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It has been observed a sharp growth in the number of diagnoses of depression (under the MDD [Major Depressive Disorder] spectrum) in the last decades, accompanied by a similarly increase in sales of antidepressants in several societies, leading to depression being currently considered an epidemic (WHO). The predominant understanding of the cause for depression, the serotonin hypothesis, conveyed by 80% of the population, dates back to the 1960s, when the first antidepressants were being developed. This article sought to verify this state of affairs from the main literature available, starting from the original pharmacological development of antidepressants and their implication in the body's physiology. Most of the literature gathered for this study did not validate the hypothesis as the most plausible main cause for depression, while nonetheless, this continues to be widespread by pharmaceutical industries and most medical practitioners as such.

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I. INTRODUCTION

The biochemical hypothesis relating depression to low levels of neurotransmitters in the central nervous system (CNS) is linked to the millennial use of *Rawolfia serpentina*. Due to the similarity of its roots with vipers, and following the theory of signatures, the ancient Hindu medicine used this species to treat snake and insect bites. The name Rawolfia was given in honor of the German physician Leonard Rauwolf who exhaustively studied the properties of this plant. Ayurvedic medicine also used the roots of this species to treat insomnia and some types of insanity. Mahatma Gandhi took an infusion of these roots every night to treat his insomnia. In 1931, the first work on the therapeutic use of the Rauwolfia root in the treatment of hypertension and psychosis was published, but with little repercussion (Alonso, 1998).

Later, reserpine was highlighted as one of its active principles, and its association with the decrease in the production of dopaminergic neurotransmitters (dopamines) affirmed (Mabey, 1988).

1.1 The Pharmacology in the Origin of Antidepressants

In 1932 the alkaloid reserpine was isolated, and started to be used with great success in the treatment of hypertension. However, in the long-term treatment, reserpine produced depressant effects that limited its use (Mabey, 1988). In addition to depressant effects, reserpine treatment could cause tremors similar to those produced by Parkinson's disease.

Subsequent studies revealed that reserpine produced the release of noradrenaline, adrenaline, dopamine, and serotonin from the nerve endings where these neurotransmitters are synthesized and released. At high doses, reserpine cause marked depletion of these neuro-transmitters and prevented their reuptake by neuronal storage granules, markedly decreasing their neuronal stores. Severe hypotension, bradycardia, gastric ulcer, tremors, fatigue and

"depression" were the symptoms produced by reserpine at high doses (Shore, 1971). These combined effects including the depressive state led researchers to the conclusion that reserpine would be a good tool for experimental studies in the search for new drugs for depression.

However, when we observe the effects it produces in experimental animals it is impossible to conclude that they are related to depression. After 24 hours of a high dose of reserpine, "to induce depression," the animals are in a deplorable state with piloerection (fur erection), elevated hypotension, salivation, intense diarrhea, gastric ulcer, and locomotor ataxia (an impairment of voluntary movements). It is really not possible to claim that these intense effects would be characteristic of a depressive condition.

Therefore, this experimental model of depression has been contested by some authors. Because of its hypotensive effects, by depleting the noradrenaline present in the endings of the sympathetic system responsible for the control of blood pressure, reserpine has been indicated for the treatment of blood pressure, evidently in doses much lower than those used in laboratory animals. However, even at low doses, reserpine, despite lowering blood pressure very effectively, produces orthostatic hypotension (the excessive drop in blood pressure), which has greatly limited its use, since the patient can barely stand upright. In fact, a person with very low blood pressure and dizziness will appear "depressed".

In the 1950s, as with many chance discoveries, researchers observing the clinical effects of iproniazid in tuberculosis patients noted that this drug produced a significant improvement in their mood. What was apparently just a side effect, in reality revealed the discovery of the first group of antidepressants, which acted by inhibiting monoamine oxidase (MAO), responsible for the metabolization of catecholamines (adrenaline, noradrenaline and dopamine) and serotonin, causing accumulation of these neurotransmitters in the nerve endings where they are predominant. In the same decade, another group of researchers, studying derivatives of chlorpromazine, an antipsychotic that originated from the antihistamine promethazine, arrived at the imipramine molecule, which had no antipsychotic effect, but rather an antidepressant one, giving rise to a new class of substances. Subsequent studies revealed that imipramine and derivatives acted by inhibiting the neuronal reuptake of catecholamines and serotonins. Because they have tricyclic chemical structure they were also known as tricyclic antidepressants (Pereira e Hiroaki-Sato, 2018). Meanwhile, experimental studies in animals found that the administration of tryptophan, a precursor of serotonin, potentiated the antidepressant effect of MAO inhibitors and tricyclic antidepressants (Coppen et al., 1963). These experiments gave rise to the monoaminergic theory and the search for drugs that would specifically inhibit serotonin reuptake.

The company Eli Lily constitutes a group of researchers that then began the search for a specific serotonin reuptake inhibitor. Again, from the molecule of antihistamines, they synthesized dozens of molecules until they came to fluoxetine (Prozac), the most potent in inhibiting the reuptake of serotonin in synaptosomes (isolated synaptic terminals of neurons) in mice (Wong et al., 1974). However, conclusions about the mechanism of action of antidepressants have always been based on *in vitro* studies, such as with synaptosomes in experimental models with laboratory animals. Transposing these studies to humans diagnosed with depression is very difficult and unlikely. Experimental models for studies of drugs that act on CNS disorders are very limited, since it is impossible to isolate the brain of an animal and monitor its function, as is done, for instance, with the heart. One can remove the heart from an animal, keep it in perfect functioning and quantitatively register the alterations produced by several substances. The same is not possible with the human brain. Therefore, conclusions about the mechanism of action of drugs in the brain are always risky to extrapolate from *in vitro* studies and behavioral observations of laboratory animals, to the human brain.

There are basically four experimental models used for studies that seek antidepressants' mechanisms of action. One of them is the study of the

potentiation of the effects of noradrenaline in the periphery, in organs stimulated by the sympathetic nervous system, such as the heart. Another model evaluates the potentiation of the central stimulant effects of amphetamine, which acts by releasing noradrenaline. The reduction of the "depressant" effects of reserpine is another model used, besides the one that studies the *in vitro* blockade of neurotransmitter capture.

These are very restricted models (*in vitro* or in animal brains) which, in our understanding, do not allow a safe transposition of their results to the complexity of the human brain.

1.2 The Adverse Effects of Antidepressant Drugs

When studying the various pharmacological effects of antidepressants, we can conclude that the actions observed are far beyond inhibition of reuptake or on neurotransmitter metabolism.

Monoamine oxidase inhibitors (MAOI) cause accumulation of serotonin, norepinephrine, and dopamine in the nerve endings where these neurotransmitters are produced and released. However, contrary to expectations, hypotension is a common side effect, and pargiline, one of the MAOIs, was used for some time as an antihypertensive drug.

The contradiction lies in the fact that MAO inhibition causes an accumulation of noradrenaline at the sympathetic endings, which are responsible for blood pressure control. Thus, with more noradrenaline the greater the chance of hypertension. This accumulation is proven by the hypertension caused by tyramine (produced by fermentation of some cheeses) in patients under MAOI treatment[1].

In the current literature, the role of acetylcholine as an important neurotransmitter in the CNS, through its action on muscarinic receptors, is not sufficiently discussed for depression. Cholinergic neurons are widely distributed in the CNS, being responsible for alertness, learning, and memory. Evidently, the blocking of muscarinic receptors of acetylcholine in the CNS by MAOIs produces alterations in brain function. The amnesia produced by atropine and derivatives is well known. This variety of pharmacological effects automatically questions the theory that the actions on mood are associated exclusively with MAO inhibition.

These same problems are observed when we analyze the adverse effects of tricyclic antidepressants (TADs), which act, according to the literature, by inhibiting the reuptake of serotonin, noradrenalin, and dopamine. Therefore, these substances act by increasing the concentrations of these amines at the sites where they are released. It is reported that in non-depressed individuals these substances cause sedation, confusion, and lack of motor coordination. These effects also occur in patients medicated with TADs, but may diminish with prolonged treatment. As with the MAOI, the TADs also act by blocking the muscarinic receptors of acetylcholine, producing effects such as xerostomia (dry mouth), blurred vision, intestinal constipation, and urinary retention. They cause postural hypotension as well, which, by the proposed mechanism of action, should not happen. On the contrary, the increase in noradrenaline concentration in the sympathetic terminals would produce an increase in blood pressure, mainly because the vasomotor tonus is maintained by the sympathetic, with continuous release of noradrenaline. TADs also have an antihistaminic effect, contributing to the observed sedation. This effect is also expected, because this group of substances was synthesized from the antipsychotic chlorpromazine, a derivative of promethazine, one of the most potent antihistamines. In the CNS, histamine is a neurotransmitter involved in several functions. In the cortex and reticular activating system histamine contributes to arousal and alertness. Therefore, histamine H1 receptor antagonists, such as promethazine, produce sedation, as do

[1] Known as the cheese reaction: the patient may have a severe hypertensive crisis, accompanied by intense pulsating headache (migraine), which can sometimes produce intracranial haemorrhage. These contradictory effects, so far, have not been explained. MAOIs also block the muscarinic acetylcholine receptors, which at the peripheral level produce xerostomia (dry mouth) by decreasing saliva production; cyclopaedia (blurred vision), urinary retention and intestinal constipation, among other effects.

antipsychotics and TADs. Antipsychotics are drugs that are widely used to treat nausea and vomiting, especially when they are consequences of chemotherapy[2].

The adverse effects common to selective serotonin reuptake inhibitors (SSRIs) - nausea, insomnia, loss of libido and of appetite, among others -[3], also observed in the use of MAOIs and TADs, classified as adverse, involve other CNS mediators besides serotonin and other systems in the body, such as the autonomic. Other antidepressant drugs that inhibit the reuptake of noradrenaline and/or serotonin, such as venlafaxine, reboxetine and bupropion, also have similar adverse effects.

In the CNS, serotonin influences numerous functions such as sleep, cognition, sensory perception, motor activity, temperature regulation, nociception (sensory capture), mood, appetite, sexual activity and hormone secretion. In the gastrointestinal system (GIT), serotonin stimulates peristalsis and intestinal secretions. In the cardiovascular system (CVS), serotonin has a complexity of effects that can produce an increase in blood pressure by the contraction of vascular smooth muscle, bradycardia (low heart rate) by vagal stimulation, or an increase in heart rate by direct activity in the heart. In platelets, serotonin stimulates their aggregation, and when there is deep vascular injury, it causes vasoconstriction, contributing to haemostasis (the stopping of blood flow) (Rang and Dale, 2020).

Other factors that, finally, contradict the serotonin hypothesis are related to the distribution of serotonin in the body and its physiological effects through the currently 14 different types of receptors, involved in the actions of this neurotransmitter. At the time of the formulation of the serotonin theory of depression, little was known about its distribution, effects and only two receptors were known at the time. About 90% of the body's serotonin is concentrated in the GIT and the rest (10%) is between the CNS and platelets and cardiovascular system. Considering that the serotonin reuptake mechanism is the same in all these systems, it would be expected that blocking its reuptake would stimulate all of its peripheral effects as well.

Therefore, in addition to the actions on the CNS, the selective blockade of its reuptake should stimulate all other peripheral effects on the TGI, SCV and platelets, which is not observed during treatment with SSRIs. Considering that 90% of serotonin is in the GIT, inhibition of its reuptake would provoke intense stimulating effects on gastrointestinal activity. Thus, the hypothesis does not hold when analysing the “adverse” effects of antidepressants and the physiological effects of this neurotransmitter throughout the body (Ibid.).

At last, we question whether these are in fact adverse effects as usually claimed, or characteristics of action of these substances that act in a very comprehensive way in the organism, which seems to be the case. And in this case, it seems that the sum of effects on CNS histamine, acetylcholine, serotonin and catecholamines would lead to the outcomes that antidepressants have in the treatment of depression.

II. THE LITERATURE OF DEPRESSION

Following this series of preliminary pharmacological studies, in 1965 Joseph Schildkraut published the hypothesis that low levels of monoamines would be related to the cause of depression, associated with low levels of norepinephrine, referring essentially to catecholamines (Schildkraut, 1965). Short after, another group of researchers ratified that serotonin was the neurotransmitter of interest in

[2] Another adverse effect of TADs is the induction of cardiac arrhythmias by blocking sodium and potassium channels, similar to that produced by phenothiazine, such as promethazine, used in the treatment of schizophrenia (Vieweg et al., 2004). Probably, the same chemical origin of these substances is related to this activity, which increases the chances of sudden death in patients treated with these drugs. This activity in cardiac conduction tissue can certainly be present in CNS neurons, increasing the possibilities of interference in the conduction of the nervous action potential, essential for communication between neurons.

[3] Still according to the Prozac package insert, also diarrhoea, fatigue, headache, flu syndrome, pharyngitis, sinusitis, palpitations, blurred vision, xerostomia, dyspepsia, arrhythmias also due to increased QT interval, attention disorder, vertigo, dysgeusia, tremor, abnormal dreams (nightmares), anxiety, pollakiuria, hyperhidrosis, pruritus, hives and flushing with hot flashes.

this hypothesis, which would be in deficit in cases of depression, and that it could be reversed with antidepressants that would restore its function in depressed patients (Coppen, 1967). Coppen's thesis remains one of the most frequently cited in the history of psychiatry (Healy et al., 2001).

In the following years, several attempts were made to identify reproducible neurochemical changes in the nervous system of patients diagnosed with depression. Researchers compared levels of serotonin metabolites in the cerebrospinal fluid of clinically depressed and potentially suicidal patients for control, but this early literature is mixed and crossed by methodological difficulties such as too small sample sizes and uncontrolled confounding variables (Lacasse and Leo, 2005). In a recent review of these studies, the chairman of the German Medical Board and his colleagues stated, "Reported associations of suicidal behavior in subgroups with low concentrations of 5-hydroxyindoleacetic acid (5-HIAA) [the serotonin metabolite] in cerebrospinal fluid (CSF) are likely to represent somewhat premature translations of findings from studies that are flawed in methodology" (Ibid., p. 1211). Attempts have also been made to induce depression by depleting serotonin levels in humans, but these experiments have not yielded consistent results either. Similarly, they found that even huge increases in brain serotonin levels - achieved by administering high doses of L-tryptophan - were ineffective in alleviating depression.

Despite little verifiable evidence, "the hypothesis" prevailed. Cowen and Browning (2015) argue that in biological psychiatry, pathophysiological hypotheses are usually not so easily disproved. More often, they simply seem to become irrelevant as new models of causality take their place. In the case of depression, a new explanatory model has not taken place yet; possibly because of its high complexity, variability, and likely multifactorial cause. "In an era of neural networks and systems-level neuroscience, theories of depression with a single neurotransmitter seem increasingly implausible" (p. 158).

In traditional etiological studies diagnosis and therapy always seem to rely on a common point, a so-called biological marker. Even though attempts have been made to determine the level of brain serotonin as a marker, this does not seem to have remained sufficiently consensual (Cowen and Browning, 2015). On the other hand, contemporary neuroscientific research has failed to confirm serotonin lesions in any mental disorder, and, on the contrary, has provided significant counter evidence to the explanation of a simple neurotransmitter deficiency (Lacasse and Leo, 2005). While at the same time, they have been showing that the brain is very complex and poorly understood.

While the field of neuroscience is knowingly rapidly advancing, proposing that one can objectively identify a chemical imbalance at the molecular level is indeed not compatible (Ibid., p. 1212). "In fact, *there is no scientifically established ideal serotonin chemical balance,* much less an identifiable pathological imbalance" (Ibid., emphasis added). The biological marker,

> This reliable witness is absent in psychiatric illnesses in general and in depression in particular, and for this very reason, it is necessary to find explanatory strategies different from those that characterize classical etiological studies (Caponi, 2009, p. 2).

However, as here mentioned, even without proven biological markers or a new explanatory hypothesis, that first comprehension (dating from the 1960s) has endured as the sustainer of the medication related to its claimed pathology. That is, the SSRIs, which have the specific function of regulating the chemical imbalance of this neuron in the brain, according to the original hypothesis, remains the most sold antidepressant (Quevedo et *al.*, 2019).

However, there is a great interest of the pharmaceutical industry in developing drugs that act on the histamine receptor (H3) in the CNS, given that they have potential for the treatment of several pathologies: Alzheimer's, Parkinson's, schizophrenia, attention deficit hyperactivity disorder, obesity, narcolepsy (chronic sleep

disorder). One of them is the reported TAD, with an important use in the treatment of chronic pain, i.e. fibromyalgia, headaches and migraines, as well as pain of neuropathic origin.[4]

Related to the latter, there is an important curious fact: studies report that many chronic pain patients are often diagnosed with depression, likely in consequence of their suffering while according to some authors, the proposed mechanism of antidepressant action is not associated with an analgesic effect (Rang and Dale, 2020). However, in ancient times, opium was used for the treatment of depression, suggesting a correlation between pain and depression (Weber and Emrich, 1988).

Anxiety/anguish, its affective correlates (to pain), are widely reported by numerous patients diagnosed as depressed, in different intensities: from the exclusively psychic/emotional reported anguishes, to the somatised (registered in the body) ones, as in fibromyalgia, panic crises and physical pains (Berlinck, 1999, p. 50). One of the consequences of this fundamental observation about the human psychic and physiological apparatus is that depression, pain, and anguish are often indistinguishable, given that they are sensations referred to as extensive helplessness.

As the literature also shows, depression seems to have had distinct expressions from the origin of its mapping to the present days. Although these expressions overlap each other to some extent, nowadays authors (mostly from psychoanalysis) point to especially present bodily clinical pictures: fatigue, generalized and non-localized pain - as in the here above mentioned fibromyalgia -, chronic fatigue, insomnia, and the inertias of the body.

2.1 The Neurobiology Of Depression

In May 2011, a two-day conference entitled "The neurobiology of depression - revisiting the 5-HT hypothesis" (hydroxytryptamine, the serotonin neuron) was held at the University of Montreal, Canada, counting the 33rd International Symposium of the CNS Research Group (*Groupe de Recherche sur le Système Nerveux Central*), which annually brings together leading researchers from around the world to discuss a specific, pre-chosen topic. As defined by its organizers from three Canadian universities, Laurent Descarries (*Université de Montréal*), Chawki Benkelfat (McGill University) and Paul R. Albert (University of Ottawa), the objective of that year's meeting was to gather experts from different disciplines to review current knowledge on the neurobiology of depression - and in particular the serotonin hypothesis, including its most recent results. The twenty lectures then delivered were the basis for the publication of two special issues.[5]

Among these lectures, the authors confirm that a variety of functional deficits of serotonin in the brain circuits known to regulate emotions, whether primary or secondary, have been consistently associated with Major Depressive Disorder (MDD)[6] , as suggested by post-modern genetic, neurochemical, neuroimaging, and pharmacological studies (p. 2379). They further state that more recently, relatives of MDD patients are reported to be more sensitive to serotonin deficits, and there is evidence that altered serotonin functions are still present in MDD patients in remission, suggesting that being found with altered or low serotonin levels may represent a risk factor and trait diathesis increasing vulnerability to MDD (Ibid.).

Some authors in the above mentioned publication report, furthermore, that over the years, the serotonin hypothesis of depression would have been refined to take into account new knowledge.

[4] SSRIs and MAOIs also have certain analgesic action, but of lesser efficacy than the one produced by TADs.

[5] Philosophical Transactions of the Royal Society B: Biological Sciences (Albert, Benkelfat & Descarries, 2012).

[6] Major Depressive Disorder (MDD) is characterized by two or more weeks of depressed mood or diminished interest, associated with symptoms such as disturbed sleep, decreased appetite and libido, psychomotor changes, reduced concentration, excessive guilt, and suicidal thoughts or attempts. It is insidious and often recurring, with each episode increasing the likelihood of a new one by 16 percent. MDD is the second leading cause of disability worldwide, in the 15–44 age group for both sexes combined, second only to heart disease. The financial cost involved in this diagnosis and treatment is billions of dollars per year (Albert et al., 2012, p. 2378).

However, they reiterate some original inconsistencies, exemplifying that induction of a transient CNS serotonin reduction obtained experimentally in healthy control cases revealed only modest effects on mood, *"if any"*. (Ibid., p. 2379, emphasis added).

> Today, it is generally accepted that a variety of genetic, environmental, and neurobiological factors are implicated in depression. All areas of neuroscience, from molecules to mind, from genes to behavior, and from the laboratory to the bedside, are actively engaged in attempts to elucidate the physiology of depression, as well as the mechanisms underlying the efficacy of antidepressant treatments (Ibid.).

And add, "The model of a mental disorder based exclusively on the dysregulation of a determined neurotransmitter system is obviously simplistic and open to criticism" (Ibid.).

2.2 Rise and Shining of Antidepressants

When Kuhn and Kline in the late 1950s announced the "discovery" that promised to treat depression, the new drugs (antidepressants) would not have become famous and immensely profitable from the start. Herzberg (2010) argues that these were first marketed only in psychiatric publications as a treatment for severe and lifelong depression; early advertisements, for example, described these drugs as substitutes for electroconvulsive therapies. It was only in the early 1960s that (mental health) experts in the United States began to spread the word about depression. Then depression - and no longer anxiety -, was responsible for the new epidemic wave of mental illness and its associated physical symptoms (Herzberg, 2010; Horwitz and Wakefield, 2010), from the belief (once hypothetical) of low levels of serotonin.

Herzberg will further reiterate from Healy (1997) that, however, this hope for brain chemical simple answers were indeed precariously supported by evidence. The author clarifies:

> Whatever psychotropic drugs are doing, they are not correcting any observable imbalance in dopamine, serotonin, or norepinephrine. Even the initial observation that reserpine caused depression turned out to be largely anecdotal and misleading, or totally incorrect (...). In the case of antidepressants, no one has explained why it takes two weeks for the drugs to work, even though they increase monoamine levels immediately, or why the drugs work only for a relatively small portion of depressed patients. Even the most positive studies preferred by drug manufacturers show improvement in approximately 60% of patients, barely more effective than a placebo (Herzberg, 2010, p. 167).

This and other mysteries, claims Herzberg (2010), do not diminish the importance of biology to emotional and mental illness, but they are simplistic and devastating models when equalizing moods with the amount of a few monoamines in the brain. The author alludes finally to other possible, more complex models, such as one in which the brain would resemble the (meteorological) weather, sufficiently complex and self-influencing, and absolute precision and control would be impossible, even in theory. Another model, also considered, would emphasize the difficulty in determining the causality of a system based on interactions between genes, biology, and one's experiences. Thus, the author understands that chemical substances would indeed play a role in moods and emotions, but it cannot be affirmed that they cause them (ibid.).

Authors consider that the possible reason why simplistic explanations such as serotonin depletion would have survived is not because they have been proven true - once they have not - but because they would have been very useful for almost everyone involved in this story: the pharmaceutical industry, which used it to prove efficacy to the Food and Drug Administration (FDA) and general advertisements; psychiatric professionals, who used them to claim a "true understanding" of their patients' psychic pain, while highlighting the drug power prescription; insurance companies, who benefited from the "objectivity of causal diagnosis"; and last but not least, the patients themselves, who often preferred a supposed physical (biological) illness to a

mental/psychiatric one, becoming consequently "grateful for the simple cure" (ibid. , p. 168).

In this direction, while antidepressants did not achieve celebrity at first (as previously stated), they were nevertheless a gateway to the awakening of the popularization of the "new brain sciences." Accompanied by simple explanations of brain functions and their "correction" such as by antidepressants, these became a prime example of the relatively objective theories of brain chemistry favored by commercial medicine (Herzberg, 2010).

Schildkraut, forerunner of the neuronal default hypothesis, himself would have recognized:

> Even if drugs are effective in treating a disorder, this does not necessarily mean that their mode of action implies that the latent abnormality will be corrected (1965, apud Horwitz and Wakefield, 2010, p.198).

In this sense, even if the hypothesis of serotonin deficiency were proven, it would explain only a part of the cases of depression, as Schildkraut, himself again, would have recognized years earlier (Ibid). On the other hand, we find in Nathan Klein, also a "discoverer" of an antidepressant produced from iproniazid, the genesis of the belief that these new drugs would do more than cure diseases: they would enhance/improve emotional states, beyond the cure. An example of this, was when in an interview with the New York Times in 1957, Klein would claim that "the beneficial action of the drug would not be limited to sick individuals, but could improve the ordinary performance (...) of essentially normal people" (1957, in Herzberg, 2010, p. 170).

The serotonin hypothesis, the driving force behind antidepressants that "corrected the deficient levels of this neurotransmitter", pointed in its early days to the (today common) idea of enhancement of the human kind: an area of pharmacology that aims at the improvement of the so-called normal human performance (without intervention), as in the sexual, intellectual and emotional human spheres.

An article in Maclean's Magazine[7] recorded the delight of some researchers of the time: *"Improve your memory! Increase your sexual potency! Relieve your anxiety! End your depression! Maximize your powers of concentration! Get rid of agonizing physical pain!* " (Ibid., p. 171); or, in some other advertisements, *"No fun? No desire? Antidepressants can bring new life to your life! "* (Ibid., p. 174).

Voices like these grew in the 1980s, with the idea of "a new brain" amenable to psychopharmacological remodeling, and the popularization of these new neurological/brain sciences were crucial to the turning point of the so-called biological revolution (ibid., p. 173). This is what the subscription magazines of the time used to publish in their cover advertisements, and sold massively in many countries.

However, at the same time (1970s and 1980s), other researchers were also reexamining the crucial question: do people diagnosed with depression suffer from a chemical imbalance that can be corrected by medication? Were the new drugs really antidotes to something chemically wrong in the brain? (Whitaker, 2017).

2.3 Returning To The Chemical Imbalance Hypothesis

> *Although SSRIs are considered antidepressants, they are FDA-approved treatments for eight separate psychiatric diagnoses, ranging from social anxiety disorder to obsessive-compulsive disorder and premenstrual dysphoric disorder.*
>
> J.R. Lacasse and J. Leo

A recurring criticism made is that supposed deficiencies of serotonin or other brain chemicals could even be consequences, rather than causes, of depression. To many authors, the most serious conceptual problem with "the hypothesis" is that there are no proper benchmarks for normal and pathological levels of serotonin or other amines, just as there are for other biological markers for

[7] Maclean's is a Canadian weekly news magazine. It was launched in 1905 under the name The Business Magazine. Its weekly circulation is 350,000 magazines. (Wikipedia)

biological diseases (Horwitz and Wakefield, 2010; Dunker, 2021).

The Clinical Science Laboratory of the US National Institute of Mental Health (NIMH), regarding "the hypothesis", in a statement made by researchers from this institute, further states that "the demonstrated efficacy of SSRIs cannot be used as primary evidence for serotonin dysfunction in the pathophysiology of these disorders" (Lacasse and Leo, 2005, p. 1211). In this sense, Cowen and Browning (2015) restate this uncertain state of affairs: to these psychiatrists the hypothesis eventually achieved the status of a "conspiracy theory whose purpose was to allow the industry to market SSRIs to a gullible public" (p. 158).

The explanation for the cause of depression (in all its intensities, from mild to a severe and chronic MDD) remains in fact unknown or at least quite controversial among different theoretical and clinical bodies, while, nevertheless, the idea that neurotransmitter imbalances cause depression is still vigorously promoted by pharmaceutical companies and psychiatric practice in general.

Consequently, today SSRIs are the most prescribed class of antidepressants in the world, besides the other classes of antidepressants[8] which, altogether, indeed report clinical efficacy.

However, in several studies, they strongly compete with placebos; as in an important study that verified a large number of clinical trials of antidepressants submitted to the FDA, showing an impressive 80% response rate to placebos[9]. However, another critic commonly made by researchers is that, lacking a biological marker, it is from the mediation of the antidepressant that an explanatory causal network is then built. "This kind of explanation is possible because there is no 'reliable witness' that allows translating human sufferings to the controlled world of the laboratory" (Pignarre in Caponi, 2009, p. 3).

Nevertheless, the message that consumers take home when buying an antidepressant by viewing the ads for SSRIs, is that they work by normalizing neurotransmitters that have gone wrong or are below the proper level in their brain. "This was a hopeful notion 30 years ago, but it is not an accurate reflection of the current scientific evidence" (Lacasse and Leo, p. 1214). Also according to these authors, what remains unmeasured, is how many people seek the help of their doctor because they have been convinced that they suffer from an insufficiency of serotonin. "These advertisements present a seductive concept of cure for an imbalance that these same people would not otherwise have access to" (Ibid.).

Thus, the paradox goes on. Nowadays the American Psychiatric Press Textbook of Clinical Psychiatry addresses serotonin deficiency as an unconfirmed hypothesis, stating, "Additional experience has not confirmed the hypothesis of monoamine depletion," while in a contemporary advertisement one could read: "Celexa helps restore the brain's chemical balance by restoring the supply of a chemical messenger called serotonin", thus revealing the contrast between the official guide, and the advertisement.

In the United States, between 1991 and 2000, the diagnosis of depression doubled in parallel with the introduction of SSRI drugs. According to publications, these drugs were not marketed by explaining the problematic correlational data; instead, "they were sold as remedies for the chemical imbalance that caused depression" (Lacasse and Leo, 2005, p. 35).

At last, scholar Nikolas Rose in an interview (Spink, 2010), questions research programs in the psycho/neuro/pharmacological field that would be "path-dependent," as when related to serotonin levels at the synapse as a deficit or abnormality of the serotonin system. He argues that "this was a very potent heuristic device for psycho-pharmacology and later for psychiatry, but almost

[8] According to MD.Saúde on 02/20/2021 https://www.mdsaude.com/

[9] Kirsch, I., Moore T. J., Scoboria, A., Nicholls, S. S. (2002) The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat 5: article 23. Available at: https://psycnet.apa.org/record/2002-14079-003 Accessed by Lacasse and Leo on 10/14/2005; and by the authors of this article on 01/19/2022.

certainly, if this is not completely wrong, it's quite wrong (p. 9)".

Rose summarizes that in a certain kind of biological psychiatric thinking and research –presumably the prevalent kind world wide-, this (assumption-dependent research) provided a gateway and a model for understanding a number of other issues that were occurring in the transmission between neurons, but that "the hypothesis" would have remained "assumed".

> ( ) Everybody thought that the locus of the disorder was the brain; somehow it was a brain thing - maybe a gene thing; maybe a neurotransmitter thing. Nobody talked about it, it was an assumption (...) There is a psychology underpinned by neurobiology. And if you talk to people, they also think of themselves as people with a neurobiology and not just brains on legs. They don't think of their minds as what their brains do, but, not surprisingly, they think they are more than that. (Rose in Spink, p. 311).

2.4 The Serotonin Cause for Depression: A Hypothesis or a Persisting Myth?

There are possibly one hundred billion neurons in the human brain. A single neuron would have between one thousand and ten thousand synaptic connections, and the adult brain altogether around 150 trillion synapses. According to experts, the brain's serotonin system is the largest brain system known and can be characterized as a gigantic neuronal system (Azmitia, 1991). However, the chemical imbalance theory of mental disorders reduces this enormity and complexity to a simple pathological mechanism that is relatively easy to describe and grasp. As mentioned, in depression, the problem would be that serotonin neurons release too little serotonin into the synaptic cleft and, therefore, the brain's serotonin pathways become underactive. Thus, antidepressants would raise and normalize serotonin levels in these clefts, allowing these pathways to transmit messages at a, now, appropriate rate.

Since the hypothesis said that this low level of serotonin caused depression, consequently, anyone with this diagnosis should have low levels of serotonin, or "lower than normal" (without knowing exactly what the cut-off level was), in their cerebrospinal fluid.

In 1969, Malcolm Bowers at Yale University, became the first to report on whether or not depressed patients had low levels of serotonin metabolites. In a study of eight depressed patients (all previously on antidepressants), Bowers announced that their serotonin levels were lower than normal, but "not significantly so" (Bowers in Whitaker, 2017, p. 85).

Two years later, other researchers, from McGill University stated that they too had not found a "statistically significant" difference in the serotonin levels of depressed patients, and that they had also found no correlation between serotonin levels and the severity of depressive symptoms.

In 1974, Bowers returned with an improved follow-up study, with a very thought-provoking result: depressed patients who had not taken antidepressants, exhibited "perfectly normal 5-HT levels" (Bowers, 1974).
In other words,

> The literature reviewed here strongly suggests that a reduction in brain norepinephrine, dopamine, or serotonin is not sufficient, by itself, to account for the development of the clinical syndrome of depression (Mendels, 1974, in Whitaker, 2017, p. 85).

Yet, other researches continued to credit the serotonin hypothesis in a positive way, and soon American psychiatrists were writing that 30% of depressed patients had low serotonin levels, while other Japanese studies revealed that 24% of patients diagnosed with depression "had high serotonin levels" (Nagayama, 1986).

Following the studies of those decades focused on this task, in 1984 researchers at the NIMH investigated the hypothesis once again, seeking to see if the biological subgroup of depressed patients with low serotonin levels responded best to an antidepressant, amitriptyline, which blocked

its reuptake. Sometime later, wrote James Maas, the team leader of these researchers:

Contrary to expectations, no relationships were found between cerebrospinal 5-HIAA and the response to amitriptyline (...). Elevations or decreases in serotonin system function, by themselves, do not tend to be associated with depression. (in: Whitaker, 2017, p. 87).

In light of the recurring lack of evidence since the inception of the stated hypothesis and, conversely, numerous counter evidence, we end up wondering, in echo with the counter evidence, whether it is still today "worth thinking of serotonin as a primary causative factor in depression" (Lacasse and Leo, 2008).

In an article from Harvard Health Publishing, a 2019 Harvard Medical School publication titled "What Causes Depression?"[10] the author designates the chemical imbalance hypothesis as a figure of speech:

> It is often said that depression results from a chemical imbalance, *but this figure of speech fails to capture the complexity of the disease*. Research suggests that depression does not arise simply by having too much or too little of certain brain chemicals. Instead, there are many possible causes for depression, including impaired mood regulation by the brain, genetic vulnerability, stressful life events, medications, and medical problems. Several of these forces are believed to interact to cause depression. (Ibid., emphasis added).

In current articles concerning depression - whether in the field of psychiatry, psychoanalysis, descriptive or fundamental psychopathology, or even in the neurosciences - in their different views and conceptualizations, the serotonin level is hardly ever addressed as a proven causal factor[11]. However, as previously stated here, the prescription of a SSRI type antidepressant is the usual response to the symptoms reported and classified in some category of MDD, whose first causative logic would be the serotonin hypothesis – not only unproven but also to some extent, currently silenced.

In our understanding, MDD or depression in its various forms would indeed not be explained by the serotonin level, but this hypothesis would be "respected" by most, crediting it with the possibility of the reason for depressive conditions. While, on the other hand, nothing proves it otherwise.

When the first antidepressants were manufactured, depression was perceived as relatively rare. "The idea that there should be a depression that could be treated on the basis of drugs had to be invented, as well as that of an antidepressant," states Healy (1997, introduction).

Interestingly, in Japan, this phenomenon that came to occur more recently than in the West, since the SSRIs were introduced to the Japanese market only in 1999; however, already accompanied by intense "disease awareness" propaganda from the beginning. Soon after, in 2000, public opinion started to perceive depression as a "common, everyday" form of mental illness; a perception strengthened by Japanese popular sayings such as *kokoro no kaze*, an expression that characterizes depression as "a common cold of the soul" (Okuda, 2015).

> Depression has become more widespread in Japanese society in the last 10-20 years, and the growing number of people with depression in Japan today is becoming a social problem (...) We find a marked change in treatment models, referred to in this article as bio medicalization and pharmaceuticalization of mental health (...). As a consequence of these trends, an inordinate number of campaigns for disease awareness have emerged as part of the promotional efforts of pharmaceutical companies to increase sales of prescription drugs. These campaigns seem to have had a significant impact on people's behavior about depression (Ibid., p. 633).

[10] What causes depression? - Harvard Health accessed on 11/11/2021

[11] In the main academic search engines: Scielo, Google Scholar/Scholar google, VHL, MeSH, EMBASE, BDTD; WorldWideScience, PubMed Central, Research Gate, among others.

The author reports that prior to the entry of SSRIs into the Japanese market, the size of antidepressant sales remained relatively low, at around 17 billion/year. With the entry of SSRIs - underpinned by the serotonin hypothesis - this same market began to skyrocket, and by 2012 had reached 137.7 billion/year - a more than eight-fold increase over the 12 years measured since their inception in Japanese pharmacies (Okuda, 2015). Okuda's publication seems to illustrate clearly, as in a mirror, the dynamics that starts to be installed with the very installation of SSRI antidepressants in the market, supported by an expanded diagnostic system (through the western standardized diagnostic manuals), which until then kept some reserve and circumscription in Japanese society. Since then, the numbers of work leaves due to depression in the country have increased considerably. Okuda names the phenomenon he observes and studies as the fabrication and contagion of a disease (Ibid., p. 637).

It is possible that the construction of a logic that made sense - that is, a failure or lack in the conduct of brain neurotransmitters that would be in the constructed hypothesis, responsible for triggering depression, remediable with antidepressants - occupies today a certain place of myth, even if not so named: the myth of the origin of depression.

Ever since, this myth - the hypothesis - is equally accepted and appropriated by society, to whom it also explains and justifies its malaise.

Rose, in the aforementioned interview with Spink (2010), reports:

> We know, for example, in the field of psychopathology, that in the last ten years there have been written, by more or less well-known people, narratives where the story is more or less this: they fell into depression (...) and the resolution, in the end, is always that they accepted their psychiatrists' view that it was a biological disorder and they medicated themselves and got better (p. 310).

Recently a new antidepressant substance, esketamine, in fact a derivative of the ketamine, has been approved by some regulatory agencies. The drugs made from ketamine have no effect on the reuptake of neurotransmitters, but inhibit the activity of glutamate, a stimulating neurotransmitter in the CNS. Since ketamine is very old and cheap, a derivative was produced to enable an abusive price tag for "a new promise for treating depression".[12]

III. CONCLUSION

“The hypothesis” has been widely assumed since its origin, already more than half a century ago, bringing about a massive manufacture of antidepressant drugs, namely the SSRIs. Fluoxetine, launched in the market in 1986 (broadly referred to as *Prozac*, its gigantic successful representative in sales), came in for the so desired reestablishment of this neuronal lack, supposedly the cause of depression.

However, pharmacological studies of antidepressant substances reveal that their adverse effects interfere with the activity of several other neurotransmitters such as histamine, acetylcholine and noradrenaline, in addition to serotonin. Furthermore, the distribution of serotonin in the body and its peripheral physiological effects oppose the hypothesis of selective inhibition of serotonin reuptake, which is widely distributed in the CNS, in the SCV and especially in the GIT, which concentrates 90% of the body's serotonin. Therefore, with the inhibition of its reuptake, whose mechanism is the same in all these systems, intense adverse effects would also be expected to happen in the BMS and in the GIT, which is not observed.

The effects of the three groups of antidepressants on histamine, acetylcholine and noradrenaline receptors are observed peripherally and classified as adverse. Nevertheless, the peripheral adverse effects, resulting from selective inhibition of serotonin reuptake, which would necessarily be intense in the digestive and cardiovascular

[12] The Antidepressant Conundrum | Super (abril.com.br) accessed on 02/11/2022.

system, are simply not observed, raising more doubts about this alleged selectivity. Moreover, the possible side effects of real selective serotonin reuptake inhibitors would be incompatible for the treatment of depression.

The literature also reveals that in fact there are no established biological markers for good levels of serotonin. There are also certain categories of antidepressants (such as TADs) that also act on physical pain, which seems to bring relief to many patients diagnosed as depressed.

Neurobiological studies also point to the complexity of the human brain and the CNS, ruling out the possibility of a hypothesis that would focus on the functions of a single neurotransmitter (serotonin), amidst the trillions of synapses that would occur, resulting from the thousands of synaptic connections of a single brain neuron, among the possible one hundred billion mapped by studies in this area.

There are also studies that question whether the supposed low levels of serotonin are in fact the cause, or the consequence, of depressed states. For all these evidences it becomes difficult to relate depression to a single neurotransmitter, as sustained until today.

Critical authors claim that a logic is established as supposedly true: since the treatment of depression starts from the serotonin hypothesis, when the patient is relieved of his pain - physical or mental - with the use of antidepressants (generally approximately 60% of medicated patients are reported to respond to antidepressants, while 40% to placebo), it is as if the hypothesis was confirmed, even though it has never been effectively proven; and it seems, in fact, to be increasingly distant from a proof.

The serotonin hypothesis has finally been proposed as *a figure of speech*, by a study at Harvard Medical School (2021). We believe it is important that this category be distinguished from a hypothesis postulated and conveyed as factual, given that it has never been fully confirmed.

Lastly, do the announcements of the World Health Organization (WHO) alarm us, or to what extent do they fulfill the prophecy? Twenty years ago the projections were that by 2020 depression would be the second most numerous disease, preceded only by heart diseases. The projections now in 2022 are that by 2030 depression is expected to be the largest in number of people affected. How much would the serotonin hypothesis for depression, sustained on the foundation of old, precarious and never proven parameters, be helping or, instead, hindering the understanding of this complex and currently rampant picture?

Our understanding is that there is something still quite unknown and misunderstood about the clinical picture of depression, being therefore, neglected; leading it, inevitably, to its ungoverned, epidemic status.

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