OVERVIEW

1) Class

a) This drug is a member of the following class(es):

Androgen
Endocrine-Metabolic Agent
Nutriceutical
Protectant, Dermatological

2) Contraindications

a) Prior hypersensitivity to dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEAS)
b) Patients with any form of cancer or at risk of cancer; dehydroepiandrosterone has promoted growth of some tumor-types (eg, breast cancer, prostate cancer)
c) Pregnancy
d) Breastfeeding period

DOSING INFORMATION

Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms

Dehydroepiandrosterone
Dehydroepiandrosterone, Micronized
Dehydroisoandrosterone
DHEA
DHEA - Dehydroepiandrosterone
Prasterone

Adult Dosage

Normal Dosage
Oral route

Aging

a) Some evidence of improved well-being was seen with doses of 50 milligrams (mg) once daily in men and women 40 to 70 years of age in a small study (Morales et al, 1994a).

Depression
a) In one 6-week study, an oral dose of 30 milligrams (mg) once daily for the first two weeks was given, followed by an increase to 30 mg twice daily for 2 additional weeks, then 30 mg three times daily for the 2 final weeks (Wolkowitz et al, 1999).

**Erectile dysfunction**

a) Dehydroepiandrosterone 50 milligrams (mg) once daily has been administered for up to 6 months (Reiter et al, 1999).

**Hereditary angioedema**

a) Oral doses of 25 to 50 milligrams (mg) have been given either daily, every other day, or every three days (Koo et al, 1983).

**Menopausal symptom**

a) Oral doses of 50 milligrams (mg) once daily for up to 6 months have been reported to reduce vasomotor/psychological symptoms in a small study (Stomati et al, 2000b). Lower doses (25 mg daily) have produced beneficial lipid changes in postmenopausal women, including increases in high-density lipoprotein (HDL) cholesterol (Lasco et al, 2001a).

**Systemic lupus erythematosus**

a) A dose of 200 milligrams (mg) daily for up to 6 months has been administered in most studies (van Vollenhoven et al, 1995a; van Vollenhoven et al, 1994a; van Vollenhoven et al, 1999). In one 6-month trial, doses were titrated gradually from 50 mg daily initially to a maximum of 600 mg daily (Barry et al, 1998a).

**Topical application route**

**Menopausal symptom**

a) Dehydroepiandrosterone 10% topical cream has been applied daily to the thigh area in postmenopausal women for up to one year. The topical dose was based on amounts to achieve dehydroepiandrosterone plasma levels of 20 to 30 nanomols/liter (nmol/L), which correlated to 3 to 5 grams (g) daily (Labrie et al, 1997a).

**IMPORTANT NOTE**

1) Insufficient documentation or other factors have limited adequate evaluation of the efficacy of dehydroepiandrosterone in any potential indication; at present it is not recommended over conventional, known-effective treatments. The following doses/routes are based on observations of at least potential efficacy in small studies. For all indications, confirmation of benefits in larger, well-controlled trials is required.

2) The long-term effects of dehydroepiandrosterone supplementation are unknown. However, the risk of breast cancer in women (including
postmenopausal women) and prostate cancer may be higher during dehydroepiandrosterone long-term supplementation.

GENDER EFFECTS

1) Pharmacokinetic data suggest that lower doses may be indicated in women (Frye et al, 2000c; Horowitz, 2000b). However, these data are mainly from older subjects and were based on higher than usual doses; variability in plasma levels has also been observed. At present, specific dose recommendations based on gender cannot be made.

PHARMACOKINETICS

Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established in any potential indication.

a) ENDOGENOUS LEVELS

1) Normal endogenous plasma concentrations of dehydroepiandrosterone are generally in the range of 2 to 4 nanograms/milliliter (ng/mL) in healthy men, whereas values in women are similar or slightly higher; levels of dehydroepiandrosterone sulfate (DHEAS) are usually 2 to 6 micrograms (mcg)/mL in men, and this range is lower in women (Frye et al, 2000b; Friess et al, 2000; LaMontagna et al, 2001; Stomati et al, 2000; Meno-Tetang et al, 2001; Horowitz, 2000a).

2) Endogenous levels decline with aging. In older men and women (mean 69 years), average endogenous levels of dehydroepiandrosterone sulfate were 1.1 mcg/mL and 0.25 mcg/mL, respectively, in a small study (Frye et al, 2000b).

B) Time to Peak Concentration

1) ORAL: dehydroepiandrosterone, 1.5 to 2 hours; dehydroepiandrosterone sulfate, 2 to 3 hours (Meno-Tetang et al, 2001; Arlt et al, 1998; Frye et al, 2000b).

a) Plasma-concentration data for dehydroepiandrosterone and dehydroepiandrosterone sulfate during dehydroepiandrosterone supplementation have varied, due at least in part to the different formulations used.

2) Young Women

a) In healthy young women (mean age, 30 years) receiving dehydroepiandrosterone 200 mg daily, mean peak plasma levels (corrected for endogenous) of dehydroepiandrosterone and dehydroepiandrosterone sulfate on day 29 (given with prednisone) were 1.3 mcg/dL (13 ng/mL) and 942 mcg/dL (9.4 mcg/mL), and occurred in 2 hours and 2.4 hours, respectively; corresponding trough levels at this time were 9 ng/mL and 3 mcg/mL (Meno-Tetang et al, 2001).
b) After single 50-mg oral doses in young women (mean, 23 years) in another study (Arlt et al, 1998), mean peak levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate were observed in 2.5 hours (26 nmol/L) and 2.9 hours (15 micromols/L), respectively.

3) Older Men and Women

a) Dehydroepiandrosterone and dehydroepiandrosterone sulfate levels were consistently higher in elderly women (mean, 69 years) than elderly men (mean, 69 years) in one well-conducted study; reasons for this difference are unclear, although differences in body weight are likely contributory (Frye et al, 2000b). In this study, mean peak plasma dehydroepiandrosterone concentrations (times to peak levels) after single 200-mg oral doses of micronized dehydroepiandrosterone, were 22 ng/mL (1.3 hours) and 27 ng/mL (1.4 hours) in elderly men and women, respectively; endogenous levels before administration were similar. Endogenous levels of dehydroepiandrosterone sulfate (DHEAS) were 3.7 times higher in men than women, and after single 200 mg dehydroepiandrosterone doses, mean dehydroepiandrosterone sulfate levels increased 5-fold in men (to 7 mcg/mL) and 21-fold in women (to 7.5 mcg/mL) relative to baseline levels; times to peak dehydroepiandrosterone sulfate levels were shorter in women (2.1 versus 3.3 hours). Plasma levels (and times to peak levels) of both dehydroepiandrosterone and its sulfated metabolite did not change significantly in either group during two weeks of daily administration (200 mg), indicating lack of accumulation. Trough (24-hour) levels of dehydroepiandrosterone averaged 4 to 6 ng/mL in men and 5 to 7 ng/mL in the women; corresponding values for dehydroepiandrosterone sulfate were more variable (1 to 4 mcg/mL in men, 0.2 to 3.5 mcg/mL in women).

4) SUBLINGUAL, CAPSULES: time to peak levels unavailable.

a) In HIV-infected patients receiving 50 mg daily sublingually, dehydroepiandrosterone sulfate levels increased from 5.2 micromols/L at baseline to 19.8 micromols/L at 16 weeks (Piketty et al, 2001).

5) TRANSDERMAL, GEL: time to peak levels unavailable.

a) Following 5 days of transdermal (abdominal) application of 5 g of a 1% dehydroepiandrosterone gel (corresponding to about 50 mg dehydroepiandrosterone daily) in healthy men, dehydroepiandrosterone plasma levels had increased from 13 nmol/L (baseline) to 20 nmol/L; levels of dehydroepiandrosterone sulfate increased from 4.5 to 5.8 micromols/L (Sulcova et al, 2000).

C) Area Under the Curve

1) With oral dehydroepiandrosterone in doses of 200 mg once daily, mean AUC values on day 29 (corrected for endogenous) for dehydroepiandrosterone and dehydroepiandrosterone sulfate were 11.5 mcg x hr/dL and 9722 mcg x hr/dL, respectively, in healthy young women (mean age, 30 years) (Meno-Tetang et al, 2001). After single 50-mg oral doses of dehydroepiandrosterone in young women
(mean, 23 years) in a further study, respective AUC(0-12) values for dehydroepiandrosterone and dehydroepiandrosterone sulfate were 176 nmol/L x hr and 122 micromols/L x hr; corresponding values after single 100-mg doses were 318 nmol/L x hr and 195 micromols/L x hr (Arlt et al, 1998).

2) During administration of dehydroepiandrosterone 200 mg daily (micronized) to older men and women (mean, 69 years), AUC values for dehydroepiandrosterone were higher in the women (approximately 225 ng x hr/mL versus 180 ng x hr/mL); AUC values for dehydroepiandrosterone sulfate after these doses were similar in each sex (about 100 mcg x hr/mL). AUC values did not change significantly with multiple versus single doses (Frye et al, 2000b).

**ADME**

**Absorption**

**A) Bioavailability**

1) Some investigators suggest good oral bioavailability (Yen et al, 1995); however, absolute data are lacking. Bioavailability can be expected to vary among nutritional supplement formulations.

**Distribution**

**A) Distribution Sites**

1) Protein Binding

a) dehydroepiandrosterone 10% to 20%; dehydroepiandrosterone sulfate 80% to 90% (Longcope, 1996).

2) OTHER DISTRIBUTION SITES

a) CEREBROSPINAL FLUID, extent unknown.

1) Dehydroepiandrosterone penetrates the blood-brain barrier. CSF levels of dehydroepiandrosterone sulfate have ranged from 0.2% to 5% of corresponding plasma levels; higher concentrations of dehydroepiandrosterone sulfate have been found in brain tissue compared to CSF (Friess et al, 2000; Barrett-Connor et al, 1999).

**B) Distribution Kinetics**

1) Distribution Half-Life

a) 17 minutes (intravenous) (Meno-Tetang et al, 2001).

2) Volume of Distribution

a) dehydroepiandrosterone, 17 to 38 L (Bird et al, 1978; Longcope, 1996); dehydroepiandrosterone sulfate, about 9 L (Gant et al, 1976).

1) Data are limited; confirmation is required.
Metabolism

A) Metabolism Sites and Kinetics

1) INTESTINE

a) Dehydroepiandrosterone is converted (sulfated) to dehydroepiandrosterone sulfate ester in the intestine after oral doses by sulfotransferases (Arlt et al, 1998; Meno-Tetang et al, 2001; Sulcova et al, 2000).

2) LIVER/OTHER TISSUES, extensive (Arlt et al, 1998; Frye et al, 2000; Meno-Tetang et al, 2001)

a) Dehydroepiandrosterone is converted (sulfated) to dehydroepiandrosterone sulfate ester in the intestine (oral doses) and liver and other tissues (oral, transdermal, or parenteral doses) by sulfotransferases (Arlt et al, 1998; Meno-Tetang et al, 2001; Sulcova et al, 2000). There is some interconversion of dehydroepiandrosterone sulfate to dehydroepiandrosterone, although this substantially favors formation of the sulfate ester (Meno-Tetang et al, 2001).

b) Dehydroepiandrosterone and dehydroepiandrosterone sulfate are converted to androgens and estrogens in peripheral tissues via several enzymes (eg, 3-beta-hydroxysteroid dehydrogenase, 5-alpha reductase, aromatase, 17-beta-hydroxysteroid dehydrogenase) (Arlt et al, 1998; Dean, 2000c; Davidson et al, 2000; Barrett-Connor et al, 1999).

c) Dehydroepiandrosterone undergoes hepatic 17-alpha- and 17-beta-hydroxylation; dehydroepiandrosterone sulfate undergoes 16-alpha hydroxylation (Frye et al, 2000b; Davidson et al, 2000). Cytochrome P450 (CYP)-3A4 is involved in the hepatic metabolism of both steroids; activity of this isoform is higher in women, which may contribute to the lower dehydroepiandrosterone sulfate levels observed in women (Frye et al, 2000b).

B) Metabolites

2) Androsterone sulfate (active) (Bird et al, 1978).
3) Estradiol (active) (Schwarz, 1990; Stomati et al, 2000).
4) Estriol (active) (Schwarz, 1990).
7) 7-Oxo-prasterone (active) (Davidson et al, 2000).

a) 3-Acetyl-7-oxo-prasterone is under investigation as an alternative to dehydroepiandrosterone for potential dehydroepiandrosterone indications (Davidson et al, 2000); it purportedly lacks androgenic activity.

a) Like dehydroepiandrosterone, it remains controversial whether pharmacologic effects are direct or secondary to conversion to androgens, estrogens, other metabolites (eg, 7-oxo-prasterone) (Davidson et al, 2000)), or a combination of these processes.


Excretion
A) Kidney

1) Renal Excretion (%)

a) 51% to 73% (intravenous dehydroepiandrosterone sulfate) (Zumoff & Bradlow, 1980).

1) Based on total excretion (including all metabolites) following intravenous administration of labeled dehydroepiandrosterone sulfate.

Elimination Half-life
A) Parent Compound

1) ELIMINATION HALF-LIFE

a) young women, 8 to 11 hours; elderly men, 5 to 7 hours; elderly women, 7 to 12 hours (Meno-Tetang et al, 2001; Frye et al, 2000b; Arlt et al, 1998).

1) Half-life values have varied somewhat, depending upon gender, age, whether values were for endogenous dehydroepiandrosterone or following exogenous administration, and possibly dose. The clinical relevance of these differences with respect to exogenous administration is doubtful.

a) Normal Men - Endogenous

1) A short half-life of endogenous dehydroepiandrosterone has been reported (about 2 hours (Frye et al, 2000).

b) Young Women - Supplementation

1) In young women receiving exogenous dehydroepiandrosterone, half-life values for dehydroepiandrosterone have been approximately 8 hours after 50 or 100 mg (single doses) and 11 hours after 200 mg daily (multiple doses) (Meno-Tetang et al, 2001; Frye et al, 2000b; Arlt et al, 1998).

c) Elderly Men - Supplementation

1) In elderly men receiving dehydroepiandrosterone supplementation, half-life values for dehydroepiandrosterone were approximately 5 hours after
doses of 50 or 100 mg (single-dose) and 7 hours after 200 mg (single or multiple doses) (Frye et al, 2000b).

d) Elderly Women - Supplementation

1) In elderly women receiving 200-mg doses, the elimination half-life of dehydroepiandrosterone progressively declined, from about 12 hours after the first dose to 9 hours on day 8, and to 7 hours on day 15 (Frye et al, 2000b).

B) Metabolites

1) young women, 12 to 13 hours; elderly men, 11 to 25 hours; elderly women, about 25 hours (Meno-Tetang et al, 2001; Frye et al, 2000b; Arlt et al, 1998).

a) Half-life values have varied somewhat, depending upon gender, age, and possibly dose. The clinical relevance of these differences is doubtful.

1) Young Women - Supplementation: In young women receiving exogenous dehydroepiandrosterone, half-life values for dehydroepiandrosterone sulfate have been approximately 13 hours after 50 or 100 mg (single doses) and 12 hours after 200 mg daily (multiple doses) (Meno-Tetang et al, 2001; Frye et al, 2000b; Arlt et al, 1998).

2) Elderly Men - Supplementation: In elderly men receiving dehydroepiandrosterone supplementation, half-life values for dehydroepiandrosterone sulfate were approximately 11 to 13 hours after doses of 50 or 100 mg (single-dose), and 20 to 25 hours after 200 mg (single or multiple doses) (Frye et al, 2000b).

3) Elderly Women - Supplementation: In elderly women receiving 200-mg doses, the elimination half-life of dehydroepiandrosterone sulfate was relatively constant after single or multiple dosing (24 to 27 hours) (Frye et al, 2000b).

CAUTIONS

Contraindications

A) Prior hypersensitivity to dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEAS)
B) Patients with any form of cancer or at risk of cancer; dehydroepiandrosterone has promoted growth of some tumor-types (eg, breast cancer, prostate cancer)
C) Pregnancy
D) Breastfeeding period

Precautions
A) Patients at risk of breast cancer in women (including postmenopausal women) and prostate cancer; risk may be higher during dehydroepiandrosterone long-term supplementation
B) Patients with hypercholesterolemia or ischemic heart disease (HDL lowering has occurred during dehydroepiandrosterone therapy)
C) Patients with or a history of psychiatric disorders (risk of exacerbation)
D) The risk of mania may be increased during concomitant use with antidepressants (tricyclic or SSRIs) and/or alcohol, or with high doses or in patients with a history of mood disorders
E) Liver disease or renal impairment (pharmacokinetic data lacking)

**Adverse Reactions**

**Cardiovascular Effects**

**Cardiovascular finding**

1) Benign premature atrial contractions and occasional premature ventricular contractions occurred in a 55-year-old man after administration of dehydroepiandrosterone 50 mg daily for 2 weeks. Six months later dehydroepiandrosterone was reinitiated with recurrence of these arrhythmias within 36 hours. On each occasion, dehydroepiandrosterone was discontinued and arrhythmias were controlled by beta-blockers (propranolol, atenolol) (Sahelian & Borken, 1998).

**Dermatologic Effects**

**Dermatological finding**

1) Endocrinologic-related cutaneous manifestations in women have included oily skin, ACNE, facial hirsutism, and enhanced perspiration odor; these have occurred with variable frequency (Morales et al, 1998; Gebre-Medhin et al, 2000; Labrie et al, 1997; Lasco et al, 2001; Davidson et al, 2000a; Barry et al, 1998).

2) ACNEIFORM DERMATITIS was seen in about half of women receiving dehydroepiandrosterone 200 mg daily for treatment of systemic lupus erythematosus (SLE) (van Vollenhoven et al, 1995; van Vollenhoven et al, 1994).

3) Mild HIRSUTISM developed in 2 of 10 women with SLE receiving dehydroepiandrosterone 200 mg/day (with concomitant prednisone) (van Vollenhoven et al, 1994).

**Endocrine/Metabolic Effects**

**Endocrine finding**

1) Significant increases in estrogens and particularly androgens, with attendant adverse effects, can occur during dehydroepiandrosterone therapy/supplementation. Acne, oily skin, facial hirsutism, hair loss, MOOD CHANGES, voice deepening, enhanced perspiration odor, and other signs of masculinization have been reported with variable frequency in women (Morales et al, 1998; Gebre-Medhin et al, 2000; Labrie et al, 1997; Lasco et al,
2001; Davidson et al, 2000a; Barry et al, 1998). Facial acne was observed to clear in one woman with continued supplementation (Morales et al, 1998). None of these effects has been clearly dose-related.

**Metabolic finding**

1) Although beneficial reductions in total and LDL cholesterol have been observed during dehydroepiandrosterone supplementation in some clinical studies, this has not been confirmed in others. Potentially deleterious reductions in HDL cholesterol, at times significant, have also been reported in various patient groups (men and women) (Morales et al, 1998; Morales et al, 1994; Villareal et al, 2000a; Mortola & Yen, 1990b). The HDL-lowering effect is likely due to increased androgenicity, and is probably dose-related. With use of low doses in postmenopausal women, one study reported increases in HDL cholesterol, as well as beneficial changes in other lipid parameters (Lasco et al, 2001).

**Hepatic Effects**

**Liver finding**

1) No significant changes in transaminases or other hepatic function tests were seen during long-term use (eg, 6 months) in some studies (Morales et al, 1998; Villareal et al, 2000a).

2) One case of hepatitis has been reported in a patient with high pretreatment antinuclear antibody (ANA) titers (Buster et al, 1992). Causality is uncertain.

**Psychiatric Effects**

**Mania**

1) Manic reactions during dehydroepiandrosterone therapy (50 to 500 mg daily) have been described in at least three case reports (Dean, 2000b; Pies, 2000). Symptoms began after 2 weeks to 2 months of supplementation in cases providing these data; psychotic features accompanied one case. Two patients had no history of psychiatric disorders (including the patient with psychotic-like symptoms), whereas the third had a history of bipolar disorder and was also receiving sertraline and abusing alcohol. In all cases, withdrawal of dehydroepiandrosterone and therapy with sodium valproate or divalproex (with haloperidol in the patient with psychotic symptomatology) resulted in improvement of symptoms.

2) There was no apparent association with patient age (31 to 68 years) in these cases. Risk factors for development of mania/psychosis are considered to be higher doses, combined use with antidepressants (tricyclics or selective serotonin-reuptake inhibitors) or alcohol or benzodiazepines, young patients (20 to 30 years, due to peaking endogenous dehydroepiandrosterone levels), and cytochrome P450 polymorphisms (poor metabolizers) (Dean, 2000b).

**Renal Effects**
Kidney disease
1) No significant changes in renal function tests were observed during long-term use (eg, 6 months) in some studies (Morales et al, 1998; Lasco et al, 2001; Villareal et al, 2000a).

Urogenital finding
1) No change in endometrial thickness was observed during 6 months of oral treatment in one study involving early and late postmenopausal women; uterine bleeding was also absent during this period (Stomati et al, 2000a).

Other
Carcinogen effect
1) dehydroepiandrosterone is capable of enhancing tumor growth; it has been associated with promotion of growth of BREAST CANCER in women and PROSTATE CANCER (Davidson et al, 2000a; Jones et al, 1997; Stoll, 1999; Skolnick, 1996a).

Drug Interactions

Drug-Drug Combinations
Acetophenazine
1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725
micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Carbamazepine

1) Interaction Effect: reduced effectiveness of carbamazepine
2) Summary: Dehydroepiandrosterone (DHEA) in a single case report was noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999c). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992c). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If carbamazepine is being used for manic
symptoms, concomitant use of dehydroepiandrosterone (DHEA) may cause a return of symptoms. Patients with a personal or family history of bipolar disorder should be advised to avoid DHEA use.

7) Probable Mechanism: proserotonergic activity of dehydroepiandrosterone may predispose patients to manic episodes; dehydroepiandrosterone is a precursor to androgenic steroids, which in high doses may precipitate mania.

8) Literature Reports

a) A 68-year-old male with no documented psychiatric history initiated dehydroepiandrosterone (DHEA) 100 milligrams (mg) daily and increased the dose to 200 to 300 mg daily for 6 months. Within 3 months, family members noted the onset of odd behavior with prominent symptoms of agitation, delusional thinking, decreased sleep and appetite, and spending sprees. The patient was not taking any prescribed medication but did ingest alcohol in amounts up to 1 case of beer daily. Another 3 months elapsed, leading to involuntary inpatient admission secondary to rapid, loud, pressured speech with grandiose thoughts. At admission, the patient reported that he had decreased alcohol intake to 2 beers daily due to family concerns about his behavior changes. There was no family history of bipolar disorder. Urinary drug screen was negative. Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient’s behavior and sleep patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdrawal symptoms. The patient was discharged with follow-up care from his primary care physician with a diagnosis of substance-induced mood disorder (Markowitz et al, 1999b).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid
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**Chlorpromazine**

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**Chlorprothixene**

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial
improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

Citalopram

1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA
with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports
a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

Clozapine
1) Interaction Effect: reduced effectiveness of clozapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992h). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992h). Patients being treated with clozapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and clozapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA)
blood levels may reduce responsiveness to clozapine

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992g).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992g).

Conjugated Estrogens

1) Interaction Effect: increased risk of estrogenic adverse effects

2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women
Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.

3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.

7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids
8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively (Mortola & Yen, 1990).

Escitalopram

1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar
disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.

7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels
8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

Esterified Estrogens

1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women (Mortola & Yen, 1990a). Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.

3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of
dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.

7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids

8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 176.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively (Mortola & Yen, 1990).

**Estradiol**

1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women (Mortola & Yen, 1990a). Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.
7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and
8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively (Mortola & Yen, 1990).

Estradiol Cypionate

1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women (Mortola & Yen, 1990a). Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.
7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids
8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment
Estropipate
1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women (Mortola & Yen, 1990a). Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.
7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids
8) Literature Reports

 Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively (Mortola & Yen, 1990).

Ethynyl Estradiol
1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has
increased endogenous estrogen levels in postmenopausal women (Mortola & Yen, 1990a). Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids (Mortola & Yen, 1990a), suggesting that increased estrogen levels may occur in all women regardless of menopausal status.

3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.

7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids

8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively (Mortola & Yen, 1990).

Ethopropazine
1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of
dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.

7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Fluoxetine
1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels
8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

Fluphenazine
1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg,
clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

**Fluvoxamine**

1) Interaction Effect: development of manic symptoms  
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.

3) Severity: moderate  
4) Onset: delayed  
5) Substantiation: theoretical  
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.  
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels  
8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he
was diagnosed with bipolar disorder, which he discontinued after 2
weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg
to 500 mg daily for the previous 2 months apparently for weight
training. Following use of DHEA for a short time, he became more
irritable, was not sleeping well, and began threatening a female
friend and family members. He also drank alcohol occasionally and
reportedly had difficulty controlling his anger when intoxicated.
Sertraline was stopped and the patient was treated with valproic
acid with the dose titrated to 500 mg twice daily. The combination of
DHEA, sertraline, and alcohol was suggested responsible for the
developing of the manic episode (Dean, 2000).

Haloperidol

1) Interaction Effect: reduced effectiveness of haloperidol
2) Summary: Dehydroepiandrosterone (DHEA) levels within the
normal range of 100 to 400 microgram/deciliter (mcg/dL) are
conducive to optimal treatment of patients with psychosis (Howard,
1992j). In case reports, patients have been resistant to
antipsychotics when DHEA levels were elevated (Howard, 1992j).
Patient being treated with haloperidol should avoid DHEA
supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of
dehydroepiandrosterone (DHEA) and haloperidol. If DHEA is
elevated, treatment with dexamethasone 1 mg orally per day may
be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA)
blood levels may reduce responsiveness to haloperidol
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant
to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40
mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus
thioridazine 300 mg. The patient appeared Cushinoid with moon
face, acne, facial hair, abdominal hair, and a 40 pound weight gain
in the previous 8 months. Dehydroepiandrosterone (DHEA)
measured as part of an endocrine panel was 725
micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL).
Dexamethasone 1 mg orally at bedtime resulted in substantial
improvement within one week. The patient appeared calmer, more
alert with improved psychotic symptoms and ability to concentrate.
At two weeks, a repeated DHEA level was within normal range (328
mcg/dL). The author concluded that elevated DHEA levels were
associated with severe psychosis resistant to conventional
antipsychotic therapy (Howard, 1992i).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992i).

**Lithium**

1) Interaction Effect: reduced effectiveness of lithium
2) Summary: Dehydroepiandrosterone (DHEA) in a single case report was noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999a). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992a). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) with lithium may cause a return of manic symptoms. Patients with a personal or family history of bipolar disorder should be advised to avoid DHEA use.
7) Probable Mechanism: proserotonergic activity of dehydroepiandrosterone may predispose patients to manic episodes; dehydroepiandrosterone is a precursor to androgenic steroids, which in high doses may precipitate mania.
8) Literature Reports

a) A 68 year-old male with no documented psychiatric history initiated dehydroepiandrosterone (DHEA) 100 milligrams (mg) daily and increased the dose to 200 to 300 mg daily for 6 months. Within 3 months, family members noted the onset of odd behavior with prominent symptoms of agitation, delusional thinking, decreased sleep and appetite, and spending sprees. The patient was not taking any prescribed medication but did ingest alcohol in amounts up to 1 case of beer daily. Another 3 months elapsed, leading to involuntary inpatient admission secondary to rapid, loud, pressured speech with grandiose thoughts. At admission, the patient reported that he had decreased alcohol intake to 2 beers daily due to family concerns about his behavior changes. There was no family history of bipolar disorder. Urinary drug screen was negative. Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient's behavior and sleep patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdrawal symptoms. The patient was discharged with follow-up care from his primary care physician with a diagnosis of substance-induced mood disorder (Markowitz et al, 1999).

b) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

c) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativevness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy
with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

Loxapine
1) Interaction Effect: reduced effectiveness of loxapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992r). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992r). Patient being treated with loxapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and loxapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to loxapine
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were
associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992q).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992q).

Mesoridazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

**Methdilazine**

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should
avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial
amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

**Molindone**

1) Interaction Effect: reduced effectiveness of molindone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992p). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992p). Patient being treated with molindone should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and molindone. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to molindone
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992o).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combative ness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated
type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992o).

**Olanzapine**

1) Interaction Effect: reduced effectiveness of olanzapine  
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992t). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992t). Patients being treated with olanzapine should avoid DHEA supplementation.
3) Severity: moderate  
4) Onset: delayed  
5) Substantiation: theoretical  
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.  
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to olanzapine  
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more
alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992s).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combative behavior. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992s).

Paroxetine
1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be
avoided due to the potential additive precipitation of mania.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels

8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).

Perazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Perphenazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to
antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye
contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Pipotiazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene,
agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Prochlorperazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL).
Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Promazine
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2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Promethazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are
conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate  
4) Onset: delayed  
5) Substantiation: theoretical  
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.  
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines  
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal
DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

Propiomazine

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included
bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

### Quetiapine

1) Interaction Effect: reduced effectiveness of quetiapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992f). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992f). Patients being treated with quetiapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and quetiapine. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to quetiapine
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA)
measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992e).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992e).

**Risperidone**

1) Interaction Effect: reduced effectiveness of risperidone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive for optimal treatment of patients with psychosis (Howard, 1992n). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992n). Patients being treated with risperidone should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and risperidone. If DHEA is
elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.

7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to risperidone

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992m).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992m).

Sertraline
1) Interaction Effect: development of manic symptoms
2) Summary: A case has been reported in which concomitant dehydroepiandrosterone (DHEA) and sertraline use was suggested to precipitate a manic episode in a patient with a history of bipolar disorder (Dean, 2000a). DHEA was also noted to cause mania in a patient with no previous personal or family history of bipolar disorder (Markowitz et al, 1999f). Elevated DHEA levels have been found in patients with mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992u). DHEA possesses proserotonergic activity which may predispose patients to manic episodes (Majewska, 1995). DHEA is a precursor to androgenic steroids, which in high doses may precipitate mania (Markowitz et al, 1999f). Patients taking medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not take DHEA until further data is available to characterize this drug-herb interaction. Concomitant use of DHEA with selective serotonin reuptake inhibitors (SSRIs) should be avoided due to the potential additive precipitation of mania.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and selective serotonin reuptake inhibitors. If patients present with manic symptoms (i.e. agitation, anger, irritability, aggressive behavior), determine if the patient is using DHEA and discontinue DHEA.
7) Probable Mechanism: serotonergic activity of dehydroepiandrosterone, possibly increased androgen levels
8) Literature Reports

a) A 31-year-old male was admitted following threats to commit suicide and injure family members. He had self-initiated sertraline 100 milligrams (mg) daily for the previous 2 to 3 weeks for depression. Sertraline had been prescribed 3 years prior when he was diagnosed with bipolar disorder, which he discontinued after 2 weeks. He had also taken dehydroepiandrosterone (DHEA) 300 mg to 500 mg daily for the previous 2 months apparently for weight training. Following use of DHEA for a short time, he became more irritable, was not sleeping well, and began threatening a female friend and family members. He also drank alcohol occasionally and reportedly had difficulty controlling his anger when intoxicated. Sertraline was stopped and the patient was treated with valproic acid with the dose titrated to 500 mg twice daily. The combination of DHEA, sertraline, and alcohol was suggested responsible for the developing of the manic episode (Dean, 2000).
1) Interaction Effect: Increased risk of adverse androgenic and hepatic effects

2) Summary: Patients electing to take both dehydroepiandrosterone (DHEA) and testosterone are at increased risk for androgenic side effects. Data are conflicting on the extent that DHEA increases the testosterone-epitestosterone (T/E) ratio (Bowers, 1999a; Bosy et al, 1998a). The effect appears to be dose-dependent, and at doses commonly used by body-builders (e.g. 1000 milligrams), androgenic effects are likely. Concomitant use is not advised.

3) Severity: Moderate

4) Onset: Rapid

5) Substantiation: Theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and testosterone. DHEA may increase testosterone levels, increasing the incidence of adverse androgenic adverse effects such as oligospermia (in men), gynecomastia, prostatic hypertrophy (especially in elderly males), and virilization in women (deepening voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Libido may increase or decrease. Adverse hepatic effects may also occur (peliosis hepatitis, hepatic neoplasms).

7) Probable Mechanism: Additive androgenic effect, since dehydroepiandrosterone appears to act as a pro-drug for testosterone

8) Literature Reports

a) Dehydroepiandrosterone (DHEA) increased the testosterone-epitestosterone (T/E) ratio in an uncontrolled study of 4 human volunteers. Two over the counter DHEA preparations were used in this study. Nature’s Pride "DHEA 50 mg+" (product A) contained DHEA 50 milligrams (mg), suma 25 mg, Korean ginseng 25 mg, muira pauma 25 mg, shitake mushroom concentration 15 mg, and green tea extract 5 mg. The second product, YourLife DHEA (product B), contained DHEA 25 mg as the only active ingredient listed on the label. Neither product contained testosterone as detected by gas chromatography-mass spectrometry (GC-MS) analyses. All subjects (except subject 4) took the product once daily for 4 days at breakfast. Subject 1 (age 47) took both preparations at 3 dosage levels at different times over a 6 month period: product A 50 mg/day, product A 100 mg/day, and product B 150 mg/day for 4 days. Subjects 2 (age 61) and 3 (age 28) took product B 50 mg/day and 100 mg/day, respectively. Subject 4 (age 27) took product A 100 mg/day for 2 days. A 24-hour urine was collected on day 3 and spot urine samples were taken in the morning and evening of day 4. Subject 1 at DHEA doses of 50 mg/day, 100 mg/day, and 150 mg/day had T/E ratios of 8.1, 11.4, and 14.4, respectively,
compared to a pre-dose ratio of 2.4. Pre-dose T/E ratios for subjects 2 and 3 were 1.3 and 1.7, respectively, and T/E ratios were 1.6 and 3.9, respectively after DHEA. Subject 4 had a pre-dose T/E ratio of 0.8 and a T/E ratio of 1.1 following DHEA. Ratios exceeding 6:1 are used by several organizations including the United States Military and the International Olympic Committee (IOC) as an indication that additional tests are warranted to rule out use of exogenous physiological steroids. Manipulation of the steroid endocrine system to improve athletic performance has led some DHEA supplement providers on the internet to recommend up to 1000 mg/day (Bowers, 1999).

b) Differences in baseline mean T/E ratios and dehydroepiandrosterone (DHEA) treatment mean ratios were not significant in 7 healthy subjects. Mean baseline T/E ratio was 0.67 (range: 0.1 to 1.2). DHEA 50 mg was taken each morning for 30 days with urinary samples collected before and two to three hours after ingestion with no voiding before collection. Individual variation was prevalent. The greatest individual variation from baseline to treatment mean T/E ratio was 1.20 to 2.11. The greatest difference from baseline mean to peak treatment mean T/E ratio was 1.2 to 3.7. A single dose of DHEA 250 mg resulted in a 40% increase in the T/E ratio relative to the pre-dose value (peak T/E ratio equal to 1.2). DHEA at this dose had a minimal effect on urine T/E ratios and would not be expected to result in a positive screen for testosterone abuse as the T/E ratio must exceed 6:1 (Bosy et al, 1998).

c) Two female volunteers demonstrated three to four fold increases in plasma testosterone levels following dehydroepiandrosterone (DHEA) 100 mg administration. In subject 1, the pre-DHEA testosterone level was 0.07 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL ninety minutes after DHEA administration. In subject 2, the pre-DHEA testosterone level was 0.08 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL sixty minutes after DHEA administration. This demonstrates that in vivo conversion of DHEA to testosterone occurs in women as well as men (Mahesh & Greeenblatt, 1962).

**Thioridazine**

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were
associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

**Triazolam**
1) Interaction Effect: increased central nervous system depression
2) Summary: Dehydroepiandrosterone (DHEA) inhibited metabolism of triazolam in humans through inhibition of CYP3A isoenzymes (Frye et al, 2000a). As a result of increased triazolam levels, patients may be at increased risk for adverse effects of triazolam.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: In patients taking dehydroepiandrosterone (DHEA) and triazolam concomitantly, monitor closely for signs of triazolam toxicity such as excessive sedation, hypotension, tachycardia, ataxia, slurred speech, and respiratory depression.
7) Probable Mechanism: inhibition of liver cytochrome P450 3A by DHEA metabolite, DHEA-S with resultant increase in triazolam levels
8) Literature Reports

a) Dehydroepiandrosterone (DHEA) metabolite dehydroepiandrosterone sulfate (DHEA-S) inhibited metabolism of triazolam in human liver microsomes and in 13 elderly subjects (ages 65-79 years). Placebo was given to subjects for 7 days, followed by DHEA 200 milligrams (mg) daily for 14 days. Triazolam 0.25 mg was administered on days 1 and 22. Triazolam clearance/bioavailability (CL/F) was reduced from 27.8 +/- 3.5 to 23.3 +/- 3.6 (p equal to 0.0067) (Frye et al, 2000).

**Trifluoperazine**
1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

**Triflupromazine**

1) Interaction Effect: reduced effectiveness of phenothiazines
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992l). In case reports, patients have been resistant to
antipsychotics when DHEA levels were elevated (Howard, 1992l). Patients being treated with phenothiazines for psychosis should avoid DHEA supplementation.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and phenothiazines. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to phenothiazines
8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992k).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye
contact. Once dexamethasone was discontinued, rapid
decompensation and florid psychosis ensued despite "substantial
amounts of psychotropic medications." DHEA increased to 536
mcg/dL. The author concluded that elevated DHEA levels were
associated with florid psychosis resistant to conventional
antipsychotic therapy (Howard, 1992k).

Valproic Acid

1) Interaction Effect: reduced effectiveness of valproic acid
2) Summary: Dehydroepiandrosterone (DHEA) in a single case
    report was noted to cause mania in a patient with no previous
    personal or family history of bipolar disorder (Markowitz et al,
    1999e). Elevated DHEA levels have been found in patients with
    mental disorders; DHEA suppression has lead to improvement in
    psychotic symptoms (Howard, 1992d). Patients taking medication
    for bipolar disorder or patients with a personal and/or family history
    of bipolar disorder should not take DHEA until further data is
    available to characterize this drug-herb interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If valproic acid is being used for manic
    symptoms, concomitant use of dehydroepiandrosterone (DHEA)
    may cause a return of symptoms. Patients with a personal or family
    history of bipolar disorder should be advised to avoid DHEA use.
7) Probable Mechanism: proserotonergic activity of
    dehydroepiandrosterone may predispose patients to manic
    episodes; dehydroepiandrosterone is a precursor to androgenic
    steroids, which in high doses may precipitate mania
8) Literature Reports

a) A 68-year-old male with no documented psychiatric history
    initiated dehydroepiandrosterone (DHEA) 100 milligrams (mg) daily
    and increased the dose to 200 to 300 mg daily for 6 months. Within
    3 months, family members noted the onset of odd behavior with
    prominent symptoms of agitation, delusional thinking, decreased
    sleep and appetite, and spending sprees. The patient was not taking
    any prescribed medication but did ingest alcohol in amounts up to 1
    case of beer daily. Another 3 months elapsed, leading to involuntary
    inpatient admission secondary to rapid, loud, pressured speech with
    grandiose thoughts. At admission, the patient reported that he had
    decreased alcohol intake to 2 beers daily due to family concerns
    about his behavior changes. There was no family history of bipolar
    disorder. Urinary drug screen was negative. Over the seven-day
    hospital stay, with the institution of valproic acid 500 mg twice daily,
    the patient's behavior and sleep patterns improved, and the patient
    believed DHEA led to his symptoms. There were no ethanol
withdrawal symptoms. The patient was discharged with follow-up care from his primary care physician with a diagnosis of substance-induced mood disorder (Markowitz et al, 1999d).

**CLINICAL APPLICATIONS**

**Monitoring Parameters**

A) Therapeutic

1) Laboratory Parameters

   a) There are no adequate data to support monitoring of dehydroepiandrosterone sulfate (DHEAS) levels during dehydroepiandrosterone therapy

   b) Systemic Lupus

1) Antibodies to dsDNA, ANA titers, serum complement (may normalize during remission), complete blood counts (improvements in anemia, leukopenia, and/or thrombocytopenia), sed rate, hepatic and renal function tests, urinalysis (resolution of proteinuria, RBCs) (periodically during therapy to assess improvements)

2) Physical Findings

   a) Systemic Lupus

   1) Body weight, V/S periodically (eg, reversal of weight loss, resolution of fever, improved pulmonary function)

   2) Sign/symptom improvement (eg, joint symptoms, cutaneous/mucous membrane lesions, pulmonary symptoms (dyspnea), GI complications (anorexia, abdominal pain, ileus) ocular symptoms (eg, conjunctivitis, photophobia, cotton-wool spots); improvement of psychiatric symptoms (eg, depression, psychotic features), which may be exacerbated by concomitant steroids

   3) Prednisone daily dosage (reduction with dehydroepiandrosterone)

   4) ECG monitoring periodically

   5) Radiologic studies in selected patients (eg, improvement of pleural effusion)

   6) Neurologic monitoring in selected patients

B) Toxic

1) Laboratory Parameters

   a) Routine chemistry periodically (to include transaminases)

   b) Plasma lipid profile periodically (reduced HDL levels)

2) Physical Findings
a) Signs/symptoms of toxicity, including libido changes, signs of masculinization in women, gynecomastia in men, psychiatric symptoms (eg, behavioral changes, mania)

**Place In Therapy**

**A)** Based on available data, the place in therapy of dehydroepiandrosterone (ie, when the steroid should be used considering all other treatment modalities) cannot be ascertained in any potential indication. This is attributed primarily to the small patient populations across all studies, limiting adequate efficacy evaluation; many studies were also of open design or suffered from other flaws (eg, lack of adequate demographic data, other medications). Dehydroepiandrosterone may very well have activity in several settings, but more intense scrutiny in well-controlled studies with enough patients to enable achievement of reliable statistical differences is needed.

**B)** Even if larger studies support benefit of dehydroepiandrosterone in selected indications, use of the steroid over conventional treatments would not be indicated until direct comparisons are conducted. Examples requiring such comparative data are depression (eg, with SSRI's), erectile dysfunction (eg, with vardenafil), menopause and prevention of bone loss (eg, with hormone-replacement therapy), and prevention of coronary artery disease (eg, with statins).

**C)** At present, the only recommendation that can be made for dehydroepiandrosterone is systemic lupus, where it may reduce concomitant steroid dosage and provide clinical improvement in some patients. However, as with other conditions, studies in this area are small, and a larger, well-controlled study is required to confirm benefits. Data are insufficient to recommend dehydroepiandrosterone for slowing or reversing any process of aging, and the drug has no proven benefit as a nutritional supplement; although dehydroepiandrosterone and dehydroepiandrosterone sulfate levels decline with age, this alone does not support a need for replacement.

**D)** No study has investigated the efficacy of dehydroepiandrosterone as an ergogenic agent in athletes; androstenedione supplementation in young men undergoing resistance training had no effect on muscle size, strength, or overall body composition in one study (Horowitz, 2000).

**Mechanism of Action / Pharmacology**

**A) MECHANISM OF ACTION**

1) Dehydroepiandrosterone (dehydroepiandrosterone, DHEA) is a steroid produced by the adrenal gland in response to adrenocorticotropic (ACTH) stimulation; production also occurs in the brain by undefined pathways (Davidson et al, 2000; Friess et al, 2000; Hayashi et al, 2000; Horowitz, 2000a). Dehydroepiandrosterone is an intermediate in the conversion of cholesterol to estrogens and androgens (Davidson et al, 2000; Horowitz, 2000a). Circulating
Dehydroepiandrosterone is predominantly (90%) in the form of its sulfate ester, dehydroepiandrosterone sulfate (dehydroepiandrosterone sulfate, DHEAS). Plasma levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate are substantially higher than those of any other adrenal steroid (Arlt et al, 1998; Hayashi et al, 2000).

2) Other than serving as precursors to androgens (eg, testosterone) and estrogens (eg, estrone) (Ahrendt, 2001; Arlt et al, 1998), the physiologic roles of dehydroepiandrosterone and dehydroepiandrosterone sulfate have remained unclear. However, the decline in plasma levels of these steroids with age (Orentreich et al, 1984; Morganti et al, 1999; Villareal et al, 2000) and low levels associated with various disease states, related or unrelated to age (Feldman et al, 2001; LaMontagna et al, 2001; Horowitz, 2000a; Barrett-Connor et al, 1999), has led to investigations of exogenous dehydroepiandrosterone as an antiaging agent and for treatment of age-related diseases and prevention/treatment of other disease states (Horowitz, 2000a; Dean, 2000c; Feldman et al, 2001; Ahrendt, 2001).

3) No specific mechanism or binding site (receptor) for dehydroepiandrosterone or its sulfate ester in any disease, condition, or setting has been confirmed. Many speculate that actions of dehydroepiandrosterone and dehydroepiandrosterone sulfate are related to their conversion to estrogens and androgens, or other metabolites, which exert effects in target tissues (Arlt et al, 1998; Davidson et al, 2000). However, others suggest more direct actions of these steroids. The following are some general or specific speculations regarding mechanisms of action of dehydroepiandrosterone and/or dehydroepiandrosterone sulfate:

a) Neurophysiologic studies have suggested both agonist and antagonist effects at the gamma-aminobutyric acid type A (GABA-A) receptor complex; some evidence of agonist effects at the sigma-1 receptor, with potentiation of N-methyl-D-aspartate (NMDA) receptor induced neuronal excitability, has also been described (Friess et al, 2000; Friess et al, 1995; Morales et al, 1994b).

b) Conversion of dehydroepiandrosterone to estrogen and an increase in nitric oxide-dependent mechanisms are speculated to contribute to antiatherogenic effects (Hayashi et al, 2000).

c) A direct effect on pancreatic beta cells to enhance glucose-simulated insulin secretion has been reported in association with antidiabetic effects in animal models; an increase in mRNA expression on beta-cell mitochondrial/peroxisomal lipid metabolic enzymes was also observed (Dillon et al, 2000).

d) An antiglucocorticoid effect has been suggested, which could possibly improve memory and treat depression (Friess et al, 2000; Horowitz, 2000a), although conflicting data obscure this mechanism.

e) Inhibition of the GABA-A receptor and potentiation of NMDA and sigma receptor function are also speculated to contribute to antidepressant effects (Barrett-Connor et al, 1999), whereas enhancement of GABAergic transmission was considered related to neuroprotective activity against ischemic stroke observed in rabbits (Lapchak et al, 2000).
B) ENDOGENOUS LEVELS - DISEASE CORRELATIONS

1) Normal endogenous plasma concentrations of dehydroepiandrosterone are generally in the range of 2 to 4 nanograms/milliliter (ng/mL) in healthy men, whereas values in women are similar or slightly higher; levels of dehydroepiandrosterone sulfate are usually 2 to 6 micrograms (mcg)/mL in men, and this range is lower in women (Frye et al, 2000b; Friess et al, 2000; LaMontagna et al, 2001; Stomati et al, 2000; Meno-Tetang et al, 2001; Horowitz, 2000a). Levels of dehydroepiandrosterone/dehydroepiandrosterone sulfate rise in early adolescence and peak in the second or third decade of life; thereafter they decline at the rate of about 2% per year; by 75 years of age, levels are approximately 10% of peak concentrations (Orentreich et al, 1992; Skolnick, 1996; Friess et al, 2000; Davidson et al, 2000).

2) In addition to normal aging, low endogenous plasma levels of dehydroepiandrosterone and/or dehydroepiandrosterone sulfate have been reported in numerous disease states/conditions, and these findings have led to enthusiastic claims for potential benefits of replacement therapy. Some conditions associated with low levels (age- or non-age related) include depression (children and adults), rheumatoid arthritis, active systemic sclerosis, schizophrenia, colon cancer, systemic lupus erythematosus, HIV infection, Huntington’s disease, stress, memory impairment/Alzheimer’s disease, Crohn's disease, ulcerative colitis, adrenal insufficiency, and polymyalgia rheumatica (LaMontagna et al, 2001; Barrett-Connor et al, 1999; Fraser et al, 2000; Horowitz, 2000a; Alberg et al, 2000; Arlt et al, 1998; Friess et al, 2000). Reduced levels correlated with a higher risk of ischemic heart disease in men aged 40 to 69 years in one study (Feldman et al, 2001). However, some associations were barely significant at times, and inconsistencies/conflicting data have been reported. The low DHEA levels in many conditions may simply be coincidental, unrelated to pathogenesis.

C) SOME PRECLINICAL STUDIES

1) In some animal studies, hypolipidemic, antidiabetic, antiatherogenic, antioxidant, neuroprotectant, antistress, and antiobesity effects of exogenous dehydroepiandrosterone have been reported (Hayashi et al, 2000; Hu et al, 2000; Dillon et al, 2000; Villareal et al, 2000; Shen et al, 2001; Brignardello et al, 2000; Lapachak et al, 2000). Specific cardiovascular effects have included inhibition of platelet aggregation, plaque formation, LDL oxidation, and plasminogen activation (Feldman et al, 2001). Antitumor activity and protection against cancer have been reported in rodent models (Nephew et al, 2000; Alberg et al, 2000). Protection against DNA damage in the brain of elderly dogs was described in one report (Shen et al, 2001).

2) The clinical relevance of any of these findings can only be determined by well-controlled studies with exogenous dehydroepiandrosterone.

D) REVIEW ARTICLES

1) Effects in chronic inflammatory diseases (Straub et al, 2000).

2) Reviews of dehydroepiandrosterone replacement therapy, including effects on

**Therapeutic Uses**

**Adrenal insufficiency**

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Oral doses of DHEA raised circulating levels of DHEA in women with adrenal insufficiency (ADDISON'S DISEASE)  
Limited studies suggest benefits of dehydroepiandrosterone 50 milligrams daily; additional well-controlled and long-term studies needed

3) Adult:

a) Treatment with dehydroepiandrosterone (DHEA) did not appear to improve subjective assessments of health or sexuality in patients with adrenal failure (Addison's disease). In a randomized, double-blind study, women with adrenal failure received a 9-month, oral daily treatment regimen with either DHEA 25 milligrams (n=19) or placebo (n=20). Potential effects of treatment on subjective assessments of health, fatigue, and sexuality were measured, respectively, by the previously validated Short Form-36 (SF-36), by an 11-question fatigue questionnaire, and a version of McCoy's Sex Scale Questionnaire. Whereas all assessment scale scores improved (from baseline) in the DHEA group without statistical significance, the apparent effects from treatment with DHEA did not differ significantly between patients receiving either DHEA or placebo. Adverse events (increased sweat odor, scalp itching) occurred in 17 of 19 patients (89%) treated with DHEA; however, 70% of patients receiving placebo also reported adverse events, although of significantly milder severity (p less than 0.001, side-effect score). There were no significant adverse events reported (Lovas et al, 2003).

b) Clinical data are limited. Oral doses of 50 mg daily were associated with improvement of well-being and sexual functioning in one 4-month randomized study involving women with adrenal insufficiency (n=24); lipid parameters improved during therapy (Horowitz, 2000b). Oral doses of 50 milligrams (mg) or 200 mg DHEA raised circulating levels of DHEA in
women with ADDISON'S DISEASE. Women with primary adrenocortical failure (Addison's disease) received a daily oral dose of DHEA 50 mg (n=5) or 200 mg (n=4) in a randomized fashion. The DHEA therapy was generally well tolerated; no patient withdrew from treatment. Adverse events including acne, oily skin, facial acne, and increased sweat odor occurred in some patients, with no difference between those taking 50 mg and those taking 200 mg DHEA. A reduction of low-density lipoprotein occurred in both groups. DHEA had no effect on body composition (Gebre-Medhin et al, 2000a).

c) Clinical data are limited. Oral doses of 50 mg daily were associated with improvement of well-being and sexual functioning in one 4-month randomized study involving women with adrenal insufficiency (n=24); lipid parameters improved during therapy (Horowitz, 2000b).

**Aging**

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference:

**RECOMMENDATION AND EVIDENCE RATINGS**

2) Summary:

Daily oral administration of DHEA 100 milligrams did not induce discernible changes in body fat composition or in urological function when given over a 3-month period

Anti-aging effects of dehydroepiandrosterone have not been clearly demonstrated

Oral administration improved the well-being of elderly subjects in one placebo-controlled study, although the small sample size limits clear evaluation of efficacy

Dehydroepiandrosterone has not demonstrated consistent benefits on memory, immune responses, body composition or bone mineral density, or insulin sensitivity in elderly subjects; deficiencies in some studies precluded adequate evaluation of results, and some changes were small and of doubtful clinical relevance

There are no data to suggest that dehydroepiandrosterone can prolong life

All available studies investigating benefits on aging have involved small populations; additional, larger studies will be required to demonstrate statistically or clinically significant benefit

3) Adult:

**a) GENERAL INFORMATION**
1) Many claims made for dehydroepiandrosterone are in regard to slowing or reversing the aging process and improving quality of life in otherwise healthy middle-age or elderly individuals, and they are discussed together here for cohesiveness. These claims include: maintenance of body composition/strength and bone mineral density; enhancement of physical/psychological well-being; memory/cognition enhancement; improvement of age-related declines in insulin sensitivity and immunity. Most relevant studies have generated conflicting results, usually due to the small sample sizes, concurrent therapies, and/or poor trial design. No study has demonstrated prolongation of life in elderly patients treated with dehydroepiandrosterone.

b) BODY COMPOSITION/STRENGTH AND BONE EFFECTS

1) In small, placebo-controlled studies evaluating benefits of oral dehydroepiandrosterone on body composition and bone mineral density in middle-age and elderly men and women (exhibiting low endogenous levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate), results have been equivocal (Villareal et al, 2000b; Morales et al, 1998b; Morales et al, 1994a; Horowitz, 2000b). With doses of 50 or 100 milligrams (mg) daily for up to 6 months, plasma dehydroepiandrosterone/dehydroepiandrosterone sulfate levels were generally restored. Either no change or slight but significant decreases in body fat mass (about 1 kilogram without a significant change in body weight were observed in elderly men; changes were also inconsistent in women (increase or no change or decrease in fat mass and increase or no change in body weight). Bone mineral density (BMD) (assessed by dual-energy X-ray absorptiometry) was either increased significantly in both men and women (total body and spine) or not altered in either sex (hip and spine). Use of estrogen replacement by most women in the study demonstrating an increase in fat mass/no change in BMD (Morales et al, 1998b) may have contributed to these discrepancies. A significant increase in muscle strength (eg, lumbar back, foot-pounds of torque) was reported in men, but not women, in one study (Morales et al, 1998b). In women subjects, increases were seen in serum androstenedione, testosterone and dihydrotestosterone but changes in men were inconsistent. Plasma lipids did not change significantly during therapy in any of these studies, although trends toward deleterious falls in HDL cholesterol were observed in women (Morales et al, 1998b).

2) Replacement therapy with dehydroepiandrosterone (DHEA) did not provide any apparent significant health benefit to older men with age-related, lowered serum concentrations of DHEA. In a randomized, double-blind, cross-over study, 22 healthy older men (50 to 69 years of age) with age-related declines in serum concentrations of DHEA were given 4-month oral regimens of either DHEA 50 milligrams or placebo. After 4 months, subjects entered a 1-month washout period prior to crossing over to the opposing treatment study arm. For all subjects, baseline serum DHEA-S
concentrations were below 4.1 micromoles/liter. Efficacy markers included changes in serum concentrations of DHEA/DHEA-S, osteocalcin, lipoproteins, and changes in exercise capacity and body composition. During 4 months of active treatment, serum concentrations of DHEA and DHEA-S significantly increased, attaining the normal range for males after only 1 month of treatment. However, this increase was not sustained, and after 4 weeks of placebo treatment, all hormone concentration levels had returned to baseline. Serum concentrations of high-density lipoproteins were also significantly increased during active treatment, yet did not persist after crossover to placebo. After 4 months of DHEA treatment, there were no significant, treatment-related changes observed in bone metabolism, lean body mass, waist-to-hip ratio, body mass index, or in exercise tolerance. The study investigators observe that such responses to treatment suggest that age-related declines in serum DHEA concentrations are not the physiological equivalent of the pathological loss of DHEA production induced by adrenal insufficiency (Arlt et al, 2001).

3) Replacement therapy with DHEA (dehydroepiandrosterone) was not effective for reversing age-related changes in lean body mass, mean body fat, or in urological function of healthy, older men. In a randomized, double-blind, crossover study, 39 men (60 to 84 years of age) were given either oral DHEA 100 milligrams (mg; 50 mg at 0700 hours, another 50 mg at 1500 hours) or placebo once daily for 3 months, after which the subjects crossed over to the other treatment arm for an additional 3 months prior to all subjects entering into a 3-month washout period. All subjects were measured every 3 months for changes in body fat composition, blood lab values, urological function, and subjective perceived changes in sexual function and other daily activities. At the end of the 9-month study period, there were no significant changes observed in percent mean body fat, lean body mass, urological function or in any self-analysis pertaining to sexual activity, lifestyle or attitudes. After 3 months of therapy with DHEA, although statistically significant decreases were seen in the mean blood values for blood urea nitrogen/creatinine ratio, alanine aminotransferase, total cholesterol and HDL cholesterol, these changes were not sustained after the withdrawal of the study drug; all prior changes reverted to baseline over the 3-month washout period. There were no adverse events reported (Flynn et al, 1999).

4) One further study employing topical dehydroepiandrosterone (10% cream daily for 12 months) reported a significant increase in hip BMD in postmenopausal women (Labrie et al, 1997a); however, this study was uncontrolled and changes barely reached statistical significance.

c) IMMUNE FUNCTION ENHANCEMENT

1) Immune function declines with aging. In studies investigating immune-enhancement effects of oral dehydroepiandrosterone in older subjects, no statistically significant improvement in the immune response to tetanus VACCINATION or influenza vaccination was observed when the steroid
was given for 4 days (50 mg two or four times daily) beginning 2 to 4 days prior to vaccine injection (Evans et al, 1996; Danenberg et al, 1997).

2) Significant increases in serum insulin-like growth factor-1 (IGF-1) and the IGF-1/IGF binding protein-1 (IGFBP-1) ratio have been reported in elderly subjects treated with dehydroepiandrosterone 50 or 100 mg daily in some studies (Khorram et al, 1997; Morales et al, 1994a; Villareal et al, 2000b) but not others (Wolf et al, 1997). Evidence of functional activation of B-cells and T-cells has been reported, as well as mitogen-stimulated release of interleukin-2 and interleukin-6; however, increases in absolute number of T-lymphocytes (total or subsets) or immunoglobulins were not observed (Khorram et al, 1997). An adverse decrease in CD4+ cell counts was observed in one study (postmenopausal women) (Casson et al, 1993).

3) No study has attempted to demonstrate clinical benefits of enhancement of immunologic parameters (eg, prevention of infection, cancer-risk outcome).

d) INSULIN SENSITIVITY ENHANCEMENT

1) INSULIN RESISTANCE tends to increase with age and may predispose to diabetes mellitus. Although some studies have reported enhanced insulin sensitivity in both young and old subjects with dehydroepiandrosterone (Lasco et al, 2001a; Casson et al, 1995), most have not (Morales et al, 1994a; Usiskin et al, 1990; Nestler et al, 1988; Schriock et al, 1994; Vogiatzi et al, 1996). Discrepancies are likely due to different methods of assessment, differing types of subjects (eg, obese versus non-obese), and small populations; however, data collectively suggest no effect. No change in glucose tolerance was reported in studies showing improved sensitivity.

2) In a further study involving postmenopausal women, insulin resistance was induced by dehydroepiandrosterone (Mortola & Yen, 1990c).

e) MEMORY ENHANCEMENT

1) Oral dehydroepiandrosterone (50 milligrams (mg) daily) failed to provide significant improvement in memory/cognitive function in elderly subjects in a double-blind, placebo-controlled study (Wolf et al, 1997). Although some benefit was seen in one open study (Wolkowitz et al, 1997), controlled studies do not support use for the purpose of memory enhancement.

f) WELL-BEING ENHANCEMENT

1) Significant improvement in parameters of physical/psychological well-being in middle-age and elderly subjects (40 to 70 years), including mood, sleep quality, energy, and reduced stress, was reported in a small 3-month, placebo-controlled study with dehydroepiandrosterone 50 mg daily (Morales et al, 1994a). There was no change in insulin sensitivity or libido. The nonspecific nature of endpoints in this study, limitations in evaluation techniques, and small population preclude adequate assessment of efficacy; a large trial is required to evaluate these effects by well-defined
criteria. Improvements in well-being have also been mentioned anecdotally in other studies investigating dehydroepiandrosterone for other potential indications.

**Anorexia nervosa**

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Favorable effects on bone were reported in a small study  
Confirmatory studies are needed  

3) Adult:

a) Long-term anorexia nervosa patients have a seven-fold greater risk of fractures and often develop early osteoporosis. In a small double-blind study (n=15), trends toward normalization of bone turnover were observed during supplementation with dehydroepiandrosterone 50, 100, or 200 milligrams (mg) daily for three months in young women (15 to 22 years) with anorexia nervosa (Gordon et al, 1999). At three months of therapy, urinary N-telopeptides decreased significantly in the 50 and 200 mg groups, accompanied by significant increases in osteocalcin levels. More than half of patients experienced at least one menstrual cycle, suggesting the therapy may have lead to estradiol levels sufficient to stimulate the endometrium (Gordon et al, 1999). However, the inconsistent dose-effects and small sample size limit confidence in results. A larger study incorporating placebo is required.

**At risk of coronary heart disease**

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

There is some evidence that dehydroepiandrosterone may produce beneficial metabolic effects and reduce some risk factors for
cardiovascular disease, including improvement of lipid profiles; however, conflicting data have been reported with regard to changes in plasma lipids, and potentially deleterious falls in HDL cholesterol have been observed in some studies. There are no studies in patients with cardiovascular disease; long-term controlled comparisons with clinical endpoints are needed, including comparison with a statin.

3) Adult:

a) Evaluated Data

1) Potentially beneficial metabolic and other effects during oral dehydroepiandrosterone supplementation (25 to 1600 milligrams (mg) daily) in young and older male and female subjects in placebo-controlled studies have included falls in total and low-density lipoprotein (LDL) cholesterol and triglycerides, decreases in platelet aggregation, increases in plasma cyclic guanosine monophosphate (cGMP), and reductions in plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen (Nestler et al, 1988; Jesse et al, 1995; Lasco et al, 2001a; Mortola & Yen, 1990c; Casson et al, 1995; Jakubowicz et al, 1995; Beer et al, 1996).

2) A beneficial increase in high-density lipoprotein (HDL) cholesterol has been observed with lower doses (25 mg daily) (Lasco et al, 2001a). However, other controlled studies have not demonstrated significant beneficial changes in any lipid parameter (Morales et al, 1994a; Sulcova et al, 2000a; Morales et al, 1998b; Villareal et al, 2000b), and several have reported a deleterious fall in HDL cholesterol levels during treatment, which at times was statistically significant (Morales et al, 1998b; Morales et al, 1994a; Villareal et al, 2000b; Mortola & Yen, 1990c). Reductions in HDL cholesterol are presumably related to increased androgenicity, have been seen in both men and women (more often women), and are probably dose-related.

3) All studies with dehydroepiandrosterone have been very small, which probably contributed to some of the discordant findings on lipid parameters; differences in types of subjects (eg, young versus older men, early versus late postmenopausal women) were also contributory. Baseline demographic data for dehydroepiandrosterone and placebo group were not always provided. There are no investigations in patients with cardiovascular disease, and thus no assessments of clinical endpoints as a result of dehydroepiandrosterone therapy (eg, incidence of nonfatal/fatal cardiac events). A large prospective study comparing various dehydroepiandrosterone doses with placebo (combined with conventional therapy) in patients with (or with significant risk factors for) ischemic heart disease is in order to more adequately assess lipid changes, the significance of putative antiplatelet and other metabolic effects, and effects
on morbidity and mortality. A comparison with statins (which also possess benefits beyond lipid-lowering) is also warranted.

b) Clinical-Study Summaries

1) In a small (n=6) double-blind, placebo-controlled, crossover study involving postmenopausal women, oral dehydroepiandrosterone 1600 mg daily significantly decreased total serum cholesterol (11%) and HDL cholesterol after one week of treatment; these reductions persisted for the following 3 weeks of the study. LDL cholesterol was also decreased, but not statistically significantly (Mortola & Yen, 1990c).

2) In a placebo-controlled, unblinded study in early postmenopausal women (n=20), significant improvement in insulin sensitivity (euglycemic clamp studies) and lipid parameters was reported after one year of treatment with low doses of dehydroepiandrosterone (25 mg daily). Significant increases in HDL cholesterol (12%) and decreases in LDL cholesterol (11%) and triglycerides (20%) were observed at 12 months. There was no change in glucose tolerance. Beneficial lipid effects were attributed at least in part to increased insulin sensitivity; the low dose was considered responsible for HDL increases, compared to decreases seen in other studies.

Carcinoma of prostate

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference:
RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Not indicated due to enhancement of tumor growth in a case report

3) Adult:

a) In a patient with advanced prostate cancer unresponsive to prior treatment, dehydroepiandrosterone alleviated some disease symptoms but ultimately promoted growth of the cancer. Following withdrawal of therapy, the previous hormonally-unresponsive malignancy in this patient responded transiently to diethylstilbestrol (Jones et al, 1997a). The authors suggest that an analogue of dehydroepiandrosterone with nonandrogenic metabolite conversion could possibly provide a treatment regimen for prostate cancer. An analogue with these properties (3-acetyl-7-oxo-dehydroepiandrosterone) is under investigation (Davidson et al, 2000b).

Constitutional delay of growth and puberty
1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class III
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Monthly injections of dehydroepiandrosterone enanthate were ineffective in one small study.

3) Pediatric:

a) Monthly injections of dehydroepiandrosterone enanthate 70 milligrams/square meter (mg/m(2)) for one year had no significant effect on growth velocity or skeletal maturation in 5 boys (11 to 13 years) with constitutional growth delay and 1 boy (13 years) with panhypopituitarism (Sizonenko & Paunier, 1986).

**Depression**

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

More effective than placebo in a small study; confirmation is required.

3) Adult:

a) A small, 6-week blinded study reported the superiority of dehydroepiandrosterone 30 milligrams (mg) one to three times daily over placebo in producing improvements on the Hamilton Depression Rating Scale in patients with major depression (n=22; 33 to 53 years) (Wolkowitz et al, 1999). b. A larger controlled study is required to confirm this benefit. Direct comparison with a selective serotonin-reuptake inhibitor (SSRI) will be mandatory.

**Diabetes mellitus**

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category C
See Drug Consult reference:

RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Insulin resistance improved in one diabetic patient treated with dehydroepiandrosterone

3) Adult:

a) No study investigating benefits of add-on dehydroepiandrosterone versus placebo in type 2 diabetics have been published.
b) Improvement of insulin resistance was reported with oral dehydroepiandrosterone 150 milligrams (mg) twice daily for one month in conjunction with dexamethasone (0.25 mg/day) in a 15-year-old female with type 2 diabetes mellitus and hyperandrogenism. While dexamethasone monotherapy increased oral glucose tolerance test values by 30% and decreased erythrocyte insulin binding by 33%, dehydroepiandrosterone in addition to dexamethasone increased insulin sensitivity, as represented by a decrease of 30% in the oral glucose tolerance test, an increase in the rate of glucose disappearance by intravenous insulin (3-fold), and a 30% increase in erythrocyte insulin binding (Buffington et al, 1993).
c) Benefits in this case report require confirmation. Insulin sensitivity has not been improved by dehydroepiandrosterone supplementation in most studies involving young or old subjects.

Dyssomnia

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference:

RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

One study has shown a beneficial effect on rapid eye movement (REM) sleep values
Further studies are required

3) Adult:
a) dehydroepiandrosterone significantly increased REM sleep values in the sigma frequency range during the first two hours of sleep following 500-milligram (mg) doses in healthy young men (n=10). No other sleep variables were affected. These data suggest the potential for modulating REM sleep with dehydroepiandrosterone (Friess et al, 1995a).

**Erectile dysfunction**

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

An oral dose of 50 milligrams (mg) daily was reported effective in a small placebo-controlled study; a larger study is needed.

3) Adult:

a) Oral dehydroepiandrosterone 50 milligrams (mg) daily slightly improved erectile dysfunction in a prospective, double-blind, placebo-controlled study involving impotent males (n=40). Success of therapy was based on the International Index of Erectile Dysfunction (IIEF) questionnaire. In addition, response was defined as the ability to achieve or maintain an erection sufficient for satisfactory sexual performance according to the National Institute of Health Consensus Development Panel of Impotence. None of the patients were able to maintain erection long enough to reach orgasm at the start of the study. Slight improvement was noticeable in the dehydroepiandrosterone group by 8 weeks, which became progressively more evident at weeks 16 and 24. Dehydroepiandrosterone had no effect on serum prolactin, prostate specific antigen (PSA), testosterone, prostate volume, or post-void residual volume (Reiter et al, 1999).

b) A larger efficacy study is needed to eliminate the problems associated with small sample size. Studies employing RigiScan(R) techniques (measure of penile tumescence and rigidity) are also required. Comparison with vardenafil or sildenafil will ultimately be needed.

**Female infertility; Adjunct**

1) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference:
RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved response to ovarian stimulation reported in a small study

3) Adult:

a) A small study (n=5) suggested the efficacy of oral dehydroepiandrosterone in improving the response to OVARIAN STIMULATION (Casson et al, 2000). Women (41 years or less) with unexplained infertility, normal FSH concentrations, and a prior poor response to gonadotropin administration were given micronized dehydroepiandrosterone 80 milligrams (mg) daily for two months, followed by a repeat ovarian stimulation cycle while still receiving oral dehydroepiandrosterone (ie, intramuscular FSH twice daily, HCG at follicular maturity, then intrauterine insemination). Improved responsiveness to ovarian stimulation was seen in all patients (by at least 2-fold); one patient conceived with a delivered twin pregnancy.

b) Confirmation of this benefit of dehydroepiandrosterone is required.

Finding of memory performance, Enhancement

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

No effect in healthy subjects

3) Adult:

a) Controlled studies in both young and elderly subjects have failed to detect memory-enhancing effects of oral dehydroepiandrosterone (Friess et al, 2000a; Wolf et al, 1997). Although suppression of cortisol levels was reported, suggesting an antiglucocorticoid action, this has not been confirmed.

Hereditary angioedema

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Potential benefits were reported in a small study
Additional controlled studies are needed

3) Adult:

a) In one small study involving patients with HEREDITARY ANGIOEDEMA (n=8), oral dehydroepiandrosterone 25 to 50 milligrams (mg) daily every one to three days was reported to improve symptoms (peripheral edema, airway obstruction) and moderately increase levels of C1 esterase inhibitor protein (normally deficient). A significant increase in C4 protein (also involved in the complement pathway) was also observed (Koo et al, 1983).

b) These benefits have not been duplicated in other open or controlled studies. A well-controlled study is required.

HIV infection

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Ineffective in producing virologic/immunologic improvement in small studies

3) Adult:

a) Oral dehydroepiandrosterone 50 milligrams (mg) given sublingually once daily for 4 months had no effect on CD4 cell counts or p24 antigen levels in HIV-infected patients in a small, placebo-controlled study (n=32). Effects on viral load (HIV-RNA) were not evaluated. A significant improvement in only 2 of 10 dimensions (self-perceived mental health and health distress) on a quality-of-life scale (MOS-HIV) was demonstrated during therapy; improvement in quality-of-life was the primary study endpoint (Piketty et al, 2001a).

b) Other small studies have also failed to demonstrate immunologic or virologic benefit of dehydroepiandrosterone therapy (Jacobson et al, 1991; Dyner et al, 1993).

Menopausal symptom
1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Some metabolic (including lipid) and clinical benefits have been reported with daily doses of 25 to 50 milligrams (mg); however, the clinical relevance of some metabolic changes requires clarification.

Increases in bone mineral density have been reported in some studies. All studies have been small, and some were not controlled.

3) Adult:

a) Evaluated Data

1) Oral dehydroepiandrosterone and its sulfate ester have produced metabolic changes considered to be beneficial in early and postmenopausal women in small open and controlled studies (total n=40) (Stomati et al, 2000b; Stomati et al, 1999); with doses of 50 mg daily of dehydroepiandrosterone or dehydroepiandrosterone sulfate (DHEAS) for up to 6 months, increases (usually significant) of serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, testosterone, dihydrotestosterone, allopregnanolone, estradiol, estrone, and beta-endorphin were observed; cortisol levels decreased and progesterone levels remained unchanged. Improvements in Kupperman scores (vasomotor/psychological complaints) were observed during treatment, but changes were not always statistically significant. The authors speculate that, in addition to estrogenic effects, many metabolic changes observed may be responsible for benefits of dehydroepiandrosterone and its metabolites in reverting aging processes and improving quality of life (eg, improved well-being due to beta-endorphin increases, anxiolytic actions of allopregnanolone, anabolic actions of androstenedione) (Stomati et al, 2000b). However, clear benefits of dehydroepiandrosterone on aging have not been clearly established, and the clinical relevance of most metabolic effects requires clarification.

2) In a further study (Lasco et al, 2001a), significant improvement in insulin sensitivity (euglycemic clamp studies) and lipid parameters was reported after one year of treatment with 25 mg daily in early postmenopausal women in a placebo-controlled (unblinded) study (n=20). Significant increases in high-density lipoprotein (HDL) cholesterol (12%) and decreases in low-density lipoprotein cholesterol (11%) and triglycerides...
(20%) were observed at 12 months. There was no change in glucose tolerance.  
3) Bone mineral density (BMD) in postmenopausal women has been increased during dehydroepiandrosterone therapy in some studies (Villareal et al, 2000b; Labrie et al, 1997a) but not in another (Morales et al, 1998b); concurrent estrogen therapy in the latter study may have been a confounding factor, masking potential antiresorptive effects of dehydroepiandrosterone, although this is speculative.  
4) All of these studies involved small numbers of patients and larger trials are necessary, especially to confirm benefits on BMD.  

b) Clinical-Study Summaries  

1) In an open study (n=14), topical application of dehydroepiandrosterone 10% cream daily to the thigh area, in amounts to achieve dehydroepiandrosterone plasma levels of 20 to 30 nanomols/liter (nmol/L) (3 to 5 grams (g) daily), was associated with slight but significant increases in hip bone mineral density (BMD) after 12 months of treatment (from 0.74 at baseline to 0.76 g/cm(2)). Significant increases in osteocalcin levels (marker of bone formation) and decreases in the urinary hydroxyproline/creatinine ratio and plasma alkaline phosphatase relative to baseline were also reported at 12 months. Atrophic vaginal smears at baseline normalized during therapy in the majority of evaluable women. Nonspecific increases in energy level and feelings of well-being were described by some women (Labrie et al, 1997a). However, in the absence of a control group in this study, it is not possible to ascribe any change directly to the actions of dehydroepiandrosterone.  

Simple obesity  
1) Overview  

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS  

2) Summary:  

Ineffective in promoting significant weight loss in obese patients in limited studies  
3) Adult:  

a) Limited studies, mainly placebo-controlled, have not demonstrated significant weight loss in obese patients with oral (up to 1600 milligrams (mg) daily) or sublingual (40 mg twice daily) dehydroepiandrosterone supplementation for up to one month (Vogiatzi et al, 1996; Usiskin et al,
Although variable effects on fat mass have been reported, a significant decrease in body weight has not been observed in normal men and women or postmenopausal women (Morales et al, 1994a; Villareal et al, 2000b; Nestler et al, 1988). However, all studies have been small, and were of relatively short duration. A larger trial is suggested.

**Systemic lupus erythematosus**

1) Overview

FDa Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class III  
Strength of Evidence: Adult, Category B  
See Drug Consult reference:  
[RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Oral dehydroepiandrosterone has reduced steroid requirements, improved disease activity, and demonstrated some evidence of bone-preserving effects in women with systemic lupus erythematosus (SLE) in small open and controlled studies; however, statistical significance for these effects was not often achieved. The main role of dehydroepiandrosterone in this setting may be to enable steroid dose reduction; additional and larger studies are required to confirm this benefit, and determine if any clinically relevant disease-modifying effect exists.

3) Adult:

a) In a 6-month double-blind, placebo-controlled study involving 28 female systemic lupus erythematosus (SLE) patients, dehydroepiandrosterone supplementation (200 milligrams (mg) daily) was associated with some improvement in the SLE Disease Activity Index (SLEDAI) and patient and physician overall disease assessment, and reduced prednisone requirements. In general, increases in SLE disease activity were seen only in the placebo group. However, statistically significant reductions in the treatment group were found only in the patient's overall assessment of the disease after 3 months. Lupus flares occurred in 8 placebo patients and 3 DHEA patients. No laboratory parameters showed significant changes. The dehydroepiandrosterone group showed a slight reduction in prednisone requirement after 3 months, whereas the placebo group showed a slight increase; however, these changes did not achieve significance (van Vollenhoven et al, 1995a).

b) Dehydroepiandrosterone supplementation, 200 mg daily for 3 to 6 months, reduced SLE symptoms in an open study of 10 female patients with mild-to-moderate SLE and various disease manifestations. At the end
of treatment, SLEDAI scores had decreased, although not statistically significantly. Physician overall assessment of disease activity improved significantly following dehydroepiandrosterone therapy (37.2 to 27.2, p=0.040). Patient overall disease assessment also improved, but this was not significant. A nonsignificant trend toward a reduction in proteinuria from baseline was observed during dehydroepiandrosterone therapy in affected patients. The required dosage of prednisone (or prednisone equivalent) per day for symptomatic treatment was significantly reduced in the dehydroepiandrosterone group at 3 months (from 14.5 to 9.4 mg/day, p=0.028) and 6 months (14.8 to 5.6 mg/day, p=0.042) (van Vollenhoven et al, 1994a).

c) Dehydroepiandrosterone supplementation in SLE (200 mg daily for 3 to 6 months) plus steroids did not significantly affect SL Activity Measure (SLAM) or SLEDAI scores in 19 female patients with mild or moderate disease in a placebo-controlled study (van Vollenhoven et al, 1999).

d) Statistically significant improvements were reported in a case-study involving 23 female patients with mild or moderate SLE. Dehydroepiandrosterone was initiated at a dose of 50 milligrams (mg) daily and increased in a step-wise fashion to a maximum of 600 mg daily. Twelve of the patients stopped the study due to adverse effects, while 10 continued with no adverse events and achieved symptom remission. The most common adverse effect was acne, not related to either serum levels of dehydroepiandrosterone or dehydroepiandrosterone sulfate, or the dose of dehydroepiandrosterone. All patients were assessed by SLEDAI, SLAM, patient and physician VAS, VAS pain, and Krup Fatigue Severity Score (FSS). SLEDAI, SLAM, and patient VAS scores over the 6-month period demonstrated a statistically significant decrease in disease activity. However, FSS did not change. Due to the variation of clinical response as well as side effects in the range of dosing, predictable levels were investigated. These levels were largely variable but did increase with dose. As FSS scores did not change over 6 months (although patients claimed to have less fatigue), FSS may have been a poor measurement tool for this group. This study suggests that benefits of dehydroepiandrosterone may vary with the individual and are not dose dependent (Barry et al, 1998a).

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