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Exercise is medicine: a new perspective for health promotion in bipolar disorder

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Abstract

Introduction: Similar effects in reducing the symptoms of the mood disorder are reported in the literature compared the action of drugs and aerobic exercise sessions, demonstrating the potential of exercise in the control and mood stabilization. Therefore, there are many reasons to believe that the increased cardiorespiratory fitness (VO_{2max}) can be an important means of protection and a reducing potential of physical and mental damage in bipolar disorders (BD). This review will highlight the current pattern of response of exercise on the pathophysiology of BD, relating the possible mechanisms, and hypotheses based on exercises.

Areas covered: The mechanism of monoaminergic action and its relationship with exercise, role of physical conditioning and increased VO_{2Max} on neurotrophin release, and new perspectives on long-term exercise will be reviewed.

Expert opinion: The adaptations to training, although little explored in the context of BD, can induce the expression of substances that co-regulate several processes related to the pathophysiology of BD. Furthermore, high intensity interval training (HIIT) can also be adjusted to improve the physical fitness and health in patients with BD. Future research is needed to adopt a training strategy that is both time efficient and adequate for the population in question.

Keywords: Bipolar disorder, monoaminergic system, catecholamines, exercise, high intensity interval training.

Article highlights

- In BD, changes in physical and neurological status are observed;
- Bipolar patients have low level of physical activity, therefore, low tolerance and ability to adhere to training;
- Exercise intervention causes anxiolytic and antidepressant effects similar to drug therapy but without additional side effects.
- Exercise seems to be an effective and economical alternative to the treatment of mood disorders, and this can be extrapolated to BD.
- Trophic factors such as BDNF, NGF, GDNF, and IGF-I have been widely explored in the pathogenesis and pathophysiology of neurodegenerative disorders.
- The improvement in VO_{2Max} could be an interesting channel to be stimulated in BD.

1.0 Introduction

The pathophysiology of bipolar disorder (BD) is closely related to changes in physical and neurological status [10, 26, 42, 80]. BD patients commonly exhibit changes in the activation relationship between prefrontal cortex and amygdala [2, 3, 33, 57, 59, 63, 103], volumetric reductions of cortical regions [34, 35, 48, 68, 84, 89, 90], significant deficits in different cognitive domains [19, 58, 61, 73, 80], and hormonal changes related to stressful processes [56, 105], on mood, as well as comorbid conditions that are triggered by physical inactivity [42, 107]. This limiting disease observed spectrum is similar to other mood disorders, and it is usually treated by drug interventions such as lithium in BD. However, there are many reasons to believe that intervention through physical exercise produces similar responses to drugs used in patients with BD [4, 45, 76], especially the anxiolytic and antidepressant effects from exercise [46, 47, 108].

In line with that, an important point that must be taken into account is that several patients on drug therapy are nowadays involved in regular physical exercise programs. However, it is surprising that there are few studies on the interaction between physical exercise and drug response in the treatment of these patients. Therefore, theoretically, both acute physical exercise and physical training influence responses to drugs due to their effects on parameters involved in the

pharmacokinetics of these drugs. The acute effects of physical exercise can be hemodynamic changes, enzymatic activities, pH, plasma protein concentration, temperature and gastrointestinal function. Thus, factors such as absorption, distribution and clearance can be influenced by acute physical exercise. However, when it comes to physical training, more permanent adaptations may occur, which are also found in the resting state. In addition, the effects of exercise vary between types of medication, as they have different physical and chemical properties. Clinically relevant interactions between medication and exercise are more expected when drugs with a sharp dose-response curve are used, or with a narrow therapeutic range, or with a need for continuous therapeutic effectiveness and a short half-life. Therefore, acute and chronic exercises may influence drug response by pharmacokinetic as well as pharmacodynamic mechanisms. On the other hand, few clinically relevant effects of exercise or exercise training on drug response have been described until now [51].

Assessing the literature extensively, reporting evidence that physical exercise especially the aerobic character, plays an important role in the regulation of the symptoms of BD [4, 20, 21, 25, 45, 53, 71, 76, 87, 92, 93, 97]. Some associations are proposed between bipolar patients and exercise, and it is observed inverse relationship between the level of physical activity and body mass index, symptoms, and comorbidities [32, 52, 106, 107]. These responses are consistently demonstrated in the literature with healthy population and may in part be extrapolated to patients with BD [54, 70]. Despite this understanding, the state of the art so far has weak foundations on the subject, still lacking important evidence to clarify the mechanisms of improvement resulting from the routine practice of an exercise program [4, 25-28, 45, 71, 75, 76, 88, 92, 101].

The hypotheses to improve the symptoms of BD are constantly tested and postulated, however, we must observe the results with caution, due to inconsistencies in the control of exercise (dose and response). For instance, Ng, Dodd, and Berk [71] observed the effect of 40 min walking in patients with BD on the symptoms of the disease assessed by scales of anxiety, depression, and stress (DASS) and global improvement (clinical global impression severity scale - CGI-S; clinical global impression improvement scale - CGI-I). Based improvement of symptoms was observed in the reduction of these scores, results that are similar to other positively favoring treatment with exercise studies [67].

Regardless of the prescribed dose-response, the maintenance of regular physical exercise seems to converge to satisfactory results related to the production of neurotrophins. These would be one of the keys to inhibit BD neuroprogression, and exercise is a potent modulator of baseline levels of brain-derived neurotrophins, such as BDNF [24, 29, 53, 62, 86, 87]. Moreover, the exercise impacts on reducing stress via the HPA axis (hypothalamic–pituitary–adrenal axis), reducing allostatic load [102], and synaptic plasticity [21, 85, 86, 98]. However, other physiological mechanisms may put the aerobic exercise as an important modulator of the release and reuptake of monoamine neurotransmitters in the classic type, specially, dopamine (DA), serotonin (5HT) and norepinephrine (NE), possibly present in the pathophysiology of BD and as a reducing physical and mental stress from the release of endogenous opioids [5, 22, 40, 44, 49, 81, 104]. The objective of this review was to establish the pattern of exercise response on the pathophysiology of BD, relating the possible mechanisms, as well as, create hypotheses based on acute and chronic responses of exercise, and establish future perspectives with the focus of the exercise as an important and innovative model of treatment.

2.0 Health promotion by physical exercise for bipolar disorder

Patients with BD have a history of severe inactivity and sedentary lifestyle [67], as well as extensive use of alcohol or drugs. Evidence also suggests a high prevalence of metabolic syndrome among patients with BD [32]. The poor employee life style, as well as disorders of eating character [107], corroborate expanding the deleterious effects presented in the pathophysiology of the disease as well, exacerbating comorbidities associated with BD [32, 55].

Given this scenario, it is clear that disciplinary actions based on different domains and needs, are important for the control of physical and mental symptoms of the disease. Therefore, aerobic exercise has been extensively studied and recommended as an co-adjuvant or adjuvant intervention for treating BD [26, 27, 71, 75, 92, 97]. Its effects can significantly affect cardiorespiratory [38, 41] and metabolic function (systemic and cerebral metabolism in regions such as the prefrontal cortex, and hippocampus), about mood swings [9, 29], as well as, improved synaptic efficiency or neurogenesis [53, 85, 86, 99]. However, these responses are still inconclusive or underused in patients with different mood disorder and in particular

with BD. In general, the hypotheses studied tend to a positive effect of exercise on regulation of symptoms and health in these patients.

About a distinct perspective of commonly presented in the medical literature, although still little studied in patients with mood disorder [36], it seems that increased cardiorespiratory fitness (VO_{2max}) can be a way of protecting health and reducing potential physical and mental damage. For example, every 1 MET (metabolic equivalent = 3.5 $mL.kg.^{-1}min^{-1}$ increased the maximum oxygen consumption, this can reduce about 13% relative risk of all-cause mortality, and also contribute to improvement of systemic metabolic profile (blood pressure, lipoproteins, glucose). More recently, Whiteman *et al.* [106] demonstrated significant and positive relationship between the level of $VO_{2max,}$ BDNF, cognitive and memory tasks. To remember, BDNF, brain-derived neurotrophin, exerts great influence on neuronal plasticity [53, 86], mainly on the hippocampal region [85], and is a highly expressed substance through exercise, and dependent on the given intensity. In addition, aerobic exercise act selectively on cognitive process (age-dependent) [96], and people with higher VO_{2max} tend to get higher cognitive performance during and after training [95]. It is observed then that the variable in question should be a more appropriate position with respect to the BD, since it has a direct impact on the disease pathophysiology. Figure 1 shows possible general mechanisms of influence of exercise on mental illness.

Moreover, it is known that the lifestyle of people with serious mood disorder contributes to low participation and adherence to training programs. Thus, patients with BD are not normally included with the minimum recommendation proposed by the American College of Sports Medicine (ACSM), 150 $min.week^{-1}$ of moderate aerobic activity or 60 $min.week^{-1}$ of vigorous activity to promote health [1]. An inverse dose-response relationship between the level of exercise practiced and the severity symptoms, and emotional well-being, adds a negative prognosis for health in patients with BD [36]. So, inclusion strategies/progression, and mostly controlled in relation to dose-response, and enabling adherence of patients with BD in aerobic exercise programs strategies is a gap still to be structured.

3.0 Exercise in the context of bipolar disorder

The literature reports the benefits of exercise on reducing the symptoms of BD. However, it is commonly observed in several studies a lack of control of the exercise, or the relationship of dose x response, which undermines the consistency of the completion of studies. A meta-analysis of Pearsall *et al.* [76], for example, met a few randomized controlled studies that made use of exercise as therapy in patients with different psychiatric disorders, including BD. The authors observed a moderate effect size (ES) on the levels of physical exercise, however, no significant results were found on the negative *(p* = 0.40) nor positive symptoms *(p* = 0.12). In another study, Ng, Dodd and Berk [71], for example, evaluation scales used for anxiety, depression, and stress (DASS), plus a scale of global improvement (CGI-I and CGI-S). Forty minutes walking in patients with BD have provided positive results only in the DASS scores (mean ± standard deviation; baseline) 58.2 ± 25.4> (post-exercise) 23.0 ± 14.9).

More favorable and consistent with the practice of aerobic exercise results are observed in studies focusing on comorbidities, however, the outcomes of the symptoms remain controversial. Daumit *et al.* [27] for example, evaluated weight reduction in patients with BD and subjected 291 patients (22% in the bipolar sample), the group of programs in cognitive and behavioral therapies, food restructuring exercise groups during a follow up of 18 months. By the sixth month, the intervention group reduced 1.8 kg while the control changed only 0.3 kg. Throughout the remainder of treatment, group intervention reduced a total of 3.4 kg, and the control is not changed. Other interventions evaluated changes on the symptoms and comorbidity with bipolar patients and found no significant effects on reducing body weight or any derived variable. Nonetheless, there was improvement of the scores of scales of depression and mania after 20 weeks of intervention with exercise and behavioral therapies (MADRS - *Montgomery Asberg Depression Rating Scale,* YMRS - *Young Mania Rating Scale,* CGI-Mania - *Clinical Global Impression Mania Subscale, CGI - Depression - Clinical Global Impression Depression Subscale,* among others) [93]. Table 1 shows the main chronic benefits with exercise intervention.

Based on the presented data, and similar studies with a use of different mood disorders, e.g., unipolar depression, that have particular pathophysiological schemes, it is assumed that the mechanisms responsible of the reduction of symptoms from the intervention exercise are common among themselves. Aerobic exercise enables

you to change or improve metabolism specifically on structures such as the prefrontal cortex (PFC) and hippocampus, better regulated monoaminergic pathways, or new synaptic connections (regardless of the specificity of the disease). The BD-specific mechanisms need to be better understood, and next topic is based on physiological, assumptions and relationships created processes to try to explain and enhance our understanding of the pathophysiology of BD.

4.0 Exercise-induced mechanisms associated with the pathophysiology of bipolar disorder

The state of the art shows that aerobic exercise can provide anxiolytic, antidepressant effects [46, 47], and anti-inflammatory [77], and promote change on the synthesis of monoamine neurotransmitters [44, 64, 65, 74, 81] and neurotrophins types during exercise [7, 8, 24, 43]. For patients with mood disorder, the studies on the subject show commonly a chronic imbalance in the operating system specific monoamine neurotransmission for each disease [22]. Pharmacological treatment appears to induce the restoration of normal levels of these substances in the brain [11, 23]. Accordingly, considering that the use of specific drugs is the primary route for treatment of BD, this can often cause side effects or the patient is refractory to such medication. Aerobic exercise could be an alternative co-adjuvant or even the main treatment of the mood disorder without the possible side effects [45]. To prove the positive effects of aerobic exercise, Blumenthal *et al.* [45] compared a 16-week intervention in elderly patients with major depression divided into three groups: a) treated with sertraline, a medication 5HT reuptake inhibitor, b) regular aerobic exercise, c) combination of medication and exercise. The authors reported similar effects between strategies for the decline in depression scores (Hamilton Rating Scale for Depression - HRSD, Beck depression inventory - BDI), however, treatment with medication only promoted faster response for reducing symptoms of depression in patients with greater severity than aerobic exercise. In subjects with less severe symptoms, the combined between aerobic exercise and medication, strategies promoted greater decline on the scores of the depression. Thereafter, the same researcher group conducted a treatment in 156 adults diagnosed with major depression for 4 months, plus 6 months of follow up. Patients were divided in three groups of similar intervention detailed in previous study (i.e., aerobic exercise, sertraline therapy, or a combination of exercise and sertraline), and also showed

significant improvement in symptoms of major depression (i.e., reduction ranging between 60.4 a 68.8%) after 4 months [6]. After the follow up, interestingly, the findings indicated increased chance of recovery, or lower frequency of depression episodes in patients that participated only the aerobic exercise group compared to treatment with sertraline, and the combined group. Moreover, the chance of relapse during this period also was lower for aerobic exercise group compared to other groups [6].

Trying to explain how aerobic exercise acts to modulate the imbalance monoaminergic regulation, we must first understand that in bipolar, this imbalance is state-dependent, i.e., associated with the cycle time of the patient (i.e., mania or depression) [15]. It is known that the serotonergic system - 5HT has extensive involvement in the pathophysiology of depression [60, 100], and drugs that increase extracellular concentration of 5HT from inhibition of their reuptake by presynaptic neurons are the first line in the prescription. The exercise seems to induce similar effects, and the intensity of training can exercise some influence gene expression of this substance. Gomez-Merino *et al.* [40], although still controversial, observed significant increases in animal model of 5HIAA (i.e., marker of serotonin levels) and extracellular 5HT in the hippocampal region after 90 min of recovery from aerobic exercise. Other studies with animal model showed increases of 47% in the extracellular concentration of 5HT, returning to baseline values after the first hour of recovery [65]. The administration of tryptophan (i.e., a precursor of 5HT) 60 min prior to acute exercise appears to promote an increase in the length of exposure to 5HT (100%) and 5HIAA (83%) [65].

Obviously, we must evaluate this information cautiously, since this increased availability of 5HT from the exercise, does not necessarily lead to greater interaction "key receiver", and increased the activity of mechanism. However, it can be said that exercise induces an up-regulation of 5HT receptors (subunits 1 and 2), and also a hypersensitivity of the $5HT_2$ receptors, suggesting the operation of the antidepressant mechanism modulated by exercise [28]. Amplifying the positive effects of exercise, it seems that the 5HT neurotransmitters type and neurotrophins such as BDNF (brain-derived neurotrophic factor) are also closely related, and have their signs in order to co-regulate, promoting neuronal plasticity in several brain areas. For better understanding of this mechanism see revision proposed by Mattson and Maudsley [62].

Evidence also supports that dopaminergic system (DA), due to its excitatory nature, also has particular importance for the BD manic phase, like the noradrenergic system (NA) [22]. It is understood that antagonists of DA receptors drugs are known to produce an anti-mania effect, however, when the process of DA and NA are stimulated, for example, by the administration of amphetamine-like effects mania or even psychosis are manifested in healthy subjects, and expanded in euthymic patients [5, 83]. Within this scenario, the literature is still not entirely clear regarding the magnitude or extent of influence of the DA circuit on the BD, however, it appears that both DA and NA neurotransmitters are found in higher concentrations in the basal transition from depression to mania [15].

Historically the behavior of this neurotransmitter DA, as well as 5HT, were studied in the context of central fatigue, the major influence on the ability to perform prolonged exercise [66]. Aerobic exercise seems to induce changes on the functioning of the DA pathways, especially in tasks that require motor control [50]. The DA system in exercise is highlighted by a high volubility in their concentrations, as well as metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanilic acid) in regions of the hypothalamus and striatum during and after aerobic exercise [44]. Because we are dealing with a manic state in patients with BD, we will have to agree that an expected positive effect with exercise at this stage of the cycle would be a significant reduction in the levels of DA and NA after exercise, a kind of latency. Acutely literature provides a reduction in post-exercise sympathetic drive, leading by example, lower levels of catecholamines, less sympathetic neural activity via mediation by GABA receptors, and increased activity of the parasympathetic tone [18, 49, 81]. Moreover, subjects with greater physical fitness, tend to more rapid inactivation of plasma catecholamines by sulfation than less trained [81]. Therefore, it is assumed that autonomic changes after acute exercise may contribute to trigger an "anti-mania" state, and the fitness level may be an important factor to be considered.

Within this perspective, extensively analyzing studies of fatigue and exercise there is evidence that in exhaustive or prolonged exercise to fatigue, a reduced sympathetic drive also suppress the levels of DA and NA released in the bloodstream [66]. However, microdialysis studies in animals support an intensity threshold point (3 to 6 m/min - moderate effort) in the release of DA, DOPAC, HVA in the striatum were minimally elevated during exercise [44]. The administration of higher training

intensities (above threshold moderate work) led to increased extracellular DA concentrations, remaining free for a longer time [44]. In healthy humans it is still controversial, Wang et al. 2000 [104], twelve volunteers were evaluated using the technique of positron emission tomography (PET scan) and showed unchanged results. The subjects ran at an average speed of 8.7 km/h with 3.3º tilt for 10 to 15 min (average total distance of 4.3 km), with no changes in the availability of D2 receptors after exercise in the cerebellum and putamen (baseline, 4:17 ± 12:29 - after exercise, 4:22 ± 0.34 - p = 0.06). Additional human studies are needed to clarify the true effect of DA as well, which exercise conditions would be more interesting to such patients.

Finally, one of the most adaptive effects seen with regular aerobic exercise is the reduction of sympathetic drive after a few weeks for the same exercise training intensity [17]. This may be a mechanism of great importance to be considered in a manic state, and along with the production of β-endorphin could favorably contribute to a reduction in euphoria and mania. In short, considering the monoaminergic changes specifically 5HT, DA, and NA during, after, and with exercise in long-term, these may exhibit potential benefits for mood regulation in BD. Furthermore, the long term could speculate that the exercise may be a means of maintaining euthymia making patients less vulnerable to stay longer in a moment of neutrality [6, 45].

5.0 Conclusion

In fact, there is still no a definitive answer about the effects of exercise on psychiatric disorders, more specifically in BD. However, the combination of aerobic exercise with specific drug strategies seem to reduce disease severity. The mechanisms for this reduction are multifactorial, and monoaminergic systems are only part of the pathophysiology of BD. Moreover, although still unclear, the monoaminergic responses manifested from exercise in general can adjust the patient with BD to a neutrality, introducing exercise as an innovative form of treatment. Future studies are needed to establish a pattern and a more effective dose of training for this population.

6.0 Expert opinion

In this article, we have reviewed some of the mechanisms related to BD, as well as, the pattern of exercise response on the pathophysiology. Additionally, new

perspectives were suggested, which in our view, is a new way of thinking about the potentiating effects of the physical conditioning. Until this moment, the acute response of aerobic exercise has been extensively studied [4, 14, 71, 92, 98], however, without focusing on chronic training which forms the basis for non-drug treatments. In line with that, the adaptations to training, although little explored in the context of BD, can induce the expression of substances that co-regulate several process related to the pathophysiology of the patient [8, 12, 13, 30, 79, 82]. Currently, skeletal muscle has been evidenced as an endocrine organ capable of modulating several responses through the production and secretion of important myokines such as interleukin 6 (IL-6) [69]. As previously mentioned, BDNF is directly related to the promotion of neuronal plasticity [53], and this growth factor may be induced by aerobic training or interval exercise linked to IL-6 secretion. Other evidence supports that the myocin-dependent PGC-1α - FNDC5 axis is mainly mediated by muscle contraction during exercise, along with IL6, and this axis stimulates an increase in BDNF expression as above [72]. Moreover, mitochondrial biogenesis and consequently the increase of oxidative metabolism are responses of this mechanism [37, 39].

In patients with mood disorder, we find a gene network involved in different pathophysiology and this is also reflected in BD, with mutations and different responses such as protein PGC-1α, which appears in abnormal concentrations compared to healthy individuals. The reduction in PGC-1α concentration in the brain is associated with neurodegenerative processes [72]. Thus, it is known that physical exercise is involved in different signaling and that exerkines are substance derived from exercise metabolism. These substances are regulated over the long term via the AMPK and p38 MAPK signaling cascade to activate PGC-1α, which can act as a neuromodulator as well as other hormones synthesized via physical exercise, thus reinforcing the possible effectiveness of physical training as a non-drug treatment in BD [37].

In a chronic context, speculating that the improvement in VO_{2Max} could be an interesting channel to be stimulated, higher growth of this variable is observed when administered higher training intensities (90-100% of VO_{2Max}) in healthy subjects [16, 38, 41], with metabolic syndrome [94], or in patients with cardiac failure [109]. It is reasonable to think that these higher training stimuli with recovery periods (high-intensity interval training - HIIT) can also be adjusted to improve the physical fitness

and health in patients with mood disorder. First, it is important to understand that the term high intensity should not necessarily be interpreted as a high effort, since the effort depends on the ratio of intensity vs. time. Thus, considering the negative effect on the affective state reported in the literature with prolonged exposure to high-intensity stimuli [31], new researches should be conducted, aiming to determine a threshold effort that simultaneously reproduce the physiological benefits of HIIT and a positive training perception (for a better understanding about HIIT, please see Gibala *et al*. [38] and Swain and Franklin [91]). Thus, future studies are needed to clarify HIIT as a new perspective of training. However, knowing that patients with BD have low physical capacity or exercise tolerance [88], a suitable training strategy, like HIIT, which is both time efficient and cited in different fields, is still a challenge to researchers regarding BD. Other factors that should be taken into account are the adherence to regular physical exercise, the patients' exercise history and the perception of disease management. Most patients with BD do not exercise regularly, nor know the positive influence of physical exercise on their disorder. In addition, with regard to adherence to physical exercise, the presence of symptoms and stigma can be the most important barrier regarding the practice of physical exercise. Thus, medical supports, specifically to the presence of symptoms, such as hypersomnia, amotivation or psychomotor retardation is critical, and also social support, especially from family and friends, could be facilitators to the practice of physical exercise [111].

In addition, it is necessary to investigate the prescription of chronic training to optimize the levels of neurotransmitters, neurotrophic and immunomodulatory factors and all factors originating from skeletal muscle in the processes involved in neurogenesis, and to investigate better response to training dose and safe prescription for patients with mood disorders [78, 79]. Therefore, we expect that, over the years, physical exercise will become a safe non-drug treatment for different mood disorders, such as BD, and that new studies are carried out from a dose-response perspective, safe and effective prescription, and that all responses on molecular pathways modulated by exercise are also better established.

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Figure and table legends:

Figure 1. Possible general mechanisms of influence of exercise on mental illness.

Table 1. Benefits with exercise intervention.

Author	Methods Features				Exercise Features			
	n	Control Group	Med	Therapy	Exercise Protocol	Level of Exercise	Total Weeks	Criteria ACSM
Ng, Dodd, and Berk, 2007 [71]	49	Y (n=35)	?	N	Walk (40 min)	Free	?	Y
Sylvia *et al*. 2013 [93]	5	N	?	Y (cogitive, lifestyle)	? (30 min) 5x/week	Moderate Effort	± 20 Weeks	Y
Daumit *et al.* 2013 [27]	64	Y (n=147)	Y	Y (lifestyle)	?	Moderate Effort	± 72 Weeks	?
Verhaeghe *et al*. 2013 [101]	173	Y (n=50)	Y	Y (social + cognitive)	Walk (30 min) 3x/week	Moderate Effort	± 10 Weeks + 6 month (follow up)	Y
Van Citters *et al*. 2010 [97]	76	N	Y	Y (behavior, lifestyle, psycological)	?	Vigorous Effort	± 36 Weeks	?

Subtitles: Med - medicines; Criteria ACSM - subjects or studies covered the minimum recomended; Y - yes; significative reduction on symptoms of BD; ↔ - non-significative change; ↑ - significative increase on mood

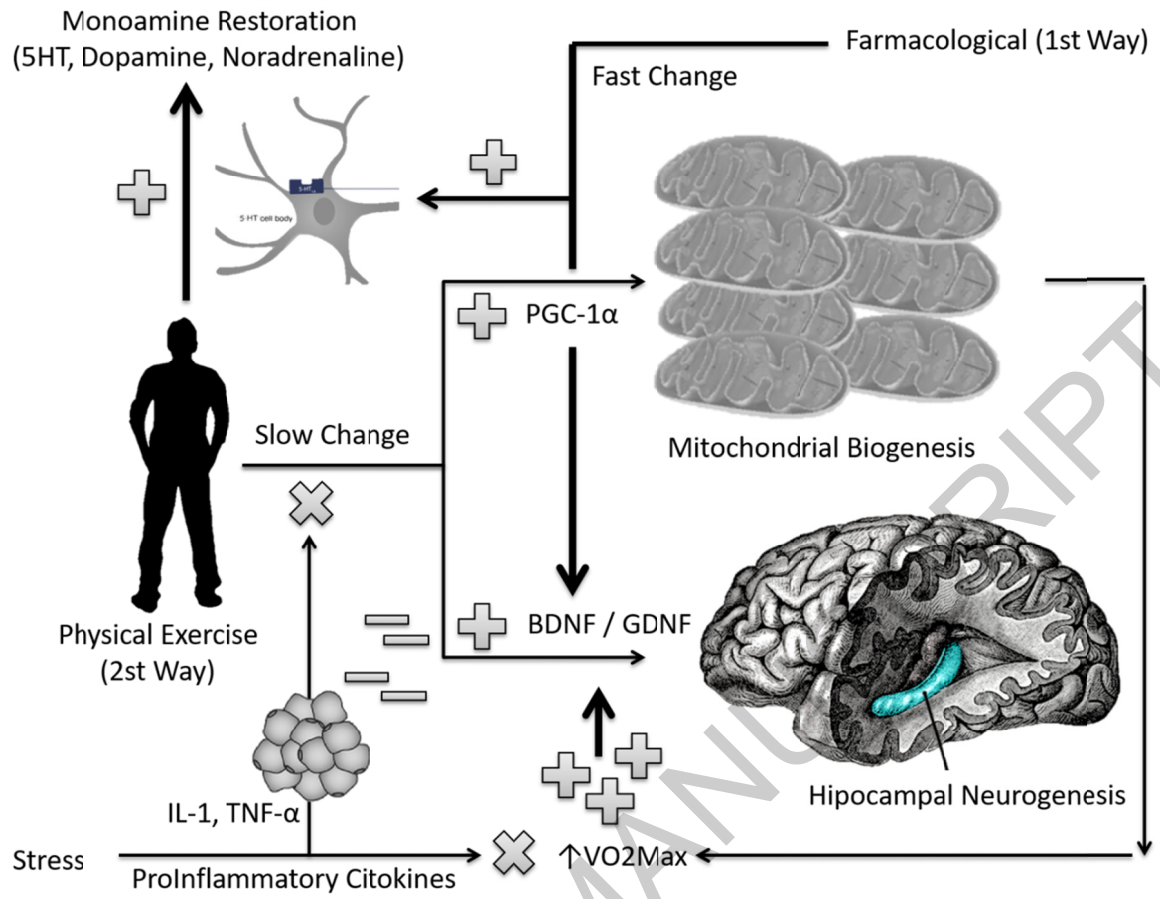

Fig 1