

# New Explanation of Bipolar Disorder in Women: Addiction to Endogenous Testosterone

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Bipolar Disorder, DHEA and Testosterone in Women: Addiction to Endogenous Testosterone

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I suggest this disorder may be caused by an inappropriate combination of stimulation caused by testosterone and dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). DHEAS is the large supply of this hormone in the blood from which the active molecule, DHEA, is converted. These hormones are connected with mania, depression, and menstrual problems.

Manic episodes have been connected with the luteal phase of the cycle (Biological Psychiatry 1993; 33: 194–203). Free testosterone levels were significantly higher in premenstrual syndrome than controls in the luteal phase and DHEA levels were significantly higher in PMS in the luteal phase (Psychoneuroendocrinology 1992; 17: 195–204). A later study also reported increased DHEA and free testosterone in the luteal phase (Gynecological Endocrinology 2004; 18: 79–87). DHEA levels are significantly lower during the luteal phase in "premenopausal healthy women" (Psychological Medicine 2004; 34: 93–102). "Early-onset menstrual dysfunction" has been reported more often in women with bipolar disorder and women with depression compared to healthy controls (Journal of Clinical Psychiatry 2006; 67: 297–304). The opposite side of this hypothesis is that low DHEA has been connected with depression (Archives of General Psychiatry 2005; 62: 154–162). When DHEA is low these individuals feel depression.

Testosterone is high in mania (European Archives of Psychiatry and Clinical Neuroscience 2003; 253: 193–6). Increased testosterone has been connected with early puberty and obesity in girls (Journal of Clinical Endocrinology & Metabolism 2006; February 21). The metabolic syndrome is "alarmingly high" in bipolar disorder (Bipolar Disorder 2005; 7: 424–30). DHEA is being considered as a treatment for metabolic syndrome (Journal of the American Medical Association 2004; 292: 2243–8).

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A common treatment for bipolar disorder, valproate, actually causes similar problems to testosterone. Valproate increases weight gain, testosterone, and DHEAS (Epilepsia 2004; 45: 1106–15 and New England Journal of Medicine 1993; 329: 1383–8). Valproate increases testosterone during the luteal phase (Journal of Affective Disorders 2005; 89: 217–25) and contributes to menstrual abnormalities (Bipolar Disorders 2005; 7: 246–59). However, valproate is effective in bipolar disorder. The effects of valproate may be used to "tease" apart the connection of DHEA and testosterone in mania and depression in bipolar disorder.

Valproate increases DHEAS. This means that valproate is reducing conversion of DHEAS to DHEA. I suggest a combination of high testosterone and high DHEA over-stimulate the brain and cause "mania." One treated with valproate will possibly experience the effects of excessive testosterone but not the stimulating effects of testosterone and excessive DHEA simultaneously. Valproate reduces this mania by reducing available DHEA. Lithium also reduces DHEA. In rats, lithium reduces DHEA and DHEA levels (International Journal of Neuropsychopharmacology 2004; 7: 71–5). When this combination of androgens declines, "depression" occurs. I suggest this may fit type 1 bipolar disorder. Type 2 may represent a state of low DHEA which results in depression interrupted periodically by the combination of simultaneous testosterone with a reduced DHEA level.

"The prevalence of the metabolic syndrome in patients with bipolar disorder is alarmingly high? and The prevalence of obesity is even higher than the already very high prevalence that has been estimated for the US general population." (Bipolar Disorders 2005; 7: 424–30). "The odds of having the MBS [metabolic syndrome] were 3.8 times higher for every quartile increase in bioavailable testosterone in girls with PCOS?" (J Clin Endocrinol Metab 2006; 91: 492–7). Bipolar disorder is increased in women with polycystic ovary syndrome (PCOS) (J Affect Disord 2006 Feb 15; Klipstein and Goldberg, ahead of print at this writing).

The Mechanism: Maybe Bipolar Disorder is Testosterone Addiction

It has been my hypothesis that DHEA is involved in all growth and development and maintenance of all tissues. My principal hypothesis is that DHEA optimizes replication and transcription of DNA. At its most basic level, I suggest cells absorb DHEA for growth. As cells form masses of cells, cell surface area is reduced so availability of DHEA is reduced as a consequence. This shifts the cellular mode from growth to differentiation. That is, lots of DHEA enables the cell to replicate. As DHEA amounts are reduced, areas of DNA are activated according to their ability to react to reduced levels of DHEA. That is, DHEA is used for reduced areas of DNA activation as DHEA is reduced. This is differentiation; tissue formation.

I suggest the addiction mechanism is controlled by the levels of DHEA that are available for the neuronal tissues that are involved. A "drug" attaches to a part of the brain. This reduces available receptors which respond appropriately. I suggest this triggers recruitment of DHEA by

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these brain parts for this purpose. Hence, DHEA levels are increased, the tissues are activated by the extra DHEA. When the drug is used again, the process is reinitiated, therefore, eventually requiring more drug. This is also how I explain growth and development. The involvement of DHEA with drugs of addiction has been reported. "These results showed that DHEAS prevented the development of morphine tolerance and dependence and suggested that the attenuating effects of DHEAS might result from the regulation of c-fos mRNA expression, which is possibly involved the signaling activation of ERK, but not of cAMP pathway." (Behav Brain Res 2004; 152: 243–5). This is a "rebound" mechanism, that is, receptors are closed by drugs of abuse which causes the rebound which stimulates DHEA.

Testosterone has this effect, that is, testosterone is reinforcing: "These results indicate that testosterone at high doses causes central autonomic depression, which may be a factor in deaths during self-administration. As well, the depressive effects of large quantities of testosterone may be mediated, at least in part, by an opioidergic mechanism." (Neuroscience 2005; 130: 971–81). In the foregoing quotation, an overdose of testosterone shuts down the nervous system just as does an overdose of morphine. Testosterone does produce an addictive effect: "These data support the hypothesis that testosterone is reinforcing." (Psychopharmacology (Berl) 2004; 171: 298–305). "We conclude that pharmacologic testosterone activates select steroid-sensitive brain regions, as well as midbrain areas involved in reinforcement of commonly-abused drugs." (Psychoneuroendocrinology 2006; 31: 237–49). "In particular, substance abuse, especially cocaine abuse or dependence and alcoholism, is a far more common phenomenon in the population of patients with bipolar affective disorder than in the general population. There is evidence that bipolar disorder patients with substance abuse have a worse course of illness." (J Clin Psychopharmacol 1992; 12 (1 Suppl): 17S–22S).

I suggest the individuals who exhibit bipolar disorder are addicted to testosterone. That is, when testosterone is released in these individuals, perhaps at ovulation to stimulate libido, their brains over-react with an abundance of DHEA. This shows as extra DHEA during the luteal phase of the cycle. This mechanism begins a cycle of DHEA use that results in over-stimulation of the brain until the adrenal glands are exhausted. This exhaustion of DHEA availability would be similar to that of cocaine or methamphetamine use. "Chronic cocaine self-administration induced elevation in brain DHEA, its sulfate ester, DHEAS, and pregnenolone. The increased brain DHEA following cocaine self-administration may serve as a compensatory protective mechanism geared to attenuate the craving for cocaine. Such anti-craving activity is further enhanced by DHEA treatment before and during cocaine self-administration." (Eur Neuropsychopharmacol 2005; Maayan, et al., in press at this writing).

The mania is due to overstimulation of testosterone with DHEA and the depression is caused by exhaustion of the adrenal glands.

