2019

The Use of DHEA in the Treatment of Depression

Bryan Tipton
University of North Dakota

The Use of DHEA In the Treatment of Depression

by Bryan Tipton PA-S and Contributing Author Daryl Sieg, PA-C, Assistant Professor University of North Dakota
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

Abstract

Dehydroepiandrosterone (DHEA) and its sulfated ester (DHEA-S) are important pre-hormones that also have direct neurohormonal effects on the central nervous system. Over the last twenty years, data have revealed that serum DHEA peaks in a person's mid-20s and steadily declines throughout their lifetime. In addition, women tend to have lower values than men. This is of note because lower serum values tend to be correlated with increased risk of depression, worse depressive symptoms, and increased risk of relapse into depression. A review of literature concerning DHEA's age related values, its association with depression, and its use in the treatment of depression was performed. It was found that supplementation with DHEA appears to alleviate the symptoms of depression even though a dose-response relationship nor a clear mechanism have been established. For providers who choose to use DHEA to alleviate the symptoms of depression, they should consider that even the best studies concerning its effectiveness are underpowered, it lacks FDA approval, and, if given as a supplement, may lack any active ingredient. Despite those warnings, the AAPA, CANMAT, and Dynamed all agree that evidence exists as to its efficacy.

Introduction

•Major depressive disorder, depression, and dysthymia are often overlooked and undertreated conditions in the primary care field. This exists for a variety of reasons: social stigma, provider experience, concerns over medication side-effects, and cost of treatment, to name a few. Considering that in very many cases treatment of depression can be the difference between life and death for a patient, using every tool available seems imperative. Dehydroepiandrosterone and its sulphate ester (DHEA(-S)), a physiological marker and predictor for depression, especially in the elderly, is established despite some conflicting studies. The purpose of this paper is to ascertain if DHEA supplementation is a viable option for the treatment of depression in comparison to current standards of treatment with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), especially considering DHEA's low cost and low side effect profile.

Statement of the Problem

•Primary care providers who do choose to treat major depressive disorder, depression, and dysthymia seem to limit their pharmacological options to only the SSRIs, SNRIs, and other prescription-only antidepressants. DHEA's low side effect profile, comparatively low cost, and availability may make it an ideal adjunct or replacement to current therapy. But is it effective? Because of DHEA's known age related decline, this paper will focus on adults only.

Research Question

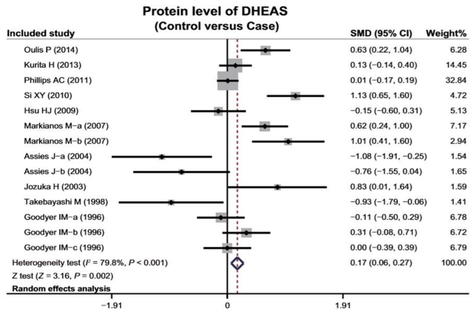
• For patients older than 30 who have major depression, depressive symptoms, or depressive episodes, does supplementation with DHEA improve symptoms or lessen episodes of depression?

Literature Review

•Bloch, Schmidt, Danaceau, Adams, & Rubinow (1999) was one of the first double blind, randomized, placebo-controlled studies of the effect of DHEA administration on the effects of depression. Though statistically significant reductions in depressive indexes as well as in itemized indicators of depression were demonstrated with promising *p* values—many at 0.01—the study is likely underpowered. Because the ANOVA data have been withheld, the effect size cannot be calculated; however, because this study only has an N of 15 participants, the effect size to reach a power of 0.8 would need to be *quite* large. Bloch et al.'s colleagues Schmidt et al. (2005) attempted to recreate and expound on some of the findings of Bloch et al. with larger N and with varying doses. Schmidt et al.'s study found similar confidence values in their double-blind, randomized, placebo-controlled study across indicators and indexes of depression; though, this time with an N of 46, the power of successive studies are growing. Differing in Schmidt et al.'s study were doses increasing up to 450 mg with washout periods in between. Finding a dose response relationship between DHEA and depression would have further cemented DHEA's effectiveness in treating depression; however, this link was not established. It is not until Piexto, Cheda, Nardi, Veras, & Cardoso (2014) that we see a meta-analysis of many of the existing, albeit underpowered, studies deliver consistent results. Though Piexto et al. (2014) did not attempt to group studies providing a single large N value due to differing methodologies between studies, the consistency of results is beginning to suggest that DHEA is effective in the treatment of depression despite all studies being likely underpowered.

Author	Year of Publication	N	Gender M/F	Age	Population	Type of Study	Daily DOSE	Treatment Time	Instruments	Results
Wolkowitz *et al* [8]	1997	6	3/3	Average: NI Range: 51 to 72	Depression	Clinical Trial	30 to 90 mg.	4 weeks	HAM-D, BDI, BH, Depression Rating Scala Global.	The use of DHEA improved scores on depression tests. One patient receiving pro-longed treatment im-proved but 72% on a scale.
Wolkowitz *et al.* [18]	1999	22	12/10	Average:44 (SD = 0) Range: 33 to 54	Depression	Randomized Clinical Trials	30 to 90 mg.	6 weeks	HAM-D	DHEA was associated with a significantly greater reduction in depression compared to placebo.
Bloch *et al.* [9]	1999	15	12/3	Average: 50 (SD = 3.8) Range: 47 to 63	Depression	Randomized Clinical Trials	90 to 450 mg.	6 weeks	HAM-D, BDI, CDS	A robust effect of DHEA on mood was observed compared to placebo. At the end of 6 weeks 60% of patients responded to treatment.
Schmidt *et al.* [19]	2005	46	23/23	Average: 50 (SD = 5.8) Range: 42 to 63	Depression	Randomized Clinical Trials	90 to 450 mg.	6 weeks	HAM-D, BDI, CDS, CES-D	The use of DHEA was associated with signifi-cant improvement in HAM-D scores and the CES-D.

Meta-analysis results of exogenous DHEA administration in depressed populations.
Peixoto, C., Cheda, J., Nardi, A., Veras, A., & Cardoso, A. (2014). The effects of dehydroepiandrosterone (DHEA) in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses: A systematic review. *Current Drug Targets, 15*, 901-914. https://dx.doi.org/10.2174/1389450115666140717111116



Forest plots for differences between DHEA-S levels in patients with depression and without.
Qiang, H., Zhang, S., Liu, F., Zhang, Y., Zhu, D., & Zang, Y. (2015). Clinical significance of decreased protein expression of dehydroepiandrosterone sulfate in the development of depression: A meta-analysis. *Journal of Affective Disorders, 174*, 416-423. https://dx.doi.org/10.1016/j.jad.2014.11.051

Discussion

- The presented data seem conclusive about the life-span and gender changes of DHEA and DHEA-S—that DHEA declines with age after peaking in our twenties, and typically men have more serum DHEA than women. However, attempts to correlate the existing data to depression, risk of depression, severity of symptoms, and remission of symptoms are less clear. Though, a trend among many smaller, under-powered studies is emerging: i.e. that lower DHEA is associated with risk of depression in the elderly, that a lower DHEA response to depression is associated with worse, or intractable depression, that higher levels of DHEA are protective against, or might signal remission of depression.
- Data suggests a mechanism to hormonally correct depression by raising levels of DHEA, but that impairment by physiologically low levels of DHEA, or low levels due to advanced age, might hinder this mechanism. Bolstering this idea is evidence that when depression is treated even with SSRIs and SNRIs, serum DHEA rises (Hough et al., 2017). The limits of this response appear to be personal and highly variable as no dose response mechanism for DHEA and depression has been identified by the literature. Specifically, Bloch et al. (1999) and Schmidt et al. (2005) found no increasing benefits with doses as high as 400 mg, whereas other studies only tested—and had success with—doses as high as 90 mg.

Applicability to Clinical Practice

- There is agreement among AAPA (Slawson, 2005), CANMAT (Ravindran et al., 2016), and Dynamed (2018) that exogenous DHEA may be useful in the treatment of depression. However, the lack of powerful studies in the data leaves us with a few questions yet about its best practice use. What dose does the literature support? What serum level is important? Is it effective only as a sole agent? Are its side effects acceptable?
- Because there has yet to be a dose-response relationship established, starting with the lowest tested dose—30 mg—and titrating up to the largest dose—400 mg (Piexto et al. 2014)—is reasonable. Indeed, because of the lack of dose-response relationship any, even the lowest, prescription of DHEA might prove effective. Furthermore, because of a lack of a dose-response relationship, in DHEA therapy for depression we are not attempting to achieve an effective serum level and if symptomatic alleviation is our goal, serum testing is moot. At least one study (Hough et al., 2018) has recommended that DHEA might be efficacious as co-therapy for treatment of depression.
- Best practice for prescriptions of DHEA might include prescribing as a sole agent for mild to moderate depression or when the patient finds the side effects of other therapy intolerable. Its use as a sole agent might be more effective in elderly men. It could be prescribed as co-therapy with more traditional antidepressants. Above all, treatment with DHEA should be done so with its particular side effects in mind, as well as the added risk of increased suicidality. Also of key clinical importance is DHEA's lack of FDA approval for the treatment of depression, meaning every provider who prescribes DHEA for depression should be prepared to plainly state why they did not treat with FDA approved drugs. Finally, if a provider chooses to treat depression with DHEA they should note that while it is available over the counter as a supplement, only pharmaceutical DHEA is sure to contain DHEA; supplements routinely fail to demonstrate they contain any claimed active ingredient. With this in mind, the aim of this paper was to provide another tool for the primary care provider to manage the sometimes life-threatening scourge of depression.

References

Bloch, M., Schmidt, P., Danaceau, M., Adams, L., & Rubinow, D. (1999). Dehydroepiandrosterone treatment of midlife dysthymia. *Society of Biological Psychiatry, 45*, 1533-1541. https://dx.doi.org/10.1016/S0006-3223(99)00066-9

DynaMed Plus. (2018, August 9). Depression alternative treatments. Ipswich, MA: EBSCO Information Services. Retrieved from http://www.dynamed.com/topics/dmp~AN~T474293/Depression-alternative-treatments#Dehydroepiandrosterone

Hough, C., Lindqvist, D., Epel, E., Denis, M., Reus, V., Bersani, F.,... Mellon, S. (2017). Higher serum DHEA concentrations before and after SSRI treatment are associated with remission of major depression. *Psychoneuroendocrinology, 77*, 122-130. https://dx.doi.org/10.1016/j.psyneuen.2016.11.035

Peixoto, C., Cheda, J., Nardi, A., Veras, A., & Cardoso, A. (2014). The effects of dehydroepiandrosterone (DHEA) in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses: A systematic review. *Current Drug Targets, 15*, 901-914. https://dx.doi.org/10.2174/1389450115666140717111116

Qiang, H., Zhang, S., Liu, F., Zhang, Y., Zhu, D., & Zang, Y. (2015). Clinical significance of decreased protein expression of dehydroepiandrosterone sulfate in the development of depression: A meta-analysis. *Journal of Affective Disorders, 174*, 416-423. https://dx.doi.org/10.1016/j.jad.2014.11.051

Ravindran, A., et al. (2016). Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 5. Complementary and alternative medicine treatments. *The Canadian Journal of Psychiatry/Le Revue Canadienne de Psychiatrie, 61(9)*, 576-587. https://dx.doi.org/10.1177/0706743716660290

Schmidt, P., Daly, R., Bloch, M., Smith, M., Danaceau, M., Simpson, L.,... Rubinow, D. (2005). Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Archives of General Psychiatry, 62*, 154-162. https://dx.doi.org/10.1001/archpsyc.62.2.154

Slawson, D. (2018). DHEA effective for midlife-onset depression. *American Family Physician, 71(11)*, 2173-2174. Retrieved from: http://www.aafp.org/afp/2005/0601/p2173a.html