Exercise and Mental Health: Many Reasons to Move

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Introduction

Neurodegenerative diseases become more prevalent as individuals age and, therefore, represent a serious issue for the healthcare system. Since inactivity is the number one risk factor for many diseases, physical activity has become an emerging topic of interest for many investigators. Exercise might act as an efficient and low-cost adjunctive factor in the treatment and prevention of age-related neurodegenerative processes [1, 2]. Recent studies have focused on the correlation between physical activity and mental health [3–6]. Clinical evidence has demonstrated that exercise has a positive relationship with the outcome of different mental diseases, such as depression, Alzheimer’s disease and Parkinson’s disease, improving not only patients’ quality of life but the disease itself [7–9]. Some authors state that the influence of exercise on brain functioning might be related to the human evolutionary process, since physical activity is associated with survival. It has been suggested that individuals who exercise might show a biological advantage over sedentary individuals [4]. Indeed, exercise is related to enhanced cognitive functioning and brain plasticity [10, 11]. Although there is an increasing interest in the mechanisms supporting the positive effects of exercise on mental health, clinical evidence is still very limited.

Key Words
Physical activity · Major depression · Alzheimer’s disease · Parkinson’s disease, elderly

Abstract
The relationship between physical activity and mental health has been widely investigated, and several hypotheses have been formulated about it. Specifically, during the aging process, physical exercise might represent a potential adjunctive treatment for neuropsychiatric disorders and cognitive impairment, helping delay the onset of neurodegenerative processes. Even though exercise itself might act as a stressor, it has been demonstrated that it reduces the harmful effects of other stressors when performed at moderate intensities. Neurotransmitter release, neurotrophic factor and neurogenesis, and cerebral blood flow alteration are some of the concepts involved. In this review, the potential effects of exercise on the aging process and on mental health are discussed, concerning some of the recent findings on animal and human research. The overwhelming evidence present in the literature today suggests that exercise ensures successful brain functioning.
This revision, which focuses on the relationship between exercise and mental health, is divided into: (1) clinical studies that investigated the effect of exercise as a non-pharmacological treatment of mental illness, and (2) studies that hypothesized a neurophysiological pathway to explain the relationship between exercise and mental health.

**Method**

A computer search of PubMed and IsiWeb was conducted using a combination of the key words exercise, physical activity, and elderly with the specific mental disorder (major depression, Alzheimer’s disease, Parkinson’s disease). Articles that did not specify methods of clinical diagnosis and that did not measure effects of exercise were excluded. Also, studies that measured other comorbid conditions were excluded. After all exclusions, the final result comprised 32 articles. They are presented in table 1 (8 articles), table 2 (8 articles) and table 3 (16 articles). The other studies referenced in this review contribute to the understanding of the mechanism of action of exercise related to maintaining a healthy brain.

**Mental Health and Exercise: Clinical Evidences in Elderly Subjects**

**Physical Exercise and Major Depression**

A recent study has shown the overall prevalence of depression in the elderly to be 22%, and that a sedentary

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**Table 1. Summary of physical exercise interventions for elderly patients with major depressive disorder (MDD)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Age, years</th>
<th>Diagnostic criteria</th>
<th>Type of exercise</th>
<th>Intervention duration</th>
<th>Primary outcomes</th>
<th>Exercise group improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al.** [24]</td>
<td>16 E 16 C</td>
<td>71.3 ± 1.2</td>
<td>DSM-IV ST</td>
<td>ST</td>
<td>20 weeks</td>
<td>BDI, HDRS, SF36</td>
<td>BDI, HDRS, SF36</td>
</tr>
<tr>
<td>Blumenthal et al.* [20]</td>
<td>41 M (sertraline) 39 E 44 M + E</td>
<td>57 ± 6.5</td>
<td>DSM-IV AT</td>
<td>AT</td>
<td>16 weeks</td>
<td>BDI, HDRS</td>
<td>BDI, HDRS</td>
</tr>
<tr>
<td>Babayak et al.* [21]</td>
<td>41 M (sertraline) 39 E 44 M + E</td>
<td>57 ± 6.5</td>
<td>DSM-IV AT</td>
<td>16-week follow-up 10 months</td>
<td>BDI, HDRS</td>
<td>Lower rates of depression (clinical diagnostic)</td>
<td></td>
</tr>
<tr>
<td>Singh et al.** [25]</td>
<td>15 E 14 C</td>
<td>71 ± 2.0</td>
<td>DSM-IV ST</td>
<td>ST</td>
<td>20-week follow-up 26 months</td>
<td>BDI, PGMS</td>
<td>BDI, PGMS</td>
</tr>
<tr>
<td>Herman et al.* [22]</td>
<td>48 M (sertraline) 53 E 55 M + E</td>
<td>56.72 ± 6.45</td>
<td>DSM-IV AT</td>
<td>AT</td>
<td>16 weeks</td>
<td>Dropout remission (HDRS)</td>
<td>Low dropout (NS)</td>
</tr>
<tr>
<td>Mather et al. [23]</td>
<td>42 E 43 C</td>
<td>63 65</td>
<td>ICD-10 AT</td>
<td>10 weeks</td>
<td>HDRS, GDS</td>
<td>HDRS, GDS</td>
<td></td>
</tr>
<tr>
<td>Singh et al. [26]</td>
<td>18 E (high intensity) 17 E (low intensity) 19 control</td>
<td>69 ± 5  70 ± 7  69 ± 7</td>
<td>DSM-IV ST</td>
<td>8 weeks</td>
<td>HDRS, GDS</td>
<td>HDRS, GDS</td>
<td></td>
</tr>
<tr>
<td>Blumenthal et al. [7]</td>
<td>53 E (home-based) 51 E (supervised) 49 M (sertraline) 49 placebo</td>
<td>52 ± 8</td>
<td>DSM-IV AT</td>
<td>16 weeks</td>
<td>HDRS</td>
<td>HDRS</td>
<td></td>
</tr>
</tbody>
</table>

ST = Strength training; AT = aerobic training; Group: E = exercise; C = control; M = medication. Depression rating scales: HDRS = Hamilton Depression Rating Scale; BDI = Beck Depressive Inventory; GDS = Geriatric Depressive Scale; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders. * and ** = Same initial sample; NS = not significant between groups; SF36 = 36-Item Short Form Health Survey; PGMS = Philadelphia Geriatric Center Morale Scale; ICD-10 = International Statistical Classification of Diseases and Related Health Problems.
lifestyle is significantly correlated to depression morbidity [12]. Dunn et al. [13] showed that only 37 studies have studied exercise in major depressed (MDD) patients, out of a thousand papers on the issue. Reviews have suggested that exercise is an effective treatment for depression [14–17]. Other studies have also examined the effect of physical exercise on the prevention of depression [18, 19]. Despite the fact that data on elderly patients are even scarcer, investigations have shown an inverse relationship between aerobic and strength training and depression in the elderly (table 1). The efficacy of these interventions is influenced by diagnosis, intensity of exercise, and instruments used to evaluate response [13, 27]. For example, aerobic exercise at an intensity consistent with public health recommendations can be regarded as an effective treatment of mild and moderate MDD. On the other hand, the effects of low-intensity exercise are comparable to placebo effects [27]. In a recent study, Blumenthal et al. [7] evaluated MDD patients with different treatments, namely sertraline, placebo, home-based exercise, and supervised exercise. Although the authors observed a higher remission rate with sertraline (47%) and exercise (45%), placebo response was also high, suggesting that a considerable portion of therapeutic response is also determined by the attention provided to the patient and to his/her own expectations regarding the treatment. Overall, there is little evidence for a possible dose-response effect of exercise on major depression.

**Physical Exercise and Alzheimer’s Disease**

Although epidemiological studies have associated exercise with reduced risk to develop Alzheimer’s disease (AD), the biological bases of such benefits remain inconclusive [28]. AD, a neurodegenerative disease, is characterized by the formation of β-amyloid plaques, neuronal loss in the hippocampus, reduced cholinergic function

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**Table 2. Summary of physical exercise interventions for elderly patients with Alzheimer’s disease**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Age</th>
<th>Type of exercise</th>
<th>Intervention duration</th>
<th>Primary outcomes</th>
<th>Exercise group improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palleschi et al. [39]</td>
<td>15 E</td>
<td>74 ± 1.5</td>
<td>aerobic</td>
<td>3 months</td>
<td>MMSE, attentional and verbal tests</td>
<td>MMSE, attentional and verbal tests</td>
</tr>
<tr>
<td>Arkin [36]</td>
<td>24 E</td>
<td>78.8 ± 8.0</td>
<td>aerobic, flexibility, strength and balance</td>
<td>at least 1 year</td>
<td>strength and aerobic capacity, GDS</td>
<td>strength and aerobic capacity</td>
</tr>
<tr>
<td>Teri et al. [39]</td>
<td>76 E</td>
<td>78 ± 6</td>
<td>aerobic, flexibility, strength and balance</td>
<td>3 months</td>
<td>SF36, SIP, HDRS, CSDD</td>
<td>SF36, CSDD HDRS</td>
</tr>
<tr>
<td>Mahendra and Arkin [40]</td>
<td>24 E</td>
<td>78.8 ± 8.0</td>
<td>aerobic, flexibility, strength and balance</td>
<td>at least 1 year</td>
<td>strength and aerobic capacity, GDS, caregiver evaluation</td>
<td>strength, aerobic capacity, caregiver evaluation</td>
</tr>
<tr>
<td>Rolland et al. [8]</td>
<td>67 E</td>
<td>82.8 ± 7.8</td>
<td>aerobic, flexibility, strength and balance</td>
<td>12 months</td>
<td>Katz ADLs</td>
<td>Restrain ADL decline</td>
</tr>
<tr>
<td>Williams and Tappen [34]</td>
<td>30 E (sw)</td>
<td>88 ± 6.32</td>
<td>aerobic, flexibility, strength and balance</td>
<td>16 weeks</td>
<td>DMAS, CSDD AMS, OAS</td>
<td>DMAS, CSDD AMS, OAS</td>
</tr>
<tr>
<td>Arkin [37]</td>
<td>24 E</td>
<td>78.8 ± 8.0</td>
<td>aerobic, flexibility, strength and balance</td>
<td>at least 1 year</td>
<td>MMSE, CDR, CERAD, ABCD, WAIS-R</td>
<td>MMSE, ABCD WAIS-R comprehension</td>
</tr>
<tr>
<td>Williams and Tappen [35]</td>
<td>16 E (sw)</td>
<td>87.9 ± 5.95</td>
<td>aerobic, flexibility, strength and balance</td>
<td>16 weeks</td>
<td>DMAS, CSDD AMS, OAS</td>
<td>DMAS, CSDD AMS, OAS</td>
</tr>
</tbody>
</table>

ADLs = Activities of daily living; SF36 = 36-Item Short-Form Health Surveys; ABCD = Arizona Battery for Communication Disorders of Dementia; SIP = Sickness Impact Profile Mobility Subscale; DMAS = Dementia Mood Assessment Scale; CSDD = Cornell Scale for Depression in Dementia; AMS = Alzheimer Mood Scale; OAS = Observed Affect Scale; HDRS = Hamilton Depression Rating Scale; E = exercise; C = control; sw = supervised walking; ce = comprehensive exercise; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; WAIS-R = Wechsler Adult Intelligence Test-Revised.
### Table 3. Summary of physical exercise interventions for elderly patients with Parkinson’s disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Age</th>
<th>Type of exercise</th>
<th>Intervention duration, weeks</th>
<th>Primary outcomes</th>
<th>Exercise group improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comella et al. [51]</td>
<td>18 E</td>
<td>66.8</td>
<td>general exercise and PT</td>
<td>4</td>
<td>UPDRS</td>
<td>UPDRS</td>
</tr>
<tr>
<td>Schenckman et al. [50]</td>
<td>23 E 23 C</td>
<td>55–84</td>
<td>individual flexibility</td>
<td>10</td>
<td>spinal flexibility and physical performance</td>
<td>functional reach and spinal flexibility</td>
</tr>
<tr>
<td>Reuter et al. [49]</td>
<td>16 E</td>
<td>65.4 ± 5.9</td>
<td>combined: aerobic gait, flexibility, strength</td>
<td>14</td>
<td>UPDRS, MMSE, BTM CURS, AMQZ, SIP</td>
<td>UPDRS, BTM and CURS</td>
</tr>
<tr>
<td>Baatile et al. [48]</td>
<td>6 E</td>
<td>72.7 ± 3.7</td>
<td>pole striding</td>
<td>8</td>
<td>UPDRS; PDQ-39</td>
<td>ADLs</td>
</tr>
<tr>
<td>Niewboer et al. [47]</td>
<td>33 E</td>
<td>66.2</td>
<td>functional training</td>
<td>6</td>
<td>UPDRS, activity scale score</td>
<td>activity scale score</td>
</tr>
<tr>
<td>Bergen et al. [46]</td>
<td>4 E 4 C</td>
<td>56.8 ± 6.5</td>
<td>aerobic</td>
<td>16</td>
<td>movement initiation, VO2 peak</td>
<td>movement initiation VO2 peak</td>
</tr>
<tr>
<td>Hirsch et al. [9]</td>
<td>9 E (B) 6 E (S + B)</td>
<td>75.1 ± 1.8</td>
<td>balance and strength</td>
<td>10</td>
<td>SOT, strength</td>
<td>strength, gait</td>
</tr>
<tr>
<td>Lun et al. [52]</td>
<td>8 E (Home) 11 E (PT)</td>
<td>65 ± 8</td>
<td>balance, flexibility and strength</td>
<td>8</td>
<td>UPDRS total and motor TUG, BBS, ABC scale</td>
<td>UPDRS motor</td>
</tr>
<tr>
<td>Protas et al. [54]</td>
<td>9 E 9 C</td>
<td>71.3 ± 7.4</td>
<td>gait and step training</td>
<td>8</td>
<td>reduce in falls, increase in steps and gait</td>
<td>reduce in falls, increase in steps and gait</td>
</tr>
<tr>
<td>Miyai et al. [45]</td>
<td>11 E (BWSTT) 9 E (PT)</td>
<td>69.5 ± 1.9</td>
<td>BWSTT and PT</td>
<td>4</td>
<td>UPDRS, ambulation speed</td>
<td>ambulation speed and number of steps</td>
</tr>
<tr>
<td>Burini et al. [44]</td>
<td>22 E</td>
<td>65.2 ± 6.5</td>
<td>aerobic and qigong</td>
<td>14</td>
<td>UPDRS, PDQ39, 6-min walk, BDI, BD’S</td>
<td>6 min walk, VO2max, double product peak</td>
</tr>
<tr>
<td>Dibble et al. [56]</td>
<td>10 E 9 C</td>
<td>64.3 ± 9.6</td>
<td>eccentric resistance</td>
<td>12</td>
<td>mobility, muscle force, quadriceps muscle volume</td>
<td>mobility, muscle force, quadriceps muscle volume</td>
</tr>
<tr>
<td>De Paula et al. [55]</td>
<td>20 E</td>
<td>61.5 ± 9.8</td>
<td>aerobic, strength and flexibility</td>
<td>12</td>
<td>NHP</td>
<td>NHP</td>
</tr>
<tr>
<td>Ashburn et al. [53]</td>
<td>65 E 65 C</td>
<td>72.7 ± 9.6</td>
<td>strength, balance and aerobic</td>
<td>6</td>
<td>BBT, SAS, QoL</td>
<td>functional reach, QoL</td>
</tr>
<tr>
<td>Herman et al. [43]</td>
<td>9 E</td>
<td>70 ± 6.8</td>
<td>aerobic</td>
<td>6</td>
<td>UPDRS, PDQ39, SPPB, gait speed</td>
<td>PDQ39, UPDRS SPPB, gait speed</td>
</tr>
<tr>
<td>Cakiti et al. [42]</td>
<td>21 E 10 C</td>
<td>71.8 ± 6.4</td>
<td>speed-dependent treadmill</td>
<td>8</td>
<td>BBT, DGI, FES walking distance</td>
<td>BBT, DGI, FES walking distance</td>
</tr>
</tbody>
</table>

BWSTT = Body weight-supported treadmill training; DGI = Dynamic Gait Index; FES = Falls Efficacy Scale; BBT = Berg Balance Test; Qigong = Chinese physiotherapy approach; MMSE = Mini-Mental State Examination; TUG = time to up and go; BD’S = Brown’s Disability Scale; E = exercise; C = control; PT = physiotherapy; B = balance; S = strength; QoL = quality of life thermometer; BBS = Berg Balance Scale; UPDRS = Unified Parkinson’s Disease Rating Scale; PDQ39 = 39-Item Parkinson’s Disease Questionnaire; AMQZ = Adjective Mood Questionnaire of Zeersen; ABC Scale = Activities-Specific Balance Confidence Scale; SAS = Self-Assessment Parkinson’s Disease Disability Scale; NHP = Nottingham Health Profile; BDI = Beck Depression Inventory; SPPB = Short Physical Performance Battery; SIP= Sickness Impact Profile; SOT = Sensory Orientation Test; BMT = Basic Motor Test; CURS = Columbia University Rating Scale.
ties of daily living (ADLs) mainly focusing on motor performance, gait, and activities related to a reduced risk of developing PD. Also, clinical studies have suggested positive effects of this non-pharmacological approach [33]. The efficacy of motor intervention was confirmed in affective status, psychosocial function, physical health and function, and caregiver distress. In another study, Teri et al. [31] observed that daily 30 min of physical training (aerobic, flexibility and strength) reduced the number of hospitalizations in 153 AD patients. It also decreased depressive symptoms and improved quality of life. Rolland et al. [8] evaluated 134 patients and demonstrated that, after a year of exercise intervention, the exercise group improved quality of life, as compared to the sedentary group. Other studies showed significant mood improvement in older adults with AD [34, 35]. In a recent study, Williams and Tappen [34] observed an antidepressant effect of exercise in severe AD. However, such investigations are still scarce and very little is known about the efficiency of exercise as a protective factor in AD [31, 34–40] (table 2).

Physical Exercise and Parkinson’s Disease

Parkinson's disease (PD) is associated with genetic, environmental, and behavioral factors. Motor alterations are expressed as tremor, rigidity and hypokinesia, as well as posture and balance changes [41]. Such alterations are directly associated with falls and fatigue experienced by the patients. Exercise might help by protecting against the disease as well as an adjunctive treatment [42–57]. Epidemiological studies have suggested that exercise is related to a reduced risk of developing PD. Also, clinical studies have investigated the effective stress and movement changes, mainly focusing on motor performance, gait, and activities of daily living (ADLs) [58, 59]. Thacker et al. [57] have demonstrated that the intensity of exercise might influence the neuroprotective response. Higher intensities of exercise would be positively related to a protective factor, when compared to lower intensities. Goede et al. [59] observed that physical activity is significantly beneficial to PD patients, improving their quality of life, walking skills, and reducing neurological symptoms. In fact, improving functional capabilities as a consequence of strength and balance training might positively influence their independence and quality of life, not necessarily because of neurochemical alterations. Therefore, strength improvement also has an essential role in daily activities. Parkinsonians (idiopathic) who accomplished a 10-week strength and balance program developed strength and reduced the number of falls [9]. Although somewhat limited, evidence suggests that exercise training is beneficial to patients with PD, especially in functional capacity and ADLs improvement (table 3).

Neurophysiological Hypothesis

The protective effect of exercise could be explained by the hormesis theory, in which low doses of toxins and/or radiation can exert beneficial effects in organisms [60]. Radak et al. [61, 62] extended the hormesis theory to include reactive oxygen species (ROS), suggesting that the beneficial effects of regular exercise are partly based on its ability to generate ROS. Exercise-induced ROS production plays a role in the induction of antioxidants, DNA repair and protein-degrading enzymes, resulting in decreases in the incidence of oxidative stress-related diseases. Exercise would, therefore, increase the circulation of the same proinflammatory cytokines that are normally upregulated during a stress response. However, exercise may also upregulate anti-inflammatory cytokines, and with time, increase the immune system threshold for stress [63].

Exercise increases the release and synthesis of several neurotrophic factors related to better cognitive functioning, neurogenesis, angiogenesis and plasticity. The brain-derived neurotrophic factor (BDNF) and the insulin-like growth factor (IGF-1) are the factors that have been investigated the most. Animal research supports the idea that BDNF is essential for hippocampal functioning, synaptic plasticity, learning, and modulation of depression [5, 64, 65]. Studies have shown that exercise elevates the level of BDNF in the rat hippocampus, acting just like a regular antidepressive drug [66]. Winter et al. [67] observed an increase in BDNF in humans running at a high intensity (blood lactate level >10 mmol/l). Moreover, the authors showed that exercise accelerates learning. The IGF-1 is another neurotrophic factor correlated with cognitive improvement. IGF-1 is also correlated with neurogenesis, since its release starts several processes related to the proliferation of progenitor cells in the subgranular zone. Exercise increases IGF-1 levels, which are diminished in elderly adults with poor cognitive performance [68]. Since strength training increases testosterone and...
IGF-1 levels, some authors argue that strength training might have an advantage over cardiovascular training. For example, Cassilhas et al. [69] observed improved cognitive functioning and higher IGF-1 levels in a group of elderly individuals after 6 months of strength training. Nottebohm [70] hypothesized that testosterone is the key to higher BDNF levels. In the brain, testosterone is aromatized in estradiol, and several studies have showed the correlation between estradiol and cognitive and mood aspects. Another important aspect is the regulation of the amyloid levels by IGF-1, since IGF-1 is inversely correlated with the β-amyloid peptide.

In addition to BDNF and IGF-1, exercise also regulates the expression of vascular endothelial growth factor (VEGF). VEGF regulates endothelial cell proliferation and angiogenesis, but also has neurotrophic, neuroprotective, and neurogenic effects. While IGF-1 and BDNF mediate behavioral improvements as a consequence of exercise, the interactive effects of IGF-1 and VEGF seem to coordinate exercise-induced neurogenesis and angiogenesis. Exercise-induced angiogenesis is associated with an increase in brain VEGF [65]. Pereira et al. [71] observed an in vivo correlation of exercise-induced neurogenesis and angiogenesis in the adult dentate gyrus, which was based on an increase of cerebral blood volume in this specific area.

Stress, depression and aging would decrease neurotrophic expression and neurogenesis in the brain, and both antidepressants and exercise would reverse these effects [5, 65]. Kempermann [72] proposed that major depression might result from a disturbance in neuronal plasticity and adult hippocampal neurogenesis. Neurogenesis in the adult hippocampus might improve cognitive processes (e.g., memory functioning) and treatment of several psychiatric diseases (e.g., depression). Voluntary exercise enhanced neurogenesis in the dentate gyrus of the adult mouse [73]. Stemming from these findings, the focus on the relationship between exercise and mental health has taken a new direction: neurogenesis in the adult human brain.

Exercise increases several neurotransmitters, such as serotonin (5-HT), dopamine (D), acetylcholine (ACh) and norepinephrine (NE). Moreover, exercise increases the activity of some subtypes of receptors for neurotransmitters changing the cortical/subcortical activity (for a review, see Sarbadhikari and Saha [74]). Winter et al. [67] observed a strong increase in peripheral catecholamine plasma levels (NE, 5-HT and D) after intense physical exercise in humans, and associated it to learning and memory improvements. However, peripheral catecholamines do not cross the blood-brain barrier. A possible mechanism, then, is the calcium-calmodulin system, since exercise leads to increased serum calcium levels, and calcium is transported to the brain. This, in turn, enhances brain dopamine synthesis through a calmodulin-dependent system, and increases dopamine levels. In addition, exercise releases anandamide, which in turn, increases the dopamine release. Sparling et al. [75] reported the first evidence that exercise at a moderate intensity activates the endocannabinoid system. They showed elevated plasma anandamide levels in runners and cyclists when compared to sedentary controls. The analgesia, sedation, anxiolysis, and a sense of well-being with physical activity would be related to this neurophysiological pathway [76]. This mechanism seems to better explain the analgesic effects of exercise rather than the endorphin hypothesis. Plasmatic endorphin levels do not necessarily represent levels in the brain, due to the blockade of the blood-brain barrier. Hence, studies have shown that the endorphin release only occurs at high exercise intensities. A recent study showed in vivo evidence that release of endogenous opioids occurs in frontolimbic brain regions after exercise, which has been related to the level of euphoria after running [77].

Cerebral activity is positively correlated with an increase in oxygen and glucose uptake and with an increase in regional cerebral blood flow (CBF). Exercise is related to an increase in CBF in several cortical and subcortical areas [78]. Adenine nucleotides play a major role in the local control of CBF. In 1979, Forrester [79] proposed that circulating nucleotides and derivatives released from active skeletal muscle achieve levels in the arterial blood that would affect cerebral metabolism, by a system of ‘metabolic communication’ in the body mediated by circulating purine compounds. The levels of adenosine triphosphate (ATP), a potent vasodilator, increase during exercise and could be a mechanism involved in CBF regulation. Cerebral perfusion is also dependent on nitric oxide (NO), and physical activity upregulates endothelial NO synthesis and improves angiogenesis and CBF [80]. Moreover, exercise increases the production of VEGF which is believed to be the primary growth factor associated with capillary formation in the developing brain [5, 65].

**Conclusion**

Although exercise improves quality of life, prevents falls, increases balance, strength, and improves ADLs, the efficacy of an exercise intervention after the onset of
the disease is not commonly assessed and, therefore, needs to be investigated with randomized clinical trials. Neuropsychological aspects, invasive measurements (e.g., neurotrophic factors, neurotransmitters, hormones), neuroimaging studies, or some physiological markers associated with clinical parameters could help elucidate the potential role of exercise as a non-pharmacological treatment of mental disorders. Our review presents recent findings in clinical and animal investigations concerning the effects of exercise on general brain functioning. Although this is a promising research topic, the study of the real effects of exercise as an adjunctive treatment of mental illness still has a long way to go.

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179

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