Depression Overview

Brain Derived Neurotrophic Factor:

Brain derived neurotrophic Factor (BDNF) may play an important role in expression and treatment of depression and other related mood disorders (Duman RS, Monteggia LM. *Bio Psychiatry* 2006;12:1116-27). BDNF is a growth factor found in the brain and peripheral tissue of humans. Its primary role is to help neurons grow and survive. High levels of BDNF are found in the hippocampus, and have been suggested to mediate, in addition to learning and memory, mood.

Robert Duman, PhD, Yale University School of Medicine, provided preclinical and clinical evidence on the role of BDNF (as well as other neurotrophic factors) in major depressive disorder (MDD). The Neurotrophic Hypothesis argues that depression is, in part, a result of a reduction in neurotrophic (eg, BDNF) support in the brain. Reduced BDNF levels and the accompanying decrease in BDNF activity may cause or exacerbate structural and/or neurochemical abnormalities in the brain. The net result of these changes may be a significant decrease in mood.

Supporting this claim is the relationship between stress, depression and BDNF. Stress has been shown to accentuate depression (Gold P, Chrousos GP. *Mol Psychiatry* 2002;7:254-75). The stress response is also correlated with atrophy in the hippocampus, decreases in neurogenesis and decreases in levels of BDNF in the hippocampus (Duman R. *Neuromolecular Med*2004;5:11-25). These reductions are reversed by the administration of antidepressants (Nibuya M, Morinobu S, Duman RS. *J Neurosci* 1995;15:7539-7547). Clinically, researchers have also noted decreases in hippocampal volume corresponding to the duration of depression.

There are also reports that administering antidepressants to animals that have been chronically stressed increase levels of BDNF in the hippocampus (Duman RS, Monteggia LM. *Bio Psychiatry* 2006;12:1116-27). That is, antidepressants reverse the effects of stress in the context of BDNF. Experimentally administering BDNF into animals, either systemically or directly into the brain, has similar effects to that of antidepressants in animal models of anxiety and depression (eg, in the Forced Swim, Tail Suspension, Learned Helplessness and Novelty Suppressed Feeding Test). Thus, the actions of antidepressants seem intimately linked to BDNF, along with its actions, in the brain.

There are also other neurotrophic factors in the brain may also be involved in depression. Of particular interest is vascular endothelial growth factor (VEGF). Antidepressants also affect VEGF levels by increasing this neurotrophic factor in the brain (Warner-Schmidt JL, Duman RS. *Proc Natl Acad Sci USA*, 2007;104:4647-52). The ultimate result of this action is an increase in the proliferation of neural cells. As such, although BDNF remains highly important, other neurotrophic factors are also being implicated in MDD and the effects antidepressants have on this disorder.

In another report on the topic, Armando Piccinni, MD, University of L'Aquila, Italy, elaborated on the clinical findings of BDNF and MDD. Plasma and serum levels of BDNF in 15 drug-free patients suffering from major depression, as well as in 15 healthy controls, were measured over the course of twelve months of

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antidepressant treatment. Compared to the control group, levels of BDNF were significantly lower in the depressed patients at the time of their baseline measurement ($p < 0.05$). Following the initiation of antidepressant treatment, BDNF levels remained lower than controls despite the improvement of depression-related symptoms. From this data it was concluded that while BDNF may not be intimately linked to the degree of depression, it may remain a strong "non-specific" trait marker for depression.

In a poster presented by Kyung Hyun Yu, MS, Samsung Biomedical Research Institute, Seoul, responsiveness to the antidepressant, fluoxetine, was evaluated in a sample of 56 patients with late-onset depression who had a Val66Met polymorphism (ie, the gene encoding for BDNF) and 34 normal volunteers. A responder was defined as anyone having a change in the Hamilton Depression Rating score (HAM-D) ≥ 50 following 6 weeks of treatment.

The results from this study suggest that those patients deficient in BDNF showed the least improvement in depression rating as compared to normal controls following fluoxetine treatment. Though these results were non-significant ($p=0.089$), Dr. Yu suggests that these findings are encouraging and that much more research in this area should be conducted.

Continuation and Discontinuation of Venlaxafine and its Metabolite in Refractory Depressed Patients:

Patrick Mbaya, MD, University Hospital of South Manchester, UK, presented his data on the efficacy, safety and serum levels of the serotonin and norepinephrine reuptake inhibitor, venlaxafine XL and its active metabolite o-desmethylvenlafaxine (ODV) in refractory depressed patients.

In a cross-sectional design, 50 patients with refractory MDD were assessed over the course of 12-months treatment with a high dose of venlaxafine XL. All patients had been on and failed or began to fail to respond to other antidepressants prior to their inclusion in the study. The primary outcome measures included Global Assessment of Functioning (GAF) scores, a self rating scale of mood and general fatigue, side effects, cardiovascular function, blood pressure, electrocardiograms and serum levels of venlaxafine and its metabolite ODV.

The results indicate that there was a significant relationship between GAF scores and the dose of venlaxafine XL ($p<0.05$). Specifically, GAF scores improved with administration of venlaxafine XL. Serum levels of venlaxafine and ODV correlated with increased dose and improvement of mood ($p<0.05$). These results indicate that the therapeutic effect of venlaxafine XL is due to the drug, as well as its metabolite ODV; the author suggests that this provides evidence that ODV is active in the context of treating depression. No major side effects, including cardiovascular events, occurred or were correlated with venlaxafine or its metabolite ODV.

Though this drug does show efficacy in treating patients with MDD who are refractory, Dr. Mbaya cautioned that venlaxafine is not recommended for everyone. Further recommendations include the close monitoring of patients on a high dose of venlaxafine, including assessments of blood pressure, elctrocardiograms and electrolytes. Overall, Dr. Mbaya notes, venlaxafine is safe and effective, and its treatment effects appear to be due to both the drug and its active metabolite ODV.