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Antidepressants are emerging potential disrupter of animal behavior, ecosystem and evolution: A review

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Abstract
Trends in prescribing antidepressants for disorders other than depression is increasing all over the world. Environmental load of this contaminant may influence neuroendocrine systems of non-target organisms mainly in aquatic ecosystems. Antidepressants in low doses have significant genotoxic effects too. Most commonly studied impacts of this group of contaminants is disruption of normal behavior. Behavioral changes due to antidepressant contamination may result in drastic alteration in population size and community composition. From microbes to mammals all classes of living organisms are affected by antidepressant pollution. Ecosystems contaminated with antidepressants may lose their normal functions like nutrient cycling, energy flow, photosynthetic efficiency and respiration. All effects exerted by such neuroendocrine disrupters may have broader consequences in terms of evolutionary process.

Keywords: antidepressant, behavior, pollution, environment, evolution

Introduction

Use of personal care pharmaceuticals has increased manifold over the last four decades. Pharmaceutical compounds are designed to modulate and interact with biological systems to produce beneficial effects for several physiological discomfort in humans and also in other animals. Most of these compounds are not completely metabolized within the treated organisms. A large amount of unaltered drugs and their metabolites are excreted. These excreta can enter and adversely affect the environment and other non target organisms [1]. Most of the pharmaceuticals do not remain long in the environment and have low toxicity. However, some medicinal products like antidepressants, antibiotics and estrogens can remain for the long time in environment and create ecotoxicological hazards on non-target organisms even at low concentrations [2].

Depression is nowadays a common chronic disease in most countries worldwide and antidepressants now represent one of the most commonly prescribed medications [3]. Patients with major depressive disorder have increased risks of developing cardiovascular disease, and increased morbidity and mortality [4]. It is estimated that more than 300 million people in the world suffer from depression, which is listed by the World Health Organization [5] as the single largest factor contributing to global disability [6]. It is reported that adolescents with severe depression are 30 times more likely to commit suicide [7]. In the last decade, many countries have reported a twofold to threefold increase in the use of antidepressant medications [8]. Increasing prevalence of antidepressants has been associated with its course of duration estimating more than 40% of antidepressants being prescribed for more than 180 days [9]. Nearly all pharmaceuticals have toxic effects in non target organisms. Impacts of antidepressants may be more adverse than other pharmaceutical compounds as because these drugs affect not only the central nervous system but are also linked with reproduction, growth and immune functions. Antidepressants act by modulating neurotransmitters serotonin, dopamine and noradrenaline through reuptake transporters and receptors. Reuptake transporters and receptors also evolved in many invertebrates like molluscs and Crustacea and aquatic vertebrates like fishes. So antidepressants can disrupt the normal biological systems of ecologically important groups of non-target organisms in aquatic environments. Processes affected include reproduction, growth, maturation, metabolism, immunity, feeding, locomotion, colour physiology and behavior [10].

Classes of Clinically Available Antidepressants

Antidepressants are designed to treat depression. Antidepressants target the pathways in brain which regulate the symptoms caused by depressive disorder. Serotonin, dopamine and norepinephrine are the three neurotransmitters which are modulated by various types of external and internal signaling to regulate different types of moods in different situations. Serotonin plays significant roles to regulate mood, appetite, sleep, memory, social behavior and sexual desire. Norepinephrine mainly regulates alertness and motor function. It also helps to regulate blood pressure and heart rate in response to stress. Dopamine plays important role in decision-making, motivation, arousal and the signaling of pleasure and reward. In people suffering from depression, these neurotransmitters show reduced availability in the brain. Antidepressants regulate the availability and function of these neurotransmitters in different ways. There are many classifications of antidepressant drugs based on their chemical structure, components, mechanism of action and duration of action.

Here we will discuss the classification based on mechanism of action (Table1).

Table 1: Classification of Antidepressants [11]

Classes	Drugs	Mechanism of action	Use
Tricyclic Antidepressants (TCA)	Amitriptyline, Imipramine, Desipramine, Nortriptyline, Clomipramine, Trimipramine, Protriptyline, Doxepin.	They work mainly by blocking the reuptake pumps of norepinephrine (NET) and serotonin (SERT), with little or no action on dopamine reuptake pumps (DAT).	TCAs are generally prescribed for depression which is unresponsive to commonly prescribed antidepressants. Other uses for TCAs include the treatment of neuropathic and chronic pain conditions, enuresis, and insomnia.
Monoamine Oxidase Inhibitors (MAOI)	Phenelzine, Nialamide, Isocarboxazid, Hydracarbazine Tranylcypromine Moclobemide, Bifemelane, Pirlindole, Ttoloxatone Selegiline, Rasagiline, Safinamide.	MAOIs act by inhibiting the activity of one or both monoamine oxidase enzymes namely monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B).	MAOIs are also used only when other classes of antidepressant have failed.
Selective Serotonin Reuptake Inhibitors (SSRI)	Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram, Fluvoxamine.	Their primary mechanism of action is via inhibition of the serotonin reuptake transporter (SERT).	SSRIs are used in panic disorder, generalized anxiety disorders, obsessive– compulsive disorder (OCD), and bulimia, post-traumatic stress disorder, premenstrual dysphoric disorder, migraine, dysthymia.
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)	Venlafaxine, Desvenlafaxine, Duloxetine, Levomilnacipran	SNRIs act by inhibiting the serotonin reuptake (SERT) and norepinephrine reuptake (NET) transporters.	SNRIs are used in major depression and in the treatment of pain disorders including neuropathies and fibromyalgia. They are also used in the treatment of generalized anxiety disorder, stress urinary incontinence, and vasomotor symptoms of menopause.
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	Bupropion.	The NDRI acts to inhibit the noradrenergic (NET) and dopaminergic (DAT) reuptake transporter pump systems.	Used in treatment of major depression
Selective Norepinephrine Reuptake Inhibitors (NRI)	Reboxetine Atomoxetine.	They act to inhibit the norepinephrine reuptake (NET) transporters.	Used for the treatment of major depression, panic disorder, attention-deficit hyperactivity disorder (ADHD), bulimia nervosa, narcolepsy, and treating therapy-resistant pediatric nocturnal enuresis.
Serotonin Receptors Antagonist With Serotonin Reuptake Inhibition (SARI)	Ttrazodone, Nefazodone, Vortioxetine	They exhibit the pharmacological property of a moderate-to-strong serotonin receptor(s) antagonism with a weak serotonin reuptake transporter (SERT) inhibition.	Used in major depression. There is some preliminary evidence that the drug may improve some aspects of neurocognitive functions in depressed patients
Serotonin 5-Ht1a Autoreceptor Partial Agonist With Serotonin Reuptake Inhibition (SPARI)	Vilazodone.	It acts as a SRI with partial agonist activity at the serotonergic somatodendritic 5-HT1A autoreceptors.	Treatment of MDD or major depressive disorder
Noradrenergic α Receptor-2 Antagonist With Specific Serotonergic Receptors-2 And-3 Antagonism (NASSA)	Mirtazapine, Mianserin.	NASSA have α2-blockade, antiserotonergic and antihistaminergic activity; They are potent antagonist or inverse agonist of the α2A-, α2B-, and α2C adrenergic receptors, the serotonin 5-HT2A, 5-HT2C, and 5-HT3 receptors, and the histamine H1 receptor.	Used in treatment of MDD and other mood disorders such as bipolar affective disorders and schizoaffective disorders.
Norepinephrine Reuptake Inhibitor With Serotonin Receptors Antagonism (NRISA)	Maprotiline.	NRISA is a strong inhibitor of norepinephrine reuptake transporter pump (NET); a moderate antagonist of the 5-HT2, 5-HT7, and α1-adrenergic receptors; and a strong antagonist of the histaminergic H1 receptor.	It acts as antidepressant and sedative.
Serotonin-Norepinephrine Reuptake Inhibitor And Serotonin Receptors Antagonism Antidepressant With Potent Antipsychotic D2 Receptor Blockade/ Antagonism (Snrisa With Potent Antipsychotic D2 Receptor Blockade/ Antagonism)	Amoxapine.	Acts as reuptake inhibition of serotonin transporter pump (SERT) and a strong reuptake inhibition of norepinephrine transporter pump (NET) and also binds to block 5-HT2, 5-HT3, 5-HT6, 5-HT7, D2, α1-adrenergic, D3, D4, and H1 receptors with varying but significant affinity.	Prescribed only when other classes of antidepressant have failed.

Atypical Antipsychotics	Olanzapine, Quetiapine, Risperidone, Lurasidone, Aripiprazole.	Atypical antipsychotics exhibit weak D2 receptor antagonism with potently strong 5-HT2A receptor blockade.	Management of MDD, acute bipolar depression, and schizoaffective disorders.
N-Methyl-D-Aspartate-Glutamatergic Ionoceptor Antagonist/ Inverse Agonist/ Partial Agonist	Ketamine. Traxoprodil Rapastinel.	It is a non-competitive and unselective antagonist for the NR2 subunits of NMDA-glutamatergic Receptor (aka channel blocker) that binds to the phencyclidine binding site inside the ion channel of the NMDA receptor, blocking the channel in a way that is similar to how Mg2+ ion blocks NMDA receptors, and is unselective for the NR2A-D subunits of the NMDA receptor channel.	Used the treatment of MDD, bipolar depression and schizoaffective depression.

Worldwide trends in use of Antidepressants

Depression along with anxiety disorder affect more than an 580 million people worldwide [5]. Most significant increase in consumption of antidepressants have been found in the countries those are members of the Organization for Economic Cooperation and Development [8]. It is reported that near about 11% of Americans over the age of 12 years are taking antidepressants regularly [12]. Cause of increase in antidepressant consumption is multifaceted. As suggested by the OECD, the current treatment courses lasts for 3-6 months. Secondly, off-label use of antidepressants have increased in significant rates [13]. The global market of drugs for depression is estimated to be worth $13 billion USD [14]. It is reported that 23.1 million Defined Daily Doses of fluoxetine were prescribed in 2003 in Germany [15]. In the UK fluoxetine were prescribed 4.2 million times between 2010 and 2011[16]. According to OCED (2019) health statistics (Table 2) a severe pattern of changes in daily defined dose (DDD) per 1000 people is found [8].

Table 2: Consumption of antidepressants in selected countries in 2017 (in DDD per 1,000 people) [8]

Sl no	Country	Consumption in DDD per 1,000 people		
		2017	2015	2000
1.	Iceland	141.4	129.6	70.5
2.	Canada	110.3	90.1	……
3.	Australia	109.2	104.2	45.4
4.	UK	107.9	94.2	37.6
5.	Portugal	103.8	95.1	32.5
6.	Sweden	96.9	92.5	44.8
7.	Belgium	78.8	78.3	38.8
8.	Spain	77.2	73.1	28.2

Antidepressants are a group drugs that are developed to treat the symptoms of depression. However, these are also used for the treatment of a different types of psychiatric disorders like anxiety disorders, obsessive compulsive disorders, adjustment disorders, eating disorders, chronic pain, neuropathic pain, attention deficit hyperactivity disorder(ADHD). Off-label use (table3) mean an atypical use of a drug, such as use of a different dosage, duration of use, dosing frequency, use of a different method of administration (e.g. orally instead of intravenously), or use by a different patient group[17]. Nearly one third (29%) of all antidepressants in Canada are prescribed for an off-label use [18]. This clearly shows the large scale use of antidepressant drugs to treat disorders other than depression.

Table 3: Off-level use of Antidepressants [17]

Sl No.	Disease	Antidepressants
1.	Hives (urticaria)	Doxepin
2.	Chronic pain of fibromyalgia	Amitriptyline, Duloxetine, Milnacipran
3.	Urinary incontinence	Amitriptyline Imipramine Duloxetine
4.	Eating disorders	Fluoxetine Sertraline Imipramine Trazadone Citalopram Duloxetine Escitalopram
5.	Premature ejaculation	Sertraline Paroxetine Fluoxetine Escitalopram Clomipramine
6.	Premenstrual dysphoric disorder	Fluoxetine Sertraline Citalopram Paroxetine
7.	Hot flashes during menopause	Escitalopram Citalopram Paroxetine Venlafaxine Desvenlafaxine
8.	Migraine prevention	Amitriptyline Nortriptyline Venlafaxine Duloxetine
9.	Smoking cessation	Bupropion Nortriptyline
11.	Sleeping disorders	Amitriptyline Doxepin Mirtazapine Trazodone
12.	ADHD(Attention-deficit hyperactivity disorder)	Desipramine

Antidepressants in Environment

Antidepressants enter wastewater treatment primarily through domestic waste from human excretion or by direct disposal of unused or expired drugs [19]. Antidepressants are clinically administered within hospital, nursing home, assisted living and

independent living healthcare facilities and these are the primary source of environmental contamination of antidepressants [20].

In addition, wastewater from drug production areas can potentially be a source of environmental load of this pharmaceutical [21].

Thus these drugs and their metabolites may enter the environment via WWTP effluent or by land application of bio solids, originating from WWTPs sludge [22].

Animals are also treated with antidepressants in several cases like in separation anxiety, fearful behavior and other behavioral problems [23].

Metabolism and Excretion of antidepressants in Environment

After oral ingestion antidepressants are metabolized and transformed into primary metabolites [24]. In most of the cases primary metabolites retain the pharmacologic activity of the parent molecule [25]. For example fluoxetine forms a metabolite called norfluoxetine which have the same pharmacologic potential as the parent compound [26]. Antidepressants undergo hepatic metabolism, in order to form more hydrophilic excretable compounds. In most cases renal clearance has been reported to be low, generally with less than 12% of each drugs excreted unaltered in urine [24].

Table 4: Excretion rates of antidepressants and metabolites [27]

Antidepressants	Excretion rates
Sertraline	Less than 0.2% are excreted unchanged in urine
Meprobamate	90% is excreted in urine. About 10–20% of the dose is excreted as unchanged drug and the remainder as metabolites
Paroxetine	2% is excreted as the parent compound in urine and 1% in feces
Venlafaxine	Excreted in urine: 1–10% as the unchanged drug, 30% Odesmethylvenlafaxine, 6–19% N, O-didesmethylvenlafaxine and 1% N-desmethylvenlafaxine. 2% is excreted in feces
Amitriptyline	50% is excreted as 10–hydroxynortriptyline and its glucuronide conjugate and 27% as10–hydroxyamitriptyline

Fate of Antidepressants in the Environment

Five most commonly found antidepressants in environment are fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram [28]. Some other antidepressant drugs like venlafaxine and duloxetine bupropion amitriptyline are also reported to contaminate aquatic environments [29]. A large number of antidepressants have already been identified in water, sludge and biological tissues of aquatic organisms [29]. Fluoxetine and its metabolite norfluoxetine are the most commonly investigated antidepressants throughout the world. However, the antidepressants found in the highest concentrations were venlafaxine, citalopram and bupropion [29]. Until now, the maximum determined concentration of fluoxetine was 0.099 ng L^{-1} in WWTP effluents in Canada [30]. Moreover, very high quantities of fluoxetine were found in bio-solids produced by a WWTP, varying from 100 to 4700 ng kg^{-1} organic carbon (Kinney *et al*., 2006).

Besides the occurrence in surface waters [30], amitriptyline, fluoxetine and risperidone were also recently found in treated drinking waters at low concentrations [31].

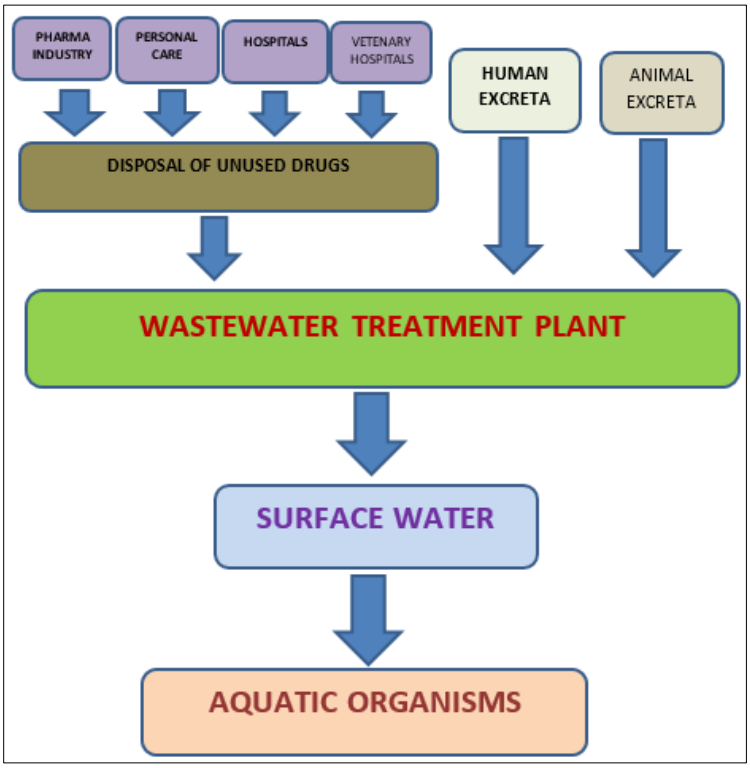

Fig 1

Impact on animal behavior

Many antidepressants are reported in surface waters and have the potential to affect non-target organisms even in very low concentrations [32]. Weinberger and Klaper (2013) reported [33] concentrations of fluoxetine varies from 0.012–1.4 µg/L in freshwater aquatic systems. Even at environmentally relevant concentrations, fluoxetine leads to alterations in reproduction, memory, cognitive function and development in many aquatic organisms [34]. Antidepressants in aquatic environment affect aquatic animals in diverse ways. The most common affect is shift in anxiety related behaviors. Alteration in anxiety related behaviors could result in various altered approaches of life skills. Some common life skills like predator avoidance, prey capture, mating attitude may be affected due to shift in anxiety related behavior.

Swimming behavior

De Castro-Català *et al*. (2017) studied [35] effects of the fluoxetine on the behavior of the freshwater invertebrate *Gammarus pulex.* They found an increase in swimming velocity at 100 ng/L concentrations of fluoxetine. Altered swimming behavior in amphipods at very low concentrations (1–100 ng/L) of antidepressant were also reported by several researchers [36]. Disruption of swimming behavior in cladocerans due to antidepressant pollution in aquatic environments were also reported by several workers [37].

Predator avoidance

Di Poi *et al*. (2014) studied [38] the impact of fluoxetine in the young cuttlefish. They observed the changes in the efficiency of cryptic behaviors, locomotor activity and brain chemistry in young cuttlefish (*Sepia officinalis*) after exposure to environmentally relevant concentrations of fluoxetine compounds. Fluoxetine significantly altered camouflage efficiencies only at 1 ng/L concentration. They also showed a significant increase in the frequency of sand digging behaviors which might make them highly vulnerable to predators in nature. It revealed that environmentally realistic concentrations of fluoxetine significantly impair the cryptic performances of newly hatched cuttlefish and it may ultimately reduce their chances of survival. Hazelton *et al*. (2014) came[39] 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. Such changes may result in their increased susceptibility to predation. Painter *et al* (2009) reported [40] changes in escape responses in larval fathead minnows. When they are exposed to 5 µg/L venlafaxine over a period of 12 days, they exhibited slow escape response. Junior *et al*., (2012) studied [41] decrease in alarm behavior in piaucu fishes after exposure to fluoxetine.

Reproduction

Péry *et al*. (2008) studied [42] the effects of fluoxetine on the life cycle of *Daphnia magna*, *Hyalella azteca*, and *Potamopyrgus antipodarum* exposed to fluoxetine. Length of newborn daphnids was effected by fluoxetine.

For *P. antiporadum*, a significant decrease in reproduction was found at a concentration about 10 µg/L. The exposure of *H. azteca* to fluoxetine resulted in a significant effect on growth. Brooks *et al*. (2003) found [43] a decrease in reproduction in *Ceriodaphnia dubia* after exposure to fluoxetine. Fong *et al*. (1998) found [44] that spawning in male zebra mussels (*Dreissena polymorpha*) was induced by fluvoxamine (1 nM) and fluoxetine (50 nM). Lazzara *et al*. (2012) studied [45] zebra mussels in environmentally relevant concentrations of fluoxetine (20 and 200 ng/L). A decrease in oocyte and spermatozoon density in fluoxetine treated groups were found. This results reflected the ability of fluoxetine to induce spawning at concentrations as low as 20 ng/L. 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[46]. Parrott and Metcalfe (2017) exposed [47] fathead minnows over their full life cycle to environmentally relevant concentrations of the venlafaxine in order to study the effect on survival, development, and reproduction. Galus *et al*. (2013) exposed [48] adult zebra fish for 6 weeks to venlafaxine at a concentration of 10 µg/L, resulting in significantly reduced embryo production.

Locomotion

Peters *et al* (2017) reported [49] that exposure of shore crabs *Hemigrapsus oregonensis* to fluoxetine at environmental concentration of 0.03 µg/L influenced both diurnal and nocturnal prey risk behaviors by increasing foraging and locomotors activity during the day time when these crabs normally stay hidden. Mesquita *et al* (2009) studied[50] increased locomotion and increased activity of muscle cholinesterases in crabs *Carcinus maenas* after seven-day exposure to fluoxetine at ≥120 µg/L. Exposure to venlafaxine and citalopram were reported to cause significant foot detachment from the substrate in two freshwater snails, *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*. 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 [51]. A disturbed circadian rhythm with decreased locomotion during the day was seen in adult mosquito fish (*Gambusia holbrooki*) exposed to 100 µg/L venlafaxine for 7 days [52].

Growth

Significant effects of fluoxetine on growth of crayfish was observed by Tierney and Andrews (2013). Pery *et al*. (2008) reported[42] that growth of juvenile *Hyalella azteca* was significantly reduced when exposed to fluoxetine concentration 100 µ g/L and in Daphnia magna at concentrations ranging from 102 to 241 µ g/L. Brooks *et al*. (2003) reported[43] reduction in growth of *Hyalella azteca* and *Chironomus tentans* exposed to fluoxetine in sediments. Sehonova *et al*. (2017) studied [53] the effects of 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. Yang *et al*. (2014) observed [54] a reduction in the body length of zebrafish (*Danio rerio*) embryos

after exposure to amitriptyline at concentrations of 1, 10 and 100 ng/L; 1, 10 and 100 µg/L; and 1 mg/L.

Feeding

Escape responses were slowed in larval fathead minnows exposed to 5 µg/L venlafaxine over a period of 12 days [40]. Time to capture prey was increased in hybrid striped bass (Morone saxatilis x Morone chrysops) exposed to 50, 250, and 500 µg/L of venlafaxine for a period of 6 days (Bisesi *et al*., 2014). Female goldfish IP-injected with fluoxetine displayed reduced food intake and a 40% decrease in weight gain [55]. Decreased prey capture and abnormal behavior were reported in fluoxetine-exposed hybrid striped bass [56].

Memory and learning

Fluoxetine can influence the process of learning and memory in cuttle fishes (*Sepia officinalis*) at concentrations between 1 and 100 ng/L [38].

Impact on Ecosystem

Ecological effects of antidepressant exposure in aquatic systems may arise through changed population sizes and subsequently altered community composition and species richness [57]. All aquatic systems are intimately connected with adjacent terrestrial systems via cross-boundary resource flows [58]. Resource flows are directly or indirectly altered if pharmaceuticals induce behavioral changes in aquatic consumer organisms. Adjacent terrestrial food webs may also be influenced by affected aquatic ecosystems.

Microbes

Zhaopeng Yang *et al* (2018) reported [59] that Sertraline upon treatment inhibited the growth of two microbial populations (the green alga, *Chlorella vulgaris*, and the cyanobacterium, *Microcystis aeruginosa*) and decreased the chlorophyll a (Chl-a) concentration in the microcosm to reduce the photosynthetic efficiency. They also showed that Sertraline treatment resulted in slight enhancement of the prokaryotic diversity by differentially stimulating bacterial growth. Sertraline could therefore be toxic to such aquatic microorganisms and change the microbial community structure. As a result, the metabolic state like reduced photosynthetic efficiency, N_2 availability or the ability to withstand predators or competitors of surviving individuals would change and alter the relationship between them (allelopathy, parasitism, mutualism, etc.) and indirectly cause the disruption of microbial ecological balance [60]. SSRI group of antidepressants have antimicrobial properties with the potential to affect composition of both bacterial and algal communities [61]. Algae exposed to fluoxetine also can be smaller in size than normal which may result in reduced photosynthetic performance, leading to lower production and respiration [62].

Species interaction, Population size and Community composition

Antidepressants influence both physiology and behaviour in a wide range of organisms from microbes to mammals. Effects of pharmaceutical on behaviour are of direct ecological importance because behaviours are tightly linked to individual fitness and population persistence [63]. However, besides these direct effects, changes in individual fitness may also produce indirect ecological effects. Such indirect effects occur via changed species interactions, such as predation or competition [64]. For example, as individual behaviours change, a number of trade-offs (e.g. to eat or being eaten) affecting individual fitness also change, resulting in population increase, decrease, or even local extinction [65]. Extinction have direct effect on population size and community structure. Gaworecki and Klaine (2008) reported [56] that striped bass decreased feeding upon prey fish after exposure to fluoxetine. Conversely, a recent study using juvenile perch showed increased feeding after exposure to a different psychotropic drug oxazepam [66]. If exposure to antidepressant increases feeding rates of a secondary consumer [66], primary consumers are likely to be suppressed, with positive consequences for primary producers. Conversely, an increased feeding rate among intermediate consumers may make them more vulnerable to top predators, resulting in a population reduction and, subsequently, an increase in primary consumers. Such cascading effects may have drastic impacts on population size and community structure of the affected ecosystem.

Ecosystem function

Alterations in basic behavioural patterns such as activity level, boldness, and sociability, especially of predatory and omnivorous organisms, can change functioning of entire ecosystems [67]. Increased activity, aggressiveness, and changed foraging behaviour can rapidly impact resources and lead to ecosystem instability, disrupting relationships in the food chain and affecting biodiversity [67]. Using functional response M. Bláha *et al* (2019) investigated [68] pharmaceutical impact on the consumer resource relationship, the basic component of ecosystems that strongly influences energy flow and stability of ecosystems. E. K. Richmond *et al* (2016) reported [62] that SSRI groups of antidepressants in rivers and streams have potential to affect several ecosystem processes like biofilm biomass and metabolism.

Impact on Evolution

It is established that exposure to chemical contaminants can result in the evolution of physiological resistance [69]. Contaminants like antidepressants can bring changes in behavior of affected organisms. There are three aspects through which antidepressants may influence evolutionary process of aquatic organisms. Changes in the function and structure of microbial communities, behavioral changes in individual organisms and mutation in genetic components----these three aspects may have direct or indirect consequences through which emergence of new taxon may be initiated.

Z. Yang *et al* (2018) reported [59] that sertraline can inhibit growth of algae and reduce photosynthetic efficiency in microcosm experiments. If we think it in larger field it may have drastic impact on the functioning of ecosystem. All aspects of nutrient cycling to decomposition may be influenced by this single impact of a single antidepressant. It may pose strong evolutionary force to emerge new taxa resulting in drastic alteration of the existing ecosystem structure and function.

Changes in behaviors like predator avoidance may result in the affected species to take more risks, spending longer foraging time and less time for avoiding predators. These altered behavior may have broader consequences like shifting of nutrient cycling, gradual decreasing of population of the affected species, arrival

of new dominant species. Indirect effects due to antidepressant-induced behavioral shifts could cause systems to respond far more strongly and quickly than an assessment of direct effects [70]. Moreover, antidepressant mediated effects could yield novel forms of ecological interactions by inducing prey-switching due to changes in predatory behavior and changes in prey abundance or quality, or by differentially altering the vulnerability of individuals or species to parasites[71].

Several studies have suggested that a large number of antidepressants have genotoxic affects [72]. Mutagenicity of antidepressants are reported in a large array of organisms starting from microbes to mammals. These mutations may also have strong influence in the evolution of organisms.

Discussion

Antidepressants act by modulating and mimicking the effects of the neurotransmitter serotonin, dopamine and norepinephrine and regulate a wide range of physiological, genetic and behavioral systems in aquatic organisms [73, 74, 75]. Already available literature suggests that exposure to this group of drugs may lead to reproduction reduction, abnormalities in embryo development, delay in physiological development and sexual maturation. Decreased aggressiveness and inhibition of feeding responses were also reported [22, 73, 74]. Studies demonstrated that in crustaceans and bivalves antidepressants can induce spawning at concentrations as low as 0.03 µg L^{-} and were found to be toxic to algae in laboratory experiments [29]. Daughton and Brooks, 2011 reported [76] the evidence of accumulating antidepressant residues in fish tissues from an effluent dominated stream (). Since then several studies have been published and it has been observed that the SSRIs concentrations in fish tissues varies in different the species and the tissue [74, 76]. Studies have also confirmed that several types of antidepressants can be bio accumulated in aquatic organisms [75]. It is important to note that antidepressants do not occur individually but as mixtures together with their metabolites and other pharmacologically active compounds. Antidepressants can interfere with several animal behaviors. Reproductive behavior, swimming and locomotion, predator avoidance behavior, feeding behavior are the most studied behaviors in response to antidepressant pollution. Antidepressants are designed to modulate adaptive stress or fear responses to treat persons with depressive disorders. In aquatic environment, some of these drugs have great potential to affect foraging and anti-predator responses of wild animals. This type of alteration in behavior have direct impact on fitness and population dynamics [77].

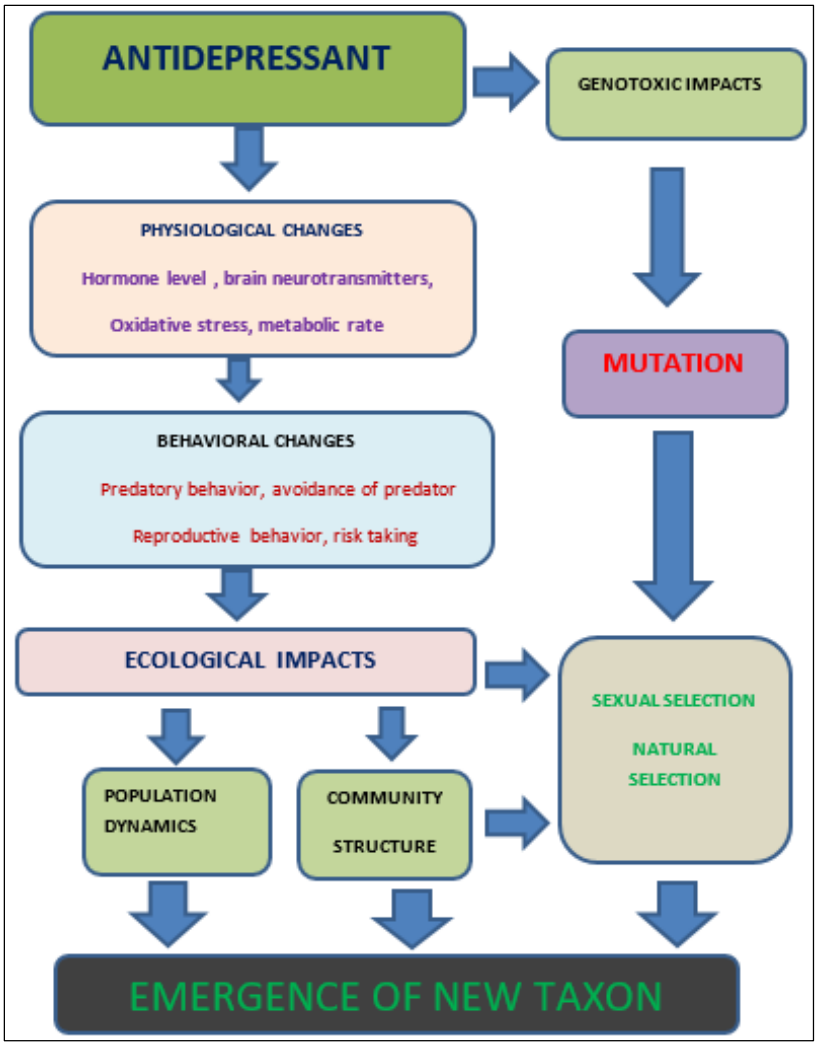

Fig 2

Conclusion

Antidepressants are the latest addition in the anthropogenic pollutant list. Increasing complexities of life and struggle result in chronic depressive disorder in human being. Use of antidepressant drugs are increasing in an exponential fashion throughout the globe. More precise research and studies are needed to evaluate the present load of all types of antidepressants in all ecosystems.

As per available reports, this group of drugs have direct physiological, genetic and behavioral effects on non-target organisms ranging from bacteria to mammals. In this review it is proposed that antidepressants may have more broader consequences in the ecosystems through changing productivity, mineral cycling, decomposition patterns, species dominance, population dynamics and community structure. Alteration in these features may initiate the emergence of new taxa in the affected ecosystems.

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