

# BDNF–TrkB signaling as a therapeutic target in neuropsychiatric disorders

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**Abstract:** Research evidence points to abnormal brain-derived neurotrophic factor (BDNF) signaling being a common and vital participant in the etiology and pathophysiology of many psychiatric disorders, including depression, schizophrenia, and bipolar disorder. To increase BDNF levels in patients is therefore a necessary goal of any treatment. This review explores the various therapeutic strategies that can increase BDNF brain expression and recover mental health disturbances. From environmental enrichment and exercise to dietary intake, it is apparent that a healthy lifestyle significantly influences BDNF signaling and mental health. We conclude that in order to combat the inefficiency of current treatment methods, more attention should be focused on holistic approaches to achieve this goal, as BDNF is proven to have dynamic responses to environmental influences.

**Keywords:** BDNF, neurotrophins, mental health

## Introduction

Neurotrophins are a family of growth-factor proteins that promote the survival, growth, maturation, and function of neurons. The family of neurotrophins to which brain-derived neurotrophic factor (BDNF) belongs also contains nerve-growth factor (NGF), neurotrophin 3, and neurotrophin 4.<sup>1,2</sup> Of these, BDNF is especially assiduous and plethoric; its importance is shown by its highly conserved structure<sup>3</sup> and by early postnatal lethality in knockout mouse models.<sup>4</sup>

Since its identification more than three decades ago,<sup>5</sup> BDNF has been found to be vital during embryonic brain development, where it is seminal in early synaptic and neuronal circuit formation.<sup>6–9</sup> Its importance also persists postnatally, where it supports neuronal maturation, homeostasis, and survival,<sup>4,10,11</sup> the regulation of synaptic transmission and neuronal plasticity,<sup>12–14</sup> and the promotion of neurogenesis via enhancing the proliferation,<sup>15–17</sup> differentiation,<sup>18</sup> and survival<sup>19</sup> of newborn cells.

The *BDNF* gene is mapped to chromosome 11p in humans and exhibits highly complex regulation of its expression. It has been found to have eleven exons and nine functional promoters that direct tissue, brain-region, and cellular spatial specificity.<sup>20,21</sup> BDNF is synthesized as a 35 kDa prepro isoform, which may then be cleaved to form a 28 kDa proBDNF or a 13.5 kDa mature BDNF. The expression of BDNF is regulated via neuronal activity through calcium-mediated mechanisms,<sup>22</sup> and its high-affinity tyrosine kinase-coupled receptor, the tropomyosin-related kinase receptor (TrkB), is also regulated in an activity-dependent manner.<sup>23</sup> BDNF also binds with a low affinity to the p75 receptor, which it shares with other members of the neurotrophin family. The

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mature BDNF isoform has a high affinity for TrkB, and upon binding activates a number of intracellular signaling pathways including phosphoinositide 3-kinase, phospholipase C $\gamma$ , and mitogen-activated protein kinase.<sup>24</sup> While it is thought that the pro or truncated BDNF isoform has little biological activity, preproBDNF is thought to form a complex with sortilin and p75 to elicit apoptotic signaling.<sup>25</sup>

Having so many fundamental and diverse influences on the brain naturally led to the linkage of abnormal BDNF expression and function with various psychiatric diseases.<sup>26–31</sup> One crucial reason is the finding that stress, a great inducer of depression, anxiety, and other psychiatric problems, impairs BDNF and TrkB signaling in limbic areas critically associated with emotionality, such as the hippocampus and frontal cortex.<sup>32–35</sup> This review focuses on the pathophysiological involvement of BDNF in psychiatric disorders, the therapeutic potential of this prolific growth factor, and the various methods in which restoration of BDNF signaling may be implemented.

## BDNF and depression

Depression is a multifarious and debilitating disorder that is among the top three contributors to the global burden of disease.<sup>36,37</sup> It is also a disease whose prevalence is on a sharp upward trend.<sup>36,38</sup> Depression is a major contributor to suicide<sup>39</sup> and is often a symptom of or highly comorbid with other neurological disorders, such as schizophrenia,<sup>40</sup> Alzheimer's disease,<sup>41</sup> Parkinson's disease,<sup>42–44</sup> and Huntington's disease,<sup>45–47</sup> as well as with major diseases such as type 2 diabetes,<sup>48</sup> cardiovascular disease,<sup>49–51</sup> and alcohol withdrawal syndrome,<sup>52</sup> to name but a few.

Depression is thought to result from an inability of the brain to make appropriate adjustments and adaptations in response to environmental stressors, due to impaired or inadequate synaptic and neural plasticity.<sup>53–56</sup> This is evidenced by studies showing altered brain structures in depressed patients, such as reductions in cell number, cell density, and body size as well as reduced glial density in frontal cortical and hippocampal brain regions.<sup>57–60</sup> These observations led to the hypothesis that a loss of neurotrophic factors, which are essential for the survival, development, and maintenance of neurons<sup>61,62</sup> and for regulating synaptic and morphological plasticity,<sup>1,63</sup> is directly involved in the pathophysiology of depression and that its restitution may lie at the heart of successful treatment – the neurotrophin theory of depression.<sup>27,35,53,64</sup> BDNF, an essential, abundant, and prolific neurotrophin conspicuous for its relationship to various neurological and psychiatric disorders, has been given particular interest.

The link between BDNF and depression has been shown by a wealth of evidence. A common single-nucleotide polymorphism in the *BDNF* gene at nucleotide 196 (G/A), which causes a valine (Val)-to-methionine (Met) substitution at codon 66 (Val66Met) has been shown to negatively affect memory and induce abnormal hippocampal activity as well as to disrupt normal activity-dependent BDNF secretion<sup>65</sup> and dendritic trafficking of BDNF mRNA.<sup>66</sup> Those with the Met allele also show reduced hippocampal and prefrontal cortex gray matter volume.<sup>65,67</sup> A recent meta-analysis suggests that the Met allele is associated with increased susceptibility to stressful life events and subsequent depression.<sup>68</sup> Another study observed a correlation between having the Met allele and increased chronicity of depression with a gene–dosage effect – Val/Met heterozygotes show intermediate chronicity between Val/Val and Met/Met homozygotes, who showed the highest chronicity.<sup>69</sup> These findings suggest that disruptions in BDNF signaling increase the propensity to depression.

BDNF can cross the blood–brain barrier,<sup>70</sup> and its serum protein levels in the periphery are strongly correlated with protein concentrations in the central nervous system.<sup>71</sup> Levels of peripheral BDNF measured in serum and plasma have largely been found to be significantly reduced in patients suffering depression and dysthymia disorder, compared with healthy people.<sup>72–74</sup> A significant negative correlation between BDNF levels and the severity of symptoms according to the Hamilton Rating Scale for Depression<sup>75</sup> as well as the Montgomery–Åsberg Depression Rating Scale<sup>76</sup> have also been observed, suggestive of a dose effect. Going hand-in-hand, successful treatment seems to correlate with the restitution of BDNF. Serum BDNF was found to be significantly lower in antidepressant-naïve depressed patients than in healthy controls, whereas patients treated with antidepressants showed a significant elevation in BDNF when compared with nonmedicated patients.<sup>77,78</sup> A recent meta-analysis confirmed reduced serum BDNF in antidepressant-free depressed patients versus healthy controls and antidepressant-treated patients, but failed to find the correlation between BDNF concentration and symptom severity.<sup>79</sup> Indeed, systematic analysis in more than a thousand patients did not find any association between decreased BDNF and specific symptoms or symptom clusters.<sup>80</sup>

In postmortem samples, both mRNA and protein expression of BDNF and its receptor TrkB were found to be reduced in the prefrontal cortex and hippocampus of suicide victims.<sup>81,82</sup> Hippocampal BDNF levels were found to be higher in both patients with major depression and suicide victims treated with antidepressants at time of death,

compared with untreated subjects.<sup>82,83</sup> Tying in with this are the neuroimaging studies that have found reductions in frontal-lobe<sup>84,85</sup> and hippocampal volume in depressed patients, which correlated negatively with duration of disease.<sup>86–88</sup> Within a cohort of patients suffering major depression, who exhibited overall reduced hippocampal volumes compared with controls, those with the Met allele had significantly smaller hippocampal volume than patients with the Val allele.<sup>89</sup> Hippocampal shrinkage is attenuated in patients undergoing antidepressant treatment.<sup>90,91</sup> Likewise, a recovery in dorsal–lateral prefrontal cortical volume was seen in patients after antidepressant treatment and was correlated with a self-reported decrease in depression level.<sup>92</sup> Orbitofrontal cortex shrinkage<sup>93</sup> was partially attenuated in geriatric patients with depression who had used antidepressants versus those who were drug-naïve.<sup>94</sup> A direct positive correlation has also been found via magnetic resonance imaging (MRI) between serum BDNF levels and hippocampal volume of first-episode, medication-free depressed patients,<sup>95</sup> suggestive of BDNF's importance in the etiology and pathogenesis of depression. Despite some inconsistencies between neuro-anatomical studies, most likely due to sample differences in illness severity, medication, sex, family history, et cetera,<sup>96</sup> the evidence nevertheless suggests that antidepressants arrest brain atrophy and symptom deterioration at least partly by increasing BDNF levels.

This supposition is further fortified by research in rodent models, where a mouse model containing the Met/Met allele exhibited abnormally increased anxiety-like behaviors when confronted by stressful settings, was unresponsive to fluoxetine treatment, and showed decreased hippocampal volume and reduced BDNF secretion, reflective of clinical data.<sup>97</sup> In rodents, early life stress (a model of depression) lowered BDNF and altered stress sensitivity later in life,<sup>98</sup> whereas increases in BDNF, either via social enrichment or direct infusion into the brain, reduced susceptibility to depression-like behaviors.<sup>99–101</sup> However, studies also found that increases in BDNF through communal nesting induced a depressive-like phenotype by increasing immobility time in the forced-swim test.<sup>102</sup> Other studies examining the role of BDNF in depression have also found that heterozygous knockout of *BDNF* did not alter anxiety as tested on the elevated-plus maze.<sup>103–105</sup> *BDNF* heterozygote mice and mice expressing the dominant negative TrkB receptor TrkB.T1 did not show any differences compared with wild-type mice in their performance on the forced-swim test, therefore suggesting that reduced BDNF signaling alone may not be sufficient to cause depression per se.<sup>106</sup>

There is accumulating evidence suggesting inflammation as a mediator of the pathophysiology of mood disorders.<sup>107,108</sup> Many studies show that depression is often accompanied by an activation of the inflammatory response system, with an increased production of proinflammatory cytokines. Two meta-analyses consisting of 24 studies and 29 studies, respectively, have shown that interleukin (IL)-6, and tumor necrosis factor (TNF)- $\alpha$  are increased in patients with major depression compared with controls;<sup>109,110</sup> the 2012 study also reported increased soluble IL-2 receptor levels in depressed patients. Cytokine administration has similar effects as psychogenic stressors through actions in the hypothalamus and limbic areas, making it a candidate in the pathophysiology of depression.<sup>111</sup> It has been suggested that the depressive effects of an increased inflammatory response is an adaptive change to encourage individuals to rest and reserve energy as the body combats disease.<sup>112</sup> The effect of inflammatory factors on BDNF is rather scant, but studies have shown that IL-1 $\beta$  and TNF- $\alpha$  can decrease BDNF mRNA in the amygdala of rats.<sup>113</sup> Interferon- $\alpha$  has been found to reduce BDNF in humans,<sup>114,115</sup> as does lipopolysaccharide in rats.<sup>116</sup> IL-1 $\beta$  has also been shown to reduce BDNF–TrkB signaling and to interfere with BDNF-induced antiapoptotic effects.<sup>117</sup> However, another study found that IL-1 $\beta$  increased BDNF mRNA expression in rat hypothalamic neuron-enriched cultures while it reduced BDNF expression in mixed neuron–astrocyte cultures.<sup>118</sup> Inflammatory cytokines also attenuated TrkB phosphorylation, thereby interfering with BDNF signaling.<sup>119</sup> Counterbalancing this, imipramine's ability to offer neuroprotection against lipopolysaccharide-induced apoptosis requires intact BDNF signaling.<sup>120</sup> The evidence therefore hints at a complex relationship, but one that could potentially compromise BDNF signaling.

Collectively, these findings suggest that BDNF may be a key molecule involved in various antidepressant treatment strategies. Therefore, restitution of BDNF may be a fundamental goal of treatments targeting depression.

## BDNF and schizophrenia

It has been suggested that altered synthesis and/or release of neurotrophins may contribute to the development of schizophrenia.<sup>29,30,121</sup> Studies on post-mortem tissue from patients with schizophrenia showed a significant reduction in both *BDNF* and TrkB transcripts as well as BDNF protein in the dorsolateral prefrontal cortex, compared with controls.<sup>122–124</sup> Another study, measuring protein concentrations determined by enzyme linked immunosorbent assay (ELISA), showed decreased BDNF levels in the hippocampus

but increased BDNF levels in the neocortex and unchanged BDNF levels in the cingulate gyrus and thalamus of schizophrenia patients.<sup>125</sup> In contrast, other studies examining the hippocampus of schizophrenia patients showed increased immunostaining of BDNF and TrkB proteins<sup>126</sup> and increased BDNF protein but decreased TrkB protein, as measured by ELISA and Western blots, respectively.<sup>127</sup> It is unclear why there are these opposite and inconsistent findings between studies, although different methods used to measure BDNF and TrkB could be responsible. For example, ELISA methods, used in the aforementioned studies, typically cannot differentiate between pro and mature BDNF isoforms, while Western blotting can distinguish the two. However, more recently, selective ELISA kits have become available that are advertised to be specific to either mature BDNF (human BDNF ELISA Kit; Adipo Bioscience, Santa Clara, CA, USA) or proBDNF (human proBDNF ELISA Kit; Adipo Bioscience). Indeed, a recent study using the above-mentioned ELISA kits demonstrated a selective reduction in mature but not proBDNF isoforms in patients with major depressive disorder,<sup>73</sup> demonstrating the importance of assessing these isoforms individually.

Most studies show significantly reduced serum BDNF protein levels in chronic and medicated patients with schizophrenia compared with healthy controls.<sup>128–132</sup> This is also true in first-episode and antipsychotic-naïve patients with schizophrenia compared with healthy people.<sup>133–135</sup> However, increased BDNF serum protein levels have also been reported,<sup>136</sup> while other studies have failed to find any significant differences.<sup>137,138</sup> Komulainen et al<sup>139</sup> reported that a reduction in plasma BDNF protein levels was associated with cognitive impairment in a large sample of women aged 57–79 years, but not in men. Further, women who reported using sex hormones (hormone-replacement therapy) performed better in tests of general cognition, memory, and executive function.<sup>139</sup> Taken together, clinical data point to a dysregulation of BDNF signaling in schizophrenia.<sup>140</sup>

The dopamine hypothesis of schizophrenia suggests that schizophrenia is caused by excessive dopaminergic neurotransmission, and consequently, most antipsychotic medications act via dopamine receptor DR2 antagonism. BDNF has been shown to play a critical role in the developmental expression of dopamine receptor DR3 in the nucleus accumbens.<sup>141</sup> Conversely, striatal BDNF expression may be altered by activation of dopamine receptors DR1 and DR2.<sup>142</sup> Hence, a strong relationship appears to exist between BDNF and dopamine signaling, and alterations to either of these systems may underlie the pathophysiology of schizophrenia and may dictate responsiveness to antipsychotic medication.

Indeed, medication-naïve patients have been shown to have lower plasma BDNF levels, suggesting a role for antipsychotics in the regulation of BDNF.<sup>143</sup> This positive effect of antipsychotics on BDNF expression is specific to atypical antipsychotics, as typical antipsychotics such as haloperidol tend to reduce BDNF expression levels.<sup>143–145</sup> However, this tends to be antipsychotic-specific, as a cross sectional survey demonstrated positive effects of clozapine, but not risperidone, on serum BDNF levels.<sup>146</sup>

Both in vitro and in vivo studies have shown a positive effect of atypical antipsychotics, such as olanzapine and lurasidone, on BDNF mRNA and protein expression in the prefrontal cortex and hippocampus.<sup>147,148</sup> Thus alterations in the levels of BDNF may represent one of the mechanisms by which antipsychotics exert their effects.

Several studies have shown an association between the Val66Met *BDNF* polymorphism and aspects of schizophrenia, including age of onset,<sup>149</sup> antipsychotic response,<sup>150–152</sup> and cognitive function.<sup>153,154</sup> Both patients with schizophrenia and healthy participants carrying the Met allele showed poorer verbal memory than their Val homozygous counterparts.<sup>155</sup> However, the Met allele was associated with visuospatial impairments that were specific to schizophrenia patients but not healthy participants.<sup>155</sup> A 2012 meta-analysis of the association between the Val66Met polymorphism and cognition, including 23 studies up to 2010, reported no significant associations with the polymorphism and measures of general cognitive ability, memory, executive function, visual processing skills, and cognitive fluency.<sup>156</sup> These discrepancies in the literature may be due to limited sample sizes, lack of consistency in the cognitive tasks assessed, or other hidden sources of variation such as ethnicity of the subjects (the frequency of the derivative allele ranges from near 0% in Africans to up to 60% in Asians and 17% in Caucasians).<sup>156</sup> In addition, it may be that the polymorphism renders the patient more vulnerable to stress-induced disruption (eg, gene  $\times$  environment). For example, Met carriers exposed to high childhood abuse showed significantly poorer cognitive function when compared with Val carriers,<sup>157</sup> suggesting a gene  $\times$  environment interaction. This gene  $\times$  environment interaction has been further explored in our laboratory, where we have shown in *BDNF* heterozygous mice that an additional environmental insult in the form of chronic corticosterone treatment leads to significant impairments in spatial memory.<sup>158</sup>

Cognitive impairments have also been reported in conditional *BDNF* knockout mice. For instance, a conditional dorsal hippocampus *BDNF* deletion in male mice impairs spatial learning in the Morris Water Maze and nonspatial



recognition memory in novel-object recognition tests.<sup>24,159</sup> Interestingly, Monteggia et al<sup>160</sup> found a sex-specific behavioral phenotype in mice with forebrain-specific *BDNF* deletions. The female conditional knockout mice exhibited normal locomotor activity but a substantial increase in depression-like behaviors, whereas male conditional knockouts showed hyperactivity but normal depression-related behaviors. Other animal models of schizophrenia have also displayed alterations in BDNF expression levels, including rat models induced by postnatal MK-801 or phencyclidine administration,<sup>161,162</sup> disrupted in schizophrenia 1 (DISC-1) and Reelin mutant mouse models,<sup>163,164</sup> and a prenatal infection (poly-I:C) mouse model.<sup>165</sup>

Cytokines have been posited to play a role in schizophrenia.<sup>166</sup> A comprehensive meta-analysis showed that schizophrenia is associated with altered cytokine profiles. IL-1 $\beta$ , IL-6, and transforming growth factor (TGF)- $\beta$  all are increased in both acute relapse patients and first-episode patients; this abnormal increase was abolished by antipsychotic treatment. On the other hand, IL-12, interferon- $\gamma$ , TNF- $\alpha$ , and soluble IL-2 receptor were found to be elevated and remained elevated following antipsychotic treatment,<sup>167</sup> suggesting that IL-1 $\beta$ , IL-6, and TGF- $\beta$  are good state markers. Furthermore, another study found increased IL-6 and TNF- $\alpha$  in first-episode psychotic patients. Linear regression showed that increased psychosocial stress predicted lower BDNF through an inflammation-mediated pathway and that the increased IL-6 correlated with reductions in BDNF and left hippocampal volume.<sup>168</sup>

Together, the studies above suggest that BDNF may underlie aspects of positive symptoms such as hyperactivity and cognitive dysfunction as well as negative symptoms associated with schizophrenia.

## BDNF and bipolar disorder

Bipolar disorder is a devastating psychiatric condition marked with severe mood symptoms, most notoriously by episodes of mania or hypomania typically followed by an episode of depressed mood. Lifetime prevalence stands between 1%–4%.<sup>169</sup> Genetic studies show bipolar disorder is highly heritable, explaining about 60%–85% of variance in risk.<sup>170</sup> Relatives of a bipolar sufferer have a significantly increased risk of developing bipolar disorder as well as unipolar major depression disorder.<sup>170,171</sup>

*BDNF* has been posited as a key candidate gene associated with the etiology of bipolar disorder. A meta-analysis of 14 studies found a significant association between the Val66Met allele and bipolar disorder.<sup>172</sup> A recent study

showed that serum BDNF levels in drug-free bipolar patients suffering either a manic or depressive episode were reduced compared with healthy controls.<sup>173</sup> This is in agreement with a meta-analysis that found reduced serum and plasma BDNF levels in both manic and depressive patients, with an association with the length of illness. It was also found that peripheral BDNF increased after treatment for acute mania, suggesting that BDNF can be a marker for mood episodes.<sup>174</sup> A recent study comparing BDNF levels in first major depressive episode patients suffering either from bipolar or major depression found that while both groups showed significantly reduced plasma BDNF, those suffering bipolar disorder had even lower BDNF levels than did the major depression patients.<sup>175</sup> However, other studies found either no decrease in plasma BDNF in patients compared with controls<sup>176</sup> or even an increase in plasma BDNF compared with controls.<sup>177</sup> One study found that improvement in symptoms resulting from quetiapine treatment was accompanied by increases in BDNF in patients with depressive episodes and decreases in BDNF in patients with manic or mixed episodes,<sup>178</sup> suggesting differential BDNF alteration according to polarity of disease, adding a layer of complexity in analyzing the role of BDNF.

Postmortem analysis found reduced BDNF mRNA expression in layer VI in the inferior temporal gyrus and layers V and VI of the superior temporal gyrus in patients with bipolar disorder, schizophrenia, or major depression disorder.<sup>179</sup> Hippocampal proBDNF levels were also found to be reduced in postmortem bipolar samples to a similar but slightly lesser degree than that of major depression disorder samples.<sup>180</sup> MRI revealed decreased gray matter in bipolar sufferers compared with controls, but there were no differences between Val66 versus Met66 allele carriers.<sup>181</sup>

Examining cytokine profiles in bipolar patients in the depressed, manic, and euthymic phases, Brietzke et al<sup>182</sup> found different state-dependent profiles. Manic phase was associated with increases in IL-2, IL-4, and IL-6 compared with controls; patients in depression phase exhibited an increase only in IL-6; euthymic patients show an upregulation in IL-4 only, suggesting that change in cytokine expression profile is a good state marker in bipolar disorder. Looking at early versus late-stage bipolar patients, it was found that BDNF was only reduced in the late stages of disease despite increased IL-6, IL-10, and TNF- $\alpha$  levels at the early phase of disease. A significant negative correlation was seen between BDNF and TNF- $\alpha$ , which continued to increase in the late stages of disease, whereas IL-6 and IL-10 decreased in late-stage patients.<sup>183</sup> However, it was found in adolescent bipolar

patients that a negative association exists between BDNF and IL-6,<sup>184</sup> suggesting negative influences of increased cytokine on BDNF signaling even in early phases of disease.

The evidence suggests that an important role is played by BDNF in mediating both the pathogenesis and symptom severity of bipolar disorder.

## Antidepressants and BDNF

In addition to its role in synaptic plasticity, the BDNF signaling pathway is now well known to interact with the serotonergic system at several different levels. A recent review by Homberg et al<sup>185</sup> suggests that alterations to the serotonin (5-HT) transporter in 5-HT transporter knockout rats reduced BDNF mRNA and protein expression in both the hippocampus and prefrontal cortex, and this reduction in BDNF may then alter 5-HT<sub>1A</sub> receptor signaling. In addition, we have shown an upregulation of BDNF protein in the hippocampus of 5-HT<sub>2C</sub> receptor knockout male mice,<sup>186</sup> but a decrease in BDNF protein and TrkB phosphorylation (activation) in the ventral hippocampus of 5-HT<sub>1A</sub> receptor knockout mice, and this was specific to female mice.<sup>187</sup> With this complex interplay between BDNF and the serotonin pathway in mind, it is not surprising then that BDNF is thought to play a role in mediating antidepressant drug effects.

BDNF seems to mediate the positive effect of several classes of antidepressants, including selective serotonin reuptake inhibitors, tricyclics, serotonin noradrenalin reuptake inhibitors, and monoamine oxidase inhibitors, which have been found to increase BDNF in patient serum, cortical astrocytes *in vitro*, and in the prefrontal cortex and hippocampus of animal models.<sup>77,188,189</sup> Gervasoni et al<sup>190</sup> found that not only was reduced BDNF in depressed patients increased following antidepressants, but in both instances BDNF negatively correlated with depression severity as measured by the Montgomery-Asberg Depression Rating Scale. Chen et al<sup>83</sup> also found increased BDNF immunoreactivity in the hilus, dentate gyrus, and supragranular zone of postmortem patients on antidepressants at the time of death compared with those who were not on antidepressants.

Rodent models allow closer dissection of the mechanism of antidepressants and further illuminate the importance of BDNF in mediating antidepressant effects. In rats, Nibuya et al<sup>191,192</sup> found that chronic but not acute treatment with various antidepressants including sertraline, desipramine, and tranylcypromine increased the gene expression of *BDNF* and TrkB in different subregions of the hippocampus, including the granule cell layer, CA1, and CA3; this effect was not found using nonantidepressant psychotropics such as

haloperidol and cocaine. Furthermore, chronic antidepressant treatment was also protective against the reduction of BDNF and TrkB induced by restraint stress. In forebrain BDNF-deficient mice, the antidepressant and learning-enhancing effects of desipramine were abolished.<sup>106,193</sup> Transgenic mice overexpressing the dominant negative truncated TrkB receptor TrkB.T1, which show reduced TrkB activation in the brain, are resistant to the effects of antidepressants,<sup>106</sup> whereas overexpression of TrkB led to resistance to depression-like behavior, with selective serotonin reuptake inhibitors unable to further increase this resistance.<sup>194</sup> TrkB agonists have been found to exert antidepressive effects in rodents,<sup>195</sup> indicating that TrkB signaling is necessary for the behavioral benefits of antidepressants.

## BDNF as a therapeutic target

A key question in the treatment of depression with antidepressants has been why it takes weeks for antidepressants to achieve beneficial effects when they are able to alter synaptic monoamine levels within a matter of hours. It has been theorized that this delay is due to the time required to achieve neuroadaptive changes<sup>196,197</sup> and that this action is mediated via BDNF.<sup>198–200</sup> It is a well-known phenomenon that fewer than half of patients treated with antidepressants derive any benefit.<sup>201</sup> Katsuki et al<sup>202</sup> found that the difference between responders and nonresponders to treatment with mirtazapine is the ability for the antidepressant to increase serum BDNF. Hence, other means of elevating BDNF is greatly sought. Infusion of BDNF directly into the hippocampus<sup>101</sup> or peripherally<sup>203</sup> produces antidepressant-like effects in mouse models. However, as a therapeutic or adjunctive treatment, peripherally administered BDNF is unsuitable due to: 1) the tumour promoting properties of BDNF;<sup>204</sup> 2) the limited ability of BDNF to cross the blood–brain barrier (which remains controversial); 3) poor bioavailability (due to enzyme degradation);<sup>205</sup> and 4) short half-life (within hours, therefore requiring multiple doses).<sup>206</sup> However, lifestyle alterations and diets including small molecules that can specifically activate the BDNF receptor are attractive candidates for potential therapeutic use.

## Environmental enrichment

As *BDNF* gene expression is triggered by neuronal activity;<sup>22</sup> enhancement of cognitive and sensory stimulation has been posited as a way to enhance BDNF expression. Much work has been done in rodent models – the first description of positive effects of environmental enrichment (EE) was made by Donald Hebb, who let his rats roam

free in his house and found that these rats performed better in problem-solving tests than rats kept in cages in the laboratory.<sup>207</sup> While the ingredients of an enriched environment can differ greatly between laboratories and studies, what it essentially involves is a housing condition that promotes and enhances sensory, cognitive, and motor stimulation relative to standard housing. This is typically achieved through group housing in large boxes with the addition of various objects like tunnels, nesting material, and running wheels to the habitat.<sup>208,209</sup>

Further investigations in rodents unearthed that environmental enrichment can lead to increased cerebral volume<sup>210</sup> as a result of increased cerebral cortical thickness, number of synapses and glial cells.<sup>211,212</sup> It has long been known that detracting of environmental stimulation, such as social isolation housing, increases stress and promotes depression-like behaviors.<sup>213,214</sup> Being the negative corollary, EE has been found to have the opposite effects – anxiolytic and antidepressant-like actions – in a variety of rodent models of psychiatric and neurologic disorders.<sup>215–220</sup> Enrichment promotes hippocampal cell proliferation and survival.<sup>221</sup> In fact, it has been found that adult neurogenesis is required to facilitate EE benefits to counter depressive-like behaviors induced by psychosocial stress in mice.<sup>222</sup> Furthermore, BDNF was seen as the intermediary of increased neurogenesis after EE, as *BDNF* heterozygous mice that did not show any increase in BDNF after EE did not show any increase in neurogenesis, unlike their wild-type counterparts that showed both an increase in BDNF and a two-fold increase in neurogenesis.<sup>223</sup> The positive behavioral effects of EE also correlate with increases in BDNF in the amygdala and hippocampus of rats.<sup>224</sup> *BDNF* heterozygote mice exhibited increased anxiety and altered nociception, which were corrected by enrichment<sup>225</sup> as well as increases in BDNF expression in the hippocampus.<sup>226</sup> Neuropathic pain is common in psychiatric diseases and this may be due to increased inflammation, which exacerbates nociceptive sensitivity.<sup>227</sup> EE has been shown to have immunomodulatory actions<sup>228</sup> that counteract inflammation, which, in conjunction with increasing BDNF, may offer a double-pronged beneficial effect in combating depression.

Due to the multifaceted nature of environmental enrichment, it is difficult to untangle the essential key elements of enrichment to allow efficient clinical translation. Systematic clinical studies looking at the equivalent of environmental enrichment are comparatively scant compared with those studying effects of pharmacological treatments. Evidence does suggest that complementary interventions that

foster social contact and mental and physical stimulation can have benefits to patients. A recent study found that the act of joining social groups had positive benefits on depression symptoms and decreased the risk of depression relapse in a dose-dependent manner.<sup>229</sup> Similarly, social networking benefited schizophrenia patients, with positive effects persisting long after implementation.<sup>230</sup> Gentle yoga intervention was seen to benefit women suffering depression by enhancing connectedness.<sup>231</sup> Likewise, patients who joined Argentine tango or meditation lessons showed a significant reduction on their depression measures.<sup>232</sup> Massage and yoga also showed anxiolytic and antidepressant effects in prenatally depressed women.<sup>233</sup> A review found an overall positive effect of massage treatment for depressed people despite large variations in effect size, most likely due to differences in the protocol used.<sup>234</sup> In schizophrenia patients, a recent meta-analysis did not find convincing benefits of yoga.<sup>235</sup> Little evidence is available on the effects of these therapies on BDNF expression.

More substantial studies have been performed in looking at music therapy. Psychodynamic music therapy has been found to reduce depression and anxiety symptoms<sup>236</sup> as well as altering frontotemporal electroencephalograph activities in patients.<sup>237</sup> A review concluded that chronic music listening can reduce depressive symptoms regardless of type of music preferred by the listener.<sup>238</sup> Systematic review of music therapy in schizophrenia patients found general positive benefits on various aspects of the disease, including global state, general mental state, depression, anxiety, and negative symptoms, but effects were inconsistent and variable due to variability in protocols.<sup>239</sup> Interestingly, rodent studies duplicated the effects of music observed in humans, with one study reporting that chronic exposure to a range of music, including vocal and instrumental (both Oriental and Western), had anxiolytic effects, which were accompanied by increases in BDNF mRNA and protein expression in the prefrontal cortex, hippocampus, and amygdala.<sup>240</sup> Interestingly, the elevation of BDNF was seen in *BDNF* (Met/Met) transgenic and wild-type mice but not in *BDNF* heterozygous mice. Chronic exposure to slow rhythm music in mice has also been shown to increase BDNF levels in the hypothalamus<sup>241</sup> and hippocampus as well as to enhance learning in the passive-avoidance task.<sup>242</sup> As music has been demonstrated to stimulate areas of the brain associated with emotionality, such as the hypothalamus, hippocampus, amygdala, and prefrontal cortex,<sup>243</sup> the evidence from rodent studies suggests that BDNF may be the mediator of the benefits of music on psychiatric disorders.

Cognitive behavioral therapy (CBT) is a widespread behavioral approach in the treatment of psychiatric disorders. It has been found to show some efficacy in the treatment of depression<sup>244</sup> and schizophrenia.<sup>245</sup> A meta-analysis however, showed dubious efficacy of CBT on schizophrenia but more robust effects on the treatment of major depression, both in reducing symptoms and preventing relapse.<sup>246</sup> This opacity of CBT effect is due to a lack of controls available in studies looking at CBT, unlike the rigorous double-blind, placebo-controlled experiments used to scrutinize the efficacy of drugs.

Physical activity has always been considered an important part of an enriched life, and the majority of EE paradigms include running wheels. Studies have suggested that in fact physical exercise is the key element mediating positive benefits of EE on psychiatric disorders. Rodent studies have indeed found that the element of running is crucial to increasing neurogenesis and mature BDNF levels in the hippocampus, whereas enrichment without running wheels did not achieve these changes in female mice.<sup>247</sup> A recent systematic study examining the different constituents of EE, separating out running, environmental complexity, and the social interaction elements, showed that running is the principal neurogenic stimulus.<sup>248</sup> Complex environment, despite not increasing neurogenesis, did increase depolarization-associated c-Fos expression in the granule cell layer and reduced stress-induced plasma corticosterone levels, which occurred regardless of running. These results suggest that while environmental complexity and social interaction have certain positive influences, physical exercise might be the prevailing mediator of BDNF upregulation and subsequent benefits.

## Exercise

Exercise has been shown to have positive effects on depression,<sup>249–251</sup> with levels of physical activity negatively correlated with depression symptoms.<sup>252</sup> It was found that within a population of patients with major depression, those who are physically active show milder symptoms compared with more sedentary sufferers.<sup>253</sup> Blumenthal et al<sup>254</sup> found that group-supervised and individual home-based aerobic exercise were equally effective in getting patients into remission as was sertraline across 16 weeks of treatment, with milder side-effects in the exercise groups. Echoing this, a study in rats found chronic running-wheel housing increased BDNF mRNA level to a similar extent as chronic antidepressant treatment. Furthermore, a joint treatment of citalopram with running wheel resulted in a greater rise in

BDNF mRNA than either treatment alone,<sup>255</sup> suggesting an additive or adjunctive effect.

Exercise has also been shown to impart benefits to schizophrenia patients, reducing both positive and negative symptoms,<sup>256–258</sup> improving memory and increasing hippocampal volume,<sup>259</sup> as well as increasing serum BDNF levels.<sup>260</sup> Exercise was found to be associated with lower depressive symptoms but more manic symptoms in bipolar disorder.<sup>261</sup> Evidence of a positive influence of exercise on schizophrenia and bipolar disorder are more scant compared with studies in depression.<sup>262</sup> A recent study looked at the effect of a 4-week exercise regimen in patients with major depression or schizophrenia matched for age, sex, education, and disease duration. Despite the relatively short duration, the authors found benefits in both groups, with reduced depressive symptoms and anxiety in the depressed patients and reduced negative symptoms in schizophrenia patients. Both groups showed increases in cognitive function and increased subjective ratings on quality of life.<sup>263</sup> The efficacy of physical exercise is difficult to gauge due to inconsistencies in regimens, types of exercises, and duration and frequency of exercises undertaken.

While the exact mechanism underlying the benefits of exercise is not understood, BDNF has been posited as a participant. Neeper et al<sup>264</sup> first reported that acute exercise can increase hippocampal and caudal neocortical BDNF mRNA in rats. Following from this, evidence is found to show that similarly, a single bout of exercise can induce an acute if transient increase in serum or plasma BDNF in depressed patients.<sup>265,266</sup> Subsequent training can augment this response, suggesting a mechanism to long-lasting benefits.<sup>267</sup> However, differences in effect are seen in different regimens. For example, 3 months of endurance training at ~70% maximum heart rate and ~65% maximal oxygen uptake for an hour a day in healthy subjects was found to increase basal serum BDNF levels but to have no influence on exercise-induced BDNF levels.<sup>268</sup> The same study found that a similar regimen in mice consisting of 5 weeks of 1-hour-long treadmill running, 5 days a week, led to an increase in hippocampal but not cortical BDNF mRNA expression. Another study instituted a 10-week strength-training regimen, after which no increase in either baseline or postexercise serum BDNF or in cognition was seen.<sup>269</sup> Similarly, a 12-week training intervention of either moderate endurance training or high-load strength training, despite having positive endurance and strength augmentation, respectively, did not increase baseline plasma BDNF.<sup>270</sup> Compared with this, a 5-week regimen of a mixture of moderate to intense endurance exercise induced in healthy



young men an increase in both basal and exercise-induced plasma BDNF. This study also examined a cohort of athletes whose plasma BDNF was found to be about three times higher than that in untrained subjects.<sup>271</sup>

Ferris et al<sup>272</sup> found that postexercise increases in serum BDNF were only achieved with a 30-minute bout of intense riding exercise at 10% above ventilator threshold and not after riding at 20% below the ventilator threshold. A recent study examined time as well as intensity of exercise and found that to achieve maximal postexercise increases in serum BDNF, a long duration (40 minutes as opposed to 20 minutes) of intense aerobic exercise (80% of heart rate reserve as opposed to 60%) was the most effective.<sup>273</sup> This evidence suggests a certain level of exercise intensity, duration, and chronicity is required to achieve reliable elevation of BDNF that might translate to therapeutic benefits. Consistent with this, it was found in a large cohort of women that those who reported a history of vigorous exercise had the lowest odds of depression symptoms, compared with more sedentary subjects.<sup>274</sup> For patients treated for depression, regular exercise after cessation of initial pharmacotherapy or exercise regimen intervention showed benefit at follow-up months later, with the amount of exercise per week correlating negatively with Hamilton Rating Scale for Depression score and positively with the probability of partial remission.<sup>275,276</sup> A very recent study examined effects of implementing a 3-month exercise regimen (3 sessions per week; 45 minutes per session) of aerobic exercise (80% maximum heart rate) versus control exercise (consisting of stretching and low-impact exercise such as catching and throwing balls) in outpatients with major depression. The study failed to find any increase in BDNF after the regimen, nor any change in hippocampal volume. However, this study suffered from poor adherence, with an average of only one attendance to exercise sessions per week instead of the planned three, making it hard to draw conclusions as to the effects of exercise on BDNF.<sup>277</sup>

In support of the clinical evidence, BDNF is found to be upregulated by exercise and environmental enrichment in rodents, contributing to beneficial effects such as induction of cell survival and proliferation and dendritic development, leading to augmented cognitive outcomes.<sup>278–282</sup> Fang et al<sup>283</sup> found that treadmill exercise in rats attenuated reductions in BDNF and phosphorylated TrkB in the hippocampus caused by chronic immobility stress. A recent study found that exercise, via running wheel, in rats compensated for high-fat diet-induced memory deficits measured in the two-way avoidance task and that this correction was associated with increases in BDNF expression in the CA3 subfield of the dorsal hippocampus.<sup>284</sup> Intensity of exercise was also a factor, with higher intensity

resulting in increased levels of BDNF in the hippocampus as well as increased cell proliferation in rats.<sup>285</sup> In mice too, a 6-week voluntary running regimen in male C57Bl/6J mice reduced anxiety-like behaviors and increased gene expression of *BDNF*.<sup>286</sup>

The positive effects of exercise may be affected by myriad other factors. A Japanese study found that cycling for 30 minutes at 60% maximal oxygen uptake induced an increase in serum BDNF in 18/33 subjects, which, when aggregated, was not significant. The authors attributed the inconsistency to lifestyle and environmental idiosyncrasies.<sup>287</sup> Another recent study conducted in Japan found that during 9 weeks of intense military training, despite increased physical activities as shown by serum levels of muscle enzymes creatine phosphokinase and lactate dehydrogenase, decreased plasma BDNF, which recovered 4–5 days after cessation of military training.<sup>288</sup> This study attributed this decrease to reduced sleep quality as well as to stress and fatigue. This suggests that any benefits of exercise may be compromised by stress and fatigue. Interestingly, a study reported that the increase in BDNF resulting from cycling was negated in those cycling near a major road where air pollution was high.<sup>289</sup> Agreeing with this, a recent Chinese study examining the effects of closure of a highly polluting coal-burning power plant found that babies born to mothers after the closure of the plant had reduced polycyclic aromatic hydrocarbons–adducts and increased BDNF compared with those born before the closure, highlighting the impact of pollution on developmental BDNF expression.<sup>290</sup> Babaei et al<sup>291</sup> indeed found that a 6-week endurance training regimen increased serum BDNF only in healthy subjects and not in subjects with metabolic syndrome. Metabolic syndrome, linked with unhealthy diet and lifestyle, is very prevalent in psychiatric illness<sup>292</sup> and may be a factor preventing obvious benefits of exercise intervention. These studies suggest a multitude of environmental and lifestyle factors can influence the effect of exercise on BDNF expression.

## Healthy diet

In 1988 Christensen and Christensen<sup>293</sup> reported that the ratio of dietary saturated to polyunsaturated fat was a major predictor of outcome for schizophrenia. Animal model studies have shown that levels of BDNF, which are reduced in schizophrenia, have been shown to be reduced in the hippocampus of rats fed a high-fat, refined-sugar diet.<sup>294</sup> This effect of a high-fat diet on hippocampal BDNF expression has recently been replicated and was also shown to disrupt performance in active-avoidance memory tasks. Furthermore, exercise recovered hippocampal BDNF and memory performance in rats

fed a high-fat diet, suggesting that a combination of healthy diet and exercise are highly effective in regards to memory performance.<sup>284,295</sup> A high-fat diet has also been shown to induce anxiety-like behaviors (burrowing and spontaneous wheel running), depressive behavior (forced-swim test), and impairments in fear-conditioning responses alongside reduced hippocampal and cortical BDNF.<sup>296–298</sup>

Offspring derived from mothers fed a high-fat diet show increased anxiety with an increase in BDNF expression in the dorsal hippocampus, suggesting significant developmental effects of a high-fat diet.<sup>299</sup> In line with the report from Christensen and Christensen on the ratio of saturated to polyunsaturated fats, perinatal and postweaning diets rich in omega-3 polyunsaturated fatty acids have been shown to increase cortical BDNF, TrkB, and nerve growth-factor expression in C57Bl/6 mice.<sup>300</sup> This would suggest that while high-fat diets rich in saturated fats may reduce BDNF, altering memory performance, anxiety, and depressive behaviors, foods rich in polyunsaturated fats increase BDNF and may therefore be beneficial to mental health. However, once again there are inconsistencies in the literature, with other reports showing no effect of omega-3 on brain BDNF expression, but increases in serum BDNF in a ketamine-induced rat model of schizophrenia.<sup>301</sup>

Overall, it is evident that a high-fat diet reduces BDNF expression and can affect learning and memory as well as anxiety-like and depressive-like behaviors. What is promising is that the effects of a high-fat diet can be reversed by exercise and other dietary supplements. Below we will discuss a variety of dietary supplements that have been shown to increase BDNF expression and improve mental health.

### Dietary flavonoids

There is a wealth of literature that describes the cognitive-enhancing effects of a group of phytochemicals known as flavonoids. A variety of different flavonoids have been shown to increase hippocampal BDNF and neurogenesis, reduce neurotoxic and neuroinflammatory cell damage/loss, and increase brain blood flow, making flavonoids prime therapeutic targets for neurodegenerative disorders.<sup>302</sup> Probably the most consistent finding is the positive effect of flavonoids on BDNF expression. Given the role of BDNF in mental health disorders (described above), more recent studies have explored the use of flavonoids in animal models of psychiatric disorders.

### 7,8-dihydroxyflavone (7,8-DHF)

One of the most commonly studied flavonoids is 7,8-dihydroxyflavone (7,8-DHF). 7,8-DHF is a naturally

occurring flavonoid from the plant *Godmania aesculifolia*, which binds with a high affinity to the TrkB receptor to initiate dimerization and autophosphorylation.<sup>303</sup> Following characterization of 7,8-DHF, one of the first behavioral studies reported antidepressant-like effects; with oral administration of 7,8-DHF shown to activate TrkB in the mouse hippocampus and to reduce immobility in the forced-swim test and tail-suspension test.<sup>304</sup> In addition, deficits in learned fear in neocortical *BDNF* knockout mice were rescued by a peripheral intraperitoneal injection of 7,8-DHF.<sup>305</sup> This same group showed beneficial effects of 7,8-DHF on appetitive and aversive memory domains in neocortical *BDNF* knockout mice.<sup>306</sup> Another group was able to show that systemic 7,8-DHF administration (5 mg/kg administered intraperitoneally) was able to activate TrkB receptors in the amygdala and enhanced fear acquisition and extinction.<sup>307</sup> 7,8-DHF has therefore been suggested as a potential therapeutic for post-traumatic stress disorder.<sup>308</sup>

Acute 7,8-DHF in striatal slices potentiated dopamine release.<sup>309</sup> In addition, treatment with 7,8-DHF improved deficits in prepulse inhibition (a measure of sensorimotor gating) in mice after administration of methamphetamine.<sup>310</sup> Furthermore, 14 days of 7,8-DHF treatment increased TrkB phosphorylation at multiple sites, promoted hippocampal synaptic plasticity, and rescued spatial working memory in a MK-801-induced animal model of schizophrenia.<sup>311</sup> Thus there is great potential for the use of 7,8-DHF as an adjunctive treatment for the cognitive and attention impairments associated with schizophrenia.

### Other flavonoids

In a recent study exploring the effects of a range of flavonoids on synthesis and secretion of neurotrophic factors, 33 flavonoids were assessed in cultured rat astrocytes. The isoflavones calycosin and genistein and the flavanol isorhamnetin were particularly strong activators of BDNF expression,<sup>312</sup> while baicalein had no effect and icariin (a flavonoid from the Chinese medicinal herb *Epimedium*) produced only mild increases in BDNF. In animal models, baicalein elevated BDNF-phosphorylated cAMP (adenosine 3'5' cyclic monophosphate)-response element binding protein signaling in the hippocampus and prevented spatial learning and memory deficits following whole brain irradiation in C57Bl/6 mice.<sup>313</sup> However, others have shown no effect of baicalein on spatial memory in the Morris Water Maze.<sup>314</sup> Nobiletin (a dietary flavonoid isolated from citrus fruit), as well as blueberry powder (*Vaccinium corymbosum*) and icariin have all been shown to increase hippocampal BDNF and improve spatial memory in rodents.<sup>315–318</sup> Soy isoflavone supplementation, including

daidzein, genistein and glycitin, have also shown beneficial effects on spatial memory in human<sup>319</sup> and rodent studies,<sup>320</sup> and this coincided with an increase in hippocampal BDNF expression in the rodent study.

Flavonoids also show antidepressant effects in several animal models. In a rat model of depression induced by chronic unpredictable mild stress, baicalein recovered hippocampal BDNF expression and extracellular-signal-regulated kinase phosphorylation and significantly reduced immobility time in the forced-swim test and tail-suspension test.<sup>321</sup> Nobiletin, as well as astilbin (a tea extract) and icariin, have also shown antidepressant properties,<sup>322–324</sup> which were proposed to be regulated by activation of the BDNF signaling pathway.<sup>323–325</sup> Phytoestrogens such as flaxseed (secoisolariciresinol diglycoside) and Tualang Honey show antidepressant effects, also thought to be regulated via BDNF.<sup>326,327</sup>

### Polyphenols

Interestingly, a recent study analyzing the effects of phenolic acids on spatial memory found that in comparison to alcohol-matched controls, aged rats receiving Champagne wine for 6 weeks showed improved spatial working memory and hippocampal and cortical BDNF protein.<sup>328</sup> Other polyphenols such as curcumin from turmeric, *Epigallocatechin gallate* from green tea, and olive polyphenols have also been shown to increase BDNF expression and alleviate depressive symptoms.<sup>329,330</sup> Theanine (a component of green tea and black tea) has also been shown to increase levels of BDNF and has been suggested as a therapeutic for a wide range of mental health disorders, including schizophrenia and depression.<sup>331</sup>

### Conclusion

Research evidence points to abnormal BDNF signaling being a common and vital participant in the aetiology and pathophysiology of many psychiatric disorders including depression, schizophrenia, and bipolar disorder. To increase BDNF levels in patients is therefore a necessary goal of any treatment. To combat the inefficiency of current treatment methods, more attention should be focused on holistic approaches to achieve this goal, as BDNF is proven to have dynamic responses to environmental influences.

Hippocrates, the father of medicine, has never been more prescient than when he remarked “walking is man’s best medicine” and “let food be thy medicine and medicine be thy food.” We have reviewed evidence in the literature that suggests that lifestyle alterations such as increased social interaction, mental stimulation, exercise, and a healthy diet

including low fat and increased flavonoids and polyphenols can have positive effects in psychiatric diseases via increasing BDNF. This “lifestyle medicine” is already advocated in developed countries for the prevention and treatment of major health issues such as obesity<sup>332</sup> and should be promoted not as a replacement but as an adjunct and iatrogenic to conventional treatments for psychiatric disorders. Advocating these lifestyle changes can potentially curtail and prevent pathogenesis in those vulnerable to developing psychiatric disorders due to environmental or genetic reasons by maintaining healthy levels of BDNF in the face of adverse circumstances. In patients with reduced BDNF, these regimens can likely complement and enhance pharmacological treatments, resulting in faster, fuller, and longer-lasting recovery of BDNF.

### Disclosure

The authors report no conflicts of interest in this work.

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