

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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HFD-550

SUBJECT: OPDRA Postmarketing Safety Review (PID 000665)
Drug: Prasterone NDA 21-239 (Dehydroepiandrosterone-DHEA)
Reaction: Summary of Spontaneous Postmarketing Case Reports

EXECUTIVE SUMMARY

This document provides an overview of postmarketing adverse events reported in association with the use of Dehydroepiandrosterone (DHEA). These cases were retrieved from the Adverse Event Reporting System (AERS), CFSAN's postmarketing database, and the medical literature.

There were 65 postmarketing adverse event cases possibly associated with the use of DHEA. Other than the single report of worsening metastatic prostate cancer¹ previously described in the review by Parivash Nourjah, Ph.D, entitled *Epidemiologic evidence of DHEA in the etiology of neoplasia*, there were no additional reports of neoplasia found in the any of the above databases or the medical literature.

Forty-two of the 65 cases fall into the following body systems: urologic/renal (5), reproductive/endocrine (5), cardiovascular (9), gastrointestinal (8), central nervous system (7), dermatological (7), and hematological (2). There were also five individuals with psychiatric adverse events and 17 cases with general symptoms or miscellaneous events that could not easily be categorized into a body system. Four of the 65 cases were published in the medical literature.¹⁻⁴

Approximately 40% of the cases were concerning. The adverse events involving the urologic/renal, cardiovascular, and gastrointestinal body systems as well as the psychiatric adverse events were particularly concerning because they had the highest number of hospitalizations ($\geq 50\%$). However, because the overall numbers of cases in

each of these body systems were small and in many cases confounded by concomitant or co-suspect medication, we identified no clear safety signals with this product.

INTRODUCTION

Dehydroepiandrosterone (DHEA) is an endogenous hormone secreted by the adrenal cortex. It has been widely available in the US as a dietary supplement and promoted for its anti-aging effects as well as other uses. Prasterone (the pharmaceutical generic designation for DHEA) is currently under review in the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), for the treatment of mild to moderate systemic lupus erythematosus (SLE) in women.

This serves as a companion document to the review by Parivash Nourjah, Ph.D, entitled *Epidemiologic evidence of DHEA in the etiology of neoplasia* which focused on a review of the literature for any published epidemiologic studies that examined cancer risk associated with exogenous DHEA administration. The primary objective in this review was to determine if there were any case reports in our postmarketing databases or the medical literature of neoplasia in association with the use of DHEA. Our secondary objective was to provide an overview of postmarketing adverse events reported in association with the use of DHEA

REVIEW OF SPONTANEOUS POSTMARKETING REPORTS

Selection of Cases

We searched AERS on February 13, 2001 for all reports with dehydroepiandrosterone and prasterone. We also requested a query of CFSAN's adverse event reporting database for case reports with DHEA. Four additional case reports were found in the medical literature. All searches resulted in a total of 64 unique reports involving 68 consumers or patients. Three AERS reports were excluded because the drug products did not appear to contain DHEA. Below is an overall summary and summary by body system of the 65 cases.

Summary of Cases

Of the 65 cases identified in the AERS database, CFSAN ARMS database, and the medical literature, there was only one report of neoplasia¹. This was summarized in Dr. Nourjah's review and is described in the urologic/renal section below.

Forty-two of the 65 cases fall into the following body systems: urological/renal (5), reproductive/endocrine (5), cardiovascular (9), gastrointestinal (8), central nervous system (7), dermatological (7), and hematological (2). There were also five individuals with psychiatric adverse events and 17 cases with general symptoms or miscellaneous events that could not easily be categorized into a body system. Four of cases were published in the medical literature.

Approximately 40% of the cases were concerning. The adverse events involving the urologic/renal, cardiovascular, and gastrointestinal body systems as well as the psychiatric adverse events were particularly concerning because they had the highest number of hospitalizations ($\geq 50\%$). The concerning cases are briefly summarized below but may be described in greater detail under the specific body system summaries.

- Urological/renal system -Literature case of worsening metastatic prostate cancer (1), increased symptoms of prostatism in patients with BPH (2), and renal failure (1).
- Cardiovascular system - Literature case of cardiac arrhythmia with a positive rechallenge (1), other arrhythmia's (4), MI (1), DVT (1), and hypertensive urgency (1).
- Gastrointestinal system– liver failure (1) and hepatitis (3)
- Psychiatric events – two patients with mania and one patient with psychosis required hospitalization.

The overall numbers of cases in each of these body systems were small and in many cases confounded by concomitant or co-suspect medication.

1. Urological and Renal Events

There are five cases involving the urologic or renal system. The cases involved all males. The patient's ages were 5, 34, 68, and 71 years old (not reported-1). The events include resurgence of prostate carcinoma (1), worsening symptoms of prostatism (2), renal failure (1), and dysuria (1). The following additional information was noted in the cases.

DHEA daily dose:	25mg-2, 50mg-1, up to 700mg-1 (not reported-1)
Time to onset:	2 to 180 days
Outcome:	Emergency room treatment/hospitalization-2, required intervention-3
Indications for use:	Short stature-1 Increase muscle strength-1 Low hemoglobin (anemia)-1 Not reported-2
Dechallenge:	Positive-3
Rechallenge:	Positive-0
Event year:	1995-1, 1996-2, 1997-2
Reporter:	Health care professional-3, Consumer-2

The literature case report (described in Dr. Nourjah's review) involves a 68-year-old male with metastatic prostate cancer who was treated with escalating doses of DHEA (200 to 700mg per day) presumably for the treatment of anemia unresponsive to erythropoetin. His blood cells increased during DHEA eliminating his need for transfusions. However, the patient began to develop facial numbness, increase in prostate size, and difficulty voiding. His PSA levels increased to greater than 10,000 ng/mL (2726 ng/mL prior to DHEA). DHEA was discontinued and DES was initiated with improvement in symptoms and decrease in PSA. Although, he exhibited a positive

dechallenge after discontinuation of DHEA, his improvement may have been due to treatment with DES.¹

There were two patients with a history of BPH who developed worsening symptoms. One case described increased symptoms of prostatism (not specified) after several months of DHEA. This patient was on Cardura and Dilacor at the time. The second case described difficulty urinating after taking DHEA for two weeks.

The renal failure case was reported by the patient's mother and was not well described. She reported that her 34-year-old son took seven different dietary supplement products (including DHEA) for about one month and developed renal failure. He was hospitalized and partial renal function returned. No additional information was provided.

The last case involves a 5-year-old who started bedwetting (coded as dysuria) two days after taking DHEA 50mg per day for central core disease. He was taking many other concomitant dietary products including enzymes, vitamins and atomadine. All products were discontinued and his event abated.

2. Reproductive and Endocrine Events

There are five cases involving reproductive or endocrine events in patients ranging in age from 39 to 50 years old (mean-44.7, median-45). The cases involved three males and two females. The events include gynecomastia (1), resumption of menstruation (1), increased estrogen levels and hot flashes (1), hyperglycemia (1), and painful intercourse and hematuria (1). The following additional information was noted in the cases.

DHEA daily dose:	25mg – 3 (not reported-2)
Time to onset:	7 days - 1, 30 days - 2, several months -1 (not reported-1)
Outcome:	No serious outcomes
Indications for use:	Menopausal symptoms-1 Immune system booster-1 Aging-1 Not reported-2
Dechallenge:	Positive-4
Rechallenge:	Positive-1
Event year:	1996-3, 1999-1 (not reported-1)
Reporter:	Health care professional-4, Consumer-1

None of the cases involved a serious outcome but four sought medical care from a physician. All cases are summarized below for your review. The first three were possibly related to the use of DHEA. Underlying disease and use of another product that was more temporally associated with the event confounded the last two cases.

AERS image # 1923242, CFSAN 11859, 1996

A 39-year-old male developed bilateral breast enlargement during use of DHEA 25mg per day for 1 to 1.5 months. They were described as very inflamed, bright red, and very

tender. He reported no relevant medical history or concomitant medications. The event reportedly abated after discontinuation of the DHEA.

AERS image # 2055734, CFSAN 12028, 1996

A 42-year-old female stated that she had not menstruated since February 1996. In December 1996, seven days after initiating DHEA 25mg per day, she started a full menstrual cycle.

AERS image # 2000126, 1997

A male consumer (age unknown) began using DHEA 10mg and then increased to 25mg after 2-3 weeks. Less than 1 month later, he experienced extreme pain during intercourse and observed large amounts of blood in both semen and urine. Urologists ruled out both cancer and STD as causes. He discontinued using the product and one week later his symptoms disappeared.

CFSAN 13543, 1999

A 48-year-old female complained of hot flashes. Was taking Rejuvex (for several months) and DHEA (duration unknown). She was status post hysterectomy with one ovary and was not receiving hormone replacement therapy. FSH, LH, and estradiol levels measured were measured and estradiol levels were noted to be markedly elevated 2777 pg/ml. Both products were discontinued for 2 months with levels normalizing (estradiol 54 pg/ml). Rejuvex was restarted and within two weeks the estradiol level was 498 pg/ml. Rejuvex contains several vitamins and ground up bovine endocrine organs.

AERS image # 1927333, CFSAN 12220, 1997

A 50-year-old Ethiopian male presented with fatigue, polyuria, and polydipsia and was found to have a blood sugar of 600. He was receiving DHEA 50mg per day for an unknown duration. His DHEA was discontinued and he was started on Glucotrol. With diet management and Glucotrol his blood glucose decreased to low normal and Glucotrol was discontinued. On follow up the reporter mentioned that the patient was subsequently diagnosed with late onset type I diabetes.

3. Cardiovascular Events

There are nine cases involving cardiovascular events in patients ranging in age from 23 to 72 years old (mean-44.7, median-45). The cases involved seven males and two females. The events include cardiac arrhythmias in five patients (unspecified-3, PVC's-1, and SVT-1). The remaining four patients experienced chest pain and palpitations (1), myocardial infarction (1), deep vein thrombosis (1), and hypertensive urgency (1). The following additional information was noted in the cases.

DHEA dose:	25mg-3, 50mg-2, 100mg-1 (not reported-3)
Time to onset:	range of 1 to 120 days; mean-49, median 30 (not reported-2)
Outcome:	Death-1, hospitalization-3, emergency room-4, required intervention (unspecified)-1
Indications for use:	Build muscle mass-1

	Maintain general health-1
	Treat decreased adrenal function expected with increased age-1
	Not reported-6
Dechallenge:	Positive-6
Rechallenge:	Positive-1
Event year:	1996-1, 1997-4, 1998-2, 1999-1 (not reported-1)
Reporter:	Health care professional-8, Consumer-1

Possible cofounders were noted in three cases including the case resulting in death. The death involved a 37-year-old male who was found dead at home. The cause of death was not reported, however the medical examiner inquired whether any of eight dietary supplements could be responsible for a cardiac arrhythmia. One case involved a 72-year-old male who developed a DVT approximately one month after he initiated use of DHEA and DMSO. Both products were listed as suspect. Another case involved a 41-year-old male with a history of increased heart rate who was admitted to the ER for unspecified cardiac arrhythmia 2.5 months after starting DHEA and creatine. The remaining cases reported both a negative cardiac history and no concomitant medication (3) or they did not provide medical history information (3). Several interesting cases are summarized below for your review.

Literature Case Report, 1998

A 55-year-old male presented to an ER with palpitations two weeks after initiating DHEA 50mg. Benign premature atrial contractions (PAC) and some premature ventricular contractions (PVC) were noted. Work-up including thyroid-stimulating hormone levels, cardiac echocardiogram, potassium levels, and exercise stress test results were unremarkable. Past medical history was not provided other than his use of Redux for the previous 12 months, which had been discontinued two weeks before initiating DHEA. He was discharged on propranolol and continued use of DHEA for three months. Three to four months later, he reinitiated DHEA (presumably off beta-blocker) and within 36 hours arrhythmias recurred and PAC and PVC was noted on a Holter Monitor. The arrhythmias were controlled with atenolol and DHEA was discontinued.²

AERS Image # 3030083-5-00, direct report, 1997

A 45-year-old male was admitted for an acute MI that occurred during exercise. He received a thrombolytic agent with resolution. Cardiac catheterization for recurrent pain showed “fairly normal coronary arteries with only mild irregularities with occluding thrombus in the right coronary artery”. His only reported cardiac risk factor was moderately elevated cholesterol. His cholesterol was 230, HDL 49, and LDL 160. Baseline values were not provided.

CFSAN # 12219, direct report, 1997

A 23-year-old male initiated use of DHEA to build up muscle tone. He was reported to have taken up to 20 tablets per day for 3 to 4 months. His mother (nurse) noticed that he had put on over 40 pounds of weight and decided to check his blood pressure, which was found to be in the range of 240/140. His blood pressure was confirmed in the ER. He was also noted to have elevated liver functions tests (LFT). . He was treated for hypertension.

Two weeks following discontinuation of DHEA his LFTs appeared to be returning to normal however his blood pressure remained labile.

4. Gastrointestinal System Events

There are eight cases involving gastrointestinal system adverse events in patients ranging in age from 21 to 63 years old (mean-41.6, median-43, not reported-3). The cases involved four males and four females. Serious events occurred in five individuals and include liver failure (1), hepatitis (3), abdominal pain requiring exploratory laparotomy, and possible GI bleed (1). Two patients experienced less severe reactions, which include unspecified stomach problems (1) and gas (1). The following additional information was noted in the cases.

DHEA daily dose:	25mg-1, 50mg-1, 200mg-1 (not reported-5)
Time to onset:	14 days – 1, 60 days – 1, 11 months - 1 (not reported-5)
Outcome:	Hospitalization – 3 (not reported-5)
Indications for use:	SLE-1 Build muscle-1 Aging-2 Not reported-4
Dechallenge:	Positive-3
Rechallenge:	Positive-0
Event year:	1996-1, 1997-1, 1998-2 (not reported-4)
Reporter:	Health care professional-5, Consumer-3

There was one study report of a 36-year-old female with SLE who was hospitalized three times for recurrent abdominal pain. She had been enrolled in a clinical trial for SLE for ~10 months and was receiving DHEA 200mg/day. On her third admission she underwent exploratory laparotomy. The findings were not provided. The report mentioned that she had a history of previous abdominal surgery with possible adhesions.

There were three consumer reports. Two did not appear to be serious and only reported gas and “stomach problems. The third consumer claimed that she experienced vomiting with blood and blood per rectum for five days. She did not mention seeking medical treatment.

There were four liver related events. One physician reported two of the cases. He reported a 43-year-old female and a 45-year-old male who developed hepatitis while taking an unknown dose of DHEA. Neither of the reports were well documented other than stating that neither patient had a relevant medical history nor were they taking concomitant OTC medications. In both of the other two cases, concomitant medications might have played a role. These cases are described below for your review.

AERS image # 3193812-6-00 , 1998

A 21-year-old male experienced cold symptoms for 1-2 weeks and began taking acetaminophen 1-2 q4-6h prn (6-10gm). He was a wrestler and was taking DHEA 50mg

per day for approximately 2-3 months prior to the event. He had 8 beers/5 shots x 3 days w/APAP. Within two weeks he developed RUQ pain, dark urine, jaundice, and was admitted with hepatic failure. Underwent liver transplant. Although acetaminophen possibly in conjunction with alcohol are suspect, the role of DHEA cannot be dismissed.

CFSAN # 13200, 1998

A 63-year-old male was diagnosed with cholestatic hepatitis while taking an unknown dose of DHEA and Pantothenic Acid 8gm/day. This was discovered during blood donation. He presented with elevated ammonia, transaminases, bilirubin, and PT/INR. All viral hepatitis screening was negative. He was hospitalized for two days neurologically intact. No additional information was provided. The pantothenic dose was > 1000 times the recommended daily allowance for adults.

5. Central Nervous System Events

There are seven cases involving central nervous system events in patients ranging in age from 49 to 59 years old (mean-54.2, median-56, not reported-2). The cases involved four males and three females. Serious events occurred in three individuals and include transient ischemic attack (1), seizure (1), and sensory peripheral neuropathy (1). The remaining four patients experienced less severe reactions which include headaches (2), numbness (1), and sleepiness (1). The following additional information was noted in the cases.

DHEA dose:	25mg-3, 50mg-1, 100mg-1 (not reported-2)
Time to onset:	range of 3 to 90 days; mean-35, median-7 (not reported-2)
Outcome:	Hospitalization-1, disability-1, saw physician-3, (not reported-2)
Indications for use:	Maintain general health-1 Muscle pain-1 Entered study (Hormone Replacement Program)-1 Not reported-4
Dechallenge:	Positive-3
Rechallenge:	Positive-2
Event year:	1997-3, 1998-1, 1999-1, 2000-1 (not reported-1)
Reporter:	Health care professional-2, Consumer-5

The four cases involving headache, numbness, and sleepiness did not appear to be serious. In one case a mother reported an event (described in Psychiatric Adverse Event section of this document) in her son but also mentioned that she experienced migraine headaches while taking DHEA. One patient experienced numbness, coldness, and tingling of her face, scalp, and neck. Her neurological exam however was found to be normal.

There were three serious cases involving seizure, TIA, and Sensory Peripheral Polyneuropathy. The case involving seizure exhibited a positive rechallenge and did not appear to be confounded by past medical history or concomitant medication. Consumers reported two cases and in one case the event appeared to be more temporally related to

the concomitant use of another product. These cases are summarized below for your review.

AERS image # 20411530, CFSAN # 12603, 1997

A 51-year-old male reported having a TIA approximately two weeks after starting DHEA 25mg per day. He was diagnosed and hospitalized for three days. According to report, he underwent numerous tests which were negative (CT, MRI, ECG, and EEG)

CFSAN # 13160, 1998

A 56-year-old male had taken DHEA for three months and experienced two seizures during that time. He discontinued use for several months and then restarted and experienced a seizure after seven days. His past medical history and concomitant medications were not reported. An EEG, MRI and exam were found to be normal.

AERS image # 3551903-1-00, 2000

A 49-year-old male reported enrolling in a Hormone Replacement Program offered by the[]. As part of the program, he began taking DHEA 50mg per day, desiccated thyroid (Armour, 1gm per day), melatonin, B complex, testosterone cream, and human growth hormone (HGH) injections (4IU per week). After one month, he started to experience numbness in both feet. He discontinued use of the HGH for a few weeks and the problem disappeared. He restarted the injections and the numbness and pain came back. A second discontinuation did not result in resolution of his symptoms. He was diagnosed with Sensory Peripheral Polyneuropathy and reported that he was partially disabled (difficulty walking, pain interrupts sleep).

6. Dermatological Events

There are seven cases involving dermatological reactions in patients ranging in age from 29 to 83 years old (mean-58.2, median-62, not reported-1). The cases involved four males and three females. The events include rash in four patients (unspecified-3, macular erythematous eruption-1). The remaining three patients experienced alopecia (2), and acne with pustules (1). The following additional information was noted in the cases.

DHEA dose:	25mg-1, 50mg-3 (not reported-3)
Time to onset:	range of 4 to 55 days; mean-14.4, median 14 (not reported-2)
Outcome:	Required (unspecified) intervention-1, saw physician-1 (not reported-5)
Indications for use:	Aging-1 Hormone deficiency-1 Impotence-1 Not reported-4
Dechallenge:	Positive-3
Rechallenge:	Positive-0
Event year:	1995-1, 1997-3 (not reported-3)
Reporter:	Health care professional-4, Consumer-3

None of these cases reported a serious outcome as a result of the events. One case is summarized below for your review.

AERS image # 1933056, CFSAN # 12099, 1997

An 83-year-old male developed a macular erythematous eruption from the mid-thigh to his toes varying in diameter from 1mm to 1cm approximately seven weeks after starting DHEA. They were non-tender with no subcutaneous hemorrhage. The rest of the physical exam was normal. He was on concomitant Nicotine patches intermittently for 18 months. The rash reportedly began to fade after the DHEA was discontinued.

7. Hematological Events

There were two individuals that experienced hematological events. One case involves a 50-year-old male that presented with fever, cough, malaise, and aching approximately six weeks after starting DHEA 50mg per day. A complete blood count revealed a platelet count of 38K. DHEA was discontinued and a repeat CBC two and three weeks later was 69K and 122K, respectively. The patient did not appear to require hospitalization. He had a history of chronic low platelets secondary to a splenectomy. He also reported receiving a flu shot 1 week prior to symptoms.

The second case involves a 46-year-old male who started taking DHEA 50mg BID on 4/14/99 and Celebrex 100mg BID on 4/26/99. On 5/3/99, he presented to his physician with bruising all over his chest, arms, and legs. He had not sustained any trauma. Celebrex was discontinued but it is unclear if DHEA was continued. No further information was provided.

8. Psychiatric Events

There are five individuals who experienced psychiatric events while receiving DHEA. Two of these cases were reported in the medical literature. The cases involved individuals ranging in age from 20 to 68 years old (mean 36.6, median-51). The cases involved three males and one female (not reported-1). The events include mania (2), manic depression (1), psychosis (1), and panic attacks (1). The following additional information was noted in the cases.

DHEA daily dose:	25mg-1, 50mg-1, 150mg-1, 200-300mg-1 (not reported-1)
Time to onset:	range of 40 to 120 days; (not reported-1)
Outcome:	Hospitalization-3
Indications for use:	General health-1 Impotence-1 To increase energy-1 Not reported-2
Dechallenge:	Positive-2
Event year:	1996-1, 1998-1, 1999-1 (not reported-2)
Reporter:	Health care professional-3, Consumer-2

All cases were confounded by either concomitant medication or other dietary products (3) and/or past psychiatric history (3). In one, the individual was taking five different dietary supplements including ephedrine and ephedra. A second was taking concomitant beef liver extract and a multivitamin. Another report listed Celexa as a co-suspect agent. Past psychiatry histories include history of panic attacks, history of manic depression, and history of daily alcohol consumption (possible alcoholism). Both literature reports is described below for your review.

Literature Case Report, 1999

A 68-year-old male with no documented psychiatric history was admitted to an inpatient psychiatric hospital after his family members noting increasingly odd behavior. Symptoms included agitation, delusional thinking, decreased sleep and appetite, and spending sprees which started approximately three months prior to admission. He had begun taking DHEA six months prior to admission at dose of 100mg daily. This dose was increased to 200-300mg per day. He had a history of daily alcohol use as much as one case of beer. On admission his use was said to be ~ two beers per day. Drug and urine screens were negative. He was treated with valproic acid and his symptoms improved. He was discharged seven days later.³

Literature Case Report, 1999

A 51-year-old male with no prior psychiatric history was involuntarily hospitalized because of grandiose delusions, expansive and irritable mood, and extreme psychomotor agitation. He had begun taking DHEA 50mg per day several months earlier to increase his energy level. He was also taking beef liver extract and a multivitamin. The severity of his psychosis necessitated the appointment of a temporary personal guardian. He was treated during his hospitalization with a combination of haloperidol and divaproex. He responded well and his symptoms disappeared after several weeks.⁴

9. General Symptoms or Miscellaneous Adverse Events

There are 17 individuals who experienced general symptoms or miscellaneous events that could not easily be categorized into one organ system. The cases involved individuals ranging in age from 28 to 84 years old (mean-49.5, median-47, not reported-4). The cases involved nine males and six females (not reported-2). The following additional information was noted in the cases.

DHEA dose:	25mg-3, 35mg-1, 50mg-5, overdose-1 (not reported-7)
Time to onset:	range of 1 day to 1.5 years; mean-98, median 5 (not reported-4)
Outcome:	Hospitalization/ER-3, life-threatening-1, saw physician-3, required unspecified intervention-2 (not reported-8)
Indications for use:	Aging/to stay young-4 Maintain general health-2 Headache-1 Hormone supplement-1 Not reported-9
Dechallenge:	Positive-12, negative-1

Rechallenge: Positive-1
Event year: 1996-4, 1997-6, 1998-1 (not reported-6)
Reporter: Health care professional-10, Consumer-7

Overall most cases were not well documented. One interesting case involves a 41-year-old female who reports taking DHEA 25mg sublingually. After 2 weeks she developed a benign submandibular tumor. She stopped taking the product for 1 week and the tumor reduced in size. She took the product again orally and the tumor returned.

There were four patients that reported requiring hospitalization, emergency room treatment, and/or reported the event as life-threatening. One involved a female (who spoke little English) who may have taken an entire bottle of DHEA for a headache. She was hospitalized with a low-grade temperature and a low blood pressure (100/50). One patient reportedly developed an anaphylactic reaction after taking one dose of DHEA 50mg. She was given epinephrine and Benadryl with good results. An elderly male listed numerous subjective “serious” adverse events to a single dose of DHEA that he reported as life threatening and requiring hospitalization. His physician noted that he has a history of reporting drug reactions. The reactions include weakness, fatigue, ataxia, insomnia, decreased appetite, SOB, rapid heart rate, and sensation of doom. The last involves a 60-year-old male with severe HTN who became hypokalemic and syncopal after four days of DHEA. This was reported life threatening, however no additional information was provided.

The remaining cases listed numerous adverse events that in most cases did not appear to be serious and generally resulted only in discontinuation of DHEA and/or other products. These events include weakness, insomnia, headache, CP, indigestion, constipation, tremors, dizziness, fainting spells, depression, muscle cramps, nightmares, guilt feelings, shortness of breath, weight gain, swelling of neck, malaise, memory loss, arm numbness, venous distension, chest heaviness, tinnitus, possible drug interaction, feet tingling, tachycardia, and hyperactivity.

CONCLUSIONS

There were 65 postmarketing adverse event cases possibly associated with the use of DHEA. Other than the single report of worsening metastatic prostate cancer previously described in the review by Parivash Nourjah, Ph.D, entitled *Epidemiologic evidence of DHEA in the etiology of neoplasia*, there were no additional reports of neoplasia found in the any of the above databases or the medical literature.

Forty-two of the 65 cases fall into the following body systems: urologic/renal (5), reproductive/endocrine (5), cardiovascular (9), gastrointestinal (8), central nervous system (7), dermatological (7), and hematological (2). There were also five individuals with psychiatric adverse events and 17 cases with general symptoms or miscellaneous events that could not easily be categorized into a body system. Four cases were published in the medical literature.

Approximately 40% of the cases were concerning. The urologic/renal, cardiovascular, gastrointestinal, and psychiatric adverse events were particularly concerning because they had the highest number of hospitalizations ($\geq 50\%$). However, because the overall numbers of cases in each of these body systems were small and in many cases confounded by concomitant or co-suspect medication, we identified no clear safety signals with this product.

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