



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

COMPOUNDING FOR MALE ANDROPAUSE

GOALS AND OBJECTIVES

Goal: The purpose of this article is to provide a discussion of the occurrence, symptoms and drug and nondrug treatment associated with male andropause and natural hormone replacement therapy.

Objectives: After reading and studying this article, the participant should be able to:

1. describe the symptoms associated with the onset of male andropause.
2. explain the value of laboratory tests providing total and free serum testosterone levels.
3. list current drug therapies available for the treatment of the symptoms of male andropause.
4. discuss current non-drug therapies available for the treatment of male andropause.

INTRODUCTION

In the United States, it has been stated that there are over 25 million men (about 408 million worldwide) between the ages of 40 and 55 that may be going through what is termed "male menopause", "or "andropause". In twenty years, the number in the US will increase to over 57 million (960 million worldwide).

Male andropause involves the hormonal, physiological, chemical and psychosocial changes that occur in men, generally between the ages of 40 and 55 (range of 35-65). It is also called viropause and is a physical condition with psychological, interpersonal, social and spiritual dimensions. Male andropause begins with hormonal and physiological changes that affect various aspects of a man's life; the condition is called hypogonadism where the levels of testosterone (testis) drops. Human growth hormone (pituitary), DHEA and androstenedione (adrenal gland) also begin to diminish. It is interesting to note that ancient Indians, Greeks and Egyptians were aware that extracts of animal testes could be used in this condition ostensibly to promote virility, potency and vigor in men. Also of note, testosterone was the first hormone to be discovered, yet its overall role is still not completely defined.

Men experience psychosocial symptoms, or "growing pains", as they enter this stage of their lives: parents are dying, job horizons are narrowing, retirement looms, friends are having their first heart attacks and the past rushes by in memories with unrealized dreams and unfulfilled opportunities. Children are leaving home to establish their own lives. Friends are getting sick. Andropause is seen by many as a threat to masculinity, macho self-image, ego, and self-esteem. Men are reluctant to discuss this issue whereas women are very open with it. Women and men may be more alike than different during the menopausal stage.

Many, but not all, men probably experience slight versions of andropause; hormones and neuropeptides diminish and bodies sag and change shape. Common medical conditions like enlarged prostate develop, stamina and temperament change and men do not seem as well equipped to deal with these extremes as women, who expect it.

Loyd V. Allen, Jr., Ph.D., R.Ph.

One method of treating male andropause is similar to that for women, natural hormone replacement therapy. Hormone replacement therapy may become as routine for men as it is now for women, leading to benefits of slowing loss of bone mass and increased heart protection. The psychosocial aspects of andropause and how elders are viewed may need to be altered and considered as they are in some cultures; older men are looked upon and valued as peacemakers, wise counselors and mentors of youth.

We are presenting this issue for the support of quality compounding of natural hormone replacement preparations for men and preparations designed for men to cope with the symptoms associated with andropause.

DEFINITIONS AND ABBREVIATIONS

Natural (bio-identical) hormones refer to those hormones that are molecularly identical to those made in the human body and have the same exact chemical structure specifically, testosterone, DHEA and estradiol. Synthetic (Patented, Conventional, Artificial) hormones are those that are not usually found in humans and are chemically different from the naturally occurring human hormones specifically, danazol, fluoxymesterone, methyltestosterone, and oxandrolone. They are not identical in structure or activity to the natural hormones they are designed to emulate.

QUESTIONS TO PONDER CONCERNING ANDROPAUSE

Are all older men hypogonadal? Is the definition of hypogonadal the same in older men as compared to younger men? Should all men receive testosterone supplementation? Will testosterone supplementation produce meaningful results in all men? How about in men with low testosterone levels and sexual dysfunction compared to men with low testosterone levels without sexual dysfunction? How should testosterone replacement therapy be administered and at what doses?



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Is it really known that testosterone replacement therapy will benefit muscle function, sexual function, well-being and quality of life in older men; and, can it be done safely? What testosterone assay should be used in older vs younger men? How about free testosterone?

One must consider that in female HRT, the debate has been carried on for 30 years and is just now really beginning in men. All men may not be hypogonadal; in fact, it may be that andropause may not even occur in the majority of men, except for the slow decrease in testosterone level.

It is established that men's testosterone levels start declining after 20 to 30 years of age. Starting at about age 40, the testosterone level declines at a rate of about 0.4% total testosterone and 1.2% free testosterone per year. At what age or at what testosterone level should a man be considered hypogonadal?

In women, reproductive aging is a definite process with overt signs, i.e., cessation of menses. However, with men, it is a very gradual process without such overt signs.

MEN'S DAILY CYCLE

In young men, the highest testosterone levels occur in the morning between 6 and 8 AM, decreasing to a low point in the afternoon between 5 and 6 PM. In elderly men, the circadian rhythm is much flatter and is not necessarily consistent between men, as it is when younger.

THE STAGES OF A MAN'S LIFE

A man's life can be divided into different stages as it relates to hormone function, from infancy into mature adulthood. Testosterone tends to thrust us into adolescence and then usher us into adulthood; as it's levels decrease, it tells us we are finished with our first stage of adulthood and ready to begin the next phase of our lives (mature adulthood).

It has been stated that during mature adulthood, men can (1) Focus more on being and less on doing, (2) Relate to other men as friends and allies rather than as competitors, (3) Lay foundation for becoming healthy, wealthy and wise, (4) Become a mentor to younger men, (5) Become a respected elder in your community, (6) Grow old gracefully and, if done properly, (7) Add life to years, not just years to life.

SIGNS AND SYMPTOMS OF ANDROPAUSE

Men are generally reluctant or unwilling to acknowledge that the syndrome has crept up on them. The symptoms are not as overwhelming as the dramatic changes women experience and it may not affect all men; however, about 40% of men in their 40s, 50s and 60s will experience some of the symptoms, including lethargy, depression, irritability, mood swings and erectile dysfunction.

Testosterone levels begin to decrease for a number of reasons, including (1) the Leydig cells begin to decrease in number and function, (2) a sex hormone binding globulin (SHBG) increases with age, resulting in greater binding of testosterone with less free testosterone. There is a higher relative amount of estradiol with less testosterone being produced.

Symptoms that may be associated with andropause are listed in Table 1. At this time, there are also other changes that are occurring in a man's life.

As men pass 50, they tend to develop an enlarged prostate. As the gland increases in size, it squeezes the urethra, often causing increased urinary frequency, a weaker flow and difficulty beginning urination. The current treatments include finasteride (Proscar) and Saw Palmetto (made from the berries of a plant native to the American Southeast) which reduces the size of the prostate in only four to six weeks and is relatively effective. Zinc is also used to maintain a healthy prostate.

In addition to enlarged prostate, other prostate problems include prostatitis, and prostate cancer. It has been stated that men have odds of 100% of experiencing one of these three disorders.

Visceral fat increase has been associated with an increased vascular risk. Body fat in men increases from 18% to 36% between 18 and 85 years of age, with the largest increases in intraabdominal fat. Also, by age 70, an average man has about 26 pounds less lean body mass than at age 25.

Low testosterone can lead to osteoporosis in elderly men. This tends to happen later in men than in women because of the general tendency for men's bones to be thicker and denser than women's. In hypogonadal men, bone mineral density tends to increase with testosterone treatment.

In men, there may be an increase in circulating estrogen levels; common causes of estrogen increase during midlife include age-related increases in aromatase activity, alteration in liver function, zinc deficiency, obesity, overuse of alcohol, drug-induced estrogen imbalance and ingestion of estrogen-enhancing food or environmental substances. Also, fatty tissue contains more aromatase activity as compared with lean tissue resulting in more testosterone being converted to estradiol. Vitamin C deficiency is associated with high levels of aromatase activity whereas zinc inhibits aromatase activity.

Low testosterone levels may tend towards depression; the decrease in sexual function may also lead to depression, irritability and mood swings....this depression further leading to decreased sexual function.

LABORATORY EVALUATION

Laboratory evaluation for andropausal men can include (1) free testosterone, (2) total testosterone, (3) estradiol levels, (4) prostate specific antigens-PSA test, (5) CBC and (6) cholesterol. Sample laboratory values are listed in Table 2.

A diagnosis of hypogonadism has been suggested if at any age the total testosterone is less than 200 ng/dL. When the total testosterone level is below 200 ng/dL, evaluation should proceed with other laboratory tests, e.g. gonadotropins, prolactin, etc. If the result is borderline, i.e. 200-300 ng/dL, then a measurement of the free or bioavailable testosterone is suggested. Hypogonadism is defined as bioavailable testosterone levels less than 60 ng/dL. If one only considers the total testosterone levels, about 5% of men are classified as hypogonadal. If the free testosterone (non-SHBG bound testosterone) is used as the definitive assay, as many as 50% of men 60 or over could be testosterone deficient.

Serum (Total) testosterone measures all the testosterone in the serum, free and bound. Free (dialyzable testosterone) estimates the fraction of testosterone in blood that is not bound to protein (requiring a dialysis procedure). Bioavailable testosterone determines the amount of testosterone not bound to SHBG and includes that which is nonprotein bound and weakly bound to albumin; it is the portion that is bioavailable to tissues (usually obtained by using a precipitation method).

In men, the total testosterone decreases and the SHBG bound testosterone increases, resulting in a decrease in free testosterone. In summary, free testosterone is decreased with age more rapidly than total testosterone.

TREATMENT

The therapeutic goal is not to produce a "Mr. Elderly Strong Man", but to enable the adult man to maintain or improve strength to function better and more consistently. Many physicians hesitate to use testosterone supplementation as it is new, they have heard stories (sometimes related to synthetic androgen supplementation), and they are unsure of the results as it takes quite some time for them to become evident. There is no evidence that exogenous testosterone stimulates the development of prostate carcinoma; there has been no relationship established between endogenous testosterone and BPH. However, a contraindication to androgen replacement therapy is the presence of prostate cancer.

The treatment of andropause is, to some degree, seeking an elusive answer to a hormone imbalance. The patient and health care provider are, in many cases, seeking a simple answer to a complex problem, or set of symptoms. One simple answer generally does not exist. A few general rules can be stated related to hormone replacement therapy.

1. There is no simple answer or single approach to HRT.
2. Treat each patient as an individual.
3. HRT may be difficult and is time consuming.
4. Generally, one cannot successfully treat hormone imbalances with hormones alone (See Table 3).

The decision to use HRT is an individual one, based on the individual's particular risks. The goals of natural HRT are to (1) alleviate the symptoms caused by the natural decrease in production of hormones by the body, (2) replace the hormones to the extent to provide positive benefits, (3) bring the body back to normal hormonal balance, and (4) imitate the body's natural processes as much as possible. Natural testosterone replacement is central to the treatment of all aspects of "male menopause".

Testosterone supplementation has resulted in decreasing body fat mass from 6.4% to 1.4% and increases in lean mass from 3.2% to 5%. Increases in strength (grip strength) also are reported.

Total cholesterol and low density lipoproteins tend to significantly decrease with testosterone administration.

Three steroids of importance in male reproductive function are testosterone, dihydrotestosterone and estradiol. By far the greatest percentage of testosterone (over 95%) is secreted by the testicular Leydig cells. The dihydrotestosterone and estradiol are derived from both the direct secretion from the testes (20%) and also from conversion in peripheral tissues on androgen and estrogen precursors secreted by both the testes and adrenal glands (80%).

Hormone preparations that have been used include testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, fluoxymesterone, methyltestosterone (methyltestosterone is toxic to the liver and heart and may have clouded the benefits of testosterone replacement therapy), oxandrolone, progesterone and estradiol. Commercial testosterone products have been administered either by injection, implants/pellets, orally or as transdermal patches.

Injections: One disadvantage to testosterone enanthate and testosterone cypionate injections is that they are injected at 2 to 3 week intervals. The blood profiles are high after the injection, followed by a slow decline over the time interval until the next injection. This clearly does not follow the normal adult physiological pattern.

Implants/Pellets: Subdermal testosterone implants produce a similar pattern to the injections. Testosterone undecanoate administered orally gives a rapid onset of action but a short duration of action, consequently it may be administered several times daily.

Transdermal: In transdermal testosterone, the hormone is released slowly through the skin to deliver a constant level in the blood, again not a routine pattern, but convenient. Transdermal testosterone can be applied either to the scrotal area or to other areas.

Compounding pharmacists can offer many options to provide for different blood level profiles and convenience of administration, including some of the novel dosage forms provided at the end of this article. Topical testosterone can be applied using different vehicles to more closely mimic the normal adult physiological pattern, i.e., apply early in the morning where it should be absorbed over a period of a few hours.

Many benefits can be derived by testosterone replacement therapy, both in the short term for the eradication of symptoms of androgen

deficiency and in the long term for the prevention of osteoporosis and for preventing and treating heart and circulatory problems. Testosterone is not, however, effective in erectile dysfunction. Androgen replacement therapy should, ideally, provide physiological serum testosterone levels, as well as dihydrotestosterone and estradiol levels while correcting the clinical symptoms of androgen deficiency in hypogonadal men.

Testosterone, the most common agent used in male hormone replacement therapy, occurs as white or slightly creamy white crystals or crystalline powder that is odorless and stable in air. It is practically insoluble in water, soluble 1 g in 5 mL of ethanol, 2 mL of chloroform and 100 mL of ether and is soluble in vegetable oils, melts between 153 and 157°C., and is subject to photodegradation in the presence of light. Testosterone is not very bioavailable when given as an oral-swallow preparation, but is absorbed when administered buccally and sublingually. The different esters of testosterone are hydrolyzed to free testosterone and, subsequently, are metabolized in the same way as testosterone itself.

MARKETING MALE HRT

Education programs can be provided to doctors and nurses as well as to the lay public. Promotional materials concerning educational programs can be provided to places where men meet. Formal or informal seminars have been very successful in presenting the topic. Pharmacists providing these seminars generally begin with a short story of their pharmacy, the importance and legal aspects of compounding, the male hormones and their function, symptoms and treatment of andropause, compliance issues and compensation and insurance billing. These are often followed up by one-on-one personal consultations. After a personal consultation, many pharmacists follow up with a communication to the physician/nurse by telephone or fax.

PATIENT FILES

A consultation is an excellent way to start the process of patient history review and the use of a symptoms chart. In addition, laboratory test values can be maintained in this chart. While laboratory tests such as serum levels, saliva levels and urine monitoring have their place in patient evaluation, they do have limitations. Using laboratory analysis in combination with clinical observation pharmacists can better recommend starting doses and dosage adjustments of hormone replacement for patients.

COMPOUNDED FORMULATIONS FOR MALE HORMONE REPLACEMENT THERAPY

Rx	Testosterone 2% and Menthol Eutectic Ointment
	Testosterone-menthol eutectic mixture* 6.33 g
	Aquabase™ 93.67 g

*The testosterone:menthol eutectic mixture can be prepared using 31.6 g of testosterone with 68.4 g of menthol. Sufficient methyl alcohol is used to dissolve both ingredients. The solution is set aside and the alcohol allowed to evaporate, with periodic stirring. This step may take one or two days. After it is dry, it should be thoroughly pulverized and packaged in a tight, light-resistant container until ready for use in the above prescription.

1. Accurately weigh each ingredient.
2. Mix the testosterone:menthol eutectic mixture with a small quantity of the base.
3. Geometrically, incorporate the remaining drug into the base and thoroughly mix.
4. Package and label.

Rx	Testosterone 20 mg/mL in Pluronic Lecithin Organogel
	Testosterone 2 g
	Propylene Glycol 20 mL
	Lecithin:Isopropyl Palmitate Solution* 20 g
	Pluronic F127 20% Gel** qs 100 mL

Procedure:

1. Prepare a paste of the testosterone and the propylene glycol.
2. Add the Lecithin:Isopropyl Palmitate Solution and mix well.
3. Add sufficient pluronic F127 20% gel to volume and mix well.
4. Package and label.

*The Lecithin:Isopropyl Palmitate Solution can be prepared by mixing 10 g of soy lecithin and 10 g of Isopropyl palmitate; allow to stand overnight for complete dissolution to occur.

**The Pluronic F127 20% Solution can be prepared by adding 20 g of pluronic F127 to sufficient cold (ice) water to make 100 mL. For complete dissolution, place in a refrigerator and allow to stand with periodic agitation.

Rx Testosterone 10 mg Troches (#24)

Testosterone	240 mg
Aspartame	500 mg
Silica gel	480 mg
Acacia	360 mg
Flavor	qs
Polyethylene glycol 1450	23 g

NOTE: The quantity of polyethylene glycol 1450 will depend upon the mold size.

1. Accurately weigh or measure each of the ingredients.
2. In a mortar, triturate the testosterone, aspartame, silica gel and acacia to a fine powder.
3. Melt the polyethylene glycol 1450 to about 55 to 60°C.
4. Add the powders and mix well.
5. Cool slightly, add the flavor(s) and pour into troche molds.
6. Allow to solidify, package and label.

Rx Testosterone 10 mg/0.1 mL Sublingual Drops

Testosterone	1 g
Saccharin	100 mg
Silica gel	200 mg
Flavor	qs
Almond oil	qs 10 mL

1. Accurately weigh or measure each ingredient.
2. Triturate the testosterone, saccharin and silica gel in a mortar.
3. Add a small amount of almond oil and triturate to a smooth paste.
4. Add sufficient flavor and almond oil to volume and mix well.
5. Package and label.

Rx Testosterone Propionate Gel

Testosterone propionate	2 g
Mineral oil, light	10 g
Polysorbate 80	1 g
Methylcellulose 2% gel	87 g

1. Accurately weigh/measure each of the ingredients.
2. Levigate the testosterone propionate with the light mineral oil.
3. Add the polysorbate 80 to the testosterone propionate:mineral oil mixture.
4. Add the methylcellulose 2% gel and thoroughly mix until homogenous.
5. Package and label.

Rx Testosterone Propionate Cream

Testosterone propionate	2 g
Peanut oil	20 mL
Purified water	8 mL
Dermabase™	qs 100 g

1. Accurately weigh/measure each of the ingredients.
2. Dissolve the testosterone propionate in the peanut oil.
3. Add the Dermabase with gentle heating until softened.
4. Add the purified water, mix well, and cool.
5. Package and label.

Rx Testosterone Propionate Ointments

	Anhydrous Hydrophilic Formula	Anhydrous Hydrophobic Formula
Testosterone propionate	2 g	2 g
Aquabase	98 g	
White petrolatum		98 g

1. Accurately weigh each ingredient.
2. Mix the testosterone propionate with a few drops of mineral oil.
3. Add the Aquabase or White petrolatum geometrically and mix until uniform.
4. Package and label.

Rx Dehydroepiandrosterone 50 mg Capsules (100 capsules)

Dehydroepiandrosterone (DHEA)	5 g
Lactose (hydrous)	33.7 g

1. Accurately weigh each ingredient.
2. Commminute each powder to a uniform particle size.
3. Geometrically, incorporate the lactose into the dehydroepiandrosterone and mix well.
4. Encapsulate the powder into 100 No. 1 capsules, each weighing approximately 387 mg.
5. Package and label.

COMPOUNDED FORMULATIONS FOR MALE SEXUAL DYSFUNCTION

Rx Prostaglandin E1/Papaverine Hydrochloride/Phentolamine Mesylate Injection

Prostaglandin E1	10 µg
Papaverine hydrochloride	30 mg
Phentolamine mesylate	500 µg
0.9% Sodium chloride injection	0.67 mL
Sterile water for injection	qs 1 mL

NOTE: This preparation should only be prepared in a laminar air-flow hood in a cleanroom. Pharmacists compounding these preparations must be validated in aseptic compounding technique. Compounding this preparation requires working with very small quantities of some ingredients. Calculations and technique must be verified.

1. Accurately weigh or measure each ingredient.
2. Add each ingredient to the 0.9% sodium chloride injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Sterile filter into a sterile container/syringe.
5. Package and label.

Rx Sildenafil Citrate 25 mg Sublingual Troches (#24)

Sildenafil citrate	600 mg
Aspartame	500 mg
Silica gel	480 mg
Acacia	360 mg
Flavor	qs
Polyethylene glycol 1450	22 g*

*Will vary depending upon mold and size of tablet used as the source of the drug.

1. Accurately weigh or measure each ingredient.
2. In a mortar, triturate the required number of sildenafil citrate tablets to a very fine powder.
3. Add the aspartame, silica gel and acacia and triturate further to a fine powder.
4. Melt the Polyethylene glycol 1450 to about 55 to 60°C.
5. Add the powders and mix well.
6. Cool slightly, add flavor, mix well and pour into troche molds.
7. Allow to solidify, package and label.

TABLE 1. SYMPTOMS ASSOCIATED WITH “MALE MENOPAUSAL SYNDROME”

Physical Symptoms

✗ Aging disorders	✗ Bone mass decrease
✗ Erectile dysfunction	✗ Fatigue and less endurance for physical activity
✗ Heart disease and atherosclerosis	✗ Libido reduction
✗ Muscle soreness and stiffness	✗ Muscle weakness
✗ Osteoporosis	✗ Prostate enlargement/cancer
✗ Reading difficulty (small print)	✗ Skin thinning
✗ Sleep disturbances	✗ Slower injury and illness recovery
✗ Thinning or loss of hair	✗ Weight gain
✗ Psychological Symptoms	✗ Anxiety and fear
✗ Anxiety and fear about losing sexual potency	✗ Depression
✗ Erectile dysfunction	✗ Forgetfulness and difficult concentration
✗ Irritability	✗ Indecisiveness
✗ Loss of self-confidence	✗ Loss of purpose and direction in life
✗ Poor concentration/memory lapses	✗ Reduced interest in sex
✗ Sexual symptoms	✗ Short term memory loss
✗ Sleep disturbances	

TABLE 2. LABORATORY VALUES OF HORMONES.

Hormone	Patient	Mean	Range
Free testosterone	Men	700 ng/dL	300-1100 ng/dL
Free testosterone	Women	40 ng/dL	15-70 ng/dL
Free androgen index			70-100%

TABLE 3. NON-DRUG RECOMMENDATIONS FOR TREATING ANDROPAUSE.

- ✗ Eat right- Eat lots of fruits, vegetables, grains and healthy meat proteins.
- ✗ Exercise- A minimum of 30 minutes three times a week.
- ✗ Vitamins and supplements- Take them wisely and consistently.
- ✗ Physical examinations- Regularly scheduled health checkups.
- ✗ Check hormone levels- As one ages, hormone levels begin to decline.
- ✗ Reduce stress and worry- Stress and worry are major contributors to ill health.
- ✗ Healthy social life- A healthy social life with emphasis on friendship, love and spirituality.
- ✗ Drink lots of water (urine should be light in color).
- ✗ Eat plenty of soy foods (containing phytoestrogens).
- ✗ Reduce the amount of saturated fat intake.
- ✗ Eat meals rich in tomatoes.

SUGGESTED READING

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1. After age 40, the total testosterone levels of males decrease at a rate of about ____% per year.

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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

- A. 0.15
B. 0.2
C. 0.4
D. 0.8
E. 1.2
2. Approximately ____% of men between the ages of 40 and 60 will experience some of the symptoms of what is called "andropause"?
A. 10
B. 20
C. 40
D. 60
E. 80
3. Free serum testosterone levels decline at a _____ rate than total serum testosterone levels.
A. faster
B. slower
4. A total serum testosterone level of 175 mg/dL would be considered:
A. normal
B. below normal
C. above normal
5. A known contraindication to testosterone supplementation is:
A. hypogonadism
B. sexual dysfunction
C. osteoporosis
D. prostate cancer
E. hypercholesterolemia
6. Which of the following commercial dosage forms of testosterone are given in a way that mimics the body's circadian testosterone levels?
A. injection in oil
B. transdermal patches
C. implants
D. none of the above
7. Which of the following would be used in natural hormone replacement therapy for males?
A. methyltestosterone
B. testosterone cypionate
C. fluoxymestron
D. testosterone propionate
E. testosterone
8. A reasonable daily testosterone replacement dose for males would be:
A. 0.01 mg
B. 0.1 mg
C. 1 mg
D. 10 mg
E. 100 mg
9. Testosterone alone appears to be effective in treating male sexual dysfunction.
A. True
B. False
10. The highest testosterone levels in males occur between what hours of the day?
A. 12 midnight and 4 AM
B. 6 AM and 8 AM
C. 9 AM and 12 Noon
D. 2 PM and 6 PM
E. 8 PM and 12 midnight
11. My practice setting is:
A. community-based
B. managed care-based
C. hospital-based
D. consultant and other
12. The quality of the information presented in this article was:
A. Excellent
B. Good
C. Fair
D. Poor
13. The test questions correspond well with the information presented.
A. Yes
B. No
14. Approximately how long did it take you to read the Secundum Artem article AND respond to the test questions? _____

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