2016-07-27

Comparison of Testosterone Replacement Therapy Medications in the Treatment of Hypogonadism

Christopher M. Williams
Brigham Young University - Provo, dgcorps30@gmail.com

Donna S. Freeborn
Brigham Young University - Provo, Donna_Freeborn@byu.edu

Karlen Luthy
beth_luthy@byu.edu

The College of Nursing showcases some of our best evidence based scholarly papers from graduate students in the Family Nurse Practitioner Program. The papers address relevant clinical problems for advance practice nurses and are based on the best evidence available. Using a systematic approach students critically analyze and synthesize the research studies to determine the strength of the evidence regarding the clinical problem. Based on the findings, recommendations are made for clinical practice. The papers are published in professional journals and presented at professional meetings.

Comparison of Testosterone Replacement Therapy Medications in the Treatment of Hypogonadism

Christopher M. Williams

An evidence-based scholarly paper submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Masters of Science

Donna Freeborn, Chair
Karlen E. Luthy

College of Nursing

Brigham Young University

July 2016

ABSTRACT

Comparison of Testosterone Replacement Therapy
Medications in the Treatment of Hypogonadism

Christopher M. Williams
College of Nursing, BYU
Master of Science

Hypogonadism is one of the most common endocrinologic syndromes seen in clinical practice. Testosterone replacement therapy (TRT) is one possible treatment option for men with hypogonadism. When TRT is a viable treatment option, routes of administration, effectiveness, patient compliance, cost, and potential side effects should be carefully considered by the Nurse Practitioner. In the United States TRT is available via intramuscular, nasal, buccal, and topical routes. All transdermal testosterone is the most effective when regulating testosterone levels. Depotestosterone, an injectable form of testosterone, promotes patient compliance, is considered safe, and is affordable. Nurse Practitioners should initiate TRT with Depotestosterone.

Keywords: hypogonadism, testosterone, medication, efficacy, side-effects, cost

Table of Contents

Title i

Abstract ii

Table of Contents iii

Introduction 1

Methods 3

Results 4

Testosterone Replacement Therapy Precautions 4

Injectable Testosterone 5

Depotestosterone (testosterone cypionate) 5

Delatestryl (testosterone enanthate 6

Aveed (testosterone undecanoate) 7

Nasal Testosterone 8

Buccal Testosterone 8

Transdermal Testosterone 10

Androderm Patch 10

Gel pumps/packets/tubes 11

Discussion 14

Implications for Nurse Practitioners 17

Conclusion 18

References 19

LIST OF TABLES

Table 1: *Types of Testosterone Medications*.. 25

Comparison of Testosterone Replacement Therapy Medications in the Treatment of Hypogonadism

Hypogonadism, a disease process whereby the body is unable to produce sufficient amounts of testosterone (Bhasin et al., 2010), is one of the most common endocrinologic syndromes seen in clinical practice (Darby & Anawalt, 2012). In males, testosterone levels normally peak in adolescence and/or early adulthood, but then gradually decline by approximately 1% per year (Mayo Foundation for Medical Education and Research, 2015). Nearly 40% of men over the age of 45 years have age-related or late-onset hypogonadism, defined as testosterone at or below 200 ng/dL (Cleveland Clinic Foundation, 2015; Urology Care Foundation, 2015).

Low testosterone levels not only cause concerning symptoms but may also have serious complications. Symptoms are varied and may include decreased libido, erectile dysfunction, low energy, trouble concentrating, reduced muscle mass, decreased bone density, increased body fat, and/or depression (Dandona & Rosenberg, 2010; Pantalone & Faiman, 2012). If untreated, low testosterone levels may lead to issues with decreased red blood cell production, bone fractures, central obesity, muscle wasting, depression/suicidal ideation, and decreased cognitive function (President and Fellows of Harvard College, 2013).

The number of testosterone prescriptions in the United States (US) has increased three fold since 2001 (Baillargeon, Urban, Ottenbacher, Pierson, & Goodwin, 2013). This may be due to publicity about the symptoms of hypogonadism making the condition more recognizable to patients and healthcare providers (Allan, Strauss, Forbes, Paul, & McLachlan, 2011). Because the overall US population is aging (Ortman, Valkoff, Hogan,

2014) and late-onset hypogonadism is associated with aging, it is likely that the use of testosterone will continue to increase. It is prudent, therefore, for Nurse Practitioners (NPs) to familiarize themselves with the diagnosis, treatment, and management of hypogonadism in the clinical setting (Lee, 2013).

Testosterone replacement therapy (TRT) is one possible treatment option for men with hypogonadism, a condition commonly referred to as Low-T, and also may be beneficial for older men in whom testosterone levels are suboptimal (Osterberg, Bernie, & Ramasamy, 2014). TRT has been shown to produce a significant improvement in quality of life (Bhattacharya & Bhattacharya, 2015) and has an important role in maintaining cardiovascular health (Oskui, French, Herring, Mayeda, Burstein, & Kloner, 2013). In addition, when hypogonadal men are treated with TRT, obesity, type 2 diabetes mellitus, and exercise capacity improve (Oskui et al., 2013). Furthermore, the 2010 Endocrine Society clinical practice guidelines for men with clearly documented androgen deficiency recommended "testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density" (Bhasin et al., 2011, p. 2537).

However, TRT may not be an appropriate treatment option for some male patients. Generally speaking, TRT is contraindicated for men with breast or prostate cancer, a prostate nodule or induration, or a Prostate Specific Antigen (PSA) above 4 ng/ml or above 3 ng/ml in male patients at high risk for prostate cancer. TRT is also contraindicated in men who have a hematocrit higher than 50%, severe obstructive and

untreated sleep apnea, severe urinary tract symptoms, or heart failure (Bhasin et al., 2011).

When TRT is a viable treatment option, routes of administration, effectiveness, cost, and potential side effects should be considered. For instance, in the US TRT is available via intramuscular, nasal, buccal, and topical routes. Therefore, the purpose of this article is to review various forms of TRT comparing their effectiveness, likelihood of promoting patient compliance, cost, and potential side effects.

Methods

Six electronic databases were searched to identify studies and literature reviews relating to TRT efficacy, side effects, and cost. The databases included *CINAHL, MEDLINE, Pubmed, Cochrane Library, Health Source: Nursing/Academic Edition,* and *Web of Science*. In addition, reference sources such as *UpToDate* and *Epocrates* were reviewed. Many websites were also reviewed, including the Mayo Clinic, Cleveland Clinic, Urology Care Foundation, American Association of Clinical Endocrinologists, Agency for Healthcare Research and Quality, GoodRx, US Food and Drug Administration (FDA), drugs.com, medicinenet.com, the Endocrine Society, and manufacturers of TRT medications currently approved for use in the US.

Inclusion criteria included: research published from 2011-2016 initially, but was expanded to include research published from 1997 to 2016 in English; research focused on treatment of hypogonadism in immunocompetent adult men; prescription medications; and, FDA approved medications for use in the US. Because efficacy and side effects were unavailable for some TRT medications in the literature, we included data from the package inserts of some medications as published either on the FDA website or the

manufacturer website. Exclusion criteria included: compounded or combination TRT medications; and, studies including subjects with other co-morbidities. Search terms included: hypogonadism, testosterone, testosterone replacement therapy, efficacy, cost, price, and Low-T.

Results

Ten studies met the inclusion criteria: five studies independently evaluated the efficacy and side-effects of a single TRT medication (Arver et al., 1997; Mattern, Hoffmann, Morley, & Badiu, 2008; Ross et al., 2004; Wang, Cunningham, et al., 2004; Wang, Swerdloff, et al., 2004) and five studies compared the efficacy and side effects of two or more TRT medications (Dobs Matsumoto, Wang, & Kipnes, 2004; Grober, Khera, Soni, Espinoza, & Lipshultz, 2008; Korbonits et al., 2004; Mazer et al., 2005; Steidle et al., 2003). The product monograph or package insert was also evaluated for all 14 prescription TRT medications for all delivery routes and strengths as published on the USFDA website and/or product manufacturer websites.

Testosterone Replacement Therapy Precautions

NPs should be aware that all TRT medications have potential side effects and should be carefully considered before initiating TRT. All of these medications can potentiate electrolyte imbalances, resulting in retention of nitrogen, sodium, potassium, and phosphorus. Additionally, TRT medications can cause decreased urinary excretion of calcium resulting in hypercalcemia (Pfizer Canada Inc., 2015).

Adverse effects can occur with any TRT medication. Some of these adverse events are clearly linked to TRT whereas others are uncommon and less clearly linked. Adverse effects that are clearly related to TRT include: 1) erythrocytosis; 2) urinary

retention; 3) acne; and 4) reduced sperm production (Bebb, 2011; Hassan & Barkin, 2016). Side effects that are less common, or not clearly linked to TRT, include: 1) gynecomastia; 2) adrenergic alopecia; 3) worsening benign prostatic hyperplasia; 4) obstructive sleep apnea (OSA) or worsening of already existing OSA; 5) fluid retention; 6) growth of an already existing prostate cancer; and 7) breast cancer (Bebb, 2011; Hassan & Barkin, 2016).

All prescription TRT medications, regardless of formula, are Schedule III controlled substances, meaning that the medications have the potential for abuse and can lead to low to moderate physical dependence or high psychological dependence (Drug Enforcement Agency, 2016). Therefore, an increase in testosterone prescriptions comes with an increased risk for abuse. Historically, testosterone misuse was found only among elite athletes, however TRT abuse is now documented among men who want to enhance their physical appearance and is commonly found among bodybuilders and weightlifters (American Society of Health-System Pharmacists, 2015).

Injectable Testosterone

Currently in the United States, there are three types of injected testosterone approved for TRT in hypogonadal men: Depotestosterone (testosterone cypionate), Delatestryl (testosterone enanthate), and Aveed (testosterone undecanoate). The side effects and potential adverse effects of all testosterone injection medications are similar to those for all TRT preparations with the addition of injection site pain although the pain is short-lived.

Depotestosterone (testosterone cypionate). According to GoodRx.com (2016), Depotestosterone is the most popularly prescribed TRT medication in the US. It is a long-

acting testosterone and only needs to be administered approximately once every 2-weeks. The most common dose is 200 milligrams (mg) in 1 milliliter (ml) (Snyder, 2016). The generic form is available in two doses: 100 mg/ml and 200 mg/ml. The 100 mg/ml is available in a 10 ml vial, while the 200 mg/ml is available in 10 ml vial or 1 ml vial. When calculated from the most commonly prescribed dose, the average cost per month is $22.70 for the 100 mg/ml (10 ml vial) and $18.45 for the 200 mg/ml (10 ml vial) (Epocrates, 2016). The 200 mg/ml in the 1 ml vial is considerably more expensive at $98.07/month (See Table 1).

Depotestosterone is commonly prescribed in the US and has been used safely for decades, however the literature does not address its effectiveness and side-effects. The benefit of Depotestosterone is the twice monthly dosing, however, the disadvantage of intramuscular administration may negatively affect patient compliance (Snyder, 2016). When administered, testosterone levels quickly increase and then gradually decrease until the next injection. Thus, there may be fluctuations in testosterone levels. This variability can be minimized by shortening the amount of time between injections (i.e. 100 mg/week rather than 200 mg/every other week) (Snyder, 2016).

Delatestryl (testosterone enanthate). Similar to Depotestosterone, Delatestryl is a long-lasting testosterone IM injection that only needs to be administered approximately every 2-weeks. Delatestryl has also been used for TRT for decades and is available at 200 mg/ml in a 5 ml vial. The most commonly prescribed dose is 1 ml every 2-weeks. Deletestryl is also available as a generic preparation and costs, on average, $23.46/month (Epocrates, 2016) (See Table 1).

Generally, Delatestryl is well tolerated by patients. Adverse reactions are very rarely reported but include the potential for anaphylaxis. Thus, patients should be observed immediately following the injection for any signs of anaphylaxis, including cough and respiratory distress. Benefits of Delatestryl for TRT include twice/month dosing. IM injection, however, may affect patient compliance (Food and Drug Administration [FDA], 2016). Since 2014, Deletestryl has been in short supply and may be difficult to obtain.

Aveed (testosterone undecanoate). Aveed is a very-long acting TRT medication that requires a 3 ml IM injection approximately once every 10-weeks to maintain normal testosterone levels. According to data from the manufacturer, testosterone peaks about 1-week following injection and gradually decreases until the next injection (FDA, 2016). Currently, Aveed has no generic substitute and is available in one dose: 750 mg/3 ml in a 3 ml vial. Because Aveed is only available as a brand name, the cost is considerably higher than other injectable TRT medications at $949.02 per vial or an average monthly cost of $379.60 (Drugs.com, 2016).

Because Aveed is associated with pulmonary oil microembolism (POME) and anaphylaxis, though only rarely, the US has restricted its availability as part of the Aveed Risk Evaluation and Mitigation Strategy or REMS program. In 18 clinical trials with a total of 3,556 subjects, a total of 9 POME and 2 anaphylaxis events occurred. As part of the REMS program, Aveed can only be administered in a clinic or hospital setting and the patient must be observed for 30 minutes following injection. Other less serious side effects occur in <5% of patients, the most common of which is acne and injection site pain (FDA, 2016).

Nasal Testosterone

Natesto is a testosterone-based nasal gel the patient self-administers three times per day. Approximately 40 minutes after administration, testosterone levels return to within normal limits, although Natesto's half-life is widely variable, between 10 and 100 minutes (Mattern et al., 2008). Each bottle of Natesto delivers approximately 60 actuations but, when taken as commonly prescribed, 180 actuations constitute a 1-month supply, therefore, three bottles are needed each month. Natesto is not available in generic form and costs $233.07 per bottle or $699.21 per month (GoodRx.com, 2016) (See Table 1).

According to the manufacturer, side effects occurred in <9% of patients during the 180-day clinical trial and most commonly included nasopharyngitis, rhinorrhea, parosmia, headache and nasal discomfort and scabbing (FDA, 2016). Benefits of Natesto, when compared to other TRT medications, include a less invasive delivery method and less risk of inadvertently transferring the gel to a partner or child (Snyder, 2016). In contrast, one notable disadvantage of Natesto is the three times per day dosing schedule, which may be inconvenient for some patients (Snyder, 2016). Because of its unique method of delivery, Natesto is not recommended for patients with chronic nasal or sinus conditions or allergic rhinitis (FDA, 2016).

Buccal Testosterone

Striant is the only available buccal form of testosterone. It is available in a 30 mg tablet and is commonly prescribed twice per day (Epocrates, 2016). Manufacturer data from one 12-week clinical study showed Striant provided steady testosterone levels for 86.6% of subjects (FDA, 2016). The most common side effect in long-term extension

trials was gingivitis (32.6%). Other side effects occurred in <10% of subjects but included gum irritation/pain/edema, bitter taste, and headache (FDA, 2016). Because no generic is available, the average cost for a 1-month supply of Striant is $724.77 (Epocrates, 2016) (See Table 1). Advantages to buccal testosterone include quick delivery of medication using a less invasive method which may increase compliance. The fact that the tablet never completely dissolves and needs to be removed before placing another one, as well as the need to recheck placement after brushing teeth, eating, or drinking are disadvantages.

Two head-to-head comparison studies have been published on Striant (Dobs et al., 2004; Korbonits et al., 2004) one of which compared Striant to the Androderm patch (Korbonits et al., 2004) and the second of which compared Striant to Androgel 1% packets. The mean total testosterone level was similar between Striant and Androgel (Dobs et al., 2004). However, Korbonits et al. (2004) concluded that Striant was superior to the Androderm patch because Striant subjects' testosterone levels were always within normal limits over a 24 hour period whereas Androderm subjects fell below the normal testosterone range during the first 2 hours of placing the patch.

Two additional studies, independent of the manufacturer, have been conducted with Striant (Ross et al., 2004; Wang, Swerdloff, et al., 2004). In both studies, Striant was found to effectively elevate serum testosterone levels within 24 hours of initiating treatment (Ross et al., 2004; Wang, Swerdloff, et al., 2004). No side effects were reported in one study (Ross et al., 2004); however, 16.3% of subjects in the Wang, Swerdloff, et al. (2004) study reported gum-related irritation.

Transdermal Testosterone

Several transdermal testosterone products are available by prescription in the US. All deliver testosterone across the skin for systemic distribution and are available as a patch or gel. Although all the gel formulas are applied to the skin in the same manner, the medications are packaged as a pump, packet, or tube. Brand names for transdermal testosterone include Androderm, Androgel, Axiron, Fortesta, and Vogelxo. One notable advantage of transdermal delivery is that it has a continuous delivery of medication and is easy to apply. Disadvantages include skin irritation, inadvertent contact transfer with others, and some restrictions on activity such as bathing or swimming.

Androderm patch. The Androderm patch is available in two different strengths: 2 mg and 4 mg, although the 4 mg dose is the most commonly prescribed (Drugs.com, 2016). The patch should be applied to non-scrotal skin and then replaced every 24 hours, rotating sites with each application. The per month cost of Androderm is $195.03 for 30 patches (Epocrates, 2016) (See Table 1). Manufacturer data show Androderm produces normal testosterone levels in 92% of patients (FDA, 2016). The manufacturer also compared Androderm to injected Deletestryl (testosterone enanthate) during a 6-month trial, reporting normalized testosterone levels in 82% of Androderm subjects and 72% of Deletestryl subjects (FDA, 2016). However, 37% of patients using Androderm had pruritis at the application site and 12% had a burn-like blister that formed under the patch (FDA, 2016).

One independent study evaluated the effectiveness and side effects of Androderm (Arver et al., 1997). Arver et al. (1997) found Androderm to normalize testosterone levels in subjects, as well as mimic the natural circadian pattern of testosterone during a day.

However, Androderm also caused skin irritation in 56% of subjects and burn-like blisters at the application site in 18% of subjects (Arver et al., 1997).

Korbonits et al. (2004) found that although Striant and Androderm both returned testosterone levels to normal, Androderm subjects had greater variability in maintaining a minimum testosterone level. This means that over a 24 hour treatment period, subjects receiving Striant maintained normal testosterone levels whereas subjects receiving Androderm had lower than normal testosterone levels for a short period of time, usually within the first two hours of applying the patch (Korbonits et al., 2004). For this reason, and the finding that there were very few subjects who suffered side effects in either group, Korbonits et al. (2004) concluded that Striant was superior to Androderm.

In two additional studies, Androderm was compared to Testim (testosterone) 1% gel tubes (Steidle et al., 2003) and Androgel (testosterone) 1% gel packets (Mazer et al., 2005). Steidle et al. (2003) concluded that treatment with two Testim 1% gel tubes per day (100 mg total) was superior to Androderm in normalizing testosterone levels. Mazer et al. (2005) reported similar efficacy and localized skin-related side effects between Androderm and Androgel 1% packets. Testim 1% gel tubes (100 mg) caused a statistically significant increase in hematocrit and hemoglobin when compared to Androderm. Furthermore, dermal-related side effects, such as erythema, rash, pruritis, and irritation occurred much more frequently in the Androderm group (Steidle et al., 2003).

Gel pumps/packets/tubes. Transdermal testosterone gel is packaged as either a pump, a packet, or a tube. When prescribed as a pump, the most common dosing

schedule is 2-4 pumps each day. Packets and tubes are both designed for single use, meaning a 1-month supply would take 30 packets or 30 tubes.

Androgel (testosterone gel) is available in a pump and packet form at 1% or 1.62% doses. Similarly, Fortesta (testosterone gel) 2% and Axiron 2% gel are available as a pump, but Axiron does not currently have a generic equivalent. Vogelxo (testosterone gel) 1% is available as a pump, a packet, and a tube. Testim (testosterone gel) 1% is only available in tubes. All transdermal gel formulations require patients to wash their hands with soap and water after application and apply clothing only after the gel has dried. Additionally, transdermal gel formulations carry the risk of unintentionally transferring medication to a partner or children. With the use of any transdermal gel, NPs should instruct patients to avoid site application contact with children and women until the area has been either washed or clothed.

Average cost for a 1-month supply of testosterone gel pumps/packets/tubes varies. The most expensive testosterone gel is Axiron 2% pump at $630.78 (Epocrates, 2016). The next most expensive testosterone gel is Androgel (testosterone gel) costing $516.41 for the 1.62% packets and $510.77 for the 1.62% pump (GoodRx.com, 2016). All remaining formulas are similar in price for a 1-month supply: Androgel 1% pump for $309.24; Androgel 1% packets for $309.25; Vogelxo 1% pump for $283.69; Fortesta 2% pump for $281.80; Vogelxo 1% packets for $270.30; Testim 1% tubes and Vogelxo 1% tubes are the same price at $268.25 (GoodRx.com, 2016) (See Table 1).

Four studies compared the efficacy and side effects of testosterone gel in packets and tubes to other testosterone medications (Dobs et al., 2004; Grober et al., 2008; Mazer et al., 2005; Steidle et al., 2003). Striant and Androderm were found to have similar

efficacy and occurrence of side effects when compared to Androgel 1% packets (Dobs et al., 2004; Mazer et al., 2005). When comparing Testim 1% gel tubes to Androderm, Steidle et al. (2003) concluded Testim 1% gel tubes were superior at achieving normal testosterone levels and that Androderm generally had a higher incidence of side effects. However, Testim 1% gel tubes had one statistically significant side effect when compared to Androderm, that of increased hematocrit and hemoglobin (Steidle et al., 2003).

Grober et al. (2008) compared efficacy and side effects between two testosterone gel packets in hypogonadal men who had suboptimal testosterone levels despite treatment with either Androgel or Testim. In the crossover study, researchers concluded that when subjects switched from Androgel to Testim, they had a more favorable response with stable testosterone levels. In the same study, researchers reported that when subjects were changed from Testim to Androgel, there were fewer side effects.

Wang, Cunningham, et al. (2004) compared the efficacy of Androgel 1% packets in varying doses (ie 1 packet daily or 2 packets daily). During the course of the study, the Androgel 1% packets could be titrated to achieve optimal testosterone levels in subjects (Wang, Cunningham, et al., 2004). The researchers reported that when titrated, Androgel 1% packets resulted in patient outcomes similar to injectable testosterone or other transdermal formulas (Wang, Cunningham, et al., 2004). Additionally, Androgel 1% gel packets did not cause skin irritation and were found to be safe and effective, even in long-term treatment.

Manufacturer data regarding efficacy, as reported in package inserts, were also reviewed. After the subjects' dose was titrated appropriately, Axiron 2% was the most

effective resulting in normal testosterone levels in 89% of subjects. Effectiveness of Androgel 1% and 1.62% was reported as 87% and 81.6% after titration, respectively. Fortesta 2% was efficacious in 77.5% of subjects after titration and Testim 1% resulted in normal testosterone levels in 74% of subjects after titration (FDA, 2016).

Package insert information regarding side effects of Testim 1%, Vogelxo 1%, Axiron 2%, Fortesta 2%, and Androgel 1% and 1.62% were also reviewed. Testim 1% and Vogelxo 1% reported the least occurrence of side effects, both reported in less than 5% of subjects. The most common side effect reported in Testim 1% and Vogelxo 1% was skin irritation at the application site. With Axiron 2% and Androgel 1% and 1.62% side effects were found in less than 10% of subjects. The most common side effect of Axiron 2% was skin irritation at the application site. Acne was the most common side effect of Androgel 1% and 1.62%. Finally, Fortesta 2% had the highest occurrence of side effects at 17% of subjects, the most common of which was skin irritation at the application site (FDA, 2016).

Discussion

In 2010, the Endocrine Society published TRT clinical practice guidelines. According to the updated guidelines, healthcare providers should recommend TRT for symptomatic men with unequivocally low serum testosterone levels that was collected from a morning serum sample. All TRT should have clear treatment goals that are aimed at maintaining secondary sex characteristics and improving sexual function, sense of well-being, and bone mineral density (Bhasin et al., 2010).

The Endocrine Society also published guidelines on contraindications for TRT and routine TRT follow-up appointments. Risk of prostate or breast cancer, hematocrit

above 50%, untreated and severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure, and desire of fertility are all contraindications for TRT (Bhasin et al., 2010). All patients undergoing TRT should be evaluated 3-6 months after initiation and then annually, aiming for testosterone levels in the mid-normal range (Bhasin et al., 2010).

The efficacy of TRT preparations should be considered when selecting a TRT medication. We confirmed that TRT medications administered every day, rather than every few weeks, most consistently maintained testosterone levels within a normal range. Since all transdermal TRT medications are prescribed on a once per day dosing schedule, it would appear that transdermal TRT preparations, in general, are more efficacious than TRT medications with more frequent or less frequent dosing schedules.

Compliance is another consideration when prescribing TRT for patients since the number of medication doses each day can have a significant effect on patient compliance. Indeed, there is an inverse relationship between the number of medication doses and patient compliance: the higher the number of medication doses in a day, the lower the patient compliance (Claxton, Cramer, & Pierce, 2001). Some testosterone medications, such as Natesto and Striant, are prescribed three times per day or two times per day, respectively. As a result, the dosing schedule for Natesto and Striant could negatively affect patient compliance. Using this same logic, however, it would seem that Depotestosterone and Delatestryl would be associated with greater patient compliance because these two injected testosterone medications only need to be administered every 2-weeks. Additionally, Aveed is only administered once every 10-weeks which would seemingly improve patient compliance further.

Cost should always be considered when prescribing any medication. A review of all testosterone medications revealed that the most cost-efficient TRT medications were injectable formulations, namely Depotestosterone and Delatestryl. Depotestosterone is commonly prescribed at 200mg/ml every 2-weeks and is available for dispense in a 10ml vial for $92.29 (Epocrates, 2016). The 10ml vial of Depotestosterone, however, would have enough medication for 5-months, for an average monthly cost of $18.45. In comparison, Delatestryl is commonly prescribed at 200mg/ml every 2-weeks and can be dispensed in a 5ml vial for $23.46 (GoodRx.com, 2016). The 5ml vial of Delatestryl would contain enough doses for 2.5-months for an average monthly cost of $23.46. When compared to the cost of transdermal patches at $195.03 per month or the cost of nasal gel at $699.21 per month, the cost difference is notable (See Table 1).

Finally, side effects of each TRT medication should be carefully evaluated. The injectable testosterone Depotestosterone is not well studied, even though it has been available the longest and is the most frequently prescribed of all types of TRT medications with seemingly few side effects. Anaphylaxis is rarely seen as a side effect of Delatestryl, another injectable testosterone. Aveed is a long-acting injectable testosterone that is rarely associated with POME and anaphylaxis, although its availability in the US is restricted because of these safety concerns.

Side effects are also associated with nasal and buccal forms of testosterone. Less than 9% of Natesto users experience side effects which are usually associated with the nasopharynx, such as nasopharyngitis. Striant is the bucally administered testosterone that is most commonly associated with gingivitis. Over 32% of patients taking Striant report gingivitis as a side effect.

There are also side effects with transdermal testosterone medications. Androderm has the highest occurrence of side effects with 57% of patients reporting skin irritation, 37% reporting pruritis, and 12-18% reporting a burn-like blister at the application site. The greatest concern regarding the testosterone transdermal gel in pumps, packets, or tubes is unintentional transdermal transfer to children or women. Androgel 1.62% manufacturer data show that average testosterone levels in female partners increased by 280% after contact with the application site. However, when the application site was covered by a shirt, average testosterone levels in female partners increased by only 6-13%. Testim is the only transdermal testosterone that showed no change in female partner testosterone levels after covering the application site with a shirt.

Implications for Nurse Practitioners

NPs are in a great position to recognize and treat the effects of hypogonadism with TRT. Hypogonadism is a problem that can be easily diagnosed and treated, improving the lives of many men who suffer with the symptoms of testosterone deficiency. When properly titrated, TRT medications return patients to normal testosterone levels increasing energy, the ability to concentrate, bone density, and libido, while lessening depression.

Selecting the best medication for TRT differs between patients and depends on delicate balance of efficacy, compliance, cost, and potential side effects. The most effective TRT medications are the transdermal preparations. The TRT medication with the best patient compliance would be the injectable formulations. The most cost-efficient TRT medications are Depotestosterone and Delatestryl, although there is a shortage of Deletestryl and, as a result, it may be difficult to obtain. While the injectable Aveed could

also improve patient compliance, it is not recommended at this time because of the prohibitive cost and potential for serious side effects. Lastly, all TRT medications have side effects. Although specific reports of Depotestosterone side effects may be lacking in the literature, it has a good track record for being safe. Therefore, in consideration of compliance, cost, and side effects of TRT medications, we recommend Depotestosterone injection as a first line therapy option. Because it is injected once every 2-weeks, Depotestosterone may not control testosterone levels as tightly as the transdermal testosterone that is administered every day. For patients who are sensitive to the testosterone peaks and troughs of Depotestosterone, we recommend altering the administration schedule to a half dose every week rather than a full dose every 2-weeks.

Conclusion

Better understanding of the diagnosis, treatment, and management of hypogonadism through continued research and best practice studies can improve the lives of the aging male population. There are different TRT treatment options that should be selected with careful consideration of efficacy, compliance, cost, and side effects. All methods of testosterone delivery improve testosterone levels in patients. The NP should select the appropriate TRT medication only when the patient is symptomatic and only after conducting a thorough medical history and confirming low testosterone with a serum testosterone level collected in the morning. In consideration of TRT medication efficacy, patient compliance, medication cost, and common medication side effects, we recommend the NP initiate treatment with Depotestosterone and then regularly follow up with the patient to reevaluate efficacy, compliance, cost, and side effects.

References

Allan, C. A., Strauss, B. J., Forbes, E. A., Paul, E., & McLachlan, R. I. (2011). Variability in total testosterone levels in ageing men with symptoms of androgen deficiency. *International Journal of Andrology, 34*(3), 212-216. doi:10.1111/j.1365-2605.2010.01071.x

American Society of Health-System Pharmacists. (2015). *Testosterone*. Retrieved from http://www.drugs.com/monograph/testosterone.html

Arver, S., Dobs, A. S., Meikle, A. W., Caramelli, K. E., Rajaram, L., Sanders, S. W., & Mazer, N. A. (1997). Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clinical Endocrinology, 47*(6), 727-737.

Baillargeon, J., Urban, R. J., Ottenbacher, K. J., Pierson, K. S., & Goodwin, J. S. (2013). Trends in androgen prescribing in the United States, 2001-2011. *Journal of the American Medical Association Internal Medicine, 173*(15), 1465-1466. doi:10.1001/jamainternmed.2013.6895

Bebb, R. A. (2011). Testosterone deficiency: Practical guidelines for diagnosis and treatment. *British Columbia Medical Journal,* 53(9), 474-479.

Bhasin, S., Cunningham, G. R., Hayes, F. J., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., & Montori, V. M. (2010). Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism, 95*(6), 2536-2559. doi:10.1210/jc.2005-2847

Bhattacharya, R. K., & Bhattacharya, S. B. (2015). Late-onset hypogonadism and testosterone replacement in older men. *Clinics in Geriatric Medicine, 31*(4), 631-644. doi:10.1016/j.cger.2015.07.001

Claxton, A. J., Cramer, J., & Pierce, C. A. (2001). Systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics, 23*(8), 1296-1310. doi:10.1016/S0149-2918(01)80109-0

Cleveland Clinic Foundation. (2015). *Low testosterone (male hypogonadism).* Retrieved from https://my.clevelandclinic.org/health/diseases_conditions/hic-low-testosterone-male-hypogonadism

Dandona, P., & Rosenberg, M. T. (2010). A practical guide to male hypogonadism in the primary care setting. *International Journal of Clinical Practice, 64*(6), 682-696. doi:10.1111/j.1742-1241.2010.02355.x

Darby, E., & Anawalt, B. D. (2012). Male hypogonadism: An update on diagnosis and treatment. *Treatments in Endocrinology, 4*(5), 293-309.

Dobs, A. S., Matsumoto, A. M., Wang, C., & Kipnes, M. S. (2004). Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. *Current Medical Research and Opinion, 20*(5), 729-738. doi:10.1185/030079904125003494

Drug Enforcement Agency. (2016). *List of controlled substances.* Retrieved from http://www.deadiversion.usdoj.gov/schedules/

Drugs.com. (2016). *Drug price information.* Retrieved from https://www.drugs.com/price-guide/

Epocrates. (2016). *Epocrates premium version*. San Mateo, CA: Epocrates, Inc., 2016.

Food and Drug Administration. (2016). *Drugs@FDA: FDA approved drug products.* Retrieved from https://www.accessdata.fda.gov/scripts/cder/drugsatfda/

GoodRx.com. (2016). *Stop paying too much for your prescriptions.* Retrieved from http://www.goodrx.com

Grober, E. D., Khera, M., Soni, S. D., Espinoza, M. G., & Lipshultz, L. I. (2008). Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. *International Journal of Impotence Research, 20*, 213-217.

Hassan, J., & Barkin, J. (2016). Testosterone deficiency syndrome: Benefits, risks, and realities associated with testosterone replacement therapy. *The Canadian Journal of Urology, 23*(Suppl 1), 20-30.

Korbonits, M., Slawik, M., Cullen, D., Ross, R. J., Stalla, G., Schneider, H., Reincke, M., Bouloux, P. M., & Grossman, A. B. (2004). A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *The Journal of Clinical Endocrinology & Metabolism, 89*(5), 2039-2043.

Lee. Y. (2013). Androgen deficiency syndrome in older people. *Journal of the American Association of Nurse Practitioners.* doi:10.1002/2327-6924.12114

Mattern, C., Hoffmann, C., Morley, J. E., & Badiu, C. (2008). Testosterone supplementation for hypogonadal men by the nasal route. *The Aging Male, 11*(4), 171-178. doi:10.1080/13685530802351974

Mayo Foundation for Medical Education and Research. (2015). *Testosterone therapy: Potential benefits and risks as you age.* Retrieved from

http://www.mayoclinic.org/healthy-lifestyle/sexual-health/in-depth/testosterone-therapy/art-20045728

Mazer, N., Bell, D., Wu, J., Fischer, J., Cosgrove, M., & Eilers, B. (2005). Comparison of the steady-state pharmacokinetics, metabolism and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. *The Journal of Sexual Medicine, 2*, (2), 213-226.

Ortman, J. M., Velkoff, V. A., & Hogan, H. (2014). *An aging nation: The older population in the United States.* Retrieved from https://www.census.gov/prod/2014pubs/p25-1140.pdf

Oskui, P. M., French, W. J., Herring, M. J., Mayeda, G. S., Burstein, S., & Kloner, R. A. (2013). Testerone and the cardiovascular system: A comprehensive review of the clinical literature. *Journal of the American Heart Association, 2*(e000272), 1-22. doi:10.1161/JAHA.113.000272

Osterberg, E. C., Bernie, A. M., & Ramasamy, R. (2014). Risks of testosterone replacement therapy in men. *Indian Journal of Urology, 30*(1), 2-7.

Pantalone, K. M., & Faiman, C. (2012). Male hypogonadism: More than just a low testosterone. *Cleveland Clinic Journal of Medicine, 79*(10), 717-725. doi:10.3949/ccjm.79a.11174

Pfizer Canada Inc. (2015). *Product monograph: Depo-testosterone.* Retrieved from https://www.pfizer.ca/sites/g/files/g10017036/f/201505/Depo-Testosterone_PM_E_181380_25_March_2015.pdf

President and Fellows of Harvard College. (2013). Considering testosterone therapy? 35% of men over 45 may have low testosterone levels. (2013). *Harvard Health Letter*, *38*(3), 5.

Ross, R. J. M., Jabbar, A., Jones, T. H., Roberts, B., Dunkley, K., Hall, J., Long, A., Levine, H., & Cullen, D. R. (2004). Pharmacokinetics and tolerability of a bioadhesive buccal testosterone tablet in hypogonadal men. *European Journal of Endocrinology, 150*(1) 57-63.

Snyder, P. J. (2016). Testosterone treatment of male hypogonadism. In A. M. Matsumoto and K. A. Martin (Eds.), *UpToDate.* Retrieved from www.uptodate.com

Steidle, C., Schwartz, S., Jacoby, K., Sebree, T., Smith, T., Bachand, R., & the North American AA2500 T Gel Study Group. (2003). AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *The Journal of Clinical Endocrinology & Metabolism, 88*(6), 2673-2681. doi:10.1210/jc.2002-021058

Urology Care Foundation. (2015). *What is low testosterone (hypogonadism)?* Retrieved from http://www.urologyhealth.org/urologic-conditions/low-testosterone-(hypogonadism)

Wang, C., Cunningham, G., Dobs, A., Iranmanesh, A., Matsumoto, A. M., Snyder, P. J., Weber, T., Berman, N., Hull, L., & Swerdloff, R. S. (2004). Long-term testosterone gel (Androgel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism, 89*(5), 2085-2098. doi:10.1210/jc/2003.032006

Wang, C., Swerdloff, R., Kipnes, M., Matsumoto, A. M., Dobs, A. S., Cunningham, G., Katznelson, L., Weber, T. J., Friedman, T. C., Snyder, P., & Levine, H. L. (2004). New testosterone buccal system (Striant) delivers physiological testosterone levels: Pharmacokinetics study in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism, 89*(8), 3821-3829. doi:10.1210/jc.2003-031866

Table 1
Types of Testosterone Medications

Trade Name	Generic	Route	Available Dosing	Common Dose	Common Frequency	Average Cost/Month (calculated from common dose)
Injectable						
Depo-testosterone	**testosterone cypionate**	**IM**	**100 mg/ml 200 mg/ml**	**200 mg/ml[1]**	**Q 2 weeks**	**100mg/ml (10ml vial) = $22.70[1] 200mg/ml (10ml vial) = $18.45[1] 200mg/ml (1ml vial) = $98.07[1]**
Delatestryl	**testosterone enanthate**	**IM**	**200 mg/ml**	**200 mg/ml[2]**	**Q 2 weeks**	**200mg/ml (5ml vial) = $23.46[2]**
Aveed	**N/A**	**IM**	**750 mg/3ml**	**750 mg/3ml[2]**	**Q 10 weeks**	**750mg/3ml (3ml vial)= $379.60[3]**
Nasal						
Natesto	**N/A**	**Nasal gel**	**5.5 mg each actuation**	**11 mg (1 actuation per nostril) [2]**	**TID**	**3 bottles (30 days) = $699.21[2]**
Buccal						
Striant	**N/A**	**Buccal**	**30 mg**	**30 mg[1]**	**BID**	**60 tablets = $724.77[1]**
Transdermal Patch						
Androderm	**N/A**	**Patch**	**2 mg 4 mg**	**4 mg[3]**	**QD**	**30 patches = $195.03[1]**
Transdermal Gel Pump						
AndroGel 1% or	**testosterone 1%**	**Gel pump**	**1%-12.5mg/1.25g**	**50mg (4 pumps) [1]**	**QD**	**2 bottles 1% (30 days) $309.24[2]**
1.62%	**testosterone 1.62%**		**1.62%-20.25mg/1.25g**	**40.5mg (2 pumps) [1]**		**1 bottle 1.62% (30 days) $510.77[2]**
Axiron 2%	**N/A**	**Gel pump**	**30mg /1.5ml**	**60 mg (2 pumps) [1]**	**QD**	**1 bottle (30 days) $630.78 [1]**
Fortesta 2%	**testosterone 2%**	**Gel pump**	**10mg/0.5g**	**40mg (4 pumps) [1]**	**QD**	**1 bottle (30 days) = $281.80[2]**
Vogelxo 1%	**testosterone 1%**	**Gel pump**	**12.5 mg/1.25g**	**50mg (4 pumps)[2]**	**QD**	**2 bottles (30 days) = $283.69[2]**
Transdermal Gel Packets						
AndroGel 1% or	**testosterone1%**	**Gel packet**	**1%-25mg/2.5g 1%-50mg/5g**	**50mg (1 packet) [1]**	**QD**	**30 packets 1% = $309.25[2]**
1.62%	**testosterone**		**1.62%-20.25mg/1.25g**	**40.5mg (1 packet) [1]**		**30 packets 1.62% = $516.41[2]**

Vogelxo 1%	testosterone 1%	Gel packet	1%-25mg/2.5g 1%-50mg/5g	50mg (1 packet) [1]	QD	30 packets 1% = $270.30[2]
Transdermal Gel Tubes						
Testim 1%	testosterone 1%	Gel tube	50mg/5g	50mg[2]	QD	30 tubes = $268.25[2]
Vogelxo 1%	testosterone 1%	Gel tube	50mg/5g	50mg[1]	QD	30 tubes = $268.25[2]

[1] Epocrates
[2] GoodRx.com
[3] Drugs.com