

## FROM CHEMICAL IMBALANCES TO NEUROGENESIS?

By David Antonuccio, Ph.D.

Dept. of Psychiatry and Behavioral Sciences

University of Nevada School of Medicine

For years we have been hearing that antidepressants work because they fix a serotonin chemical imbalance that causes depression despite a lack of evidence that depressed patients are deficient in serotonin (Leo & Lacasse, 2005). The lack of support for the serotonin deficiency theory may be one reason physicians don't typically order lab tests of serotonin levels in depressed patients. The serotonin theory has been so effectively marketed that psychologists have often felt pressure to refer their clients for an antidepressant evaluation despite strong evidence that psychosocial treatments are just as effective as medications in the short term and appear to offer more enduring benefits (Antonuccio et al., 2002).

The recent press release from the European College of Neuropsychopharmacology (2008) on neurogenesis in the adult brain, suggests that the discredited chemical imbalance theory of depression may be morphing into the neurogenesis theory of depression, i.e., the notion that there is a deficiency of neurons in the hippocampus of the brain and that antidepressants work by helping the brain generate new neurons thought to affect mood (e.g., Malberg et al., 2000; Santarelli et al., 2003).

While the neurogenesis hypothesis may be a reasonable hypothesis, there are at least two issues that must be answered to understand how neurogenesis might affect depression. One is to explain what role neurogenesis might play in the positive response of many depressed patients who are randomly assigned to receive a placebo, a group that does about 82% as well as those randomly assigned to receive an antidepressant (Kirsch et al., 2002). Another issue has to do with whether neurogenesis is always a good thing and whether it might even be harmful under some circumstances. For neurogenesis to be positive, it would have to occur in just the right locations and not in unwanted locations in the brain.

The ECN article notes that physical exercise, hormonal influences, and learning can also cause neurogenesis and gliogenesis (formation of specific glial support cells that are critical for survival of neurons in the brain). The ECN article also notes that while antidepressants appear to be able to stimulate similar cell genesis, "so far the existence of a causative relationship remains speculative".

There have been open label studies with no placebo control group (e.g., Vermitten et al., 2002) showing an increase in hippocampal volume in patients receiving paroxetine for PTSD. Had there been a control group, it is possible, perhaps even likely, that patients who improved in the placebo condition or a psychosocial comparison condition would have shown similar brain changes. There are several studies showing that psychosocial interventions (like CBT or IPT) cause comparable metabolic brain changes in those who improve (e.g., Brody et al., 2001; Martin et al., 2001; Kennedy et al., 2007)

As noted, many activities may cause what is thought to be mostly positive neurogenesis (e.g., jogging, learning Spanish, good nutrition). But neurogenesis could be just as likely a cause for concern as celebration, especially if it is induced by an ingested chemical with unknown long-term risks. For example, antidepressants have been linked to cancer in human epidemiological studies (e.g. Bahl et al., 2003 ; Cotterchio et al., 2000; Halbreich et al., 1996; Moorman et al., 2003; Sharpe et al., 2002). There are also controlled animal studies showing that antidepressants can be carcinogenic (a form of cell genesis). We have been able to establish carcinogenesis in animals because we humans consider it ethical to expose animals to suspected carcinogens in controlled studies. Such designs are obviously not considered ethical in humans so we are left with epidemiological studies in humans which are essentially correlational in nature and don't prove causation (though some of them are as well controlled as is possible in an epidemiological study). Therefore, human epidemiology studies do not

necessarily prove that antidepressants are carcinogenic in humans (as an aside, a similar lack of controlled human trials permitted the tobacco industry to claim for decades that tobacco had not been proven to cause cancer in humans) but they make it clear that this possibility cannot be ruled out in humans. The odds ratio of developing cancer in those patients taking antidepressants has been as shown to be as high as 7 times more than someone who does not take them in some of these epidemiological studies.

In conclusion, the neurogenesis theory of antidepressants must be considered unproven and open to scientific skepticism until more controlled trials in humans are available to address the issues outlined here. Unfortunately, that will not prevent the drug industry from using neurogenesis theory as a marketing tool, just as was done so effectively with the chemical imbalance theory.

Antonuccio, D.O., Burns, D., & Danton, W.G. (2002). Antidepressants: A triumph of marketing over science? **Prevention and Treatment, 5**, Article 25. Available on the World Wide Web: <http://www.journals.apa.org/prevention/volume5/pre0050025c.html>.

Bahl S., Cotterchio, M., & Kreiger, N.. (2003). Use of antidepressant medications and the possible association with breast cancer risk. A review. *Psychotherapy and Psychosomatics*, 72, 185-194.

Brody et al. (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: Preliminary findings. *Archives of General Psychiatry*, 58, 631-640.

Cotterchio, M., Kreiger, N., Darlington, G., & Steingart, A. (2000). Antidepressant medication use and breast cancer risk. *American Journal of Epidemiology*, 151, 951-957.

Halbreich, U., Shen, J., & Panaro, V. (1996). Are chronic psychiatric patients at increased risk for developing breast cancer? *American Journal of Psychiatry*. 153, 559-560.

Kennedy et al. (2007). Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *American Journal of Psychiatry*, 164, 778-788.

Martin et al. (2001). Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. *Archives of General Psychiatry*, 58, 641-648.

Moorman, P.G., Grubber, J.M., Millikan, R.C., & Newman, B. (2003). Antidepressant medications and their association with invasive breast cancer and carcinoma in situ of the breast. *Epidemiology*, 14, 307- 314.

Sharpe, C.R., Collet, J.P., Belzile, E., Hanley, J.A, & Boivin, J.F.. (2002). The effects of tricyclic antidepressants on breast cancer risk. *British Journal of Cancer*, 86, 92-97.

European College of Neuropsychopharmacology (2008). Neurogenesis in the adult brain: The association with stress and depression. Presented at the 21<sup>st</sup> Congress of the European College of Neuropsychopharmacology 2008, Barcelona, Spain

Leo, J. & Lacasse, J. (2005). Serotonin and depression: A disconnect between the advertisements and the scientific literature. *PLoS Med*, 2 (12), e395.

Kirsch, I., Moore T.J., Scoboria, A., & Nicholls, S.S. (2002), The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment. 5:Article 23*. Available at: <http://journals.apa.org/prevention/volume5/pre0050023a.html>

Malberg, J.E. et al., (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of Neuroscience*, 20, 9104-9110.

Santarelli, L. et al., (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, 301, 805-809.

Vermetten E, Douglas-Palumberi H, Vythilingam M. Effects of paroxetine on memory and the hippocampus in PTSD. Program and abstracts of the XII World Congress of Psychiatry; August 24-29, 2002; Yokohama, Japan. Symposium S-27-2.