. UVC irradiation for the degradation of antidepressants.

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
citalopram, fluoxetine, norfluoxetine, paroxetine, duloxetine, bupropion, venlafaxine, sertraline, norsertraline (among other CECs)	WWTP effluent and deionized water	5 mg/L	UVC and chlorination	None of the target compounds were fully transformed by either chlorination or UV treatment at plant scale. Only citalopram, duloxetine, norfluoxetine, and venlafaxine after chlorination showed statistically significant decrease.	Molé et al., 2019
imipramine	WWTP effluent; output of the filtration pool and tap water	5 mg/L	Vacuum UV (VUV_{185} /UV_{254})	HO· oxidation and UV_{254} direct photolysis led to IMI degradation. Quantum yields of deprotonated and protonated IMI were 1.31×10^{-2} and 3.31×10^{-3} respectively. Increasing the initial IMI concentration lowered the degradation efficiency, while elevating reaction temperature significantly improved it. 64.7% and 97.0% removal efficiency in UV_{254} and VUV systems respectively after 30 min.	Xie et al., 2019
fluoxetine (among other CECs)	3 different secondary effluents and 1 primary effluent	10 mg/L	UVC	Chemical properties of CECs and the quality of treated effluent were key factors of the photodegradation. At full-scale: the low UV doses were not sufficient to reduce the concentration.	Paredes et al., 2018
citalopram, trazodone, paroxetine venlafaxine (among other CECs)	UV effluent of municipal WWTP located in a highly industrialized area	190 ng/L	UVC based	Removal higher than 80% for paroxetine. Medium removal by UV radiation (40–50%) was for venlafaxine. No UV effect for citalopram. The UV process coupled to primary and secondary treatment is not sufficient for the complete removal.	Collado et al., 2014

Molé et al. (2019) studied the transformation of thirteen target compounds (citalopram, fluoxetine, norfluoxetine, paroxetine, duloxetine, bupropion, venlafaxine, sertraline, and norsertraline, among others) using chlorination or UV irradiation by both bench-scale and field experiments. Samples were collected from the effluent of two water reclamation plants, one using a UV disinfection system and the other chlorination/dechlorination process. The team investigated whether the transformation of the target substances was achieved during the experiments at both scales. Most compounds were partially transformed at a large scale after disinfection by either chlorination (3 ppm sodium hypochlorite for 15 minutes) or UV (9.6×10^{-5} E/L at a maximum flow rate). The transformation of over 60% was achieved after UV treatment for paroxetine, duloxetine and sertraline and after chlorination for citalopram, norfluoxetine, and sertraline. At bench-scale, the compounds were spiked into deionized water or effluent and treated in a process similar to plant-scale. A correlation was observed between compounds that were transformed at bench-scale and those in post-disinfection plant effluent (10/13 compounds). Chlorination produced some by-products that recovered to the parent compound after dechlorination. Laboratory UV disinfection was generally more effective under stirred conditions, suggesting that indirect photo-induced reactions may predominate over direct photolysis.

On the other hand, Xie et al. (2019) studied the degradation of imipramine using the vacuum UV (UV_{254nm} and VUV_{185nm}) system and evaluated its applicability. The factors that influence imipramine's degradation were evaluated, and degradation pathways were proposed to examine the toxicity of the by-products. Ultrapure water and two realistic water samples were used; Sample A was collected from the output of the filtration pool, and Sample B was tap water after chlorine disinfection. In ultrapure water experiments, degradation efficiency was high in both UV_{254} and VUV systems at neutral pH. Through direct and indirect photolysis, imipramine was removed after 30 minutes by 64% and 97.0% in UV_{254} and VUV, respectively. VUV high-energy photons (185 nm) produce reactive species and UV_{254} high-intensity photons (around 20 times VUV_{185}) are the main source of direct photolysis. The quantum yields of UV_{254} direct photolysis of deprotonated and protonated imipramine were 1.31×10^{-2} and 3.31×10^{-3}, respectively. The activation energy was calculated to be 26.6 kJ mol^{-1}. Increasing initial imipramine concentration lowered the degradation efficiency, while higher temperature improved the degradation. Negative relationships between imipramine degradation and the presence of radical scavengers HCO^{3-} /CO_3^{2-}, NOM, and Cl^- were identified. Degradation pathways of imipramine were proposed (Figure 8). In addition, some high toxic intermediate products were identified but can be further transformed to less toxic products. Four initial reactions would occur in the system, including PW1, PW2, PW3, and PW4. In PW1, hydroxylation of one methyl group through $HO^{\bullet}$ attack formed P1. Cleavage of the side chain of IMI through UV_{254} direct photolysis in PW2 produced P3. In PW3, the hydroxylation of one active carbon

site on the aromatic rings via HO• attack formed P4. The simultaneous hydroxylation of two active carbon sites in PW4 produced P7. In realistic water samples, >85% removal after 30 minutes was achieved due to photon inhibition and consumption of HO• by NOM. Sample B with lower NOM concentration had the highest degradation rate.

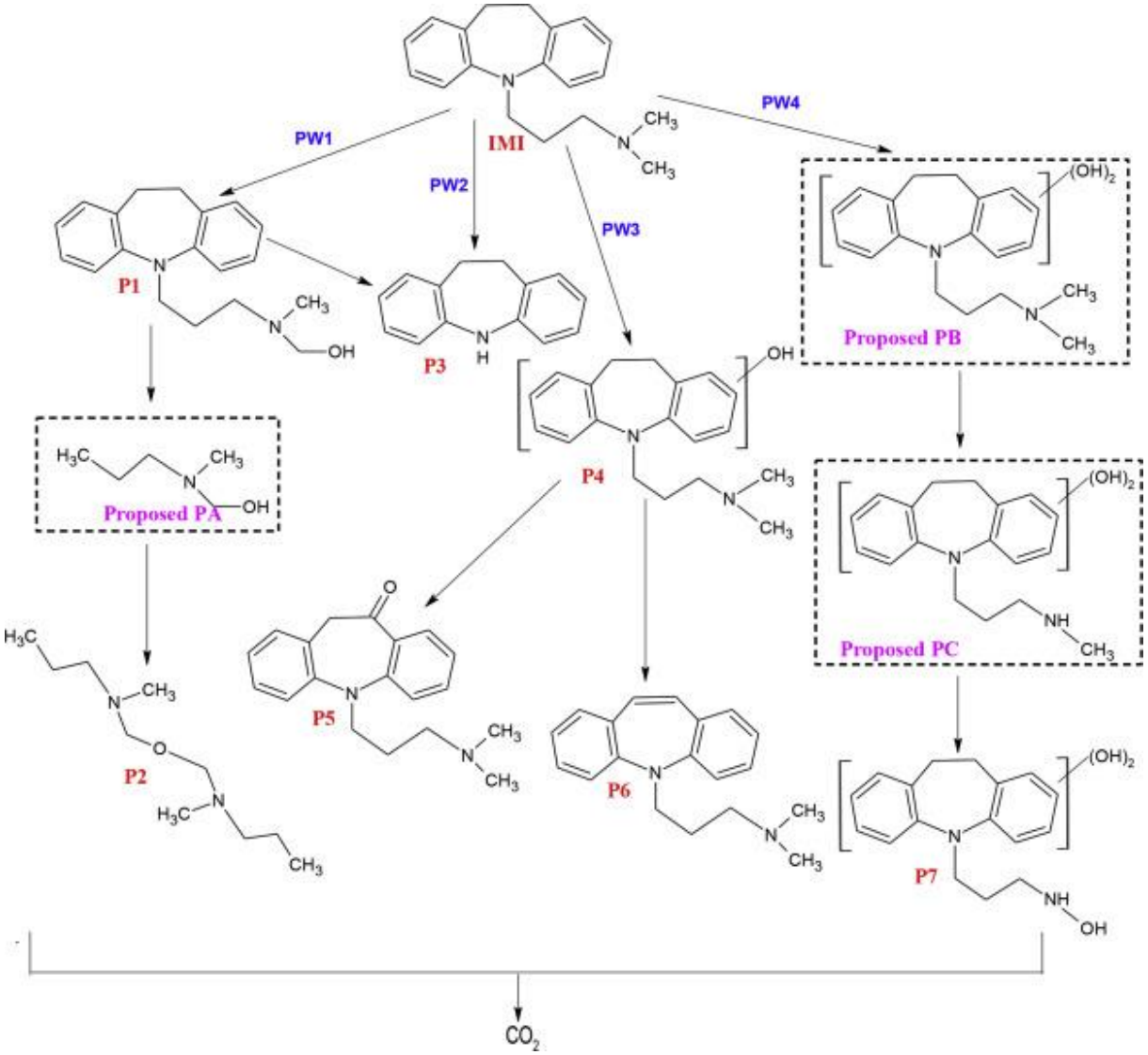


Figure 8. Proposed degradation pathways of imipramine in VUV (UV_{185} plus UV_{254}) system (Xie et al., 2019).

The team of Paredes et al. (2018) examined the transformation of different contaminants, including fluoxetine, at three secondary and one primary effluent after UV irradiation at lab-scale and full-scale. At lab-scale, different factors were examined for possibly affecting the efficiency of the degradation, such as UV dose, temperature, water matrix, and contaminant properties. After 30 minutes of UV irradiation, fluoxetine was highly transformed (>99%), regardless of effluent matrix used or the temperature, with $k_{effluentA}$= 1.03, $k_{effluentC}$= 0.74, $k_{effluentD}$= 0.29 min^{-1}. The higher effluent A constant is explained by the higher matrix quality (in terms of TSS and turbidity), while the effluent D constant being much lower is directly linked to higher TSS and CODs. At a large-scale

it was determined that removal with the use of the usual UV doses (10–50 mJ/cm^2) was very low (30-35%), so increasing the UV dose would improve the transformation of the contaminants.

A different team, Collado et al. (2014), investigated the use of UV treatment, combined with the biological process for the removal of several compounds, including citalopram, paroxetine, trazodone, and venlafaxine in a WWTP with significant industrial contribution. Water samples were collected from different points in the WWTP and the receiving river along three seasons. The contaminants differed in influent concentration, removal efficiencies, and seasonal variation. Primary and secondary treatment led to low removal of venlafaxine and paroxetine, medium of trazodone (~ 40%), and high of citalopram (~70%). Higher degradation efficiencies were noticed at warmer temperatures, as biodegradation works less efficiently at lower water temperatures. After UV irradiation, paroxetine was removed by >80%, while trazodone and venlafaxine were degraded by 40-50%. Despite the complimentary part of UV to the biological treatment, the combination was insufficient to remove the different compounds completely.

4.1.1 Other types of radiation

Table 10 contains studies investigating antidepressant degradation by other radiation types than UVC.

Table 9. Other types of radiation used for antidepressant degradation.

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
fluoxetine (among other CECs)	Ultrapure water and wastewater effluent after partial nitration(anammox)	1 mg/L	UV radiation (λ≥220 or λ≥280 nm) in the presence of NO_2^- or partial nitritation and UV (λ ≥ 220 or ≥ 280 nm)	When fluoxetine is irradiated at λ ≥ 280 for 120 minutes 57% removal is achieved (2033.1 mJ cm^{-2}) while at λ ≥ 220 for 60 minutes 90% removal is observed (23 969.2 mJ cm^{-2}). Direct photolysis did contribute, although the reaction with ˙OH accounted for ∼70–90% of pharmaceutical removal	Hora et al. 2019
duloxetine	spiked distilled water and WWTP wastewater samples	4 mg/L	hydrolysis, photodegradation (40%–48% UV and 40%–43% visible range) and chlorination	Complete degradation after 30 min by UV irradiation (0.37 W/cm) and 24 hr of chlorination (5 mg/L free chlorine). Eleven TPs, nine from reaction with UV light and two from chlorine contact, were detected. Almost all TPs were completely degraded in the experiments. DUL and one TP were detected in the wastewater effluent.	Osawa et al. (2019)
Fluoxetine and Fluvoxamine	Spiked Milli-Q water and NaOH/pure water. Dilution in Tyrod solution	10mg/L	Solar simulated photodegradation in the presence of photolabile compounds diclofenac (DCF) and triclosan (TCS)	Direct photodegradation and standard indirect photodegradation with humic acids (HA) were applied. Irradiation was > 290 nm for 3h. The following mixtures were tested: FLX, FLX + DCF, FLX + TCS, FLX + HA, FLV, FLV + DCF, FLV + TCS, and FLV + HA. FLX did not degrade either with or without the tested additives and FLV isomerized to cis-FLV.	Wawryniuk et al. 2018
Amitriptyline, citalopram, maprotiline, memantine and	ammonium acetate buffer at pH 7, unfiltered river water and filtered river water matrices	1000 ng/L	UV irradiation (λ > 290 nm)	Irradiation for 28 d in ammonium acetate buffer, filtered and unfiltered river water. Photolysis was the major removal process for the majority of CECs indirect photolysis the major pathway. The kinetics highly depended on the water chemistry with shortest half-lives	Blum et al. 2017

venlafaxine (among other CECs)				in unfiltered river water, due to additional organic carbon, which promotes indirect photolysis.	
Amitriptyline and nortriptyline	deionized water and fulvic acid solution	10 mg/L	simulated sunlight photodegradation in the presence of fulvic acid	The photodegradation of nortriptyline was slower than amitriptyline. Neither underwent direct photodegradation, but rapid photosensitized degradation did occur in fulvic acid (FA) solutions. The photodegradation of amitriptyline and nortriptyline followed pseudo-first-order kinetics with rate constants 0.24 and 0.16 h^{-1}, respectively, at pH 8.0 in air-saturated FA solutions.	Chen et al. 2017
paroxetine	Milli-Q water, Milli-Q water spiked with river organic matter and raw filtered surface water	1 mg/L	Solar simulated photochemical degradation by hydroxyl radical and singlet oxygen	Rate constants ($M^{-1}s^{-1}$) were determined for the reaction of hydroxyl radical and singlet oxygen $(8.65 \pm 0.12) \times 10^9$, $(1.18 \pm 0.13) \times 10^8$ respectively. The presence of humic and fulvic acid and NOM favored degradation by $^{\bullet}OH$ and $^1\Delta O_2$.	Santoke et al. 2017
desipramine	Ultrapure water	5-100mg/L	Simulated sunlight and UV degradation (200–440 nm)	DPM is not degraded by sunlight but it is degradable in response to UV-irradiation. It was highly eliminated after 130 min of UV irradiation with first-order kinetics and TPs were formed. pH showed a significant impact on the photolysis rate of DPM and TPs in terms of formation kinetics and mechanisms. Temperature showed no significant impact.	Khaleel et al. 2016
Venlafaxine (among other CECs)	Ultrapure and river water	2 and 0.7 μg/ L	UV irradiation ($\lambda > 290$ nm) plus natural sunlight	Photodegradation at laboratory and field scale experiments. Degradation followed a first-order kinetic model. The Hg lamp provided half-life of 1 d for venlafaxine and 2 d for natural sunlight. Indirect photodegradation is the dominant degradation process	Rúa-Gómez et al. 2013
Duloxetine, venlafaxine and bupropion	Deionized water and Humic acid solution	1mg/L	direct and indirect photodegradatio	Duloxetine was the most susceptible to direct photolysis, with a half-life of less than an hour. Bupropion degrades at a much slower rate and	Santoke et al. 2012

			n by UV light at 350 nm	venlafaxine did not undergo direct photolysis at all. The compounds degraded faster in the presence of humic acids; venlafaxine degraded 25% after 7 h. Bupropion degraded about twice as rapidly. Several reaction pathways and by-products were identified.	
Amitriptyline (among other CECS)	river water and purified water	0.5 mg/ L	Artificial sunlight irradiation	No degradation was observed for AMT in purified water while photosensitized reaction occurs in river water. Under ultra-violet (254 nm) irradiation in purified water amitriptyline was degraded. Quantum yield of photodegradation was 7.6×10^{-3}. Second order rate constant of reaction with hydroxyl radicals was 8×10^{9} $mol^{-1}\,s^{-1}$. Finally, the structures of photoproducts were proposed.	Nassar et al. 2017
Amisulpride and desipramine	ultrapure water and wastewater	10 mg /L	simulated solar photolysis	For amisulpride short irradiation times were adequate for degradation while longer exposure period was required for desipramine. A significant number of TPs were identified for both pharmaceuticals. In wastewaters collected from treatment lagoons, only amisulpride and one of its major TPs, TP 357, were detected.	Gros et al. 2015
sertraline	surface river water	1000 ng/ L	Sunlight photolysis and UV irradiation < below 300 nm	Sertraline degrades by pseudo-first order kinetics by direct photolysis assisted by •OH, CO3−• and 3CDOM*. Quantum yield for sertraline is $\Phi_{SER} = 0.95$. Half-live of sertraline depending on the addition of photosensitizers, pH or initial concentration. and was calculated to be 1.4 days. Five TPs were detected, with same or less toxicity than sertraline.	Gornik et al. 2020
Venlafaxine (among other CECs)	Reverse osmosis retentate	1.2 ng/L	γ-radiation	The removal of CECs approached 80 to 100%. Removal of CECs is correlated with reduction of protein-like fluorescence of reverse osmosis retentate, so changes of florescence peak provides quantitative estimation of CECs degradation.	Abdelmelek et al. 2011

The study of Hora et al. (2019) examined the addition of UV irradiation in between partial nitritation and annamox processes in order to improve the removal of certain pharmaceuticals, including fluoxetine. The matrices used were ultrapure water, a synthetic nitrogen-containing matrix and nitrogen-containing wastewater matrix. The possible generation of ·OH, due to the nitrite in solution being irradiated with UV, that would promote indirect photolysis was tested. In nitrogen-containing wastewater matrices, after 120 minutes of irradiation at $\lambda \geq 280$ nm about 50% of fluoxetine was degraded primarily by indirect photolysis (~78–90% of removal). Irradiation for 60 minutes at $\lambda \geq 220$ nm led to 90% removal. Reaction with ·OH contributed mostly at the degradation (~70–93%), as much of the radiation was absorbed by the buffer and the wastewater. A kinetic model was developed to determine the formation or degradation of nitrosamines, especially N-nitrosodimethylamine, by UV. Significant total N-nitrosamine formation could occur from nitrite photolysis.

At the same period Osawa et al. (2019) worked on identifying possible TPs of duloxetine on spiked distillated water and wastewater samples after hydrolysis, chlorination and photodegradation, using ultra-high-performance liquid chromatography (UHPLC) coupled to quadrupole time-of-flight mass spectrometer (QTOF/MS) (Figure 9a). In distilled water experiments duloxetine was fully removed after 30 min by UV irradiation and after 24 hours by chlorination. Hydrolysis showed no effect. During photodegradation nine TPs were formed (Figure 9b), but after 45 minutes were all degraded. Chlorination led to the formation of two TPs. Using in silico tools, mutagenicity and ecotoxicity were assessed, with most TPs presenting low ecotoxicity. Only one TP, TP-332, formed during chlorination and was about 40% degraded showed higher toxicity than duloxetine. All TPs with positive mutagenicity

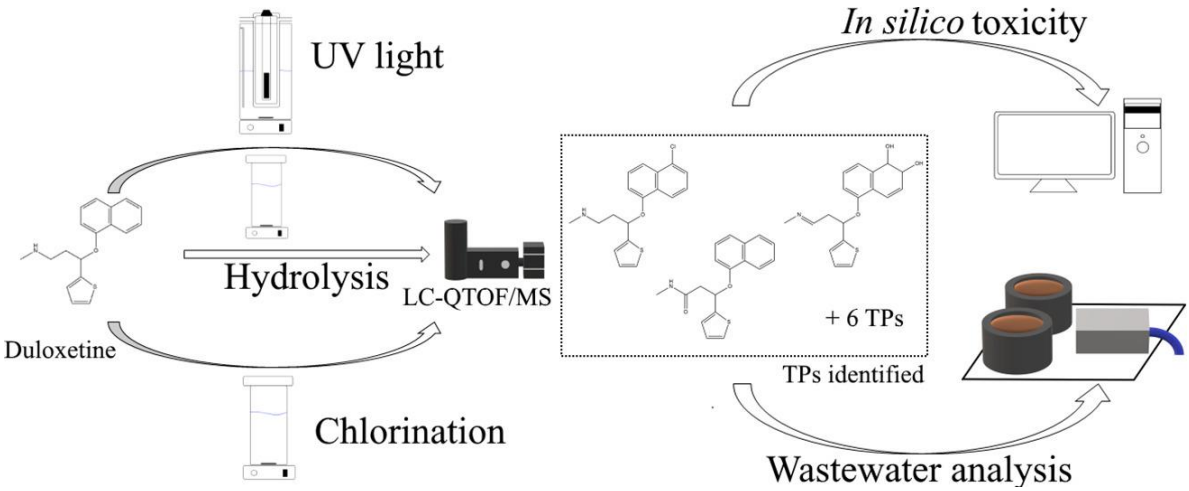
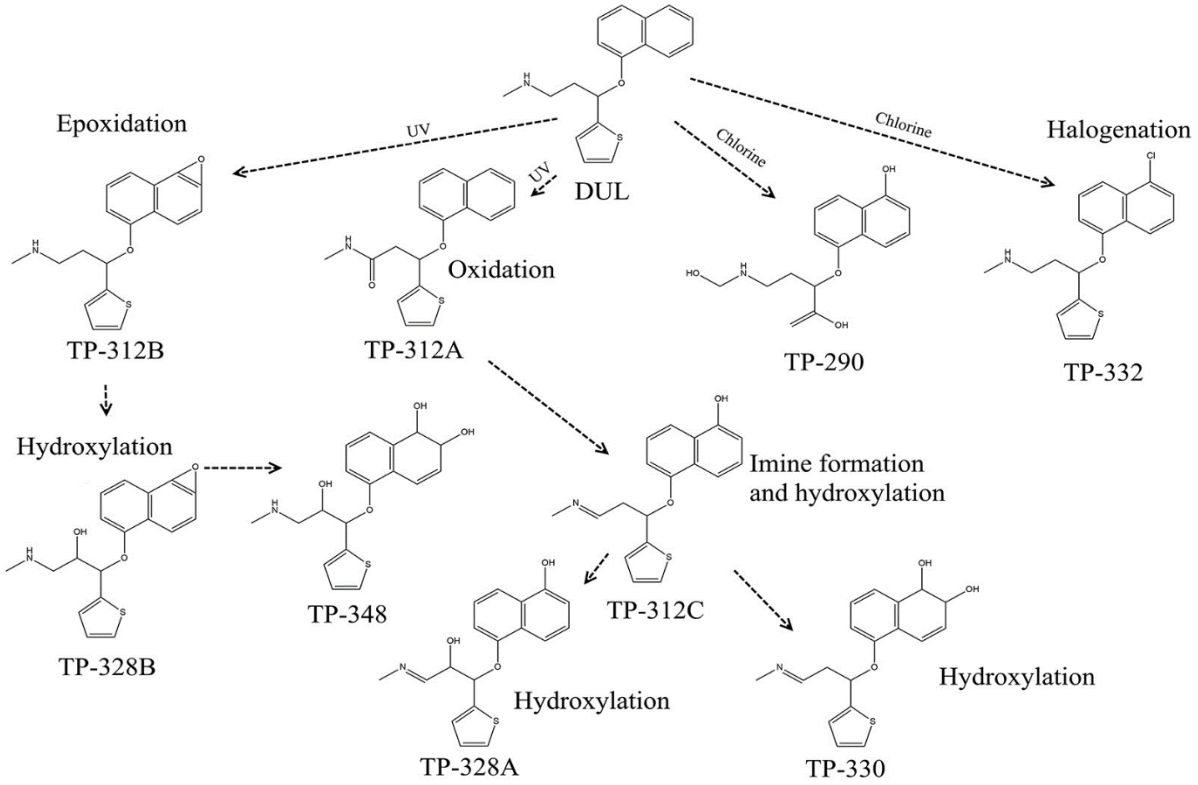


Figure 9a. Graphical abstract of Osawa et al., 2019 study

Figure 9b. Proposed pathway of TPs formation (Osawa et al. 2019).



that were formed were completely degraded during 90 minutes of UV irradiation. After analyzing wastewater samples duloxetine was detected in both influent and effluent, with 17% removal, along with TP-332.

Moreover Wawryniuk et al. (2018) evaluated the phototransformation of fluoxetine and fluvoxamine in the presence of the photolabile compounds diclofenac and triclosan or humic acids, by HPLC analysis and bioassays. Under UV and visible irradiation fluoxetine did not degrade (does not absorb light at $\lambda > 290$ nm) despite the addition of the photolabile compounds, although small amounts of desmethyl fluoxetine and 4-(trifluoromethyl)phenol were formed. On the other hand, while irradiating fluvoxamine, it isomerized to cis-fluvoxamine (half-life was 6 h), a reaction that was promoted mainly by humic acids (half-life was 1h) and secondly by diclofenac and triclosan. Thus, the composition of the matrix should be considered in the environmental risk assessment of pharmaceuticals. The ecotoxicity of samples before and after irradiation was assessed with a Spirotox assay with a ciliated protozoan Spirostomum ambiguum. Fluoxetine was slightly more toxic than fluvoxamine, but triclosan was the most toxic. The decrease in the toxicity of tested drugs was related only to the decrease in their concentration.

On the other hand, Blum et al. (2017) investigated the fate of different pharmaceuticals, including amitriptyline, citalopram, maprotiline, memantine and venlafaxine during long-term laboratory experiments. Total removal and reaction kinetics were determined in filtered and unfiltered river water and ammonium acetate buffer during 28 d of artificial UV irradiation. Amitriptyline was highly degraded in all matrices, with half-life in unfiltered water being the shortest at 6 hours and longest in buffer at about 35 hours. Venlafaxine and maprotiline had medium degradation efficiency

but half-life times were extremely long in all matrices. Memantine was stable after 28 days. In unfiltered water half-lives were generally shorter compared to the other matrices, due to the particular organic carbon presence. Degradation was primarily affected by indirect photolysis for most pharmaceuticals and can explain high degradation rate in filtered water compared to ammonium acetate buffer, because of the presence of dissolved organic carbon.

The indirect photodegradation of amitriptyline and its active metabolite nortriptyline was also investigated by Chen et al. (2017) by simulated sunlight in the presence of fulvic acids and the effect of pH was studied. Both of the compounds did not photodegrade directly, but transformed when fulvic acids were present. The two substances degraded by pseudo-first order kinetics and rate constants were 0.24 and 0.16 h^{-1} for amitriptyline and nortriptyline respectively, at pH 8.0 in air-saturated fulvic acids solutions. The photodegradation increased with increasing pH. The main reactive species in the indirect photodegradation pathway were the triplet excited state of fulvic acids (3FA*). The presence of dissolved oxygen in the solutions decreased the triplet excited state (3FA*) and as a result hindering the indirect photodegradation. So, the deoxygenation promoted the indirect photodegradation of substrates. After removing the dissolved oxygen, the degradation of amitriptyline and nortriptyline was enhanced 10- and 16-fold, respectively. TPs of both amitriptyline and nortriptyline were identified by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI (+) -MS/MS). Demethylation and hydroxylation were two main processes for the photosensitized degradation of amitriptyline and nortriptyline in the fulvic acids solution.

Another antidepressant's degradation, paroxetine's, was studied by Santoke et al. (2017) using solar simulated radiation in raw and reconstructed samples with isolates of the Suwannee Rive (humic acid, fulvic acid, and natural organic matter). The effect of two reactive species, hydroxyl radical and singlet oxygen, was studied and bimolecular rate constants were determined 8.65×10^9, 1.18×10^8 M^{-1} s^{-1}, respectively. The steady-state concentration of the hydroxyl radical was on the order of 10^{-17}–10^{-18} M, and for singlet oxygen, 10^{-12}–10^{-14} M. Paroxetine is not fully removed and has a slow reaction rate with half-lives over 100 hours in all samples. Hydroxyl radical highest contribution can be found in the raw water samples and its impact is greater in the presence of humic acid compared to fulvic acid. The opposite applies for singlet oxygen. Generally, the two species do not affect greatly the degradation.

Simulated sunlight was also used by Khaleel et al. (2016) in order to examine the fate of desipramine and its TPs in ultrapure water and the impact of different conditions on the reaction (temperature, initial concentration, pH). Desipramine's degradation followed first-order kinetics and the quantum yields were very low. The photolysis rate was inversely proportional to the initial desipramine concentration, with the smallest initial concentration (5mg L^{-1}) degrading in less than 40

minutes and the largest (100 mg L^{-1}) not being fully removed after 120 minutes. Direct photolysis (quantum yields) and degradation rates are decreasing when increasing the initial concentration. No mineralization was achieved when using simulated sunlight. The pH had a significant impact on the photolysis rate. A large number of TPs was identified during photolysis. High-resolution mass spectrometry identified three main photolysis pathways: isomerization, hydroxylation, and ring opening. Biodegradation tests and QSAR analysis revealed that desipramine and its TPs are not fully biodegradable and that some TPs may be mutagenic and toxic.

The team of Rúa-Gómez et al. (2013) investigated the degradation by UV and natural sunlight and biodegradation of three pharmaceuticals including venlafaxine and its metabolite O-desmethylvenlafaxine. Photodegradation experiments were performed either at laboratory using a medium pressure Hg lamp and ultrapure water or at field by natural sunlight and natural river water. Degradation of the target compounds followed first-order kinetic model. Half-life was about 9 days for venlafaxine in ultrapure water irradiated with the Hg lamp and about 20 days with natural sunlight. O-desmethylvenlafaxine' s half-life was about 6 days, during irradiation with the Hg lamp and almost 9 days during the sunlight experiments. The target compounds were degraded faster in natural water (hydroxyl radical formation); rates of indirect photodegradation in river water were 8 and 13 times higher than ultrapure water, for venlafaxine and O-desmethylvenlafaxine, respectively. Biological treatment was insufficient on its own. The combination of all mechanisms in river water (direct photodegradation, indirect photodegradation and biodegradation) led to half-life times 51 and 18 hours for venlafaxine and O-desmethylvenlafaxine, respectively.

Venlafaxine's photodegradation was also examined by Santoke et al. (2012) together with duloxetine and bupropion in deionized water and Suwannee Rive humic acid solutions and measured their reaction rate constants with three reactive species: hydroxyl radical (radical ·OH), hydrated electrons (e^-_{aq}) and singlet oxygen ($^1\Delta O_2$). Duloxetine degraded highly due to direct photolysis, with half-life about 1 hour. Bupropion degrades slower and venlafaxine does not degrade at all. All substances degraded faster in the humic acid samples due to the assistance of indirect photolysis. Hydroxyl radicals are the primary reactive species in the photodegradation and all the compounds react highly with them and hydrated electrons with rate constants of $\sim 10^8$ to 10^{10} M^{-1} s^{-1}, but significantly slower with singlet oxygen ($\sim 10^3$ to 10^5 M^{-1} s^{-1}). In humic acid samples it was determined that hydroxyl radicals were an order of magnitude more effective than singlet oxygen in solar photodegradation. Excited state DOM affected the degradation of duloxetine, decreasing its half-life by 27% during the irradiation. Reaction pathways and TPs were identified using gamma-irradiation followed by LC–MS analysis. All three molecules transform by hydroxylation at several sites, due to the high reactivity of the hydroxyl radical.

The team of Nassar et al. (2017) studied the photodegradation of amitriptyline among other compounds, using simulated sunlight irradiation and UV alone or with hydrogen peroxide in purified water and river water samples. Quantum yields of direct photodegradation were also calculated under a 254 nm irradiation. Amitriptyline did not degrade after seven hours of irradiation in purified or river water due to lack of absorption above 290 nm on the UV–visible spectrum. Under UV irradiation in purified water amitriptyline was degraded and quantum yields were calculated (7.6×10^{-3}). UV combined with H_2O_2 enhanced the degradation. The second order rate constant with hydroxyl radicals was calculated to be 8.0×10^9 $mol^{-1}\,s^{-1}$. Three degradation products were formed during UV irradiation through hydration and their structures were proposed.

Another group focusing on the TPs of antidepressant degradation was Gros et al. (2015), that studied the degradation of amisulpride and desipramine in ultrapure and wastewater treatment lagoons using simulated solar irradiation. Amisulpride was degraded with half-life of 3 hours in pure water and 4 hours in wastewater while a longer exposure was required for desipramine with half-life over 30 hours in pure water. A significant number of TPs was determined for both pharmaceuticals by high-resolution mass spectrometry. Generally, the TPs were not persistent although some of them may be more toxic than the parent compound. After analyzing samples collected from treatment lagoons, only amisulpride and one of its by products, TP 357, were detected, pointing out the importance of long solar exposure times for the removal of these substances.

Using a different approach, Gornik et al. (2020) aimed to determine the rate constants of sertraline during photodegradation in order to predict its kinetics by "Aqueous Photochemistry of Environmentally occurring Xenobiotics" (APEX) software. Sertraline degrades by pseudo-first order kinetics and the reaction is pH dependent, with higher degradation at alkaline pH. The reaction is dominated by direct photolysis, with quantum yields (Φ_{SER}) = 0.95. Reactive species including •OH, • $CO3^-$and 3CDOM* enhance the degradation rate; reaction rate constant of ·OH was $2 \times 10^{10}\ M^{-1}\,s^{-1}$. To validate the predictions, sertraline was spiked in surface water and was irradiated by sunlight. Half-life ranged from <1 day to about 3–5 days, depending on water conditions and five TPs were identified. By the ECOSAR toxicity prediction, TPs were found to be of the same or lower toxicity than sertraline. Those that were found more toxic were unstable in the aqueous environment.

Abdelmelek et al. (2011) screened different pharmaceuticals, including venlafaxine in a reverse osmosis retentate saturated with N_2O and determined a model of their degradation by γ-radiation radiolysis, based on the absolute hydroxyl radical (HO•) reaction rate constants, and that of the reverse osmosis retentate (EfOM and inorganic constituents). Using excitation−emission matrix (EEM) fluorescence spectroscopy, the HO• oxidation of the EfOM could be observed through decreases in the retentate fluorescence. The results showed effective removal of the compounds.

Reaction rate constants were used to predict the degradation and the calculated results are close to experimental (experimental and calculated degradation rate for venlafaxine 0.04 and 0.05 nM min^{-1}).

4.2 Degradation by UV/H_2O_2

The studies that used UV radiation combined with H_2O_2 are presented in Table 10.

Table 10. Oxidation of antidepressants caused by UV radiation combined with H_2O_2.

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
venlafaxine	Milli-Q water and real municipal WWTP secondary effluent	10 mg/L	UVC/H_2O_2	Degradation under UVC depends on incident radiation; at 3619 W/m^3 maximum k was 4.3×10^{-4} s^{-1} and 4.0×10^{-4} s^{-1} in Milli-Q and WW, respectively. Degradation under UVC/H_2O_2 depends on H_2O_2 dose and incident radiation. Maximum k in the UVC/H_2O_2 process at 10 mg/L H_2O_2 was 3.5×10^{-3} s^{-1} at 3619 W/m^3.	Hollman et al. 2020
Citalopram and venlafaxine (among other CECs)	Municipal WWTP tertiary effluents	210 and 490 ng/L	UVC/H_2O_2	UV fluence of 800 mJ/ cm^2 and H_2O_2 dosage of 10 mg/ L. Average removal was ~50 %. Observed photolytic degradation rate constants in the range of 1– 4.8 $x10^{-4}$ cm^2/ mJ resulting in moderate removal at 600 mJ/cm^2 Removal from tertiary effluents by UV/H_2O_2 is highly dependent on nitrite concentrations.	Miklos et al. 2018
venlafaxine and O-desmethylvenlafaxine	ultrapure millipore water	20 mg/L	UVC/H_2O_2	The depletion of both venlafaxine and O-desmethylvenlafaxine was very significant, with the 99.9% of both compounds eliminated after 5 and 30 min of reaction, respectively with use of 700 mg L^{-1} H_2O_2. Eleven TPs for VFX and six for DVFX were detected.	García-Galán et al. 2016
Fluoxetine, paroxetine and venlafaxine (among other CECs)	MilliQ water	1 µg/L	UVC (LP)/H_2O_2 (10 mg/L)	Computational fluid dynamics model combined with an advanced kinetic model predicted the degradation. Comparison between measured and modeled degradation resulted in good model predictions for most of the compounds.	Wols et al. 2015
Paroxetine fluoxetine and venlafaxine	Milli-Q water, tap water and river pre-treated water	4.91 0.79 0.89µg/L	UV/H_2O_2 (200–300 nm/ 10 mg/L H_2O_2). MP or LP lamps	Degradation increases with MP lamps. Tap water shows lower degradation than Milli-Q, while river water shows higher degradation. With UV/H_2O_2 Milli-Q water shows the largest improvement. For natural matrices, the degradation is lower due to scavenging.	Wols et al. 2013

Nortriptyline (among other CECs)	ultra-pure water	263μg/L	UVC/H_2O_2	Photolysis rate followed first-order kinetics, with rate constant value $13.8 \times 10^{-3} - 15.0 \times 10^{-3}$ mol E^{-1}. The UV/H_2O_2 process enhanced the oxidation rate compared to direct photolysis. Identification of the parent compounds and their TPs, which allowed the proposal of the degradation pathways.	Benitez et al. 2013
Fluoxetine (among other CECs)	pre-treated urban wastewater	1110 ng/L	UVC/H_2O_2	FLX was degraded >80% during UV photolysis after 45 min. The addition of even 5 mg L^{-1} of H_2O_2 led to a degradation of 98%. An optimal H_2O_2 dosage of 20 mg L^{-1} was determined. FLX required 385 (mJ cm^{-2} UV_{90}) to be reduced to a tenth of their initial concentration.	Afonso-Olivares et al. 2016
Fluoxetine (among other CECs)	municipal wastewater effluent	200-400 ng/L	UV/H_2O_2	Addition of peroxide increased the removal of all target compounds at each test condition compared to the UV only case. Highest removal efficiency at the 23 L/min, 5 mM peroxide condition, with highest estimated detention time. Lowest removal under highest flow rate (125 L/min)	Parry et al. 2016
Fluoxetine (among other CECs)	Secondary-treated wastewater effluent	1ng/L	UV/H_2O_2	Pseudo-first-order kinetics during degradation. Adding H_2O_2 (3 and 6 mg L^{-1}) had no significant increase in the degradation. UV direct photolysis leads to dominant elimination. Even an UV exposure at 100 mJ cm^{-2} without additional peroxide, resulted in 30% degradation; a UV dose of 700 mJ cm^{-2} is needed to achieve 90% removal (3mgL^{-1} H_2O_2)	Yu et al. 2015
Amitriptyline, Dosulepin (among other CECs)	Contaminated groundwater	7.46 μg/L 7.58 μg/L	UVC/H_2O_2	In the UV/H_2O_2 process combined with aeration pretreatment for 4 months, the overall decontamination efficiency ranged from 72% to 99. After 150 min (ret. time in photo-oxidation reactors 8.8 min; H_2O_2 dose 3.5 L m^{-3}), the observed removal efficiency was higher than 80%.	Lhotský et al. 2017
Nortriptyline (among other CECs)	ultrapure water, public reservoir lake and two secondary effluents	263 μg/L	UV/H_2O_2	Positive effect of the combined UV/H_2O_2 system in compared to UV direct radiation. Concentration of 5×10^{-5} M H_2O_2 in UV/H_2O_2 process provided degradation >90% in about 50min. The rate constant with the hydroxyl radicals was, 0.87×109 mol^{-1} L s^{-1}. A higher oxidation rate was found in the ultrapure water.	Benitez et al. 2012

Hollman et al. (2020) studied the degradation of venlafaxine by UV disinfection combined with H_2O_2 in a WWTP and at bench scale (ultrapure water and secondary effluent samples). During UV photolysis venlafaxine degrades with pseudo- first order kinetics and the total light dose was the dominant factor in the process. Kinetics were slower at the effluent samples due to shadowing effect. Adding H_2O_2 increased the pseudo first order rate constant by up to 2.5 times. Decreased degradation rates were found in wastewater samples due to the presence of radical scavengers. Venlafaxine degrades at the WWTP UV disinfection unit 0.4% at standard operating conditions. With the addition of 10 mg/L of H_2O_2, it increases ten times over the UV treatment. The breakdown pathway that has been observed in these experiments is visually represented in Figure 10.

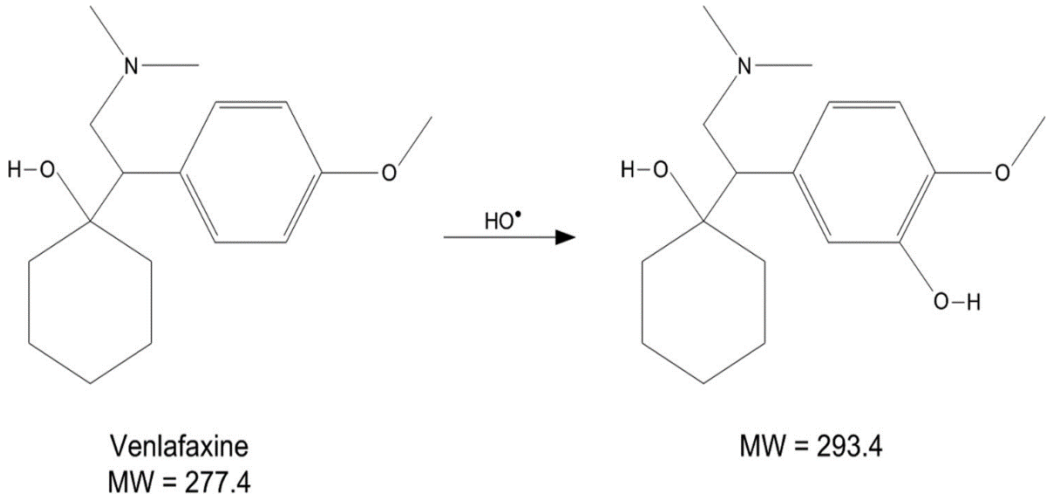


Figure 10. Reaction for the formation of breakdown product (Hollman et al. 2020)

Venlafaxine's degradation was also examined Miklos et al. (2018), along with citalopram by UV/H_2O_2 in municipal wastewater effluents in pilot-scale lab-scale and. A lab-scale collimated beam device (CBD) was used to verify the up-scaling effort. The effect of different potential OH-radical scavengers, like dissolved organic carbon (DOC), nitrite, nitrate and alkalinity was examined. The average observed removal for the moderately photo-susceptible citalopram and venlafaxine (10^{-4}<kUV<10^{-3} cm^2/mJ) was about 50%. During the OH-radical scavenging model validation experiment, the second-rate constants of the scavengers' nitrite, nitrate, DOC and bicarbonate were used as inputs; DOC ($3.0 \cdot 10^8$ $Mc^{-1}s^{-1}$) can contribute > 90% to the scavenging, nitrite ($1 \cdot 10^{10}$ $M^{-1}s^{-1}$) reacts higher with ·OH than the contaminants and its concentration can affect the degradation efficiency.

García-Galán et al. (2016) also investigated the removal and transformation of the antidepressant venlafaxine and its main metabolite O-desmethylvenlafaxine with UV/H_2O_2 under lab conditions and the different TPs were identified. Venlafaxine and its metabolite were transformed over 99% after 5 and 30 min, respectively. Hydroxyl radical constants for venlafaxine and its metabolite were calculated 8.8×10^9 L mol^{-1} s^{-1} and 4.6×10^9 L mol^{-1} s^{-1}, respectively. Eleven TPs

for venlafaxine and six for O-desmethylvenlafaxine were identified and their structures and degradation pathways were proposed. An increase in ecotoxicity is associated with the higher abundance of the TPs.

Another approach was made by Wols et al. (2015), by presenting a computational fluid dynamics model in combination with an advanced kinetic model in order to predict the degradation of fluoxetine, paroxetine and venlafaxine, among other micropollutants in UV/H_2O_2 reactors. This model takes into account the contribution of the hydraulics, fluence rate, photochemical reactions in the water matrix and the interactions between these processes. The model includes degradation by means of direct UV photolysis, OH radical and carbonate radical reactions. Temperature does not affect the degradation during direct photolysis. However, it has an important effect when H_2O_2 is added. The lowest OH radical rate constants are found at the lowest temperature and so the degradation rate of the pharmaceuticals is lower. The results of direct photolysis alone and with the H_2O_2 addition agree between measured and modeled data for most of the 35 pharmaceuticals.

The same team Wols et al. (2013) had previously tested UV and UV/H_2O_2 treatment, with the use of monochromatic low pressure and polychromatic medium pressure lamps in different water matrices (Milli-Q water, tap water and river pre-treated water) for the degradation of fluoxetine, paroxetine and venlafaxine among other pharmaceuticals. A collimated beam apparatus was used. When using photolysis alone degradation with LP lamps is limited, but increasing with MP and if using both UV (either LP or MP) combined with H_2O_2 most compounds are removed. For LP lamps, the compounds degrade similarly in the three water matrices. However, differences in degradation rates between the water matrices can be large when using MP laps. Tap water shows a lower degradation rate than Milli-Q water, whereas river water shows a much higher degradation for about half of the compounds. When adding H_2O_2, the removal is higher, with Milli-Q water showing the largest improvement with almost no hydroxyl radical scavenging (bicarbonate and NOM).

UV radiation combined with H_2O_2 was also used by Benitez et al. (2013) for the degradation of nortriptyline, among other compounds in ultrapure water by the combination of UV and H_2O_2. Photodegradation rates followed first-order kinetics and the rate constant values were affected by the nature of the compound, the pH, and the presence or absence of the scavenger tert-butanol. Quantum yields were also determined in the range $13.8 \times 10^{-3} - 15.0 \times 10^{-3}$ mol E^{-1}. The degradation was enhanced by UV/H_2O_2 compared to direct photolysis. High-performance liquid chromatography coupled to electrospray ionization quadrupole time-of-flight mass spectrometry (HPLC-ESI-QTOF-MS) technique was applied for the identification of the TPs and the degradation pathways. Finally, the aquatic toxicity was assessed in the photodegradation and the results indicated that the toxicity

values increased continuously due to the continuous formation of intermediates more toxic than the parent compound.

Moreover, Afonso-Olivares et al. (2016) examined the effectiveness of UV and UV/H_2O_2 in the degradation of twenty-three pharmaceutical compounds, including fluoxetine in secondary effluent of an urban wastewater treatment plant. Fluoxetine was degraded about 80% by photolysis with UV-C after 45 min of reaction. When adding even 5 mg L^{-1} the degradation increased over 90%. Fluoxetine removal was also studied in continuous mode in a custom-made photochemical reactor with flow rate of 333 mL min^{-1} for 75 minutes and was fully degraded.

Parry, et al. (2016) also studied the degradation of fluoxetine among twelve other pharmaceuticals and personal care products that were added to a reactor influent by the use of UV and H_2O_2. Removal was limited under UV only, with average fluence for the reactor during the 45 L/min UV only test condition being 116 mJ/cm2. By adding H_2O_2 the removal rate increased. The highest removal efficiency (> 80%) was observed at the 23 L/min, 5 mM H_2O_2. The worst removal was under the highest flow rate conditions (125 L/min, 10.4 s HRT). The longest reactor retention time and a medium H_2O_2 dose resulted in the highest removal of the compounds. In order to enhance the reactor's performance, the UV dose could be increased by increasing the reactor retention time.

The team of Yu et al. (2015) tried to predict the degradation efficiency of different compounds, including fluoxetine, by using low pressure (LP)-UV/H_2O_2 connected to an online sensor-based monitoring system, in two separate secondary wastewater effluents. The degradation followed first-order kinetics and the rate constant for direct photolysis and radical reaction were calculated, in order to assess the contribution to the overall removal. The selected pharmaceuticals were divided into groups, with fluoxetine being placed in photo-susceptible but with minor degradation by radical ·OH oxidation compounds ($k_{\cdot OH}/k_{UV} < 0.1$). The parameters that impact the reaction of direct photolysis (quantum yield and absorption coefficient) and radical ·OH oxidation (second order rate constant) are, Φ (10^{-2}, mol E^{-1}) = 41, ε (10^3, M^{-1} cm^{-1}) =0.79 and kOH (10^9, M^{-1} s^{-1}) =9.0. Direct photolysis is the dominant degradation pathway. For 90% removal, the UV dose is calculated at 700 mJ cm^{-2}, despite the addition of H_2O_2 due to their high photo-degradability of fluoxetine. TOC, UV absorbance, and fluorescence are the parameters used to examine the organic content of the matrices and can be used in order to assess the efficiency of the removal.

On the other hand, Lhotský et al. (2017) used UV radiation combined with H_2O_2 simple aeration pretreatment for disinfecting groundwaters with heavy loads of pharmaceuticals, including amitriptyline and dosulepin. After 150 min (ret. time in photo-oxidation reactors 8.8 min; H_2O_2 dose 3.5 L m^{-3}), the degradation was higher than 80% for amitriptyline and higher than 90% for dosulepin.

Aeration treatment had no effect on its own on the pharmaceuticals. However, by combining the photo-reactor UV/H_2O_2 with aeration pretreatment for 4 months the efficiency of the decontamination was high and ranged from 72% to 99%. This demonstrated the necessity of using the aeration step.

Lastly, Benitez et al. (2012) studied the degradation of nortriptyline, among other compounds in ultrapure and natural lake water and two secondary effluents. At first the compounds were dissolved in ultrapure water in order to determine the quantum yield (14×10^{-3} mol Einstein^{-1}) and the second-order rate ($10.87x10^{-9}$ L mol^{-1} s^{-1}) by using UVC radiation and the Fenton's reagent. The degradation rate was higher when UV and H_2O_2 were combined, with nortriptyline degrading over 90% in less than an hour. The compounds degraded faster in ultrapure water and slower in waste water effluents with high organic matter levels, as it competes with pharmaceuticals for UV absorption. In order to predict the degradation a kinetic model was established in all water matrices, by using as parameters the quantum yields and the radical rate constant with valid results.

4.2.1 Degradation by UV/other oxidants

Table 11 presents the studies that used UV radiation combined with different oxidants for antidepressant degradation.

Table 8. Studies using UV/other oxidants to degrade antidepressants

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
Venlafaxine, fluoxetine (among other CECs)	Pure water with pharmaceutical mixture	5 mg/L	UVC/PAA-UVA/PAA Compared to UVC/H_2O_2	UVC/PAA followed pseudo first-order kinetics. Increasing PAA dosage or UVC intensity resulted in a linear increase in pseudo-first order rate coefficient. For similar oxidant dosages UVC/H_2O_2 was found to be faster than UV/PAA by 55% and 33% for VFX and FLX respectively. Increase in the proportion of H_2O_2 to PAA in UVC/PAA/H_2O_2 improved kinetics of degradation compared to PAA alone	Hollman et al. 2020
Venlafaxine (among other CECs)	Inlet of of UVC reactor of WWTP Outlet of UVC reactor of WWTP	~0.3 mg/L	UVC and hydrogen peroxide, peroxymonosulfate (PMS), persulfate anions (PS)	UV/H_2O_2 and UV/PMS are more efficient than UV/PS or UV-C radiation at low dosages (0.05–0.5 mM) and very low UVC contact time (4–18 s). Photolysis of PMS and had highest efficiency with 0.5 mM and 18 s of contact time. PMS/UVC treatments reached slightly higher removal than H_2O_2/UVC. H_2O_2/UVC is more cost-efficient than PMS/UVC.	Rodríguez-Chueca et al. 2018
Nortriptyline (among other CECs)	Spiked deionized water,surface water and two secondary WWTP effluents	263 μg/L	UVC/PS	Efficient degradation by $SO_4^{\bullet -}$ and $^{\bullet}OH$ at high pH. Second order rate constants for the reaction with $SO_4^{\bullet -}$ were 2.0×10^{10} at pH 7. Excess of PS can lead to $SO_4^{\bullet -}$ self-scavenging. Bicarbonate inhibited the removal. The presence of humic acids inhibited the degradation, due to light screening and radical scavenging.	Acero, et al. 2018
Venlafaxine (among other CECs)	wastewater effluent and spiked pure water	1245/630 ng/L 0.5 mg/L	UVC/H_2O_2 and UV/peroxydisulfate (PDS)	UV/PDS degraded VFX more efficiently than UV/H_2O_2 in buffered pure water. DOC and chloride were the most efficient scavengers for UV/H_2O_2 and UV/PDS, respectively. The efficiency of pilot-scale UV/PDS was affected by the water matrix and higher UV fluences and oxidant doses are needed.	Nihemaiti et al. 2018
Amitriptyline (among other CECs)	Spiked deionized water	0.27 g/L	UVC/PS	Oxidation with UV/$S_2O_8^{2-}$ in presence of 0.01mol L^{-1} $NaHCO_3$. AMT was removed after 2 min of reaction. Oxidation by thermally activated persulfate at 56 °C in the absence of UV irradiation was 15–50 times less reactive than the UV/persulfate system. Second-order rate constant for the reaction between sulfate radical and AMT was determined $(4.8 \pm 0.6) \times 10^9$ M^{-1} s^{-1}	Real et al. 2015

Hollman et al. (2020) evaluated the degradation of venlafaxine and fluoxetine, among others in spiked pure water by the UV (A or C)/Peracetic acid (PAA) process compared to UV/H_2O_2 as well as a combination of the two oxidants at different ratios while using UV radiation. Both PAA in dark conditions and UVA/PAA (λ = 360 nm) were unable to degrade the pharmaceuticals; indicating that UVC irradiation is necessary for activating PAA. UVC/PAA (λ = 254 nm) fully degraded the compounds by pseudo first-order kinetics in 400s for venlafaxine and 300s for fluoxetine. When the dose of PAA or UVC intensity were increased the rate, coefficient increased as well in a linear way. Complete degradation was also achieved by UVC/H_2O_2, with pseudo first-rate constants k = 0.011 $s^{-1}$and 0.009 s^{-1} for fluoxetine and venlafaxine, respectively. When using same quantities (50 mg/L), UVC/H_2O_2 was faster than UV/PAA for degrading by 55% venlafaxine and 33% fluoxetine. Increasing the ratio of H_2O_2 to PAA in the UVC/PAA/H_2O_2 process, improved the degradation compared to PAA alone. Tests on TOC showed that 70% of PAA was converted to acetic acid and remained in the treated solutions. The main degradation mechanism of UV/PAA is suggested to be hydroxyl radical attack as the intermediates were the same with by-products identified during UV/H2O2 process.

Rodríguez-Chueca et al. (2018) studied the efficiency of UV-C photolytic activation of peroxymonosulfate (PMS) and persulfate anions (PS), in terms of pharmaceuticals' degradation, including venlafaxine at large scale, as well as cost demands to assess the ability to apply them as routine treatment (Figure 11a). Their efficiency is compared to UV/H_2O_2.

When using only UVC irradiation the removal of venlafaxine is negligible. The degradation

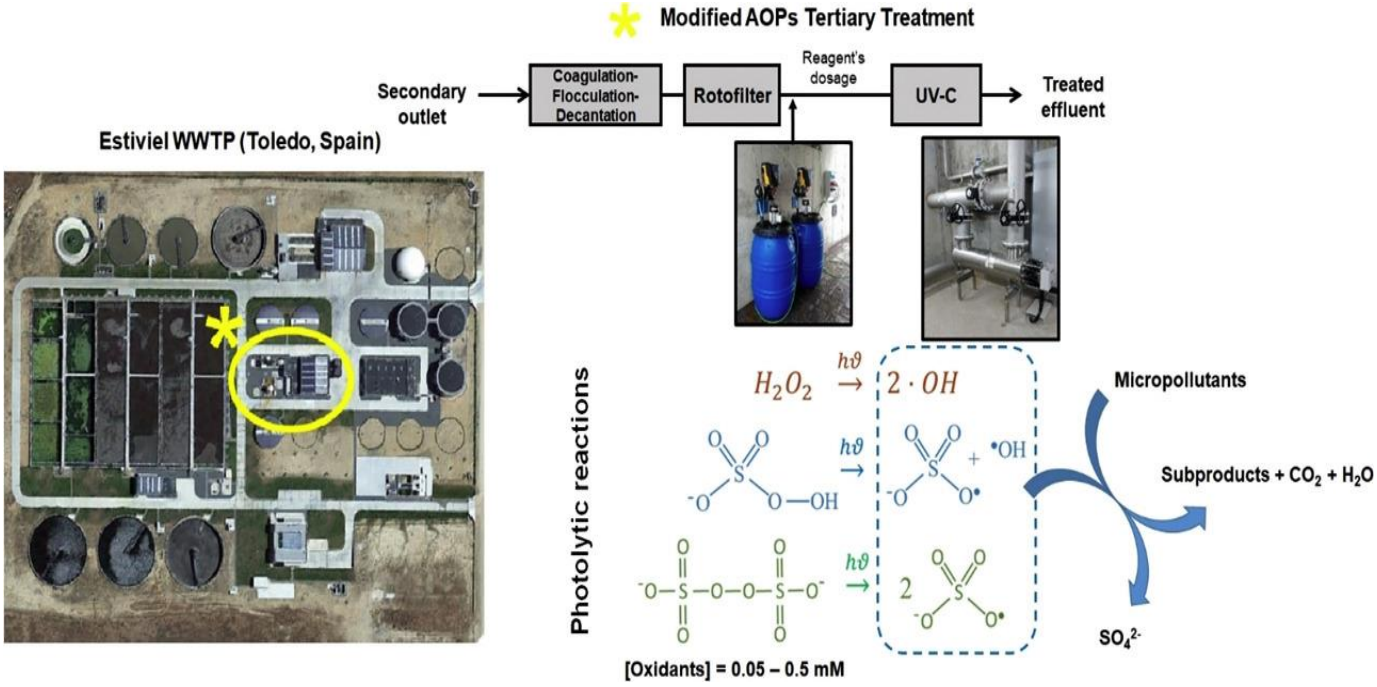


Figure 11a. Graphical abstract of Rodríguez-Chueca et al., 2018

was improved when H_2O_2 was used at different concentrations and different UVC contact times. Venlafaxine was degraded almost by 60% in 18s and 0.5 mM of peroxide. After adding PMS, the generated sulfate and hydroxyl radicals lead to degradation higher than 70% in 18s contact time and 0.5 mM PMS concentration. PS had a moderate effect with less than 40% removal at the same conditions. The best choice in terms of operational cost is UVC/H_2O_2, because when the highest dose is used, maximum removal is achieved (compared to single UV) with lower cost than PMS (Figure 11b).

UV-C contact time (s)	[Reagents]	UV-C**			H_2O_2/UV-C			PMS/UV-C			PS/UV-C		
		€/m³	% Removal	€/m³-order	€/m³	% Removal	€/m³-order	€/m³	% Removal	€/m³-order	€/m³	% Removal	€/m³-order
18	0.05				0.017	18	0.189	0.072	20	0.727	0.022	4	1.24
18	0.2				0.023	26	0.179	0.243	29	1.65	0.045	11	0.919
18	0.5	0.012	13	0.200	0.035	55	0.102	0.585	48	2.03	0.090	10	2.00
7	0.5	0.004	8	0.120	0.026	31	0.164	0.576	25	4.71	0.081	5	3.32
4	0.5	0.003	4	0.153	0.025	14	0.365	0.574	12	10.6	0.079	3	6.05

*H_2O_2, PMS and PS.

**No reagents required.

Most demanding operating conditions: highest UV-C contact time and reagents dosages.

Figure 12.Economical estimation of operating cost of proposed oxidation treatments in the tertiary step (Rodríguez-Chueca et al., 2018.

Acero et al. (2018) used a different oxidant in order to examine the degradation of nortriptyline, among others, in aqueous matrices by using UV-activated persulfate (UV/PS). Direct UV photolysis or dark PS could not degrade nortriptyline. However, the addition of PS during

photolysis increased the removal rate and led to almost complete degradation in 5 minutes due to the generation of $SO4^{-}$ and OH radicals. Second order rate constant with $SO4^{-}\cdot$ was calculated $2.0 \times 10^{10}\ M^{-1}\ s^{-1}$ compared to $1.09 \times 10^{10} M^{-1}\ s^{-1}$ for OH·. Pseudo-first order rate constants increased when increasing the initial concentration of PS, indicating a positive influence. The influence of water matrices was determined by the presence of inorganic ions (bicarbonate) or humic acids. Bicarbonate and humic acids inhibited the removal rate, due to radicals' scavenging and light screening. As a result, the degradation rate in real water samples was lower than in deionized water.

Nihemaiti et al. (2018) was another team that also used persulfate- based AOPs to study the removal of venlafaxine. They used UV/peroxydisulfate (PDS) and compared it to UV/H_2O_2 in buffered pure water and spiked wastewater effluent. UV/PDS degraded venlafaxine more efficiently (total removal) than UV/H_2O_2 (60% removal) in buffered pure water to due to its higher quantum efficiency (i.e., 0.7 moL/E for PDS and 0.5 moL/E for H_2O_2) and higher molar extinction coefficient (i.e., 21.1 $M^{-1}\ cm^{-1}$ for PDS and 18.6 $M^{-1}\ cm^{-1}$ for H_2O_2) at 254 nm and therefor higher photolysis rate at the same initial molar dose. PDS selectively degraded the compounds with electron-rich moieties, such as venlafaxine. Degradation was halted in wastewater samples, because of the scavenging effect of organic matter. However, UV/PDS was more efficient compared to UV/H2O2 because its SO4•− radicals react highly with the specific compound and can more easily overcome the scavenging impact of organic matter. In pilot-scale experiments with UV/PDS, venlafaxine was degraded over 70% at 1200 mJ/cm^2 and 0.6 mM PDS. Higher concentrations of DOC and nitrite were observed compared to lab-scale experiments, leading to 1.5- and 5-times higher scavenging capacity of the wastewater matrix on SO4•−.

Persulfate was used by Real, et al. (2015) to investigate the elimination of amitriptyline in spiked deionized water combined with UVC irradiation. The main operating conditions, such as persulfate dose, temperature, pH and buffer used varied. The oxidation of amitriptyline showed a positive effect of pH, since HO radicals are promoted at high pH. The influence of the buffer used was also investigated by examining two buffers H_3PO_4/HPO_4^{2-} and $HClO_4/ClO_4^{-}$. Complete degradation after 90 s in both cases, although the oxidation rate was slightly slower in the $HClO_4/ClO_4^{-}$ buffer (pseudo first-order rate constant of 6.85×10^{-2} and $3.72 \times 10^{-2}\ s^{-1}$ for H_3PO_4/HPO_4^{2-} and $HClO_4/ClO_4^{-}$, respectively). The presence of the scavenger carbonate/bicarbonate ions caused a great decrease in the rate constant to $1.14 \times 10^{-2}\ s^{-1}$ when using a concentration of 0.01 mol L−1 of sodium bicarbonate at pH 7. The second-order rate constant with sulfate radicals was $(4.8 \pm 0.6) \times 10^{9}\ M^{-1}\ s^{-1}$ and $1.0 \times 10^{10}\ M^{-1}\ s^{-1}$ for hydroxyl radicals. Moreover, thermally activated persulfate was around 15–50 times less reactive than the UV/persulfate system.

4.3 Photocatalysis

The following table summarizes the studies conducted for the removal of antidepressants using different types of heterogeneous catalysts combined with radiation from various light sources (UV, visible or solar).

Table 12. Photocatalysis studies for antidepressant degradation

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
Fluoxetine	Milli-Q water	10 mg/L	Photocatalytic (UV) degradation by TiO_2 nanoparticles synthesized by different methods (sonochemical US, microwave hydrothermal MW, and polymeric precursor PP)	The TiO_2-US sample performed best due to its lipophilic surface. Adsorption rate and photodegradation were optimized by adjusting pH ~ 8. Degradation was 64% (photolysis), 71% (TiO_2-PP), 80% (TiO_2-MW), and 85% (TiO_2-US) after 10 min of irradiation. After 30 min, removal increased to 92.6% (photolysis), 95% (TiO_2-PP and TiO_2-MW), and 96% (TiO_2-US). Seven TPs were identified which compete each other in the degradation mechanisms.	Moreira et al. 2020
Venlafaxine and fluoxetine (among other CECs)	Biologically treated urban wastewater effluent	349 21.7 ng/L	Photocatalytic degradation (visible light, 417 nm) by Metal-free graphitic carbon nitride (g-C_3N_4)	The photocatalytic performance was compared to the commercial TiO_2-P25, confirming that g-CNT had higher removal efficiency. Removal was achieved in less than 10 min to levels below the limit of quantification. Indirect photolysis partially contributed to the elimination. The g-CNT photocatalyst was immobilized on glass rings for continuous mode operation; a minimum residence time of 25 min being required to attain significant removal efficiencies. Phytotoxicity experiments showed no enhancement of toxicity in wastewaters.	Moreira et al. 2019
venlafaxine, fluoxetine, sertraline, fluvoxamine, citalopram, paroxetine, bupropion, mirtazapine and amitriptyline (among other CECs	hospital wastewater treatment plant effluent	~400 ~36 ~68 ~8.5 ~102.4/ 55.9/39 .4 ~32 ~15.8 ~43.2 ~23 ng/L	Photocatalytic degradation (simulated solar irradiation) by TiO_2-P25, graphitic carbon nitride (g-C_3N_4) and a heterojunction of perovskite strodium titanate and graphitic carbon nitride $SrTiO_3$/g-C_3N_4 (20% g-C_3N_4)	Depending on their initial concentrations and removal efficiencies, the compounds were discriminated: (a) Those that presented frequent detection and their photocatalytic degradation was assessed (VFX) and (b) to those that were sporadically detected (e.g., FLX and bupropion). In the case of VFX after 90 min of irradiation with CN, 96% was degraded, with TiO_2 78%, while 20CNSTO presented the lowest performance of 31%. In total 11 TPs were formed along the degradation processes and were identified.	Konstas et al. 2019

Amitriptyline, trazodone and venlafaxine	spiked tap water	10 mg/L	Photocatalytic degradation by UV–Visible radiation employing cobalt doped titanate nanowires as catalyst	Faster degradation of AMT and VFX when Co-TNW as photocatalyst, in both single and mixed solutions. Trazodone showed a similar degradation rate in photolysis and photocatalysis. More AMT and VFX TPs were formed during the photocatalytic degradation compared to photolysis.	Osawa et al. 2019
Amitriptyline	Distilled water and Tap water	10 mg/L	Photocatalytic degradation by simulated UV-Visible radiation employing cobalt doped titanate nanowires as catalyst at 100 mg/L concentration	Under visible light irradiation, amitriptyline was stable in distilled water and partially degraded in tap water after 8h irradiation. AMT degradation was 41% by photocatalytic oxidation, compared to 22% degradation by photolysis under visible light. The pseudo-first order constants in photocatalysis and photolysis were =0.0617 h−1 and = 0.0366 h−1, respectively. Nine TPs were identified and their degradation pathways were proposed.	Osawa et al. 2020
duloxetine and fluvoxamine	simulated urban wastewater	10 mg/L	Photocatalytic degradation (UVA and visible) by TiO_2 P25 as catalyst and photo-Fenton	All experiments were performed with the addition of hydrogen peroxide. In presence of H_2O_2 almost 35% of the organic load was mineralized within 180 min, while in the absence of H_2O_2 the mineralization barely reaches 20%. The highest mineralization was achieved at pH 5 and 7, while at pH = 10 the photocatalytic process barely reached 20% DOC removal after 180 min of treatment. In photo-Fenton, increasing ferric ions caused a higher degradation process which was improved even more by the addition of H_2O_2.	Tsoumachidou et al. 2018
Fluoxetine (among other CECs)	Pharmaceutical stock solution mixture	500 µg/L	Photocatalysis (UV/LED) using TiO_2 as catalyst and Biodegradation	The UV-TiO_2 based photocatalysis effectively removed FLX (>80%) after 2 hours of illumination, with rate constant 15.4×10^{-3} min^{-1}. During single biological treatment (biotic and abiotic batches), by day 3, >99% removal by sorption. In mild photocatalytic pretreatment 35% of FLX was degraded followed by biological treatment. It was found that high removal (>99%) was observed after 21 days in the biological experiments of the MP + B protocol.	de Wilt et al. 2020

Amitriptyline (among other CECs)	double distilled (DDW) and environmental waters	5 mg/L	Photocatalytic (UV 300-400 nm) decomposition using bare TiO_2 nanoparticles and TiO_2/polyaniline nanocomposites (TP-50, TP-100, and TP-150)	The efficiency of photocatalytic degradation was higher in environmental waters. Initial pH in DDW was ~3.5, while in environmental waters from 7.6 to 8.0. Higher value of pH increases efficiency of the photocatalytic degradation. After 60 min of irradiation and 0.5 mg mL^{-1} of catalyst (bare TiO_2 or TP) 45.4% of amitriptyline has been removed from the aquatic suspension. Of the all catalysts applied, TP-100 was found to be the most effective.	Šojić Merkulov, et al. 2018
Fluvoxamine	Double distilled water	0.01 g/L	Heterogeneous (TiO_2 P25) and homogeneous photocatalytic degradation using UV-A or visible radiation with (H_2O_2) and Fe^{3+} addition	The optimum concentration considering cost and efficiency was determined to be 0.25 g L^{-1}. Over 80% of FVX was eliminated within 20 min of reaction with optimum H_2O_2 concentration 0.75 g $L^{-1.}$ With increase of pH from 3 to 7 an increase in the degradation rate is observed. During homogeneous photocatalytic oxidation the increase of ferric ions from 0.00175 to 0.014 g L^{-1} led to a remarkable improvement in both UV-A and visible-irradiated process efficiency of FVX mineralization. On the other hand, the use of extra H_2O_2 dosage did not result to any remarkable improvement.	Tsoumachidou et al. 2017
Fluoxetine (among other CECs)	distilled water	20 mg/ L	Heterogeneous photocatalytic degradation using UV and visible radiation by supported titania-based catalysts produced from petrochemical plant residue	The presence of Mg (4.4%) and Ti (2.5%) resulted in a catalyst that was active over the UV and visible spectral regions.). The highest drug degradation that was observed under UV (48.6%) and visible (45.2%) radiation (60 min of irradiation) with the synthesized photocatalyst (0.7 g L−1) was compared to commercial P25 (titania) catalyst. Under the same conditions, P25 achieved 66.3% and 50.2% degradation, for UV and visible radiation, respectively.	Silva et al. 2015
Trazodone	Distilled water	5 mg/L	Simulated visible light photocatalytic degradation using (Co, Fe and Ru) doped titanate nanowires as catalyst	Photocatalytic performance of four catalysts (20mg/150ml), pristine titanate nanowires, cobalt-doped titanate nanowires, iron-doped titanate nanowires and ruthenium-doped titanate nanowires was compared. The iron-doped titanate nanowires presented the best catalytic activity by the catalyst surface area. Additionally, thirteen TPs were identified	Osawa et al. 2020
amitriptyline	Spiked ultrapure water	3 mg/L	Photocatalytic degradation by the photoactive heterojunction zinc tin oxide nanoparticles (ZnO/SnO_2) under simulated solar and UVA irradiation	In the case of heterojunction ZnO/SnO_2 (1.0 mg/mL), after 60 min of irradiation 82.6% of amitriptyline was removed, compared to other catalysts. ZnO and TiO_2 Degussa P25 removed 76.8% and 43.6% of amitriptyline, respectively. The value of the pseudo-first order rate constant k′x was calculated 3.91 10^2 (min^{-1}). UVA irradiation is more efficient compared to solar. Free •OH radicals played the crucial part in the photocatalytic degradation of amitriptyline while holes play a secondary role.	Ivetić et al. 2015

Fluoxetine (among other CECs)	Distilled water and WWTP effluent	5 mg/L	UV (365nm) photocatalysis using hydroxyapatite (HAp)-based materials as catalyst	The most effective was a multiphasic material constituted of HAp and TiO2 (HApTi); single phase HAp with lattice oxygen vacancy was also effective (Ca_2). Both single-phase HAp and HAp–titania multicomponent materials (1 wt% TiO_2) were employed as UV light photocatalysts (1–4 g/L), the latter showing better performance. The HAp- titania photocatalyst showed excellent degradation. The materials exhibited good photostability, as the degradation rate did not decrease when the material was reused. Tests were also performed in treated wastewater; Photocatalyst was still effective, even if with lower efficiency.	Moreira et al. 2016
Venlafaxine, norfluoxetine and fluoxetine (among other CECs	spiked pharmaceutical solutions	0,2 mg/L	Photocatalytic Degradation (UV 264 and 365 nm) and Adsorption using titanium dioxide (TiO_2) anatase and rutile nanowires and TiO_2 (P25) nanoparticles	For surface adsorption, TiO_2 nanowires are considerably more effective than commercial TiO_2 nanoparticles, while photocatalytic degradation effectiveness varies on a PPCP and nanomaterial-specific basis. Intermediate analysis displays a higher mineralization can be obtained in photocatalytic degradation with TiO_2 nanomaterials compared to UVC photolysis. The UV-exposed anatase-phased nanowires was more effective at degrading VFX, while the rutile-phased nanowires were more effective for FLX.	Hu et al. 2012
fluoxetine, venlafaxine (among other CECs	Ultrapure water	100 µg/L	Photocatalytic degradation by free standing TiO_2 nanowire membranes	Pseudo-first order kinetic degradation was observed for fluoxetine and venlafaxine; k_{fluo}= 0.0408 and k_{ven}= 0.0319. TiO_2 nanowire membranes display a better degradation effect under UV radiation by possessing a stronger photocatalytic effect due to improved energy harvesting.	Hu et al. 2011
venlafaxine		10 mg/L	Photocatalytic degradation by UVA radiation using TiO_2 as catalyst	Photocatalytic degradation of venlafaxine (>99%) has been achieved after 30 min of irradiation using 400 mg L^{-1} of TiO_2. Degradation was mainly affected by pH> catalyst load > initial venlafaxine concentration. Higher degradation at alkaline conditions (pH = 10), while rate constant is decreasing with the increase of the initial concentration of venlafaxine. A great number of TPs generated during the treatment was investigated.	Lambropoulou et al. 2017

Moreira et al. (2020) studied the impact of three different synthesis methods: microwave hydrothermal (TiO_2-MW), sonochemical (TiO_2-US), and polymeric precursor (TiO_2-PP) on TiO_2 nanoparticles used for the degradation of fluoxetine. MW and US methods were more effective than PP, as they presented anatase phase and smaller-size particles The TiO_2-US sample had the best performance at the photodegradation due to its lipophilic surface, which is attributed to the C-H groups therein. By performing the experiments at pH ~ 8, the adsorption rate and photodegradation were enhanced. The degradation mechanism of fluoxetine's degradation was proposed and three TPs were identified (PPMA, MAEB, and

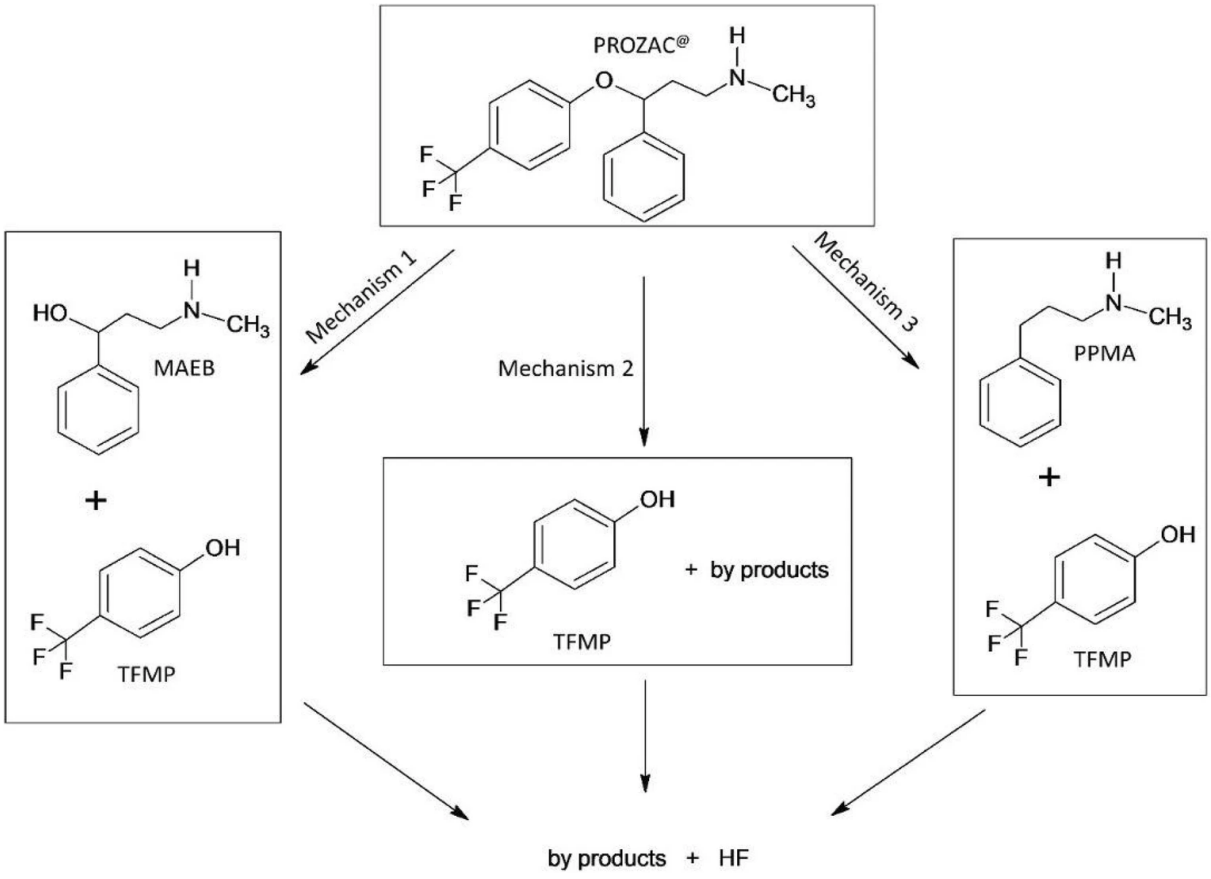


Figure 13. Preliminary degradation mechanism of Prozac® after application of photolytic and photocatalytic processes (Moreira et al. 2020).

TFMP) by using HPLC which were also degraded during the process. Due to their structural characteristics, MAEB and PPMA cannot be obtained simultaneously during Prozac® degradation

and they compete with each other in the degradation mechanism (Figure 13). TFMP was the most abundant.

A different catalyst was used in the Moreira et al. (2019) study. A metal-free graphitic carbon nitride (g-C3N4) catalyst was applied under visible light (400–500 W m^{-2} LEDs) for the degradation of pharmaceuticals, like fluoxetine and venlafaxine in biologically treated wastewater effluent and its efficiency was compared to commercial TiO_2-P25. Limited degradation was observed when only visible light was used, due to indirect photolysis. Almost complete removal was succeeded after 10 minutes of irradiation with apparent rate constants k_{app} ($\times 10^{-2}$ min^{-1}) for fluoxetine being 27.4 ± 4.5 for gC3N4 and 1.9 ± 0.2 for TiO2 and for venlafaxine 41.3 ± 1.2 and 0.9 ± 0.2, respectively. g-C3N4 had a higher performance than TiO_2, as the latter requires UV light for activation. During degradation in continuous mode the catalyst was immobilized on a glass ring in order to avoid the separation process afterwards. However, degradation rate is expected to decline due to limited contact area, with fluoxetine and venlafaxine reaching about 50% removal in 55 minutes.

Accordingly, Konstas et al. (2019) examined the degradation of venlafaxine, fluoxetine, sertraline, fluvoxamine, citalopram, paroxetine, bupropion, mirtazapine and amitriptyline among other pharmaceuticals by photocatalysis, using different catalysts (TiO_2-P25, graphitic carbon nitride (g-C_3N_4, CN) and a heterojunction of perovskite strodium titanate and graphitic carbon nitride $SrTiO_3$/g-C_3N_4 (20% g-C_3N_4, 20CNSTO). The samples were taken from hospital wastewater treatment plant effluent and simulated solar irradiation was used. The degradation efficiency was higher in the cases of CN and TiO_2. Venlafaxine was transformed over 90% in 90 minutes when CN catalyst was used, over 70% with TiO_2 and just 30% with 20CNSTO presented lower photocatalytic performance. Several TPs were identified. For venlafaxine, four TPs including the metabolite O-desmethylvenlafaxine were identified.

Moreover, Osawa et al. (2019), (2020) used cobalt-doped titanate nanowires (Co-TNW) as a catalyst for the transformation of amitriptyline, venlafaxine and trazodone in spiked tap water by UV-visible light irradiation. Amitriptyline and venlafaxine were degraded highly during photocatalysis (~80% in 30 minutes) compared to photolysis and trazodone had a similar performance in both processes (~90% removal in 15 minutes). More TPs were identified during photocatalysis for amitriptyline and venlafaxine. Twenty TPs were identified (eight for amitriptyline, seven for trazodone and five for venlafaxine). Some of amitriptyline's TPs were found to have higher ecotoxicity than the parent compound and one presented possible mutagenicity but were degraded during the experiments. All trazodone TPs had positive mutagenicity and most of them were not fully degraded (Figure 12). Then amitriptyline's degradation was examined using the same catalyst but visible light irradiation in spiked in tap and distilled water. In tap water amitriptyline's degradation

was limited for photolysis (~20%) and moderate for photocatalysis (~ 40%). In distilled water no degradation was detected. Nine TPs were detected in the tap water samples for photolysis and photocatalysis, which were not fully degraded during the experiments.

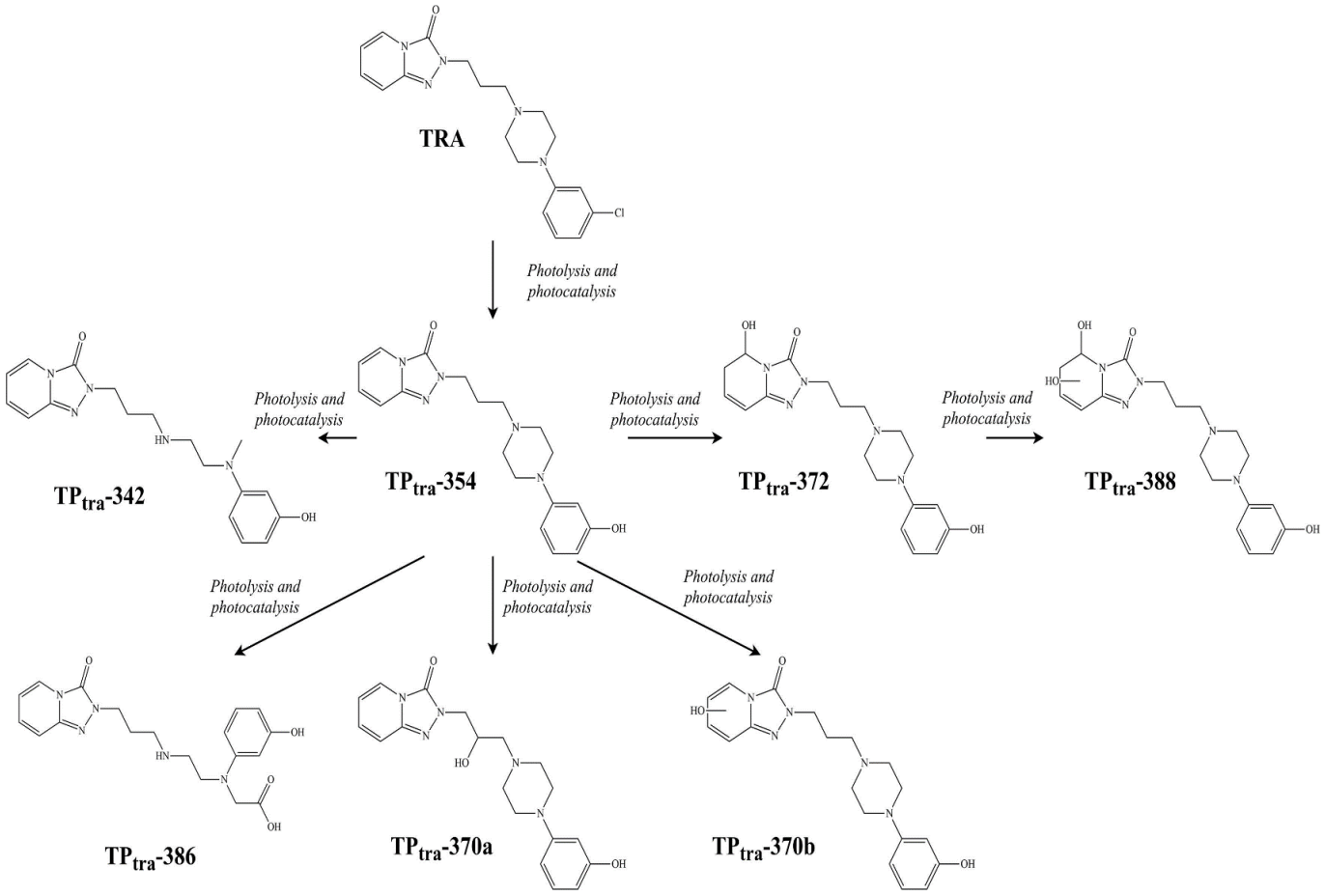


Figure 14. Degradation pathways proposed for TRA photolysis and photocatalysis (Rodrigo A. Osawa, et al. 2019).

The same year, Osawa et al. (2020) also tested the photocatalytic efficiency of four catalysts, undoped titanate nanowires, cobalt-doped titanate nanowires, iron-doped titanate nanowires and ruthenium-doped titanate nanowires, in the degradation of trazodone under visible light radiation. Undoped-TNW catalyst led to the highest degradation, with almost complete removal after 5 hours of artificial solar irradiation, followed by Fe-TNW catalyst, with 50 % smaller surface area, with 88% removal when photolysis could only lead to 57% removal. Taking this into account, Fe-TNW has the best catalytic performance. Thirteen TPs were identified, with two of them being the most abundant in the solution (TP-354 and TP-402). TP-354 was removed after 8 hours of irradiation, while TP-402

increased in quantity during the photocatalytic experiments. The results of in silico predictions showed toxic potential for all endpoints and for some TPs mutagenic potential.

Another team, Tsoumachidou et al. (2018) assessed the efficiency of the photocatalytic degradation of duloxetine and fluvoxamine in simulated wastewater samples using natural and artificial solar light (UVA and visible light 400-500 nm). The catalyst used was TiO_2 P25, but due to its limited effect (~20%), H_2O_2 was added in all experiments in order to enhance the degradation rate. After 180 minutes of UVA irradiation 35% of organic matter was transformed. pH affects highly the process, by changing the particles' surface charge and as a result the adsorption capacity of the catalyst, as well as the stability of H_2O_2. Optimal pH was 5 and 7, where highest removal was observed (~40%). Additionally, the photo-Fenton process was employed separately, producing additional OH radicals. For the same irradiation time Fenton led to a 60% removal with visible light and 70% with UVA. Then, ferric ions were combined with the H_2O_2-photocatalytic process. During these experiments the degradation rate increased to over 60% when the highest ferric concentration was used (0.014 g L^{-1}). Natural light experiments were also conducted and after 3 hours of solar irradiation similar results were acquired.

The same group, Tsoumachidou et al. (2017) examined the removal of fluvoxamine by heterogeneous (TiO_2 P25) and homogeneous (Fenton) photocatalysis. In the heterogeneous photocatalysis, increasing the catalyst's concentration increases the reaction rate and the dissolved organic carbon removal (>80% in 2hours,1 g L^{-1} TiO_2). H_2O_2 was added to the process, in order to improve the efficiency. More than 80% of fluvoxamine was degraded in 20 minutes when using 0.25 g L^{-1} catalyst at different peroxide doses. Moreover, Fe^{+3} was added to the solution and by increasing Fe^{+3}, the reaction rate increased from 0.23 to 0.45 mg L-1 min-1. The catalytic efficiency of TiO_2 is pH-dependent, so when pH increases the efficiency increases and higher mineralization is observed. In the homogeneous photocatalysis (photo-Fenton), increasing ferric ions from 0.00175 to 0.014 g L-1 enhanced DOC removal to 85% (UVA) and 74% (visible light). During the phytotoxicity analysis untreated fluvoxamine samples did not show toxic effects, but TiO_2 and photo-Fenton processes in the treated samples resulted in growth and germination inhibition due to the toxic metabolites formed.

Titanium dioxide was also used in the investigation of de Wilt et al. (2020) in fluoxetine's degradation by a combination of mild photocatalysis (TiO_2) and biodegradation, in batch experiments, compared to single intensive photocatalysis and biodegradation. After 2 hours of single intensive photocatalysis fluoxetine was degraded over 80% and followed first order kinetics, with rate constant 15.4×10^{-3} min^{-1}. During the biodegradation process over 99% transformation was observed by day three, with sorption being the dominant process. For the combined treatment 30

minutes of irradiation caused a 35% degradation at 75% less energy input and over 99% of the remaining pharmaceutical was degraded in the following biological process.

Šojić Merkulov et al. (2018) also used in their study of amitriptyline's photocatalytic degradation TiO_2 nanoparticles and TiO_2/polyaniline (TP-50, TP-100, and TP-150) nanocomposite powders, in double distilled water and environmental waters. TP-100 demonstrated the highest performance compared to the other catalysts, leading to amitriptyline's degradation by 45%, after 60 min of irradiation and 2% mineralization. TiO_2 and TP-150 had similar performance (33 and 32%) and TP-50 had the lowest efficiency with 20% removal. In environmental waters higher degradation was observed, ~ 60%, due to higher pH and SO_4^{2-} ions, compared to distilled water. Limited cytotoxicity (~ 20%) was determined in HT-29, H-4-II-E and Neuro-2a cells by the interaction of amitriptyline and the TP-100 catalyst.

On the other hand, Silva et al. (2015) assessed the removal of fluoxetine and other pharmaceuticals by photocatalysis, using UV and visible radiation and a catalyst containing Ti and Mg, coming from the residue of a petrochemical plant. The catalyst was characterized and its composition was determined by SEM–EDX to include Mg (4.44%), Si (13.13%) and Ti (2.54%). This catalyst was compared to the commercial P25 (titania). The two catalysts had similar moderate performance during UV irradiation (~20%) and during visible irradiation the synthesized catalyst's performance fell to about 10%. The catalytic activity was found to be constant and stable after recycling up to 5 times, compared to the commercial catalysts, which did not present such properties.

A different catalyst was used by Ivetić et al. (2015) to assess the photocatalytic degradation efficiency of amitriptyline by the heterojunction zinc tin oxide with molar ratio of 2:1 (ZnO/SnO_2) nanoparticles with simulated solar and UVA irradiation. The catalyst was prepared using solid-state method and annealing afterwards and its properties were characterized. The catalyst's performance is compared to the ZnO, the commercial TiO_2 Degussa P25 and photolysis. ZnO/SnO_2 had a higher degradation performance than ZnO and TiO_2 P25. Over 80% of amitriptyline was transformed after one hour of simulated solar irradiation by the ZnO/SnO_2 catalyst, while ZnO and TiO_2 Degussa P25 caused a 75% and 40% removal, respectively. The degradation followed pseudo-first order kinetics, with reaction constant for the heterojunction being 3.91×10^2 (min^{-1}), compared to commercial TiO_2 with 1.17×10^2 (min^{-1}). Amitriptyline degrades more efficient under UVA irradiation, with over 80% removed in the first five minutes. The effect of OH radicals in the degradation was examined by the use of inhibitors (Tert-butanol, NaI, NaF). Tert-butanol had the higher inhibition effect and underlined the role of radicals in the degradation.

Moreover, Moreira et al. (2016) investigated the possible photocatalytic activity of hydroxyapatite-based biomaterials in fluoxetine's degradation under UVA radiation. After processing fish bones three different catalysts were constructed: HAp, consisting of hydroxyapatite and β-tricalcium phosphate, single-phase HAp and HApTi, consisting of HAp, β-tricalcium phosphate and TiO_2. HAp had low degradation efficiency, similar to simple photolysis (~15%). The other two catalysts showed high degradation efficiency, 75% and 95% for single-phase HAp and HApTi respectively. Further tests with the HApTi catalyst showed that the catalyst' s and not fluoxetine's concentration affected the degradation rate more. The stability of HApTi in a reuse process was tested. The crystallinity was not affected as a minor 3% decrease in the degradation was observed when using the recycled catalyst. At wastewater samples the efficiency was again high (−4% in the degradation). Mineralization was not complete but high during TOC analysis (maximum 80%).

The popular TiO_2 was used by Hu et al. (2012), when they investigated the degradation and adsorption of different micropollutants like venlafaxine, fluoxetine and norfluoxetine by the catalysts titanium dioxide (TiO_2) anatase and rutile nanowires and TiO_2 (P25) nanoparticles under UV light. Both anatase and rutile nanowires were synthesized by modified hydrothermal growth techniques. The adsorption experiments demonstrated that P25 strongly adsorbs fluoxetine. Venlafaxine is degraded more efficiently by anatase-phased nanowires, while fluoxetine and norfluoxetine by the rutile-phased nanowires. Venlafaxine's degradation follows pseudo-first order kinetics with an apparent rate constant of 0.0375 min^{-1} and 90% removal after 60 minutes. For fluoxetine, in less than 30 minutes 90% degradation is observed.

The previous year, the same team, Hu et al. (2011) had studied the photocatalytic degradation of fluoxetine and venlafaxine (among others) by free standing TiO_2 nanowire membranes and UV irradiation. TiO_2 nanowires were directly synthesized by hydrothermal growth on Ti substrates at 180 °C by using different organic solvents to oxidize Ti. The catalyst's properties (growth mechanism, microstructure and phase transition of TiO_2 nanowire membranes) were characterized. Limited removal was observed during photolysis and adsorption. Photocatalysis presented the highest degradation removal (~70) in one hour.

Finally, Lambropoulou et al. (2017) studied the photocatalytic removal of venlafaxine by the UVA/TiO_2. After 30 min of UVA irradiation and 400 mg L^{-1} of TiO_2, led to complete degradation of venlafaxine (>99%). The reaction follows first-order kinetics and the reaction constant is affected by the initial venlafaxine concentration and catalyst dose; decreases when the initial venlafaxine concentration is increasing and increases with increasing catalyst dose up to the optimum activation level (600 mg L^{-1}). When the effect of pH was examined, it was determined that the rate constant increased by four times when pH was elevated from acidic pH 2 to basic pH 10. Many TPs were

identified. Even though venlafaxine was rapidly degraded, TOC degraded slower (in 240 minutes, 70% removal). During the UVA/TiO_2, TPs were determined to have higher potential toxicity than venlafaxine but were degraded during the irradiation time of the experiment (240 minutes).

4.4 UV/Chlorine

The last method studied for the removal of antidepressants is the combination of UV radiation with chlorine. Table 13 summarizes the relevant studies.

Table 13. UV/chlorine studies for antidepressant removal.

Compound(s)	Aqueous Matrix	Initial concentration	Treatment Process	Results/findings	Reference
Venlafaxine (among other CECs)	simulated drinking water and wastewater	1mg/L	UV/chlorine and UV/H_2O_2	In pure water VFX degraded faster by UV/H_2O_2 than UV/chlorine at pH 7. At simulated drinking water and wastewater, the UV/chlorine process performed better than the UV/H_2O_2. The UV/chlorine was less affected by the water and wastewater matrices. The UV/chlorine process was also more cost-efficient than UV/H_2O_2.	Guo et al. 2018
venlafaxine (among other CECs)	Pure water	2 mg/L	Simulated solar photolysis/ chlorination	The reactive species were (HO·), (RCS, i.e., Cl· and ClO·) and ozone. Solar photolysis had low effect; chlorination lower than 50% while the solar/chlorine system higher than 50%.	Hua et al. 2019
Amitriptyline (among other CECs)	ultra-pure water, surface water and secondary effluents from municipal WWTPs	277 μg/L	UVC/Cl_2 compared to UVC/H_2O_2 or UVC/$S_2O_8^{2-}$	In ultrapure water UV had low efficiency compared to the UVC/Cl_2 process (chlorine 10×10^{-6} M and 7 min irradiation) with 90% removal. The UV/Cl_2 system had the best degradation rates; intermediate rates were obtained with the UV/ and UV/H_2O_2.	Benitez et al. 2017
Venlafaxine (among other CECs)	Simulated Drinking Water	1 μg/L	UV/Chlorine	Direct photolysis at 254 nm was not effective. Venlafaxine was primarily degraded by HO•. Degradation by the UV/chlorine was more efficient for all the CECs.	Guo et al. 2017

Guo et al. (2018) examined the degradation of venlafaxine, among other compounds using UV irradiation combined with chlorine compared to the UV/H_2O_2 processes in pure, simulated drinking water and wastewater. In pure water, venlafaxine degraded with higher rate by UV/H_2O_2 than by UV/chlorine at neutral pH. Hydroxyl radicals were the dominant oxidant species compared to reactive chlorine species. In simulated drinking water the degradation was higher by the chlorine reactive species from UV/Chlorine than by UV/H_2O_2. Natural organic matter was the main scavenger of HO• (93.4%) during the UV/H2O2 process, while scavenging on Cl• was limited (only 3.6%). In UV/H_2O_2, the $HO^{\bullet}$ concentration decreased from pure water to wastewater, causing a decrease in the degradation rate. Effluent organic matter and Br^- were the main $HO^{\bullet}$ scavengers (60% and 30%, respectively). For Cl•, the main scavengers were $HCO3^-$, H_2O and chlorine (38%, 32% and 21%, respectively). While effluent organic matter resulted in the scavenging of hydroxyl and chlorine radicals, Br^- and HCO_3^- formed secondary radicals that continued the degradation. An electrical energy per order (E_{EO}) test was applied to determine the energy demands of each process. UV/chlorine process was more energy efficient compared to UV/H_2O_2 and saved 3.5–93% and 19–98% of the EE/O in drinking water and wastewater, respectively.

In addition, Hua et al. (2019) examined the degradation of different pharmaceuticals, including venlafaxine by the solar irradiation/chlorine process. The solar/chlorine system (pH 7-1 mg L^{-1} chlorine) in pure water in led to a degradation of 60% in 20 minutes, compared to single solar irradiation or chlorination, which had limited effect. The radicals of solar/chlorine system are HO·, RCS and ozone (in dissolved oxygen presence). The degradation of venlafaxine, containing strong electron-donating functional groups, was enhanced by the solar chlorine system, being more susceptible to RCS, ozone or chlorine. When pH value was increased from 6 to 8, in 20 minutes degradation was almost complete (~100%), with the concentrations of HO· and Cl· decreasing by 61% and 56%, respectively, while ClO· increased by 400% and the exposure of ozone increased by 130% in 90 min. When dissolved oxygen was not present the degradation rate of venlafaxine was decreased (<40%), due to inhibition of ozone generation. Total organic chlorine's formation was increased by 60% during solar/chlorine process.

Moreover, Benitez et al. (2017) studied the degradation of amitriptyline, among others, in different water matrices using UV irradiation with chlorine. In ultrapure water, single photolysis or chlorination had moderate effect on the degradation. On the other hand, UV/chlorine presented over 90% degradation within seven minutes (10μM Cl_2) and followed pseudo first-order kinetics. Initial concentration of chlorine had a positive effect on the degradation, while the efficiency decreased by increasing the pH. Moreover, the efficiency of UV/chlorine was compared to other oxidation processes (UV/H_2O_2 and UV/S_2O_8), in different matrices (ultrapure water, reservoir water and two

WWTP secondary effluents). By the UV/Cl_2 process the highest degradation rates were achieved, followed by moderate rates with the UV/ S_2O_8 and UV/H_2O_2 and lastly by single photodegradation. Generally, higher degradation was observed in ultrapure water and lower in reservoir secondary effluents, due to the competition with dissolved organic matter and bicarbonate ions for UV radiation and oxidation.

In the same year, Guo et al. (2017) investigated the removal of venlafaxine in different water matrices with the UV/chlorine system. In pure water direct photolysis and single chlorination did not show high degradation results for venlafaxine, compared to UV/chlorine, where the reaction with hydroxyl and not chlorine species enhances the removal. pH had a negative effect on the degradation rate (highest rate at pH 6), as in increasing pH, OCl^-, an OH radical scavenger is more abundant. The degradation was not affected by the presence of natural organic matter, as chlorine species are more likely to be scavenged compared to hydroxyl species. Venlafaxine presents an even higher rate constant value in the presence of organic matter, which may be due to its sorption to it. Bicarbonate scavengers did not affect the degradation of venlafaxine.

5 Conclusions

This project attempts to provide a review on the presence of antidepressant pharmaceuticals in environmental matrices as well as different methods to remove them, based on UV radiation. The review was based on scientific papers published in the last decade (2010-2020). The selection of the papers used was accomplished through the Scopus database after using the specific years and the antidepressants' names. The large number of studies had to do with the presence of the antidepressants in the environment, their possible toxicity to non-target organisms and different methods of removal. This project was focused on the degradation methods, mostly the Advanced Oxidation Processes based on UV radiation.

UV based processes are a well-established technology used at full-scale in water treatment and reuse facilities. For the evaluation of these processes, one must take into account the operational costs (i.e., energy consumption, chemical input), sustainability (i.e., resource use, carbon footprint), and general feasibility (e.g., physical footprint and oxidation byproduct formation). An economically feasible process is one of the most important aspects of a treatment system to be adopted in industrial environment. The cost of treatment consists of the capital, operational, and maintenance costs. Figure 13 refers to a few important components that are involved in cost estimation. The cost of the processes used on the UV system depends on the type of contaminants, properties of wastewater, flow rate of the effluents, and also the design of the reactor (Rodrigues et al. 2014, Buthiyappan et al., 2015).

An absolute comparison between these methods is very difficult and challenging to be made in terms of their efficiency, as all the AOPs treatments have different advantages and of course, some kind of limitation, which affects the degradation process and as a result its efficiency. This is even more obvious when extremely persistent contaminants are concerned.

During UV direct photolysis, the main removal mechanism is the absorption of impacting radiation from the UV light. Therefore, the application is usually restricted to the contaminants that strongly absorb UV radiation (the ones that have high quantum yields). Thus, the degradation rates were generally moderate and as Collado et al. (2014) comments, insufficient. Reaction kinetics depends also on water matrix characteristics (water constituents like absorbers, photosensitisers and suspended solids, pH, ionic strength, concentration of dissolved oxygen and temperature (Advanced Oxidation Processes for Water and Wastewater Treatment, IWA publishing, 2004). To improve the degradation efficiency, UV radiation could be combined with different radical promoters, such as H_2O_2, sulfate radicals, catalytic materials or chlorine.

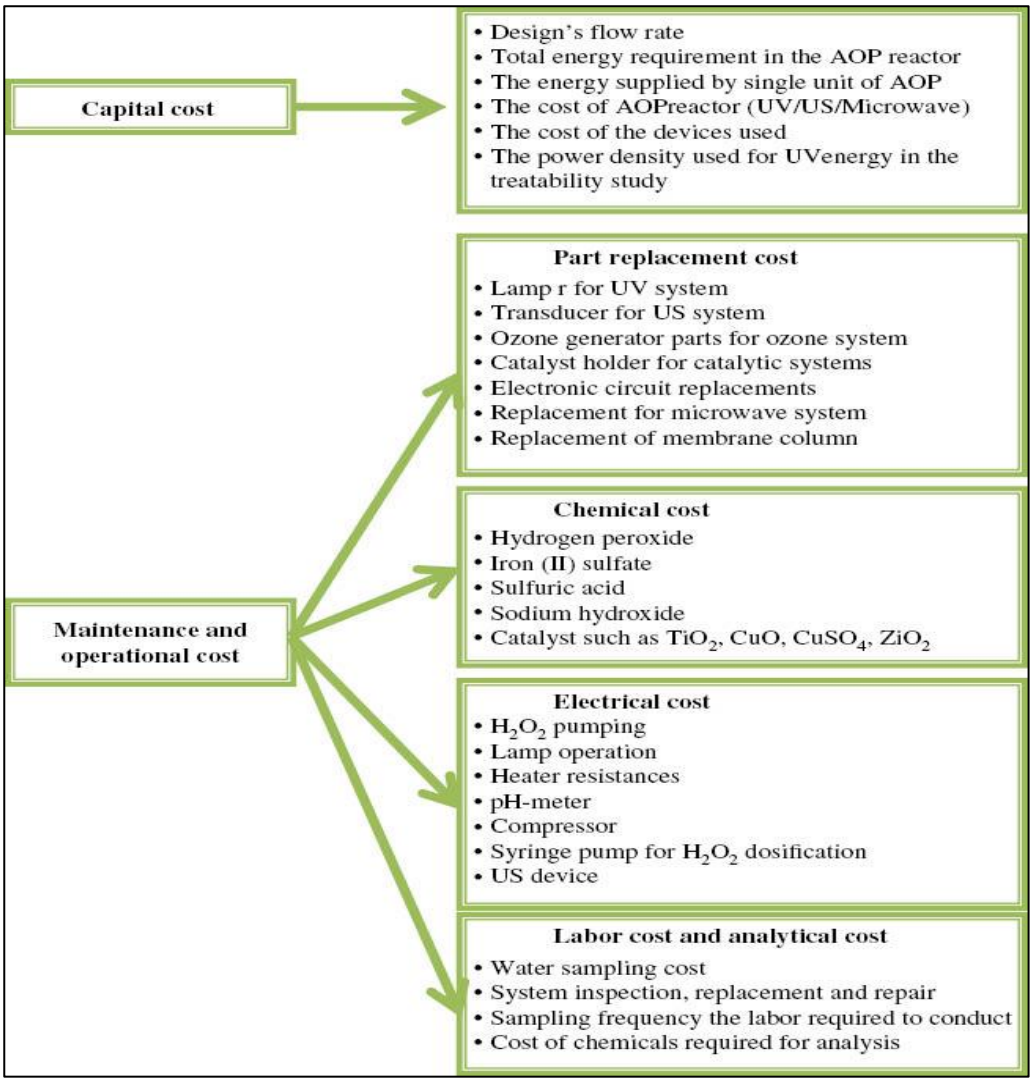


Figure 13. The elements to be included in treatment system cost estimation based on capital, maintenance, and operational cost for UV-based AOPs (Buthiyappan et al, 2015).

The most common UV based AOPs combination is UV radiation coupled with H_2O_2, which certainly raises the efficiency of pharmaceuticals' removal. For example, García-Galán et al. (2016) observed almost complete removal of venlafaxine in 5 minutes by the UV/H_2O_2 process, while Afonso-Olivares, et al. (2016) succeeded 98% removal by the addition of 5 mg L^{-1} of H_2O_2. A major drawback of this method is the considerable chemical cost of UV/H_2O_2 as low UV absorbance by H_2O_2 and organic matter scavengers' presence require additional H_2O_2 dosing. In most cases, only 5–10% of H_2O_2 is used (Guo et al., 2018). The unreacted peroxide's removal further increases the cost.

An alternative to UV/H_2O_2 is the UV/chlorine process that produces reactive chlorine species (RCS). RCS were dominant in organic matter matrices compared to hydroxyl radical as observed by Guo et al. (2018), while Hua et al. (2019) identified that venlafaxine was almost completely degraded by solar radiation/chlorine in 20 min. However, the oxidants used (hypochlorite and chlorine dioxide),

show pH dependency (for hypochlorite; HOCl/OCl ratio) and that influences the molar absorption coefficient significantly. Also, Cl· based reactions involve the formation of oxidative chlorine species (e.g., ClO·, OCl^-), which might lead to the formation of halogenated by-products.

One must also take into consideration that wastewater with high COD and total organic carbon values may not be easily treated with these processes, as hydroxyl radicals and RCS are being scavenged significantly by water matrices' components, like carbonate/bicarbonate and dissolved organic matter, with identified concentrations in real water at mg L^{-1} level (much higher than CECs). This may lead to a pre-treatment stage requirement to improve the degradation, which rises the general treatment cost.

Similarly, sulfate radicals (PS, PMS, PDS) seem to improve the degradation process. They offer several advantages over other oxidants such as longer half-life, higher stability than hydroxyl radical, greater transport distances in the sub-surface level, and ability to work in a wide range of pH and can be activated by low-cost oxidant precursors. Rodríguez-Chueca et al. (2018) managed to degrade venlafaxine over 70% in 18 s contact time with the addition of 0.5 mM PMS. However, compared to hydroxyl radicals, the high selectivity towards organic matters makes it less efficient.

Photoactive catalysts for oxidation processes have been investigated and although many catalysts have been tested, research has mainly been concentrated on TiO_2 based photocatalysis. As Moreira et al. (2020) observed, only 10 min of reaction time were enough for fluoxetine to degrade more than 80%. Also, the same compound was found to degrade very highly (90%) by Hu et al. (2012) with the use of free standing TiO_2 nanowire membranes. However, other promising catalysts appear, such as metal-free graphitic carbon nitride (g-C3N4) by Moreira et al. (2019). Almost complete removal was succeeded after 10 minutes of irradiation for venlafaxine and fluoxetine.

Despite these promising results, many of the studies using photocatalysis in large-scale conditions present moderate to low efficiency. One of the major problems in semiconductor photocatalysis is the even distribution of light in the photoreactor, due to absorption, reflection or scattering. Moreover, when the catalyst is in powder form, an extra filtration step is required which instantly influences the system's economic viability. Fixed-bed photocatalytic reactors appear to offer an attractive alternative, but their initial construction costs are comparatively high and their reaction efficiency is reduced. When the catalyst was used in continuous mode, immobilized on a glass ring (Moreira et al. 2019) efficiency dropped to 50%. In addition, with fixed-bed systems, if regular photocatalyst replacement is necessary then maintenance costs are going to be extremely high. The overall process of semiconductor photocatalysis is itself intrinsically low (typically <10%), mainly

due to significant electron–hole recombination at the typical light intensities (Advanced Oxidation Processes for Water and Wastewater Treatment, IWA publishing, 2004).

AOPs seem to have obvious advantages in terms of degradation efficiency of antidepressants, however mineralization rates are not yet satisfying as these pharmaceuticals are still detected partially oxidized as TPs and add complexity to the matrix of the treated water. Although they are found present at low concentrations, they may possess toxicity risk for water living organisms. Several of the studies mentioned above searched for possible TPs and the toxicity risk they may possess. Single photolysis, photocatalysis and UV/H_2O_2 were identified to produce TPs. In some cases, these products were not identified as toxic. For instance, Santoke et al. (2012) determined several reaction pathways and by-products during direct and indirect photodegradation of venlafaxine, duloxetine and bupropion by 350 nm UV light. Moreira et al. (2020) identified three TPs (TFMP, MAEB, and PPMA) during photocatalytic degradation of fluoxetine with TiO_2 nanoparticles with different synthesis methods (TiO_2-MW, TiO_2-US, TiO_2-PP) that compete with each other during degradation. The TPs were produced in different amounts when different catalysts were used. Moreover, except having high fluoxetine degradation efficiency TiO_2-MW, TiO_2-US had also high TP removal efficiency.

On the other hand, García-Galán et al. (2016) during the degradation of venlafaxine and desmethylvenlafaxine by UV/H_2O_2, identified several TPs and observed their ecotoxicity at different treatment times. It was determined that ecotoxicity increased with the production of TPs and later decreased after the TPs were degraded. Also, Osawa et al. (2019) proposed the structures of twenty TPs during the photodegradation of amitriptyline, trazodone and venlafaxine with modified cobalt-titanate nanowires. Some of these TPs presented high ecotoxicity by in-silico analyses, but were generally degraded quickly. Regarding trazodone TPs, all of them resulted in positive mutagenicity in at least one prediction model and some of them were not degraded even after 120 min. Gros et al. (2015) and Lambropoulou et al. (2017) identified as well, by-products that indicate high toxicity highlighting the importance of taking into consideration the TPs formed during persistent contaminant removal since many of them affect the removal efficiency and may be toxic to aquatic organisms.

In conclusion, it is obvious that UV-based AOPs as a method of antidepressant removal are now commonly used and are highly efficient for wastewater treatment. In this review, an effort was made to sum up all present UV-based AOPs methods used by different scientific teams for the degradation of antidepressants and present the results so far. UV radiation coupled with different radical promoters is a promising technological tool in the service of wastewater management, with

each process having advantages and disadvantages. It is very challenging to make a comparison between these processes in order to decide the most suitable for each occasion, due to the limited amount of research in large scale facilities, which does not permit a proper evaluation of results as well as the formation of different TPs, that affects the degradation in ways of process efficiency and ecotoxicity. Lasty, the operational costs of UV-based technologies, especially at large scale, are restrictive at many occasions despite having promising results. All of the above, point out the need of further research in this field, in order to improve these processes' efficiency specially in wastewater treatment plants in order to maximize its benefits.

References

Acero, J.L., Javier Benítez, F., Real, F.J., Rodríguez E., 2018. Degradation of selected emerging contaminants by UV-activated persulfate: Kinetics and influence of matrix constituents. Separation and Purification Technology 201, 41–50. https://doi.org/10.1016/j.seppur.2018.02.055

Afonso-Olivares, C., Fernández-Rodríguez C., Ojeda-González R. J., Sosa-Ferrera Z., Santana-Rodríguez J. J., Doña Rodríguez J. M., 2016. Estimation of kinetic parameters and UV doses necessary to remove twenty-three pharmaceuticals from pre-treated urban wastewater by UV/H2O2. Journal of Photochemistry and Photobiology A: Chemistry 329, 130-138. https://doi.org/10.1016/j.jphotochem.2016.06.018

aus der Beek T., Weber F. A., Bergmann A., Hickmann S., Ebert I., Hein A., Küster A., 2016. Pharmaceuticals in the environment-Global occurrences and perspectives. Evironmental Toxicology and Chemistry 35, 823-835. https://doi.org/10.1002/etc.3339

Benitez J. F., Acero J. L., Real F. J., Roldan G., Rodriguez E.,2013. Modeling the photodegradation of emerging contaminants in waters by UV radiation and UV/H2O2 system. Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances and Environmental Engineering 48, 120-128. https://doi.org/10.1080/10934529.2012.707864

Blum K. M., Norström S. H., Golovko O., Grabic R., Järhult J. D., Koba O., Lindström H.S., 2017. Removal of 30 active pharmaceutical ingredients in surface water under long-term artificial UV irradiation. Chemosphere 176, 175-182. https://doi.org/10.1016/j.chemosphere.2017.02.063

Bound J., Voulvoulis N., 2005. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environmental Health Perspectives 113, 1705-11. https://doi.org/10.1289/ehp.8315

Brodin T., Piovano S., Fick J., Klaminder J., Heynen M., Jonsson M., 2014. Ecological effects of pharmaceuticals in aquatic systems—impacts through behavioural alterations. Philosophical Transactions of the Royal Society B Biological Sciences 369. https://doi.org/10.1098/rstb.2013.0580

Brooks B.W., Foran C.M., Richards S.M., Weston J., Turner P.K., Stanley J.K., Solomon K.R., Slattery M., La Point T.W., 2003. Aquatic ecotoxicology of fluoxetine. Toxicology Letters 142,169-183.https://doi.org/10.1016/S0378-4274(03)00066-3

Calisto V., Esteves V. I., 2009. Psychiatric pharmaceuticals in the environment. Chemosphere 77, 1257-1274. https://doi.org/10.1016/j.chemosphere.2009.09.021

Carlsson C., Johansson A. K., Alvan G., Bergman K., Kühler T., 2006. Are pharmaceuticals potent environmental pollutants? Part I: Environmental risk assessments of selected active

pharmaceutical ingredients. Science of The Total Environment 364, 67-87. https://doi.org/10.1016/j.scitotenv.2005.06.035

Castillo-Zacarías C., Barocio M. E., Hidalgo-Vázquez E., Sosa-Hernández J. E., Parra-Arroyo L., López-Pacheco I. Y., Barceló D., Iqbal H. N. M., Parra-Saldívar R., 2021. Antidepressant drugs as emerging contaminants: Occurrence in urban and non-urban waters and analytical methods for their detection. Science of The Total Environment 757. https://doi.org/10.1016/j.scitotenv.2020.143722

Chen Y., Liang J., Liu L., Lu X., Deng J., Pozdnyakov I. P., Zuo Y., 2017. Photosensitized degradation of amitriptyline and its active metabolite nortriptyline in aqueous fulvic acid solution. Journal of Environmental Quality 46, 1081-1087. https://doi.org/10.2134/jeq2017.05.0181

da Silva W. L., Lansarin M. A., Livotto P. R., dos Santos J. H. Z., 2015. Photocatalytic degradation of drugs by supported titania-based catalysts produced from petrochemical plant residue. Powder Technology 279, 166-172. https://doi.org/10.1016/j.powtec.2015.03.045

De Castro-Català, N., Muñoz I., Riera J. L., Ford A. T., 2017. Evidence of low dose effects of the antidepressant fluoxetine and the fungicide prochloraz on the behavior of the keystone freshwater invertebrate Gammarus pulex. Environmental Pollution 231, 406-414. https://doi.org/10.1016/j.envpol.2017.07.088

de Wilt A., Arlos M. J., Servos M. R., Rijnaarts H. H. M., Langenhoff A. A. M, Parker W. J., 2020. Improved biodegradation of pharmaceuticals after mild photocatalytic pretreatment. Water and Environment Journal 11, 704-714. https://doi.org/10.1111/wej.12634

Fong P. P., Ford A. T., 2014. The biological effects of antidepressants on the molluscs and crustaceans: A review. Aquatic Toxicology 151, 4-13. https://doi.org/10.1016/j.aquatox.2013.12.003

García-Galán J. J., Anfruns A., Gonzalez-Olmos R., Rodríguez-Mozaz S., Comas J., 2016. UV/H_2O_2 degradation of the antidepressants venlafaxine and O-desmethylvenlafaxine: Elucidation of their transformation pathway and environmental fate. Journal of Hazardous Materials 311, 70-80. https://doi.org/10.1016/j.jhazmat.2016.02.070

Ginebreda A., Muñoz I., López de Alda M., Brix R., López-Doval J., Barceló D., 2009. Environmental risk assessment of pharmaceuticals in rivers: Relationships between hazard indexes and aquatic macroinvertebrate diversity indexes in the Llobregat River (NE Spain). Environment International 36, 153-162. https://doi.org/10.1016/j.envint.2009.10.003

Gogoi A., Mazumder P., Tyagi V. K., Chaminda T. G. G., Kyoungjin An A., Kumar M., 2018. Occurrence and fate of emerging contaminants in water environment: A review. Groundwater for Sustainable Development 3, 169-180. https://doi.org/10.1016/j.gsd.2017.12.009

Gornik T., Vozic A., Heath E., Trontelj J., Roskar R., Zigon D., Vione D., Kosjek T., 2020. Determination and photodegradation of sertraline residues in aqueous environment. Environmental Pollution 256. https://doi.org/10.1016/j.envpol.2019.113431

Grabicová, K., Grabic R., Fedorova G., Kolářová J., Turek J., Brooks B. W., Randák T., 2020. Psychoactive pharmaceuticals in aquatic systems: A comparative assessment of environmental monitoring approaches for water and fish. Environmental Pollution 261. https://doi.org/10.1016/j.envpol.2020.114150

Gros M., Williams M., Llorca M., Rodriguez-Mozaz S., Barceló D., Kookana R. S., 2015. Photolysis of the antidepressants amisulpride and desipramine in wastewaters: Identification of transformation products formed and their fate. Science of The Total Environment 530–531, 434-444. https://doi.org/10.1016/j.scitotenv.2015.05.135

Guo K., Wu Z., Shang C., Yao B., Hou S., Yang X., Song W., Fang J., 2017. Radical Chemistry and Structural Relationships of PPCP Degradation by UV/Chlorine Treatment in Simulated Drinking Water. Environmental Science and Technology 9, 10431-10439. https://doi.org/10.1021/acs.est.7b02059

Halling-Sorensen B., Nors Nielsen S., Lanzky P. F., Ingerslev F., Holten Liitzhofl H. C., Jorgensen S. E., 1998. Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment-A Review. Chemosphere 36, 357-393. https://doi.org/10.1016/S0045-6535(97)00354-8

Heberer T., 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicology Letters 131, 5-17. https://doi.org/10.1016/S0378-4274(02)00041-3

Hignite C., Azarnoff D. L., 1977. Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Sciences 20, 337-342. https://doi.org/10.1016/0024-3205(77)90329-0

Hollman J., Dominic J. A., Achari G., 2020. Degradation of pharmaceutical mixtures in aqueous solutions using UV/peracetic acid process: Kinetics, degradation pathways and comparison with UV/H_2O_2. Chemosphere 248. https://doi.org/10.1016/j.chemosphere.2020.125911

Hollman J., Dominic J. A., Achari G., Langford C. H., Tay J. H., 2020. Effect of UV dose on degradation of venlafaxine using UV/H_2O_2: perspective of augmenting UV units in wastewater treatment. Environmental Technology 41, 1107-1116. https://doi.org/10.1080/09593330.2018.1521475

Hora P. I., Novak P. J., Arnold W. A., 2019. Photodegradation of pharmaceutical compounds in partially nitritated wastewater during UV irradiation. Environmental Science Water Research & Technology 5, 897-909. https://doi.org/10.1039/C8EW00714D

Hu A., Zhang X., Oakes K. D., Peng P., Zhou Y. N., Servos M. R., 2011. Hydrothermal growth of free standing TiO2 nanowire membranes for photocatalytic degradation of pharmaceuticals. Journal of Hazardous Materials 189, 278-285. https://doi.org/10.1016/j.jhazmat.2011.02.033

Hua Z., Guo K., Kong X., Lin S., Wu Z., Wang L., Huang H., Fang J., 2019. PPCP degradation and DBP formation in the solar/free chlorine system: Effects of pH and dissolved oxygen. Water Research 150, 77-85. https://doi.org/10.1016/j.watres.2018.11.041

Ivetić T.B., Finčur N.L., Abramović B.F., Dimitrievska M., Štrbac G.R., Čajko K.O., Miljević B.B., Đačanin Lj. R., Lukić-Petrović S.R., 2016. Environmentally friendly photoactive heterojunction zinc tin oxide nanoparticles. Ceramics International 42, 3575-3583. https://doi.org/10.1016/j.ceramint.2015.10.169

Kessler R.,Berglund P. A., Chiu W.T., Deitz A.C., Hudson J.L., Shahly V., Xavier M., 2013. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biological Psychiatry 73, 904-914. https://doi.org/10.1016/j.biopsych.2012.11.020

Khaleel N. D.H., Mahmoud W. M. M., Olsson O., Kümmerer K. 2016. UV-photodegradation of desipramine: Impact of concentration, pH and temperature on formation of products including their biodegradability and toxicity. Science of The Total Environment, 566–567, 826-840. https://doi.org/10.1016/j.scitotenv.2016.05.095

Kim M.K., Zoh K.D., 2016. Occurrence and removals of micropollutants in water environment". Environmental Engineering Research 21, 319-332. https://doi.org/10.4491/eer.2016.115

Kinney C. A., Furlong E.T., Werner L.S., Cahill J.D.,2006. Presence and distribution of wastewater-derived pharmaceuticals in soil irrigated with reclaimed water. Environmental Toxicology and Chemistry 25, 317-326. https://doi.org/10.1897/05-187R.1

Kümmerer K., 2010. Pharmaceuticals in the environment. Annual Review of Environment and Resources 35, 57-75. https://doi.org/10.1146/annurev-environ-052809-161223

Kolpin D.W., Furlong E.T., Meyer M.T., Thurman E.M., Zaugg S.D., Barber L.B., Buxton H.T., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. Environmental Science & Technology 36, 1202-1211. https://doi.org/10.1021/es011055j

Küster A., Adler N., 2014. Pharmaceuticals in the environment: Scientific evidence of risks and its regulation. Philosophical Transactions of the Royal Society 369. https://doi.org/10.1098/rstb.2013.0587

La Torre A., Giupponi G., Duffy D., Conca A.,2013. Sexual dysfunction related to psychotropic drugs: A critical review - Part I: Antidepressants. Pharmacopsychiatry 46, 191-199. https://doi.org/10.1055/s-0033-1345205

Lajeunesse, A., Gagnon C., Sauvé S.,2008. Determination of basic antidepressants and their N-desmethyl metabolites in raw sewage and wastewater using solid-phase extraction and liquid chromatography-tandem mass spectrometry. Analytical Chemistry 80, 5325-5333. https://doi.org/10.1021/ac800162q

Loganathan B., Phillips M., Mowery H., Jones-Lepp T. L., 2009. Contamination profiles and mass loadings of macrolide antibiotics and illicit drugs from a small urban wastewater treatment plant. Chemosphere 75, 70-77. https://doi.org/10.1016/j.chemosphere.2008.11.047

Lambropoulou D., Evgenidou E., Saliverou V., Kosma C., Konstantinou I.,2017. Degradation of venlafaxine using TiO_2/UV process: Kinetic studies, RSM optimization, identification of transformation products and toxicity evaluation. Journal of Hazardous Materials 323, 513-526. https://doi.org/10.1016/j.jhazmat.2016.04.074

Lhotský O., Krákorová E., 2017. Pharmaceuticals, benzene, toluene and chlorobenzene removal from contaminated groundwater by combined UV/H_2O_2 photo-oxidation and aeration. Water Research 120, 245-255. https://doi.org/10.1016/j.watres.2017.04.076

Luo Y. Guo W., 2014. A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. Science of The Total Environment 473–474, 619-641. https://doi.org/10.1016/j.scitotenv.2013.12.065

Márquez Brazón, E., Piccirillo C., Moreira I. S., Castro P.M.L., 2016. Photodegradation of pharmaceutical persistent pollutants using hydroxyapatite-based materials. Journal of Environmental Management 182, 486-495. https://doi.org/10.1016/j.jenvman.2016.08.005

Mehrnoosh A., Dobaradaran S., Torabbeigi M., Jorfi S., Gholamnia R., Koolivand A., Darabi H., Kavousi A., Saeedi R., 2019. Health risk of phthalates in water environment: Occurrence in water resources, bottled water, and tap water, and burden of disease from exposure through drinking water in Tehran, Iran. Environmental Research 173, 469-479. https://doi.org/10.1016/j.envres.2019.03.071

Miklos D. B., Remy C., Jekel M., Linden K.G., Drewes J.E., Hübner U., 2018. Evaluation of advanced oxidation processes for water and wastewater treatment – A critical review. Water Research 139, 118-131. https://doi.org/10.1016/j.watres.2018.03.042

Miklos D. B., Remy C., Jekel M., Linden K.G., Drewes J.E., Hübner U., 2018. UV/H_2O_2 process stability and pilot-scale validation for trace organic chemical removal from wastewater treatment plant effluents. Water Research 136, 169-179. https://doi.org/10.1016/j.watres.2018.02.044

Molé R. A. Stebe E.K., Edmiston P.L., 2019. Correlating effluent concentrations and bench-scale experiments to assess the transformation of endocrine active compounds in wastewater by UV

or chlorination disinfection. Chemosphere 226, 565-575. https://doi.org/10.1016/j.chemosphere.2019.03.145

Moreira A. J., Campos L. O., Maldi C.P., Freschi G.P.G., 2020. Photocatalytic degradation of Prozac® mediated by TiO_2 nanoparticles obtained via three synthesis methods: sonochemical, microwave hydrothermal, and polymeric precursor. Environmental Science and Pollution Research 27, 27032-27047. https://doi.org/10.1007/s11356-020-08798-x

Moreira Nuno F.F., José M.Sousa, Gonçalo Macedo, Ana R.Ribeiro, Luisa Barreiros, Marta Pedrosa, Joaquim L. Faria, M. Fernando R.Pereira, Sérgio Castro-Silva, Marcela A. Segundo, Célia M. Manaia, Olga C. Nunes, Adrián M. T. Silva.,2016. Photocatalytic ozonation of urban wastewater and surface water using immobilized TiO_2 with LEDs: Micropollutants, antibiotic resistance genes and estrogenic activity. Water Research 945, 10-22. https://doi.org/10.1016/j.watres.2016.02.003

Moreira Nuno F.F., Maria J. Sampaio, Ana R. Ribeiro, Cláudia G. Silva, Joaquim L. Faria, and Adrián M.T. Silva.,2019. Metal-free g-C3N4 photocatalysis of organic micropollutants in urban wastewater under visible light. Applied Catalysis B: Environmental 248, 184-192. https://doi.org/10.1016/j.apcatb.2019.02.001

Nassar Rania, Aurélien Trivella, Samia Mokh, Mohamad Al-Iskandarani, Hélène Budzinski, Patrick Mazellier., 2017. Photodegradation of sulfamethazine, sulfamethoxypiridazine, amitriptyline, and clomipramine drugs in aqueous media. Journal of Photochemistry and Photobiology A: Chemistry 336, 176-182. https://doi.org/10.1016/j.jphotochem.2016.12.008

Osawa R. A., Carvalho A. P., Monteiro O. C., Oliveira C. M., Florêncio M. H., 2019. Degradation of duloxetine: Identification of transformation products by UHPLC-ESI(+)-HRMS/MS, in silico toxicity and wastewater analysis. Journal of Environmental Sciences 82, 113-123. https://doi.org/10.1016/j.jes.2019.02.025

Osawa R. A., Barrocas B. T., Monteiro O. C., Oliveira C. M., Florêncio M. H., 2019. Photocatalytic degradation of amitriptyline, trazodone and venlafaxine using modified cobalt-titanate nanowires under UV–Vis radiation: Transformation products and in silico toxicity. Chemical Engineering Journal 373, 1338-1347. https://doi.org/10.1016/j.cej.2019.05.137

Osawa R.A., Monteiro O. C., Oliveira C. M., Florêncio M. H., 2020. Comparative study on photocatalytic degradation of the antidepressant trazodone using (Co, Fe and Ru) doped titanate nanowires: Kinetics, transformation products and in silico toxicity assessment. Chemosphere 259. https://doi.org/10.1016/j.chemosphere.2020.127486

Osawa R. A., Barrocas B. T., Monteiro O. C., Oliveira C. M., Florêncio M. H., 2020. Visible light photocatalytic degradation of amitriptyline using cobalt doped titanate nanowires: Kinetics and

characterization of transformation products. Journal of Environmental Chemical Engineering 8. https://doi.org/10.1016/j.jece.2019.103585

Paredes L., Omil F., Lema J. M., Carballa M., 2018. What happens with organic micropollutants during UV disinfection in WWTPs? A global perspective from laboratory to full-scale.Journal of Hazardous Materials 342, 670-678. https://doi.org/10.1016/j.jhazmat.2017.08.075

Parry E., Young T. M., 2016. Comparing targeted and non-targeted high-resolution mass spectrometric approaches for assessing advanced oxidation reactor performance. Water Research 104, 72-81. https://doi.org/10.1016/j.watres.2016.07.056

Parsons S., 2004. Advanced Oxidation Processes for Water and Wastewater Treatment, IWA publishing. https://doi.org/10.2166/9781780403076

Patel V., Saxena S., Lund C., Thornicroft G., Baingana F., Bolton P., 2018. The Lancet Commission on global mental health and sustainable development. The Lancet Commissions 392, 1553-1598. https://doi.org/10.1016/S0140-6736(18)31612-X

Prieto-Rodriguez L., Miralles-Cuevas S., Oller I., Agüera A., Puma G. L, Malato S., 2012. Treatment of emerging contaminants in wastewater treatment plants (WWTP) effluents by solar photocatalysis using low TiO2 concentrations. Journal of Hazardous Materials 211–212, 131-137. https://doi.org/10.1016/j.jhazmat.2011.09.008

Radjenovic J., Petrovic M., Barceló D., 2007. Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. Analytical and Bioanalytical Chemistry 387, 1365–1377. https://doi.org/10.1007/s00216-006-0883-6

Real F. J., Acero J.L., Benitez J.F., Roldan G., Casas F., 2016. Oxidation of the emerging contaminants amitriptyline hydrochloride, methyl salicylate and 2-phenoxyethanol by persulfate activated by UV irradiation. Journal of Chemical Technology and Biotechnology 91, 1004-1011. https://doi.org/10.1002/jctb.4670

Redshaw C. H., Cooke M.P., Talbot H.M., McGrath S., Rowland S.J., 2008. Low biodegradability of fluoxetine HCl, diazepam and their human metabolites in sewage sludge-amended soil. Journal of Soils and Sediments 8. https://doi.org/10.1007/s11368-008-0024-2

Rodríguez-Chueca J., Laski E., García-Cañibano C., Martín de Vidales M. J., Encinas Á., Kuch B., Marugán J., 2018. Micropollutants removal by full-scale UV-C/sulfate radical based Advanced Oxidation Processes. Science of The Total Environment 630,1216-1225. https://doi.org/10.1016/j.scitotenv.2018.02.279

Rúa-Gómez P. C., Püttmann W., 2013. Degradation of lidocaine, tramadol, venlafaxine and the metabolites O-desmethyltramadol and O-desmethylvenlafaxine in surface waters. Chemosphere 90, 1952-1959. https://doi.org/10.1016/j.chemosphere.2012.10.039

Sanderson H., Johnson D.J, Wilson C.J. Richard A.B., Solomon K.R., 2003. Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSAR screening. Toxicology Letters 144,388-395. https://doi.org/10.1016/S0378-4274(03)00257-1

Santoke H., Cooper W.J., 2017. Environmental photochemical fate of selected pharmaceutical compounds in natural and reconstituted Suwannee River water: Role of reactive species in indirect photolysis. Science of The Total Environment 580, 626-631. https://doi.org/10.1016/j.scitotenv.2016.12.008

Santoke H., Song W., Cooper W.J., Peake B.M., 2012. Advanced oxidation treatment and photochemical fate of selected antidepressant pharmaceuticals in solutions of Suwannee River humic acid. Journal of Hazardous Materials 217–218, 382-390. https://doi.org/10.1016/j.jhazmat.2012.03.049

Schnell S., Bols N.C., Barata C., Porte C., 2009. Single and combined toxicity of pharmaceuticals and personal care products (PPCPs) on the rainbow trout liver cell line RTL-W1. Aquatic Toxicology 93. https://doi.org/10.1016/j.aquatox.2009.05.007

Schultz M. M., Furlong E.T., 2008. Trace analysis of antidepressant pharmaceuticals and their select degrades in aquatic matrixes by LC/ESI/MS/MS. Analytical Chemistry 80, 1756–1762. https://doi.org/10.1021/ac702154e

Scott G. R., Sloman K.A., 2004. The effects of environmental pollutants on complex fish behavior: Integrating behavioral and physiological indicators of toxicity. Aquatic Toxicology 68, 369-392. https://doi.org/10.1016/j.aquatox.2004.03.016

Shaliutina-Kolešová A., Shaliutina O., Nian R.,2020. The effects of environmental antidepressants on macroinvertebrates: a mini review. Water and Environment Journal 34, 153-159. https://doi.org/10.1111/wej.12448

Starling M. C. V.M., Souza P.P., Le Person A., Amorim C.C., Criquet J., 2019. Intensification of UV-C treatment to remove emerging contaminants by UV-C/H_2O_2 and UV-C/$S_2O_8^{2-}$: Susceptibility to photolysis and investigation of acute toxicity. Chemical Engineering Journal 376. https://doi.org/10.1016/j.cej.2019.01.135

Stumm-Zollinger E., Fair G.M., 1965. Biodegradation of Steroid Hormones. Water Pollution Control Federation. 37, 1506-1510. https://www.jstor.org/stable/25035413

Theodore B. H., Black M.C., 2007. Mixture and single-substance acute toxicity of selective serotonin reuptake inhibitors in Ceriodaphnia dubia. Environmental Toxicology and Chemistry 26, 1751-1755. https://doi.org/10.1897/06-265R.1

Tsoumachidou S., Antoniadis A., Poulios I., 2018. Artificial and solar photocatalytic mineralization of psychoactive drugs-loaded urban wastewater: Inorganic ions and phytotoxicity assessment.

Process Safety and Environmental Protection 120, 37-44. https://doi.org/10.1016/j.psep.2018.08.023

Tsoumachidou S., Kouras A., Poulios I., 2018. Heterogeneous and homogeneous photocatalytic degradation of psychoactive drug Fluvoxamine: kinetic study, inorganic ions and phytotoxicity evaluation. Chemical Technology and Biotechnology 93, 1705-1713. https://doi.org/10.1002/jctb.5543

Tufail A., Price W.E., Hai F.I., 2020. A critical review on advanced oxidation processes for the removal of trace organic contaminants: A voyage from individual to integrated processes. Chemosphere 260. https://doi.org/10.1016/j.chemosphere.2020.127460

van der Ven K., Keil D., Moens L.N., van Leemput K., van Remortel P., de Coenl W.M., 2006. Neuropharmaceuticals in the environment: Mianserin-induced neuroendocrine disruption in zebrafish (Danio rerio) using cDNA microarrays. Environmental Toxicology and Chemistry, 2645-2652. https://doi.org/10.1897/05-495R.1

Vasskog T., Berger U., Samuelsen P.J., Kallenborn R., Jensen E., 2006. Selective serotonin reuptake inhibitors in sewage influents and effluents from Tromsø, Norway. Journal of Chromatography A 1115, 187-195. https://doi.org/10.1016/j.chroma.2006.02.091

Wawryniuk M., Drobniewska A., Sikorska K., Nałęcz-Jawecki G., 2018. Influence of photolabile pharmaceuticals on the photodegradation and toxicity of fluoxetine and fluvoxamine. Environmental Science and Pollution Research 25, 6890-6898. https://doi.org/10.1007/s11356-017-0973-3

Wilkinson J., Hooda P.S., Barker J., Barton S., Swinden J., 2017. Occurrence, fate and transformation of emerging contaminants in water: An overarching review of the field. Environmental Pollution 231, 954-970. https://doi.org/10.1016/j.envpol.2017.08.032

Wols B. A., Hofman-Caris C. H. M., 2012. Review of photochemical reaction constants of organic micropollutants required for UV advanced oxidation processes in water. Water Research 46, 2815-2827. https://doi.org/10.1016/j.watres.2012.03.036

Wols B. A., Harmsen D. J.H., Wanders-Dijk J., Beerendonk E. F., Hofman-Caris C. H. M., 2015. Degradation of pharmaceuticals in UV (LP)/H_2O_2 reactors simulated by means of kinetic modeling and computational fluid dynamics (CFD). Water Research 75, 11-24. https://doi.org/10.1016/j.watres.2015.02.014

Wu Z., Fang J., Xiang Y., Shang C., Li X., Meng F., Yang X., 2016. Roles of reactive chlorine species in trimethoprim degradation in the UV/chlorine process: Kinetics and transformation pathways. Water Research 104, 272-282. https://doi.org/10.1016/j.watres.2016.08.011

Xie P., Zou Y., Jiang S., Wang J., Zhang L., Wang Z., Yue S., Feng X.,2019. Degradation of imipramine by vacuum ultraviolet (VUV) system: Influencing parameters, mechanisms, and

variation of acute toxicity. Chemosphere 233, 282-291. https://doi.org/10.1016/j.chemosphere.2019.05.201

Yu H. W., Anumol T., Park M., Pepper I., Scheideler J., Snyder S.A., 2015. On-line sensor monitoring for chemical contaminant attenuation during UV/H_2O_2 advanced oxidation process. Water Research 81, 250-260. https://doi.org/10.1016/j.watres.2015.05.064