SCREENING FOR ANDROGEN DEPRIVATION THERAPY RELATED SIDE EFFECTS IN MEN WITH PROSTATE CANCER

by

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Abstract

Androgen deprivation therapy (ADT) is a common method of treatment for prostate cancer. There are a variety of side effects associated with its use that can negatively impact health and quality of life, yet a significant gap exists in the literature around comprehensive screening recommendations. As a result, this project seeks to answer the question: For Nurse Practitioners (NPs) practicing in a primary care setting, what screening is required to identify side effects in men with prostate cancer receiving ADT? Eligibility criteria for this literature review included data related to ADT and men with prostate cancer, with no limitation to age or stage of disease. The majority of the participants in the primary studies included at least one study group receiving ADT in the primary care setting. This review presented findings based on the physical, cognitive and psychological side effects of ADT, followed by a description of clinical practice guidelines, clinical reviews and editorials in order to highlight the gaps in screening recommendations. Through this process, recommendations for the screening of each individual side effect were developed. It was determined that patients should undergo follow-up within 3 months of ADT initiation, followed by every 3-6 months. Limitations of this project include a scarcity of studies on specific side effects. Implications for practice include patient and primary care provider (PCP) education as well as the development of comprehensive guidelines. Moreover, further research is required for newly defined side effects. It is through appropriate screening that ADT related side effects are identified and treated, thus limiting their impact on health and quality of life.

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Glossary

Androgen are male hormones, primarily testosterone and dihydrotesterone (American Cancer Society, 2014).

Andropause generally occurs in men between the age of 45 and 55, in which testosterone levels fall leading to reduce sexual drive and vigour (andropause, 2015). Alternatively called male menopause (andropause, 2015).

Anorgasmia is the inability to achieve orgasm (International Society for Sexual Medicine, 2015).

Anti-androgens are also known as androgen biosynthesis. They work by inhibiting adrenal and intra-tumour production of testosterone. Examples in Ketoconazole and Cyrotereone (Locke & Elliot, 2015).

Asthenia is characterized by generalized weakness and can also include physical and mental fatigue (Bruera & MacDonald, 1988).

Brachytherapy is a type of cancer treatment that refers to the placement of radioactive 'seeds' into the body, either inside or next to a tumour. The seeds deliver radiation to the cancerous tumor while minimizing the surrounding tissues exposure to radiation. This method of radiation therapy is commonly used for prostate cancer, which is called Transperineal Implantation of the Prostate (TPIP). During TPIP radioactive seeds are inserted into the prostate under general anesthesia (British Columbia Cancer Agency [BCCA], 2014a).

Cryotherapy is a form of prostate cancer treatment that freezes and destroys prostate cancer cells (National Cancer Institute [NCI], 2015).

Erectile dysfunction is defined as the persistent inability to achieve or maintain an erection (Buttaro, Trybulski, Polgar Bailey, & Sandberg-Cook, 2013).

External beam radiation is the use of high energy rays to kill or shrink malignant tumour cells (BCCA, 2014a).

FRAX is a fracture risk assessment tool developed from the World Health Organization. The tool incorporates individual patient risk factors in combination with bone mineral density results and gives a 10 year probability of fracture (World Health Organization Collaborating Centre for Metabolic Bone Disease, n.d.).

Gynecomastia is defined as the benign enlargement of the male breast and is the result of proliferation of ductular elements of the breast (Buttaro et al., 2013).

Gonadotropin releasing hormone (GnRH) is a synthetic analog of luteinizing hormone releasing hormone agonist (LHRH) with essentially the same mechanism of action (BCCA, 2012a).

Hemoglobin is a laboratory test that determines the total amount of hemoglobin in the blood. Hemoglobin itself acts as a vehicle for the transportation of oxygen and carbon dioxide throughout the body. The test is an important part of the complete blood cell count (CBC) and can be helpful in evaluating for anemia (Pagana & Pagana, 2013).

Hemoglobin A1C or glycosylated hemoglobin is a measurements used commonly in diabetic patients for diagnosis and to monitor response to treatment (Pagana & Pagana, 2013). The value reflects an average blood glucose levels in the blood over a 100 to 120 day span (Pagana & Pagana, 2013).

High density lipoprotein (HDL) is often referred to as 'good cholesterol' as it is responsible for collecting cholesterol from the body's tissues and endothelium and returning it to the liver. Removal of cholesterol from the tissues and endothelium provides protection against heart disease (Pagana & Pagana, 2013).

Hypogonadism occurs when sex glands, such as the testes in men and ovaries in women produce reduced or absent amount of sex hormones (Martel, 2012).

Impotence refers to the inability to achieve or maintain an erection (Silverberg, 2015).

Insulin resistance is the "decreased sensitivity of tissue to glucose uptake with normal concentrations of insulin" (Buttaro et al., 2013, p. 1062).

Libido is ones sexual drive or instinct (libido, 2015).

Low density lipoprotein (LDL) is part of the lipid profile. LDL carries cholesterol from the liver to different cells in the body. LDL is often referred to as 'bad cholesterol' (Pagana & Pagana, 2013).

Luteinizing hormone releasing hormone agonist (LHRH) are medications used for prostate cancer. Mechanism of action is the overstimulation of the hypothalamus-pituitary-adrenal testes axis which stops the production of testosterone. Example include Goserelin and Leuprolide (Locke & Elliot, 2015).

Mean corpuscular volume (MCV) refers to the volume or size of a single red blood cell. Its measurement is commonly used to help classify anemia (Pagana & Pagana, 2013).

Metastasis is the term used to describe when cancer cells spread from its original (primary) location to another area in the body. When this occurs the cancer continues to grow in its new location (Canadian Cancer Society, 2014a).

Neo-adjuvant refers to cancer treatment that is given prior to the main treatment prescribed (NCI, n.d.).

Orchiectomy is the surgical removal of the testicles (Canadian Cancer Society, 2014a).

Osteopenia refers to abnormal (low) bone density, but not as low as bone density in the osteoporotic range (Karaguzel & Holick, 2010).

Osteoporosis is a disease in which bones become more fragile with increased susceptibility for fracture (Buttaro et al., 2013).

Prostate Specific Antigen (PSA) is an enzyme released by the prostate gland. Levels can be elevated related to both benign and malignant conditions. A normal PSA level is under 4 ng/mL. Levels can be measured with a serum laboratory test (Buttaro et al., 2013).

Psychometrician is a psychologist who is skilled in administering and interpreting psychological tests (Psychimetrician, 2015).

Quality of life definitions can vary widely. The World Health Organization (1997) defines quality of life as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" (p. 1).

Radical prostatectomy is a surgical procedure done for localized prostate cancer (BCCA, 2014b). The surgery involves removing and sampling pelvic lymph nodes, and if negative for malignancy, the removal of the prostate gland and seminal vesicles (BCCA, 2014b). Common side effects include incontinence and erectile dysfunction (BCCA, 2014b).

Testosterone is a hormone which is primarily produced in the testes, with small amounts produced in the ovaries and adrenal cortex. This hormone is primarily responsible for the development of male secondary sexual characteristics (Testosterone, 2015).

Triacylglycerol also refers to triglycerides, which are naturally occurring fatty acids and glycerol found in oils and fats (Triacylglycerol, 2015).

Very low density lipoprotein (VLDL) is another laboratory component of the lipid profile. VLDL carries triacylglycerol from the liver to adipose tissue in the body (Pagana & Pagana, 2013).

Introduction

The diagnosis of cancer can be a life-altering event. Both cancer and its treatments can impact physical, cognitive and psychological function, all of which can influence self-esteem; intimate and social relationships; and overall health and quality of life. Prostate cancer is the second most commonly diagnosed cancer in men worldwide (Tadros & Garzotto, 2011). Consequently, with such significant prevalence rates the likelihood that primary care providers (PCPs), such as Nurse Practitioners (NPs) will be involved with the diagnosis and management of this disease is substantial. Moreover, extensive progress in prostate cancer treatments have extended life expectancy, meaning patients are living longer with the disease and obtaining care and treatments by PCPs in the communities in which they live (Institute of Medicine, 2008).

Naturally, the level of interaction between PCPs and patients depends on the method of treatment and symptomology related to both cancer and treatments. For example, androgen deprivation therapy (ADT), which is a form of hormone therapy, is commonly prescribed by specialists but administered and managed by PCPs. ADT is the most common method of treatment for prostate cancer, with estimations that at least 50% of patients with prostate cancer will be treated with ADT at some point in their illness (Mohile, Mustian, Bylow, Hall, & Dale, 2009; Tadros & Garzotto, 2011). ADT reduces testosterone to castrate levels that inhibits or slows the growth of hormone dependent cancer cells (Mazzola & Mulhall, 2012). Androgen deprivation is achieved through suppressing the production of androgens by the testes, which produce 90-95% of the body's total androgen, or by blocking the effects of androgen at androgen receptors (Mazzola & Mulhall, 2012).

With the reduction of testosterone comes a variety of early and late side effects, as well as an increased risk for other health conditions such as cardiovascular disease, diabetes,

osteoporosis and functional decline. Furthermore, the literature has demonstrated that overall those with cancer die of non-cancer related causes at a much higher rate than the general public (Brown et al., 2003 as cited in Stull et al., 2007). Finally, those treated with ADT demonstrate significantly worse quality of life with changes to both mental and emotional well-being (Cary, Singla, Cowan, Carroll, & Cooperberg, 2014; van Andel & Kurth, 2003). This highlights the necessity to acknowledge the long term health and psychological sequelae associated with ADT and the subsequent need to consider screening and identification of side effects in order to commence appropriate treatment.

Primary care providers, such as NPs, are often the first and most frequent point of contact for patients when accessing care with continued responsibility for providing patient care for a variety of health problems (American Academy of Family Physicians, 2015; Health Force Ontario, 2013). This ongoing established relationship between patients and PCPs is pivotal for the identification of ADT related side effects to ensure treatment is provided to maximize health and quality of life during this treatment. However, an important consideration for providing this complex speciality care is availability and knowledge of up to date resources and tools. Until recently, the focus of prostate cancer research has been largely focused on treatment and achieving long-term survival. As a result, the literature illustrates an abundance of data regarding the effectiveness of ADT and its associated side effects, however specific recommendations or practice guidelines for the evaluation of side effects are sparse (McIntosh et al., 2009). Similarly, although risks of developing additional health conditions related to ADT are documented in the literature, guidelines related to screening for these health conditions are not well defined or comprehensive. Consequently, PCPs have little evidence to guide care with regards to methods and frequency of assessment for those receiving ADT. Without comprehensive guidelines readily

available, PCPs will have limited awareness of the substantial impact of ADT on health related quality of life and appropriate treatment of side effects cannot be adequately provided. Furthermore, the literature has identified gaps in care with regard to follow up and screening for side effects in those receiving ADT demonstrating a further need.

The objective of this integrative literature review is to answer the following question: For NPs practicing in a primary care setting, what screening is required to identify side effects in men with prostate cancer receiving ADT. The review will begin by describing prostate cancer in primary care, the role of the NP as a PCP, prostate cancer incidence as well as prostate anatomy and pathophysiology. Prostate cancer treatments, ADT and its side effects will then be discussed. Next, the literature search process will be described. Findings from the integrative review will then be presented followed by implications and recommendations for primary care practice, education and research.

Chapter One

Background and Context

Prostate Cancer in Primary Care

Primary care is central to the diagnosis and management of cancer (Summerton, 2000 as cited in Allgar & Neil, 2005). Primary care often refers to a patient's first contact for medical care, in which PCPs, such as General Practitioners and NPs, assume responsibility for continuous, comprehensive and co-ordinated care (Starfield, 1994 as cited in Allgar & Neil, 2005). Primary care includes health promotion, disease prevention, health maintenance, counseling, patient education, diagnosis and treatment of illness as well as facilitating access to specialty care (American Academy of Family Physicians, 2015). As a result, PCPs provide a focal point for continuous health care and thus are generally involved in care prior to diagnosis and have a well-established relationship and role in ongoing care (Department of Health, 2000 as cited in Allgar & Neil, 2005). Although traditionally health care management of those on active treatment for cancer has been limited to specialist and outpatient oncology clinics, care for those receiving hormonal treatment regimens such as ADT has now shifted to the PCPs. Thus, PCPs have increasing responsibility for greater aspects of cancer care, such as follow up, assessment and management of side effects and co-morbidities, and for ambulatory treatment in the community (Allgar & Neal, 2005). Additionally, with ADT's demonstrated improvements in longevity of life, patients are living longer with persistent disease that creates additional considerations for PCPs in regards to incorporating appropriate screening for both disease and treatment related side effects.

The Role of the Nurse Practitioner

Nurse practitioners (NPs) are autonomous health care providers. NPs have undergraduate

education and experience in nursing, with additional Masters or PhD level education from across health disciplines, including medicine. NP's bring together the medical knowledge required of a PCP, such as the ability to diagnose diseases and conditions, order diagnostic tests and prescribe and manage medications and treatments, with the values and skills of the nursing profession (Canadian Nurses Association, 2011). Moreover, NP's provide direct patient care, addressing health promotion, illness prevention, diagnosis and treatment of acute and chronic illness within the scope of a holistic nursing perspective (Canadian Registered Nurses of British Columbia [CRNBC], 2015a). Since inception of the role in Canada in the early 1960's, the value of the NP's role in the Canadian health care system has been identified by numerous studies, demonstrating "timely access to individualized, high quality, cost effective care" (Canadian Nurses Association, 2011, para. 10). Although NP's are currently restricted in prescribing ADT, the NP's role as a PCP serves as a continuous focal point for managing patients throughout the cancer trajectory. Thus, throughout cancer treatments patients will continue to access care in which NP's can provide competent assessments, support, education and counselling with regards to diagnoses, management and therapeutic interventions. Additionally, NP's can perform any appropriate screening and diagnostic investigations required for cancer and its treatments using standardized tools, laboratory and diagnostic imaging (CRNBC, 2015b).

Prostate Cancer Incidence

In Canada, prostate cancer is the most common type of cancer diagnosed in men, accounting for 24% of all new cancer diagnoses in men in 2014 (Canadian Cancer Society, 2014a). Similarly, prostate cancer is the most frequently diagnosed cancer in men in British Columbia, with approximately 3600 men diagnosed in 2014, and over 25 000 men throughout Canada in 2011 (Canadian Cancer Society, 2014b; Venkateswaran, Margel, Yap, Hersey, Yip, &

Fleshner, 2012). Despite the high incidence, due to the nature of the disease as well as the development of successful treatment modalities, mortality rates are relatively low. Five year relative survival rates remain high at 96%, with an overall death rate of 17 men for every 100,000 people (Canadian Cancer Society, 2014a). The average age of diagnosis is 79 years old, with over 70% of cases in men over the age of 65 years old (Mohile et al., 2009).

Anatomy and Pathophysiology

The prostate is a small gland found in men, part of both the male urinary and reproductive system (Canadian Cancer Society, n.da). The gland surrounds the base of the bladder as well as a portion of the urethra and sits in front of the rectum (Canadian Cancer Society, n.da; Prostate Cancer Foundation, n.d.). Prostate size varies in men, but on average the prostate is the size of a walnut (Prostate Cancer Foundation, n.d.). Surrounding the prostate are the seminal vesicles, which are small glands involved in the secretion of semen, and nerves that control erectile function run alongside and attach to the prostate gland (Prostate Cancer Foundation, n.d.). Although not essential for life, the prostate gland plays an essential role in reproduction through the production of protein and mineral rich fluid that nourishes and maintains sperm (Canadian Cancer Society, n.da). Further, due to the prostate surrounding the urethra, muscle cells in the prostate gland also play a role in controlling the flow of urine under involuntary nervous system control (Canadian Cancer Society, n.da.). The gland itself is divided into anatomic regions, reported as the peripheral, transitional and central zones (Prostate Cancer Foundation, n.d.). The majority of prostate cancer tumors develop in the peripheral zone, which is the largest area of the prostate (Canadian Cancer Society, n.da). This area is closest to the rectum and can easily be felt during a digital rectal examination (Canadian Cancer Society, n.da). The transitional zone is the middle of the prostate gland and can enlarge with age, while the

central zone is farthest from the rectum and thus cannot be examined via digital rectal examination (Canadian Cancer Society, n.da).

Androgens such as testosterone and dihydrotestosterone (DHT) play a crucial role in the normal development and biology of the prostate gland (Girling, Whitaker, Mills, & Neal, 2007). However, these potent male hormones are also required for the development of prostate cancer which is often referred to as a hormone dependent cancer (Girling et al., 2007). These androgens exert their devastating effect by binding to androgen receptors (AR) in the cytoplasm of the cell that allows the AR complexes to enter the cell's nucleus via nuclear translocation (Girling et al., 2007). Once in the nucleus, the AR complexes bind to specific DNA sequences known as androgen response elements that promote growth of androgen responsive genes (Girling et al., 2007). These genes are responsible for many different cellular events, including increase growth, survival and the expression of prostate specific antigen (PSA) (Girling et al., 2007). It is because of this process that treatment for prostate cancer is often aimed at targeting the androgen receptors by reducing androgens levels or by inhibiting androgen receptor activation (Girling et al., 2007) which will be discussed further below.

Prostate-specific antigen (PSA) is a protein produced by the cells in the prostate gland (NCI, 2012). It is commonly found in semen with small amounts found in the blood of healthy men (Canadian Cancer Society, n.db). Measuring PSA levels in the blood was originally approved to monitor for prostate cancer disease progression in those diagnosed with prostate cancer, however with time it was recommended for use in conjunction with a digital rectal examination to screen for prostate cancer (NCI, 2012). This test continues to be used as a 'tumor marker' to monitor prostate cancers response to treatment and to monitor for progression or recurrence of disease (Canadian Cancer Society, n.db). As such, changes to PSA levels in the

blood, such as an increase in PSA during active treatment or following treatment can indicate poor response or recurrence (Canadian Cancer Society, n.db). While a decrease in PSA levels often indicate response to treatment (Canadian Cancer Society, n.db).

Until recently, screening for prostate cancer via a PSA test was recommended for all men over the age of 50, however as more has been learned about the test, recommendations are changing (NCI, 2012). Test results are not definitive. Elevated test results (>4 ng/mL) do not indicate prostate cancer, as other benign conditions can cause PSA elevations such as inflammation of the prostate (prostatitis) or enlargement of the prostate (benign prostatic hyperplasia) (NCI, 2012). Moreover, activities such as recent sexual intercourse, digital rectal examination or prostate biopsy can temporarily increase PSA readings (Canadian Cancer Society, n.db). PSA testing has also been associated with false positives, meaning the results suggest cancer though no cancer is present as well as false negatives, meaning the test fails to identify cancer (Canadian Cancer Society, n.db). It is further identified that PSA testing has led to the over diagnosis of prostate cancer, as testing may find cancer that poses no serious risk to a man's health, leading to unnecessary testing and treatment (Canadian Cancer Society, n.db). Consequently, the majority of medical organizations and guidelines suggest patients are informed of the potential benefits and harms of screening in combination with assessing personal risk factors for developing prostate cancer (Canadian Cancer Society, n.db; NCI, 2012).

Prostate Cancer Treatments

Androgen deprivation therapy (ADT) is the most widely used treatment modality for prostate cancer, most frequently used in those with metastatic or with high risk disease (Canadian Cancer Society, 2014a; Mohile et al., 2009). It is estimated that at least 50% of those diagnosed with prostate cancer will receive this method of treatment at some point in their

disease (Tadros & Garzotto, 2011). It can be given as a single treatment modality or in combination with radiation therapy, either prior to radiation (neo-adjuvant) or after radiation therapy (Canadian Cancer Society, 2014a). Other methods of treatment for prostate cancer include surgery such as a radical prostatectomy or transurethral resection of the prostate, active surveillance (physical assessment and PSA testing every 3 to 6 months), radiation, and chemotherapy (Canadian Cancer Society, 2014a).

Androgen Deprivation Therapy

The clinical effects of suppressing testosterone levels (androgen deprivation) in those with advanced prostate cancer was first identified by Huggins and Hodges in 1941 (Perlmutter & Lepor, 2007). Androgen deprivation was found to be related to either surgical castration or through suppressing the production of luteinizing hormone releasing hormone (LHRH) by the hypothalamus using diethylstilbestrol (DES) (Perlmutter & Lepor, 2007). Since that time hormonal suppression has been a widely accepted form of managing advanced prostate cancer (Perlmutter & Lepor, 2007). DES was eventually identified to be associated with significant cardiovascular risks (Perlmutter & Lepor, 2007), so in 1971 new forms of hormone suppression were developed through the manipulation of the sixth amino acid of gonadotropin releasing hormone (LHRH), resulting in a potent LHRH agonist called Leuprolide (Perlmutter & Lepor, 2007). Leuprolide was studied and accepted to be equally equivalent in efficacy to DES with less risk of cardiovascular toxicity (Perlmutter & Lepor, 2007). Over the next several decades several other forms of LHRH agonists were developed and are currently in use today such as goserelin and triptorelin (Perlmutter & Lepor, 2007). Currently, there are four pharmacological classes of medications used for androgen deprivation: luteinizing hormone releasing hormone agonists (LHRH), GnRH antagonists, anti-androgens and CYP17 inhibitors. LHRH agonists are currently

the preferred means of androgen deprivation in practice (Harris, Mostaghel, Nelson, & Montgomery, 2009). These include Leuprolide, Goserelin and Buserelin, which are administered as either intramuscular or subcutaneous injections, most commonly every 3 months (BCCA, 2012a; BCCA, 2012b; BCCA, 2012c; Harris et al., 2009). Please refer to Appendix A for more information on the mechanism of action, indications and methods of administration.

Duration of ADT remains highly debated in the literature with regard to intermittent versus continuous treatment (American Cancer Society, 2014). Regardless of duration of dosing, patients will eventually become resistant to hormone ablation and the cancer will progress despite treatment, this can occur over a period of month or years (American Cancer Society, 2014). Intermittent treatment can be given for fixed periods of time, for example 6 months on and 6 months off or given based on PSA level response to treatment (American Cancer Society, 2014). Intermittent dosing allows for a break in treatment and thus a break from treatment related side effects (American Cancer Society, 2014). Consensus regarding disease free survival between continuous and intermittent hormone therapy remains unclear, with some studies suggesting continuous hormone ablation has a small survival benefit (American Cancer Society, 2014).

Generally, ADT is used primarily for those with metastatic disease; however it has been shown to be effective as neo-adjuvant therapy prior to radiotherapy for those with high risk localized disease (Perlmutter & Lepor, 2007). Additionally, use has been demonstrated in those with localized prostate cancer, locally advanced disease, and those with a biochemical recurrence, such as an increase in PSA after a prostatectomy (Perlmutter & Lepor, 2007).

The clinical benefits of ADT are not only related to slowing the progression of disease, but use is also associated with improving symptoms for those with symptomatic metastatic

disease. For example, improvements in pain related to bony metastases, post void residual urine, urinary symptoms such as urgency and frequency and quality of life have been demonstrated (Perlmutter & Lepor, 2007). One initial limitation to initiation with ADT is the 'flare phenomenon' which is related to the initial surge of testosterone in the body due to the stimulation of LHRH receptors (Perlmutter & Lepor, 2007). This is most frequently prevented with the administration of anti-androgens, which inhibit the effects of testosterone stimulation of the androgen receptors (Perlmutter & Lepor, 2007).

Side Effects of Androgen Deprivation Therapy

Commonly reported early adverse effects include hot flashes, loss of libido and erectile dysfunction, all of which coincide with achievement of castration levels of testosterone, which occurs in only a few weeks (Perlmutter & Lepor, 2007). Prevalence rates of these early side effects vary depending on type of androgen suppression; however rates related to LHRH agonists for hot flashes are approximately 40-77%, loss of libido 100%, and erectile dysfunction 90% (BCCA, 2012a; BCCA, 2012b). These adverse effects will continue as long as treatment is continued (BCCA, 2012a). A variety of other side effects that have been documented in the literature are outlined in table 1.

Table 1 *Androgen Deprivation Side Effects*

Physical side effects	Cognitive side effects	Psychological side effects
Impaired physical function Metabolic syndrome and Diabetes Cardiovascular disease Andropause syndrome Anemia Cataracts Impaired bone mineral density Acute kidney injury	Impaired cognitive function	Depression and distress Altered body image and loss of masculinity

(Al-Shamsi et al., 2012; Beebe-Dimmer et al., 2011; Braga-Basaria et al., 2006; Bylow et al., 2008; Cherrier, Aubin, & Higano, 2008; Curtis, Adam, Chen, Pruthi, & Gornet, 2008; Grunfeld, Halliday, Martin, & Drudge-Coates, 2012; Harrington, Jones, & Badger, 2009; Hervouet et al., 2013; Keating, O'Malley, & Smith, 2006; Lapi et al., 2013; van Londen, Levy, Perera, Nelson, & Greenspan, 2008).

A comprehensive overview of side effects is provided below, described in relation to physical, cognitive and psychological side effects. To begin, physical side effects will be described in detail in the following order: impaired physical function, metabolic syndrome and diabetes, cardiovascular disease, andropause, anemia, cataracts, impaired bone mineral density, and acute kidney injury. This will be followed by cognitive side effects. Lastly, psychological side effects, such as depression and distress, as well as body image and loss of masculinity will then be described.

Physical Side Effects

The following physical side effects will be presented below: impaired physical function, metabolic syndrome and diabetes, cardiovascular disease, andropause, anemia, cataracts, impaired bone mineral density, and acute kidney injury.

Impaired physical function. Functional decline with age can occur naturally due to normal senescent changes, however specific illnesses and their treatments, such as ADT, can further increase decline, which puts patients at further risk for morbidities and mortality.

According to Soyupek, Soyupek, Perk and Ozorak (2008) testosterone plays an important role in muscle strength as well as the function of the nervous system (Bonifazi, Ginanneschi, Volpe et al. as cited in Soyupek et al., 2008). As such ADT related depletion in testosterone has demonstrated declines in endurance, upper extremity strength and dexterity, as well as self-reports of physical function, role and vitality (Alibhai et al., 2010; Soyupek et al., 2006). Despite this knowledge, discussion of physical and functional decline have not been well described in the prostate cancer literature (Bylow et al., 2008).

Metabolic syndrome and diabetes. Goldenberg and Punthakee (2013) defines metabolic syndrome as at least three of the following criteria: waist circumference greater than 102 cm in men or 88 cm in women, elevated triglycerides (greater than or equal to 1.7 mmol/L), reduced HDL (less than 1.0 mmol/L in men or 1.3 mmol/L in women), blood pressure greater than or equal to 130/85 and a fasting glucose greater than or equal to 5.6 mmol/L. In Braga-Basaria et al.'s (2006) cross sectional study, more than 50% of men undergoing long term ADT had evidence of metabolic syndrome. This association is likely related to the profound hypogonadism associated with ADT which has been correlated with an unfavorable metabolic profile such as increased insulin resistance, increased body mass index (BMI), and reduced lean body mass (Basaria, Muller, Carducci, Egan, & Dobs, 2005; Braga-Basaria et al., 2006). Male hypogonadism has therefore emerged as an independent risk factor for metabolic syndrome, which in itself is associated with the development of diabetes and cardiovascular disease (Braga-Basaria et al., 2006; Ford, Giles, & Dietz, 2002 as cited in Braga-Basaria et al., 2006). Tsai et al. (2015) confirms the association between ADT and diabetes by highlighting three large cohort studies reporting an increased risk of diabetes in those with prostate cancer receiving ADT when compared to non ADT users. Moreover, ADT has been associated with increased total

cholesterol by up to 10%, triglycerides by 26% and high density lipoprotein by approximately 8-11%, all of which has been demonstrated within 3 months of ADT initiation (Saylor, Keating, & Smith, 2009). This association suggests risk stratification, routine assessment of metabolic profiles and cardiovascular risk should be incorporated into primary care.

Cardiovascular disease. As demonstrated above, ADT has several adverse physiologic effects, such as increased fat mass, decreased insulin sensitivity, and elevated LDL, cholesterol and triglycerides, all of which are independent risk factors for cardiovascular disease and mortality (Efstathiou et al., 2009). A variety of studies have been done to ascertain whether there truly is an association between ADT and cardiovascular morbidity and mortality with conflicting results. Keating et al. (2006) and Tsai, D'Amico, Sadetsky, Chen and Carroll (2007) studies both demonstrated an increased risk of cardiovascular disease associated with ADT, while a 2009 study by Nanda et al. demonstrated an increase in all-cause mortality in men receiving ADT among those with pre-existing cardiovascular disease. Efstathiou et al. (2009) did not find the same associations as their study findings were not statistically significant.

Andropause symptoms. Asthenia, gynecomastia, night sweats, hot flashes, loss of libido and sexual dysfunction are collectively known as andropause symptoms (Grunfeld et al., 2012). These male climacteric symptoms are associated with hypogonadism and are reported as one of the most physically and psychologically bothersome ADT related effects (Grunfeld et al., 2012; Nishiyama, Kanazawa, Watanabe, Terunuma, & Takahashi, 2004). Although some of these symptoms may be reported with the normal aging process, onset of andropause symptoms occur quicker and with greater severity in those receiving ADT due to the drastic and rapid drop in testosterone from the androgen depletion of ADT (Grunfeld et al., 2012). The most commonly reported symptom of andropause are hot flashes, with up to 80% of men treated with ADT

experiencing this adverse effect (Grunfeld et al., 2012). It has been reported that hot flashes related to ADT are more frequent, more severe and last longer than those related to female menopause (Grunfeld et al., 2012). Consequently hot flashes and resultant night sweats can have a significant impact on daily functioning as both symptoms can have a negative effect on sleep which results in deleterious effects with cognitive functioning, daily accomplishments, enjoyment of relationships and activities, and overall feeling of well-being (Chevalier et al., 1999; Roth & Ancoli-Israel, 1999; Leger et al., 2008 as cited in Hanisch et al., 2011).

Gynecomastia associated with hypogonadism occurs very early on in ADT, usually within a month or two. Although not physiologically significant, this condition can cause significant distress and embarrassment impacting psychological well-being.

Hormonal changes related to ADT can significantly impact sexual function. Declines in sexual function were reported as soon as two months after the initiation of ADT and continued for the duration of treatment. For those receiving short term or intermittent ADT the negative effects on sexual function have been reported to last two or more years after treatment completion (Gay et al., 2013). Impotence, reduced libido and anorgasmia are frequently reported in the ADT literature and are often associated with altered perceptions of masculinity, conflict within intimate relationships, a sense of loss of intimacy and ultimately can significantly impact the quality of life of both the patient and their partners (Gay et al., 2013; Grunfeld et al., 2012).

Anemia. Anemia frequently occurs in those with cancer, occurring in more than 40% of cases (Dicatol, Plawny, & Diederich, 2010). An association between testosterone and hemoglobin levels have been in the literature since it was first identified in 1948 (Hamilton, 1948 as cited in Curtis et al., 2008). These findings have been further confirmed by several studies with the knowledge that both surgical and pharmacological (ADT) castration can impact

hemoglobin, often into the anemic range. This drop in hemoglobin is likely related to the decline in androgens and thus loss of the erythropoietic stimulating effects of androgens in the bone marrow (Curtis et al., 2008). Anemia is defined as a hemoglobin less than 14 g/dl in men and less than 12 g/dl in women (Dicatol et al., 2010). The reported anemia is normocytic in nature with declines in hemoglobin most often seen within three to nine months of initiating treatment (Curtis et al., 2008). Clinical consequences of anemia in men receiving ADT for prostate cancer include impaired quality of life as it can contribute to fatigue and dyspnea on exertion, but has also been identified as an adverse prognostic factor (Curtis et al., 2008; Dicatol et al., 2010).

Cataracts. Cataracts are a chronic, progressive, age related eye disorder that commonly affects those over the age of 50 years old (American Academy of Ophthalmology, 2011). Without treatment visual and physical functioning will progressively decline (American Academy of Ophthalmology, 2011). Very few studies are available that discuss the association between ADT and cataracts. Beebe-Dimmer et al.'s (2011) study used data from the Surveillance, Epidemiology and End Results Medicare Database (SEER) that demonstrated an elevation of cataract incidence among those receiving ADT. This association is suspected to be related to the onset of other identified adverse effects of ADT such as metabolic syndrome (Beebe-Dimmer et al., 2011).

Impaired bone mineral density. The potential effect of ADT on bone mineral density has been widely explored in the literature. Those receiving ADT have demonstrated a 5-10 fold increase loss of bone mineral density at multiple skeletal sites that is related to the hypogonadal state induced by ADT. The significant decline in circulating estrogen and testosterone levels causes increased rates of bone resorption as well as impairment of new bone formation (Al-Shamsi et al., 2012). Changes to bone mineral density can be seen within months of ADT

initiation, with maximal loss noted within the first year of treatment (Al-Shamsi et al., 2012). Annual bone loss in the older male population is estimated to be 1% while bone loss in those receiving ADT is more rapid with many studies estimating the loss to be 1-4.6% annually (Mohile et al., 2009). This loss of bone mineral density alongside ADT associated declines in lean muscle mass increases the risk of osteoporosis, falls and fractures (Nadler et al., 2013). Some studies have reported the risk of fractures to be as high as 20% by 5 years of ADT treatment which is twice the risk identified in men with prostate cancer not receiving ADT or healthy controls (Nadler et al., 2013). Implications of osteoporotic fractures include pain, depression, fatigue, functional impairment, increase mortality rates by up to 20% and a significant cost to the health care system (Nadler et al., 2013).

Acute kidney injury. Recent developments in ADT research have identified a possible connection between the hypogonadal state induced by ADT and acute kidney injury (Lapi et al., 2013). Lapi et al. (2013) highlight that other ADT related adverse effects such as dyslipidemia and hyperglycemia associated with metabolic syndrome may impact renal glomerular function via the expansion and thickening of the interstitial tubular membrane (Lapi et al., 2013). It is also suggested the vasodilator effects of testosterone are lost when ADT depletes testosterone to castration levels impacting renal tubular function (Lapi et al., 2013). Lapi et al.'s (2013) case control study is currently the only observational study investigating this association and did demonstrate an increased risk of acute kidney injury with ADT. As a result of this relatively new finding, data is relatively limited in the literature regarding ADT and its associated effects on the kidney, which accounts for the limited data provided here. Nonetheless, this side effect must be considered for this patient population. As the above has highlighted, there are a variety of

physical side effects to ADT that must be considered when providing care to this patient population. Moving forward, the cognitive effects of ADT will be addressed.

Cognitive Side Effects

The following will present the adverse effects of ADT on cognition. Cognitive changes have long been associated with a variety of cancer treatments, however education, screening and support do not appear to be incorporated into cancer care. Cherrier, Aubin and Higano (2008) note a positive relationship between testosterone and cognitive functions such as executive functions, spatial memory and abilities. As such, studies have identified the hypogonadism associated with ADT was related to impairments in verbal memory, attention and spatial abilities (Cherrier et al., 2008). Further, as demonstrated by Cherrier et al.'s (2008) study, cognitive changes were noted as early and most pronounced within three months of ADT and some but not all cognitive changes related to ADT might return to baseline following cessation of ADT. The literature also identifies that often cognitive changes in those receiving ADT are erroneously believed to be associated to age rather than the treatment by both patient and provider which may be related to a lack of information regarding the potential impact of treatments on cognition. Moreover, identifying cognitive impairments in this patient population is essential as impairments can negatively impact cancer care, outcomes, treatment tolerability and patient decision-making (Mohile et al., 2010). Finally, the psychological side effects and their impact on health and well-being will be discussed below.

Psychological Side Effects

The psychological sequelae of ADT, such as depression and distress followed by altered body image and loss of masculinity will be presented.

Depression and distress. The overall prevalence of depression in those with cancer is estimated to be between 15-25%, while those receiving ADT are proposed to be at an even higher risk based on current research (NCI, 2014). However, despite its prevalence, depression and distress are under recognized and undertreated which can impact medical adherence, increased morbidity and possibly mortality (Pirl, Siegel, Goode, & Smith, 2002; Herrmann et al., 1998; Richardson et al., 1990; Spiegel & Kato, 1996 as cited in Pirl et al., 2002). Due to the potential impact, the identification and treatment of psychological issues related to cancer and its treatments have become increasingly identified as an important aspect to comprehensive cancer care (Vodermaier, Linden, & Siu, 2009). Moreover, in an attempt to increase reporting of psychological issues and lessen the stigma associated with psychological conditions, terminology has shifted from language such as depression, psychiatric, emotional or psychosocial issues to the term distress. The link between testosterone depletion and depressive symptoms was first identified in 1995, however since there has been conflicting results of the impact of ADT in relation to mood disorders (Hervouet, Savard, Ivers, & Savard, 2013). Animal models have demonstrated altered neurotransmitter levels, such as serotonin with low systemic testosterone, which can negatively affect mood (Saini et al., 2013). Further, studies involving elderly, non-cancer patients have demonstrated an association between low testosterone and depressive symptoms that resolved with testosterone hormone treatment (Saini et al., 2013).

Altered body image and loss of masculinity. Body image can be defined as "the dynamic perception of one's own bodily appearance, function, and sensations as well as feelings associated with this perception. It occurs largely at a subconscious level and is normally regulated by the condition of the body" (Dropkin, 1999, p. 310 as cited in Harrington, Jones & Badger, 2009). Evans (2001) as cited in Oliffe (2006) notes men traditionally place a high value

on specific qualities and characteristics such as physical strength and the ideal male body, which is intricately connected with embodied masculinity. Therefore adverse changes to body aesthetics, such as breast tenderness and enlargement and the loss of penile length and volume can create significant psychological distress (Saini et al., 2013). Other literature suggests that ADT related changes associated with declines in testosterone, such as 'feminine behaviours' like hot flashes and mood changes are emasculating and worsen self-image and perception (Eziefula, Grunfeld, & Hunter, 2013). Worsening self-image and perceived loss of masculinity can be further perpetuated by other effects of ADT treatment, such as declining libido, energy, body shape, ability to work (Harrington et al., 2009). Navon and Morag (2003) as cited in Harrington et al. (2009) identify these changes to body image can create emotional distance in intimate relationships impacting the quality of life of both partners. Provided above is a comprehensive description of the physical, cognitive and psychological side effects of ADT highlighted in the literature. The next chapter, research and methods, will provide a description of the literature search that was completed in order to answer the research question. The process, such as the identification of search terms, inclusion and exclusion criteria, and screening and search outcomes will be described.

Chapter Two

Research and Methods

The goal of the literature search was to answer the question: For NPs practicing in a primary care setting, what screening is required to identify side effects of ADT in men with prostate cancer. Search terms for the literature review were selected as they represent the various terms applicable to the question being searched. Search terms included *prostate cancer, prostatic neoplasm, androgen ablative therapy, androgen deprivation therapy, primary care assessments, screening, and follow up*. In order to narrow the search and yield findings relevant to ADT and screening of side effects, a combination of terms were selected, using subject headings and the Boolean phrase 'and'. For example, *androgen deprivation therapy and patient assessment, androgen deprivation and screening, androgen deprivation and screening for side effects, androgen deprivation and follow up.* However, very few findings accumulated from this search criteria, therefore slightly broader search terms such as *androgen deprivation therapy and side effects, depression and androgen deprivation therapy, anemia and androgen deprivation therapy, metabolic syndrome and androgen deprivation therapy, and sexual dysfunction and androgen deprivation therapy.* The inclusion and exclusion criteria applied consisted of the following:

Table 2 *Inclusion and Exclusion Criteria*

Inclusion Criteria:
No limitations to date of published papers
Articles written in the English language
Men with prostate cancer (all ethnicities)
No limitations to age or stage of disease
Included at least one study group receiving androgen deprivation therapy (ADT)
Both quantitative and qualitative studies were included
Published papers were not limited to Canada alone due to limited search results
Primary care setting
Exclusion Criteria:
Published papers without recommendations for screening/assessment of side effects
Acute care
Survivorship care

Inclusion criteria included men with prostate cancer (all ethnicities), however was not limited to age as ninety-seven percent of all prostate cancer diagnoses occur in those over the age of 50, however some individuals are diagnosed at a younger age (Prostate Cancer Foundation, 2014). All stages of disease were included. Further, the search was not limited to recent studies as the effects of androgen suppression have been reported in the literature since Huggins and Hodges' initial study of androgen deprivation in the 1940's (Perlmutter & Lepor, 2007). Treatment with ADT was included in all studies, however selection of studies was not limited to prostate cancer patients receiving ADT alone in order to allow for comparison of adverse events between other treatment modalities and healthy controls. Both qualitative and quantitative study designs were included in order to identify a broad account of ADT side effects and themes, identify how these side effects were screened in a research capacity, and whether these methods of screening such as validated screening tools may prove relevant or be recommended for clinical practice assessment of side effects. Qualitative studies were specifically considered as

open ended questions allowed for descriptive reflections on side effects which may identify further adverse effects or themes that should be considered for screening but may not be identified through quantitative design.

As Canadian guidelines and literature were limited, inclusion criteria included other countries. Overall, inclusion criteria remained broad as data pertaining to screening and follow up was limited. Broad criteria also allowed for the ability to gain in-depth insight into adverse events related to ADT in order to highlight gaps in screening in primary care. Exclusions included articles that did not provide screening recommendations for primary care, acute care, post treatment care and follow up (survivorship).

The literature search began with a search of the following four electronic databases: Cochrane library, CINAHL, Pubmed and Joanna Briggs Institute Library. The majority of the searches utilized medical subject headings in order to facilitate appropriate data retrieval by accounting for various terminology and subject matter for the topic of interest (National Institute of Health, 2012). Based on the above search terms, a total of 1198 articles were identified.

Using the University of Northern British Columbia's library resources for direction, a search of the grey literature was then done. This included a search of the following: clinical practice guidelines and protocols for British Columbia, Canadian Nurses Association standards and best practices, Canadian Medical Association InfoBase, National Guideline Clearinghouse, Canadian Agency for Drugs and Technologies in Health and Standards and Guidelines Evidence (SAGE). Guidelines were scanned and included in the search results if they included any aspect of screening, recommendations or follow up. Google Scholar and the World Wide Web were also searched using the same search terms and phrases as above. The search revealed an additional 140 potentially relevant materials. Finally, the reference lists for all full text eligible

papers were scanned and a total of three additional papers were identified. In the end, a total of 1341 potentially relevant materials were identified, retrieved, and exported into Endnote.

Screening and Search Outcome

The literature review identified a total of 1341 potentially relevant papers. After screening titles and abstracts for suitability, this number was narrowed down to 50 articles for further review. Full text articles were then reviewed, 28 of which were excluded based the on inclusion and exclusion criteria. After this process, 22 eligible papers were available for review (see Appendix B for flow chart). The next chapter will discuss the findings of the 22 papers identified in the review. This will begin with twelve individual research studies, followed by five clinical practice guidelines, four clinical reviews and one editorial.

Chapter Three

Findings

The search strategy described above identified 22 articles to assist in answering the research question: For NPs practicing in a primary care setting, what screening is required to identify side effects in men with prostate cancer receiving ADT. The following chapter will present 12 individual research studies, using both quantitative and qualitative designs to provide insight into specific screening recommendations. The literature frequently describes ADT side effects by a focus on physical, cognitive and psychological alterations of function; therefore data from the individual studies will be presented in a similar fashion. Following individual study findings, the findings from five current clinical practice guidelines, four clinical reviews and an editorial will be analyzed with regard to recommendations for screening for those receiving ADT for prostate cancer. Findings from clinical practice guidelines, clinical reviews and editorials are deliberately presented as a whole rather than through individual physical, cognitive, and psychological side effects in order to demonstrate the gaps, limitations and strengths of each.

To begin, current recommendations for screening of physical, cognitive and psychological side effects from 12 individual research studies will be highlighted. Several topics are noticeably absent from these studies, such as follow up intervals, cardiovascular disease, cataracts and acute kidney injury, which accounts for the diversion from previously organized paper subheadings. However, recommendations for these topics are described in other research materials, such as clinical practice guidelines, clinical reviews and editorials, which will be presented following individual studies.

Physical Side Effects

Physical function. Of the 12 research studies reviewed, only one study described

physical and functional impairment with screening recommendations. Bylow et al.'s (2008) study investigated the prevalence of falls, physical and functional impairment in those receiving ADT for symptomatic metastatic prostate cancer. Fifty patients over the age of seventy were recruited from a convenience sample of men being treated at the University of Chicago Genitourinary Oncology clinics. All patients underwent a comprehensive geriatric assessment at baseline, which was then repeated after three months of ADT treatment (only 40 patients had the repeat assessment as 10 patients were lost to follow up). The comprehensive geriatric assessment included an assessment of functional measures, risk for functional decline, physical function, history and risk of falls, mental status, nutritional assessment, social support, and fatigue using tools that have been validated in the elderly population. Functional measures such as activities of daily living (basic self-care), instrumental activities of daily living (activities required to live independently such as banking, meal preparation and shopping), and the Vulnerable Elders Survey (VES) were done to assess risk of functional decline. The VES is a 13 item, self-reported screening tool used to identify geriatric patients who are risk for functional decline. Physical function was assessed using the Short Physical Performance Battery (SPPB), which assessed the physical function of the lower extremities through three tests of balance, gait speed and quadriceps strength. The other tools utilized in the geriatric assessment included the Short Portable Mental Status Questionnaire, Charlston Comorbidity Index, Medical Outcomes Study Social Support Scale, the Mini Nutritional Assessment, and the Medical Outcomes Study Short Form 36 item health survey. Deficits were noted in balance, walking and chair stands in 56% of patients, 24% had impairments on activities of daily living while 42% had impairments in instrumental activities of daily living. At baseline, 22% of patients had reported falls within the previous three months and 56% noted additional falls after treatment had been initiated. As a

result of the increased risk for falls, the study authors identified a need for routinely screening for abnormal physical performance and risk for falls in this patient population. A major strength to this study is the use of tools that have been validated for use with the elderly population. However, due to a small sample size and the nature of the cross sectional study, a temporal relationship between ADT, abnormal physical performance and falls could not be reliably established or generalizable.

Metabolic syndrome and diabetes. Two individual research studies identified metabolic syndrome and diabetes as side effects to ADT. A cross sectional study by Basaria et al. (2005) evaluated the effects of long term ADT use on fasting glucose levels, insulin levels and insulin resistance in men with prostate cancer. Three groups were studied: Group 1 consisted of 18 men with prostate cancer who were receiving ADT for 12 months prior to the study, group 2 included 17 men with non-metastatic prostate cancer who had not received ADT, and group 3 was made up of 18 healthy controls. Parameters such as age, race, and BMI were documented along with objective measures of total and free testosterone levels, leptin, fasting glucose and insulin levels. Leptin is involved with long term regulation of energy balance, suppression of food intake and weight loss (Klok, Jakobsdottir, & Drent, 2007). However, interestingly, obese individuals typically demonstrate high leptin levels, which suggests leptin resistance (Klok et al., 2007). Fasting glucose refers to a serum blood sample that reflects the glucose (sugar) concentration to which the body tissues are exposed (Hess-Fischl, 2015). Insulin is a hormone produced by the pancreas that allows the body to use glucose derived from food intake for energy or to store glucose for future use (Hess-Fischl, 2015). Elevations in fasting glucose levels demonstrates the bodies' inability to produce enough insulin or the development of insulin resistance, both of which increase the risk of developing diabetes (Hess-Fischl, 2015).

A significant negative correlation was noted between testosterone and fasting glucose, insulin and leptin levels. Additionally, men who had received ADT had higher fasting glucose levels when compared to the non ADT group ($p=0.01$) and the control group ($p<0.01$). Insulin levels were also much higher in the ADT group (45 +- 7.25 uU/mL) in comparison to 24.0 +- 7.24 uU/mL in the non ADT group ($p=0.05$) and 19.0+- 7.39 uU/mL in the control group ($p=0.02$). Finally leptin levels were also higher in the ADT group when compared to the non ADT group ($p<0.01$) and control group ($p<0.01$). This study demonstrated that those who received long term ADT were at increased risk for developing insulin resistance; however results may not be entirely generalizable as the majority of subjects were Caucasian. The use of a non ADT and control groups does however help account for any influence prostate cancer and aging may have on metabolic parameters. Nonetheless, study authors identified individuals on long term ADT, greater than 12 months, be screened for hyperglycemia or elevated blood sugars.

Tsai et al.'s (2015) retrospective cohort study supports the above findings with regard to insulin resistance through demonstrating the potential to develop diabetes related to this treatment regimen. A total of 12,191 participants with localized prostate cancer between the ages 35 and 100 were recruited between 1995 and 2008. Participants were identified from one of three health care delivery systems within the HMO Cancer Research Network. These systems collect a variety of data regarding inpatient and outpatient diagnosis, clinical encounters, laboratory values, tumour registry and pharmacological dispensation. Men with prostate cancer were included if they received ADT within one year of diagnosis, did not have diabetes, or had not had a prostatectomy, radiation or chemotherapy one year after diagnosis. Data regarding diabetes diagnosis was obtained from inpatient and outpatient diagnosis codes, diabetes medications prescribed and hemoglobin A1C values. Of the 12,191, 22% (N=2648) received ADT within one

year of diagnosis and the remaining 78% (N=9543) did not receive ADT. Study findings demonstrated 9.9% of patients developed diabetes during follow up, which was a median of 4.8 years. Incidence rates were 2.48 per 100 persons in the ADT group and 1.6 events per 100 persons in the non-primary ADT group. Factors associated with the incidence of diabetes included treatment with ADT after 12 months from prostate cancer diagnosis, hypertension, and obesity.

As a result of findings, study authors reinforce the need to screen this patient population for insulin resistance during ADT treatment. Moreover the study authors identify the American Diabetes Association (ADA) guidelines as a method for screening, however encourage more frequent monitoring for those receiving ADT. As noted by the ADA guidelines, recommendations for screening of the general public is suggested via a serum hemoglobin A1C, fasting blood glucose and a 2 hour post prandial blood sugar every three years among any individuals who are overweight (BMI >25), obese (BMI >30) or over the age of 45. For those receiving ADT for prostate cancer, study authors identify screening should occur prior to the initiation of ADT and then repeated annually.

Study strengths include use of a control group, a large sample size and a long period of follow up. Further, potential cofounding effects such as age, race/ethnicity, year of diagnosis, comorbidities and health plans were adjusted for. However, there is no mention as to whether the study controlled for all risk factors associated with diabetes. Three study limitations were noted with the first being potential for selection bias given the study design was an observational study. Secondly, a hemoglobin A1C of 7% was used to establish the diagnosis of diabetes rather than the 6.5% which may have missed some participants with early diabetes. Finally, as the participants were selected from the HMO system generalizability to non-HMO systems may be

limited as HMO likely promotes and supports prevention and early detection of diabetes.

Andropause syndrome. Of the 12 individual research studies, only one specifically looked at andropause syndrome in relation to screening recommendations. Through qualitative interviews, Grunfeld et al. (2012) explored the prevalence and impact of andropause symptoms in men with metastatic prostate cancer undergoing ADT. Twenty-one patients were recruited and underwent semi- structured in person or telephone interview. Interview questions were developed based on previous research, and discussions with a urology nurse specialist, psychologists and urologist. Interviews were conducted using open ended questions, with loose structure that focused on areas of predefined interests such as side effects of ADT and coping strategies, however allowed for discussion of issues as they emerged in the interviews. Four main side effects to ADT were identified, gynecomastia, cognitive decline, change to sexual function, hot flashes and night sweats. Approximately half of the patients reported gynecomastia and or breast tenderness, while 71% experienced night sweats and hot flashes, all of which were a source of embarrassment. Night sweats also significantly contributed to disturbed sleep patterns which resulted in daytime sleepiness.

Additionally, reported changes to sexual function such as interest and physical capability, varied depending on the patients age and marital status. For example, sexual dysfunction such as impotence or reduced libido was more commonly accepted in those that were single or if their partner had a low libido. Others deemed sexual dysfunction to be a major concern, particularly related to concerns about disappointing their wives, while others discussed the impact on masculinity. Disclosure of symptoms was variable, with most limiting disclosure to close family. Surprisingly this study found many of the participants had a desire to commence sexual activity, however very few had received treatment for erectile dysfunction (ED) or were offered

counselling either for themselves or their intimate partners. This leads one to consider whether patients are being adequately screened for sexual dysfunction. Based on hesitancy to disclose andropause symptoms, study authors emphasized the importance for the PCP to ask about side effects to assist men in actively and openly discussing bothersome concerns. Study strengths include an appropriate sized sample group with an adequate number of meaningful and descriptive quotations that emphasized the occurrence and meaning of ADT side effects. Additionally, interview questions appeared to be evidence based and piloted which allowed for gathering of specific information sought by the study authors and participants were also provided an opportunity to discuss other issues allowing for the potential development of new themes. Limitations may include limited information regarding the interviewers, such as age and sex which may alter participants' willingness to disclose sensitive issues.

Anemia. Only one research study identified anemia as an ADT related side effect in conjunction with screening recommendations. Curtis et al.'s (2008) retrospective chart review of metastatic prostate cancer patients receiving ADT attempted to confirm the association between anemia and ADT and identify whether patients were clinically symptomatic with their anemia. A total of 135 cases were reviewed, all of which had received some form of ADT. Case review included treatment type (single or combination ADT), hemoglobin and mean corpuscular volume (MCV) levels prior to initiating ADT followed by measurements of these three and nine months after starting treatment. Patient charts were reviewed to assess for references noting the presence of symptomology related to anemia (such as dyspnea and fatigue). Of the 135 charts reviewed, 43 patients had laboratory data sufficient to be included in the final analysis. A decline in hemoglobin values, by -1.11 g/dL, was noted in all patients receiving ADT ($p<0.001$). Normal hemoglobin values for men are approximately 13.2 to 17.5 g/dL, mean values of hemoglobin

prior to ADT treatment initiation were 14.12 g/dL, while values between three and six months revealed a hemoglobin value in the anemic range (13.01). MCV levels also demonstrated a decline at six months, with a volume of 93.5 fL. Finally, 37% (16 out of 32) patients experienced symptoms of anemia. A major limitation to this study was that many of the patients received a variety of ADT treatments, therefore the changes to hemoglobin could not be solely attributed to one method of ADT alone. Based on these study findings alongside similar study findings from previous studies, it was suggested by study authors to screen for anemia and its symptoms after starting ADT, although specifics are not included.

Impaired bone mineral density. Three of the twelve studies reviewed looked at bone mineral density. Yu et al.'s (2012) study demonstrates these changes through investigating the change in bone mineral density and fracture risk with intermittent treatment with ADT. Fifty-six patients with non-metastatic prostate cancer were recruited for the study. Patients were treated with nine months of ADT and then discontinued until prostate specific antigen (PSA) reached 1 ng/mL for those who underwent a radical prostatectomy and 4 ng/mL for those who underwent radiation and ADT. When these PSA thresholds were met, ADT was reinitiated for another 9 months of treatment. Dual energy x-ray absorptiometry (DEXA) scans, CT scans, bone scintigraphy and lumbar spine x-rays were done prior to starting ADT and repeated with each subsequent change in therapy (beginning and end of each treatment). Of the 56 patients, 38 had normal baseline bone mineral density. Of the 38 patients with normal baseline results, 13.2% developed osteopenia during ADT treatment. Further, results demonstrated an 80% decrease in bone mineral density of the spine and 56.4% decline in bone mineral density of the left hip during the first treatment period. Additionally, bone mineral density recovery of the spine was seen during the first off treatment periods, with an average change of 1.4%. Unfortunately,

several patients dropped out of the study due to ADT treatment failure which may limit the statistical power of the results. Results may also be influenced by individual biologic and environmental factors. Although not specified, if DEXA scans were performed with different machines at different facilities, these small inconsistencies could potentially influence the results as well. Based on variability of bone mineral density changes throughout treatment periods and the known effects of ADT, continued and regular monitoring with DEXA scans was identified by the authors of the study.

Based on the well documented effect of ADT on bone density in the literature, Al-Shamsi et al. (2012) examined care gaps with regarding to screening, prevention and treatment of osteoporosis in men with prostate cancer receiving ADT. This retrospective study consisted of men with non-metastatic prostate cancer who received ADT between 2008 and 2009. Patients were selected based on treatment at the Juravinksi Cancer Centre in Hamilton Ontario and identified by their hormonal therapy treatment billing number. A total of 149 men's charts were reviewed and data such as age, date of prostate cancer diagnosis, stage of disease, and last PSA value were documented. Risk factors for osteoporosis such as previous fractures, hyperthyroidism, use of corticosteroids, diabetes, smoking or alcohol use was also obtained. Finally, presence of osteoporosis screening characterized by a baseline or subsequent dual x-ray absorptiometry (DEXA) was documented. Study results determined a large population of participants had risk factors present for osteoporosis, with five participants having previous fractures, 13.3% alcohol abuse, 49.3% had a history of smoking, 16.7% were current smokers, 3.3% had a history of corticosteroid use and 2% had a history of hyperthyroidism. Baseline DEXA scans were done in 58.8% of men receiving ADT and 20.3% of which had repeat scans at some point as follow up. Only 28% of participants had both a baseline and follow up DEXA

scan. Of those screened at baseline 12 were found to have a bone mineral density in the osteoporotic range (T score of -2.5 or greater) and 13 patients had a T score in the osteopenic range (-1 to 2.5). It was also found that those with increased numbers of ADT injections were more likely to be screened, while age, stage or PSA at initial visit did not impact screening.

It is noted by the study authors that screening for osteoporosis with tools, such as the World Health Organization fracture risk assessment tool (FRAX) as well as a baseline DEXA scan prior to ADT initiation should be considered. Study findings were limited to data being retrieved from a single cancer center that may impact generalizability. Further, data was obtained from a retrospective chart review; therefore data may not accurately reflect the clinical care patients received. Strengths include an adequate discussion regarding implications for practice as well as specific recommendations that may contribute to improved care for this patient population. As mentioned above, although the data was obtained from one care center, data found in this current study was supported by other studies done in other institutions that assist in validating the study findings.

Similarly, Morgans, Smith, O'Malley, and Keating (2013) assessed bone density testing among men with prostate cancer receiving ADT for one year or greater. Men were identified from the Surveillance, Epidemiology, and End Results (SEER) which is a National Cancer Institute program that collects data from cancer registries in the United States. Patients selected were diagnosed between 2001 and 2007 and over the age of 65. Ultimately 28,960 men were selected with local/regional disease. Men with metastatic disease were excluded from the study as bone mineral density testing in this population is not reliable. Bone density testing data was documented six months before ADT initiation for a total of 18 months. Results demonstrated only 10.2% of those receiving ADT for more than one year had bone mineral density testing

done 6 months prior to ADT initiation to one year after treatment. Rates of screening increased over time as 14.5% of men who initiated ADT in 2007-2008 had bone mineral density testing versus 6% of those who started ADT in 2001-2002. Further, older men (over age 85) had less bone mineral density testing done than those in the 66 to 69 age range as did black men versus white men and those with lower educational attainment. Study authors continue to endorse bone density screening and encourage additional efforts to promote screening.

Strengths of the study include a large sample size, moderate length of follow up, and broad patient characteristics which would account for generalizability. Limitations however include timing of the study, as the study began prior to significant evidence in the literature regarding ADT's effect on bone health. Therefore, limited knowledge of risks likely impacted the very low screening rates in the early years of this study. Secondly, recommendations for testing by PCPs versus patient refusal to complete testing was not able to be determined. Further, testing was done in those enrolled in Medicare therefore participation in testing may vary depending on medical coverage.

Unfortunately, the literature failed to identify a large number of studies discussing specific physical side effects alongside screening recommendation for many of the side effects. This is true for physical function, metabolic disease, diabetes, andropause and anemia, with only one study found for each. In this case, one must be cautious when interpreting the results and consider study methods, design and number of participants which can limit or strengthen study findings. For example, Tsai et al. (2015) and Morgans et al. (2013) study's included very large samples with long follow-up, which helps to establish creditability of study results. The next section will present study findings related to the cognitive side effects of ADT.

Cognitive Side Effects

Although several studies have been conducted to identify ADT effects on cognition, only one study was identified in the literature search that met the inclusion and exclusion criteria for this review. Mohile et al.'s (2010) study sought to identify the prevalence of cognitive impairment and changes to cognitive performance over time in thirty-two men with prostate cancer receiving ADT. A variety of standardized neuropsychological assessment tools were used to assess attention, language, verbal memory, visual memory, visuospatial planning and motor processing. These tools were specifically selected based on their established reliability, validity and sensitivity. Assessment tools included were: The Trail Making test (attention), Digit span (attention), Controlled Oral Word Association Test (language and semantic fluency), The Rey Complex Figure Test-Copy Trial (visuospatial planning), Hopkins Verbal Learning Test-Revised (verbal memory), Brief Visual Spatial Learning Test-Revised (visual memory), Grooved Pegboard and Finger Tapping tests (motor speed and dexterity), Becks Depression Inventory-2 (depression), and The State Trait Anxiety Inventory (anxiety). Assessments were done by a trained psychometrician within two weeks of starting ADT, and repeated six months later. Surprisingly, at the time of baseline measurements 45% of participants scored greater than 1.5 standard deviations below the mean on two or more neuropsychological measures, with no changes in cognition noted after treatment initiation. However, 38% of the total cohort demonstrated a decline in executive functioning at the six month assessment. Based on these findings study authors suggest patients be screened for cognitive impairment prior to considerations of ADT and possibly throughout treatment regimens, particularly if patients are more vulnerable to developing life altering conditions such as dementia.

Study strengths include considering potential cofounders such as anxiety, depression and education. Limitations include a short follow up time of 6 months which leaves long term effects

of ADT still unknown. Further limiting the study results is poor completion of follow up assessments, with only 65% of men completed the post treatment follow up evaluations, which may have impacted the results. Additionally, the small sample size without the use of a control group limited the studies ability to identify the impact of ADT on cognitive changes. These study findings may be used in conjunction with other findings in the literature which suggest ADT impacts cognitive function. The psychological side effects of ADT were identified in three individual research studies and will be presented below. Psychological side effects include depression and distress followed by altered body image and loss of masculinity.

Psychological Side Effects

Two studies identified depression and distress as ADT related side effects. Lee et al.'s (2014) longitudinal study aimed to identify depressive symptomology in men receiving ADT for non-metastatic prostate cancer. Participants were recruited between September 2008 and October 2012 as part of a larger study examining quality of life in those receiving ADT for prostate cancer treatment. The sample consisted of three groups: 61 patients with prostate cancer receiving ADT, 61 patients with prostate cancer not receiving ADT (instead a radical prostatectomy) and 61 healthy controls. Each prostate cancer patient receiving ADT was matched to a participant in the non ADT group (prostatectomy) and control group. Self-report questionnaires were completed by all participants with the first questionnaire done prior to the initiation of ADT and again six months later. Depressive symptomology were assessed using a validated tool called the Center for Epidemiological Studies Depression Scale (CES-D). With this measure, scores range from 0 to 60, with scores above 16 indicating clinically significant depressive symptoms.

Study results revealed an increase in depressive symptomology ($p<0.05$) and increased

rates of clinically significant depressive symptomology ($p<0.001$) in the ADT group between baseline and follow up assessments. Rates of depressive symptomology for the ADT group at baseline were statistically significant at 28%, compared to the non ADT group (5%) and control group (12%). At the six month follow up assessment, the ADT group reported depressive symptomology rates of 39%, while the non ADT and control group had rates of 9% and 11%. There were two limitations to this study; first the time between assessments was brief, only six months, which does not allow for long term impact of ADT to be adequately assessed. Second, overall those in the ADT group had a poorer prognosis; therefore it is possible the depression rates were related to awareness of prognosis rather than the effect of ADT. Moreover, it is possible that increased depressive symptomology is related to ADT related side effects, such as hot flashes. Consequently, study authors recognize identifying and treating symptoms of depression should be a priority in the research and practice domains, however suggestions for screening are not provided by the author.

Pirl et al. (2002) reported similar findings in their study. Forty five patients with prostate cancer were recruited, all of which were receiving ADT, either alone or in combination with chemotherapy. Patients were classified according to form of ADT (GnRH agonist or orchiectomy), response to treatment (stable or progression), androgen dependent or independent, treatment with concurrent chemotherapy (yes or no) and history of depression (yes or no). Functional status was assessed using the Karnofsky Performance Scale (KPS) which has been shown to have good reliability and validity (Heinrish & Ganz, 1984), while the Becks Depression Inventory (BDI), a valid screener for depression, and Structured Clinical Interview for DSM-IV (SCID) was used to assess for depression and dysthymia. Fatigue was assessed using the Fatigue Severity Scale, a 7 item scale validated in several populations such as cancer,

multiple sclerosis, Parkinson's and fibromyalgia with excellent validity and internal reliability (Neuberger, 2003). All assessments were administered by a trained registered nurse. The authors reported, the mean KPS score was 91, indicating a high level of function. Although there were no cases of new onset depression noted in the sample, 12.8% of men receiving ADT were found to have major depressive disorder as assessed by the SCID. This statistic is eight times the national rate of depression in men. Further, BDI results demonstrated 13.3% of men reporting mild to moderate depression with no reports of moderate to severe depression. However, results should be viewed with caution as other variables related to depression could confound the data. Further, as the majority of patients were identified as high functioning, reported rates of depression may not be generalizable to those with severe disease and poorer function. Due to study findings, the authors emphasize the need to provide appropriate and regular assessment for depression to this patient population.

Body image and loss of masculinity. One study identified altered body image and loss of masculinity as an ADT related side effect while meeting the inclusion and exclusion criteria. An exploratory, descriptive non-experimental study by Harrington et al. (2009) described changes to body image in those receiving ADT for the treatment of prostate cancer. The study consisted of 132 men, all over the age of 60 representing all four stages of prostate cancer. The sample was divided into two groups, with 66% receiving ADT and 34% who had never received ADT. The Body Image Scale (BIS) was used, which is a ten-item scale that measures changes to body image in cancer patients. Scores range from 0-30, with higher scores identifying greater degree of body image dissatisfaction. Unfortunately, the study does not mention whether the BIS is a validated tool, however study findings demonstrate the BIS to have acceptable psychometric properties to support its continued use in men with prostate cancer. Overall, the mean scores in

the sample were 6.13 out of the possible 30, with the mean score of the ADT group being higher (X=2.23, SD=1.44) than the non ADT exposure group (X=1.52, SD=1.44), demonstrating greater body dissatisfaction in the ADT group. The highest areas of dissatisfaction pertained to perception of sexual attractiveness, masculinity, and feeling less whole as the result of body changes. A positive correlation was noted between body image dissatisfaction and a higher BMI.

Authors suggest PCPs anticipate changes to sexuality and intimate relationships and should screen, educate and provide treatment for these areas of health. Study strengths include implications for practice as well as provide relevant information into potential interventions to aid in relieving distress in this area, such as diet and nutritional services that have been deemed successful in female breast cancer patients and men with prostate cancer receiving ADT. A limitation to the study however is age as all men were 60 years or older, which does limit the information to this age group. Previous studies on female breast cancer patients have demonstrated significantly more distress regarding body perception in younger populations which lends one to consider whether this may prove true for younger men with prostate cancer, however this study sample does not allow for this consideration.

In summary, these 12 research studies indicate that ADT has the potential to cause a variety of complex and multi-dimensional side effects. However, despite the acknowledgement of these potential side effects, individual research studies provide very few recommendations with regard to specific methods or intervals for screening side effects to ADT. Many recommendations are simply comprised of blanket statements to encourage screening however remain overall ambiguous. For example, of the five described physical side effects, only two studies provided specific recommendations with regard to methods and intervals for screening. Similarly, methods of screening for cognitive impairment and depression are not presented.

Moreover, many of the initially defined side effects provided in the background, such as cardiovascular disease, cataracts, and acute kidney injury are noticeably absent as the literature search failed to provide any research studies that included recommendations for screening for these side effects. Finally, although a variety of tools are presented as methods of assessment in the research studies themselves, very few studies actually advocate for the use of specific screening tools or propose a method of assessment. In the upcoming paragraphs, screening recommendations from five clinical practice guidelines will be presented.

Current Clinical Practice Guidelines

Clinical practice guidelines are evidence based, systematically developed recommendations and statements which are designed to support practitioners in decision making regarding health care and clinical circumstances (Watters, 2015). Current clinical practice guidelines regarding the screening and management for men receiving ADT are quite limited in the literature. Five clinical practice guidelines were identified in the literature search, one from Alberta Canada, the United States, and Australia and two from Europe. All five guidelines were developed through a critical evaluation of evidence found in the literature via a systematic literature review and through expert consensus and clinical interpretation (Alberta Provincial Genitourinary Tumor Team, 2013; Australian Cancer Network, 2010; EAU, 2015; NCCN, 2015a; NICE, 2014). Findings pertaining to the five pertinent guidelines are discussed below.

The only Canadian guidelines that appear to be available come from the Alberta Provincial Genitourinary Tumor team, published in 2013. Recommendations include follow up within three to six months of initiating therapy and as clinically indicated (Alberta Provincial Genitourinary Tumor Team, 2013). Duration for follow up is noted as 'age dependent', which does not provide a specific reference for PCPs (Alberta Provincial Genitourinary Tumour Team,

2013). Further, Alberta Provincial Genitourinary Tumour Team (2013) proposes ADT use over six months to be a high risk factor for the development of osteoporosis, therefore this guidelines suggests all patients have a baseline dual energy x-ray absorptiometry (DEXA) scan prior ADT initiation. It is also identified that patients should undergo assessment of fracture risk using the World Health Organization FRAX tool (Alberta Provincial Genitourinary Tumour Team, 2013).

The second guideline to be reviewed was published in 2015 in the United States from the National Comprehensive Cancer Network (NCCN, 2015a). This guideline provides a brief overview of the work up and diagnosis for prostate cancer, management for low, intermediate, high risk and metastatic disease including a variety of treatment modalities. In terms of ADT very little information is provided regarding screening. The only specific endorsement presented is for the National Osteoporosis Foundation's recommendation that all patients with prostate cancer receiving ADT be assessed for fracture risk using the Fracture Risk Assessment (FRAX) tool. It is further suggested that those who demonstrate an increased risk based on the FRAX assessment should undergo a DEXA scan prior to ADT initiation followed by a repeat scan after one year of treatment (NCCN, 2015a). Finally, screening for and prevention of cardiovascular disease and diabetes are also mentioned in the NCCN guidelines, however it is highlighted that it is unknown if strategies for screening and prevention should differ from the general population and therefore no formal suggestions are made (NCCN, 2015a).

The Australian Cancer Networks guidelines were published in 2010 and pertain to the management of locally advanced and metastatic prostate cancer. The guidelines discuss prevalence and possible treatments for side effects of ADT such as depression, anxiety, and osteoporosis but do not provide recommendations around screening. Statements such as "health professionals should be aware of risk factors for the development of anxiety and depression and

be prepared to treat appropriately" (Australian Cancer Network, 2010, p. 11) are included with no discussion as to methods or frequency of screening. Otherwise, the only clear recommendations refer to bone mineral density measurements prior to initiating ADT and subsequently during the treatment with the possibility of instituting preventative measures (Australian Cancer Network, 2010).

The National Institute for Health and Care Experience (NICE) guideline originates in the United Kingdom with its most recent revision occurring in 2014. Recommendations include screening for fatigue and sexual dysfunction, however no methods, tools or frequencies are provided. Recommendations are made however to consider screening for fracture risk in men initiating long term (>6 months) ADT (NICE, 2014). It is also endorsed by the NICE (2014) guidelines that men receiving ADT should have access to erectile dysfunction services, PDE5 inhibitors and psychosexual counselling, however methods and frequency of screening are not provided. Additionally, it is recommended that assessment for gynecomastia is done within the first month of treatment with ADT in order to offer appropriate treatment such as prophylactic radiotherapy or tamoxifen (NICE, 2014). Algorithms for diagnosis of cancer and treatment are provided, however screening algorithms are not included.

Finally, the fifth guideline to be reviewed comes from the European Association of Urology (EAU) Prostate Cancer guidelines. This guideline was published in 2001 and most recently updated in 2015. The EAU (2015) guidelines address follow up, psychological coping, as well as laboratory and diagnostic investigation for screening for diabetes, anemia, renal function, and bone mineral density. Clinical follow up is emphasized as mandatory for all patients receiving ADT for the treatment of prostate cancer. Although specific recommendations for timing and methods of screening are made, it is noted that follow up should be tailored based

on individual symptoms, treatment modality and prognostic factors. Generally, follow up appointments were recommended for 3-6 months after ADT initiation, followed by timed intervals depending on stage of disease. For example, those with no evidence of metastatic disease were recommended to be reviewed in clinical follow up every six months with a focus on evaluation of symptoms, response to treatment and side effects, digital rectal examination and recommended lab screening. Those with metastatic disease should be evaluated as described above, however follow up should occur every three to six months. Moreover, it is suggested that those with adequate treatment response, a PSA of 4 or less, improving symptoms, and evidence of psychological coping can be reviewed at longer periods such as every six months. Finally, the G8 screening tool is suggested as an adjunct method for evaluating the health status of older adults with prostate cancer. This geriatric screening tool is designed to assess overall health status, with results identifying whether patients should receive the same treatment as younger patients or if patients are vulnerable to impairment thus requiring a more thorough assessment or alteration in treatment.

The EAU (2015) also provides guidance for specific laboratory studies based on stage of disease and individual comorbidities. All patients receiving ADT are suggested to undergo both PSA and testosterone screening with each follow up visit. The PSA is identified as an important marker for following the course of prostate cancer, as changes to PSA levels help identify response to treatment and can also identify complications of treatment. A rise in PSA is often seen prior to the onset of clinical symptoms by several months. Testosterone is monitored regularly to ensure patients achieve initial castration goals (<1 nmol/L) and to ensure this level is achieve in order to control disease progression. Other recommended laboratory tests for all patients receiving ADT include a fasting glucose and hemoglobin A1C as well as fasting lipids,

both suggested to be done at baseline and then repeated every three months. Vitamin D and calcium may also be considered. For those with metastatic disease, laboratory screening is also recommended to include hemoglobin, creatinine, and alkaline phosphatase. Hemoglobin is recommended in order to screen for anemia which commonly occurs after three months of treatment. Creatinine is suggested to identify issues related to renal function such as bladder retention or ureter obstruction, while alkaline phosphatase helps identify the livers response to the disease process and treatment.

Diagnostic imaging, in the form of a bone mineral density test is identified as an important intervention to assess risk for osteoporosis and thus is suggested for all those receiving ADT by the EAU (2015). Bone mineral density testing is suggested by the EAU (2015) to be completed two years after castration and then repeated annually if osteoporosis risk factors or every two years if no risk factors. Finally, for those with a history of cardiovascular disease or those over the age of 65 years old, consultation with a cardiologist prior to ADT initiation is recommended. Similarly, those with impaired glucose while on ADT warrants a referral to an endocrinologist.

Although the EAU (2015) guideline does provide some excellent recommendations it is incomplete. For example, screening recommendations for physical function, cognition and mood are not specifically identified. It is only briefly suggested patients be screened for psychological coping however suggestions as to what PCPs are to screen for, such as mood changes, depression or body image concerns are not provided nor are methods or frequency of screening. Other commonly noted symptoms associated with ADT such as andropause and sexual dysfunction are not addressed.

In summary, the guidelines available for PCPs providing support to patients with prostate

cancer receiving ADT are limited. Although some appear to be more comprehensive than others, it is apparent that none of the available guidelines screen for all or even half of the documented side effects of ADT. The importance of bone mineral density testing was consistently identified in all guidelines with recommended methods of screening which is helpful for PCPs; however variabilities in frequency were noted. The remainder of ADT side effects are sporadically and inconsistently addressed. Moreover, the language in which recommendations for screening are vague in terms of specifics such as tools and frequency. Interestingly, only two of the five guidelines recommend psychological screening, two discuss screening for sexual dysfunction, two mention cardiovascular screening, one discusses cognitive changes and only one addresses andropause symptoms. Moving forward, screening recommendations for follow up and ADT related side effects will be presented from four clinical reviews.

Clinical Reviews

Clinical reviews are concise, up to date articles intended to provide health care providers with updates of recent development and accounts of a specific topic. Reviews aim at providing clinical applications to both primary and secondary care (The BMJ, 2015). Four clinical reviews will be presented by Saylor et al. (2009), Saylor and Smith (2013), Wilkinson, Brundage, and Siemens (2008) and Mohile et al. (2009). Saylor et al. (2009) completed a clinical review which focused on reviewing the common and recognized side effects of ADT with recommendations for prevention and treatment. Recommendations include screening for diabetes, cardiovascular disease, osteoporosis, and hyperlipidemia and were adapted based on commonly accepted guidelines such as the American Diabetes Association (ADA), American Heart Association (AHA), National Osteoporosis Foundation (NOF) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). The authors emphasized the lack of

evidence based guidelines and research studies that focus on screening and management of prostate cancer patients receiving ADT and suggest this is related to ADT hazards being relatively newly identified but not fully defined. Bone mineral density testing is recommended for those receiving medications in which increases ones risk of bone loss, such as ADT, at baseline prior to initiation of treatment, repeated one year after ADT treatment and then every two years or as clinically indicated. Screening for pre-diabetes or diabetes is recommended in all those receiving ADT, starting with a baseline measurement prior to initiation of treatment and then annually. Fasting plasma glucose is the screening test proposed, with serum levels of 100-125 mg/dL considered positive. Hemoglobin A1C is not recommended for the diagnosis of diabetes in this review. Fasting lipoproteins are also recommended at baseline, within the first year of ADT treatment and then every five years or as clinically indicated. Further, recommendations include assigning a target LDL based on cardiovascular risk factors and projected risk category as outlined in the NCEP ATP III guideline. According to this guideline, determining projected cardiovascular risk involves determining serum fasting lipid levels, establishing risk based on cardiovascular risk factors and presence of atherosclerotic disease, as well as establishing category of risk with the Framingham risk calculator (National Institute of Health, 2001). Based on all this criteria, a LDL target goal is established and interventions such as lifestyle or pharmacologic can then be considered. Of note, persistent concerns have evolved regarding the validity and reliability of the available cardiovascular assessment tools, including the Framingham risk assessment (Goff et al., 2014). However, the tool continues to be supported by a variety of cardiovascular organizations and guidelines to aid in risk discussion and decision making about lifestyle and pharmacological preventative interventions (Goff et al., 2014). Noticeably absent from this clinical review is discussion or recommendations regarding physical

functioning, andropause symptoms, anemia, cataracts, acute kidney injury, cognitive changes or mood changes related to ADT.

Saylor and Smith (2013) reviewed metabolic complications of ADT, specifically obesity, insulin resistance, and alteration in lipids. Evidence regarding incidence of side effects as well as recommended management is provided. However very little is presented in regards to screening. Authors suggest methods of screening for pre-diabetes and diabetes according to the American Diabetes Association (ADA) guidelines. Differing from the ADA guidelines however is the suggested intervals for screening, as authors suggest those receiving ADT to be at high risk for insulin resistance, thus suggest yearly assessment via a fasting plasma glucose (preferred) or a 2 hour 75 gram oral glucose tolerance test for diagnosis. Lastly, screening and management of lipids based on NCEP ATP III guidelines is encouraged.

A third review completed by Wilkinson et al., (2008) examined available resources for PCPs to provide appropriate follow-up for patients with prostate cancer. It identified the role PCPs have with regard to providing care to this population, but highlights the paucity of information regarding follow up. Accordingly, a brief overview of the incidence of prostate cancer in Canada, available treatment modalities and indications, recommendations for PSA monitoring (either during therapy, after primary therapy or during active surveillance) and expected PSA responses to treatment is presented. Most relevant is the algorithm provided regarding the care for patients with systemic disease on ADT. Although this algorithm is not comprehensive it does provide some guidance to PCPs. Recommendations include follow up visits with family physician every six months in which clinical inquiry, management of treatment related side effects, and PSA testing should be considered. Further, bone mineral density testing is endorsed every two years while on ADT and a bone scan if PSA levels rise above 20 nm/mL

or when clinically indicated.

In the fourth and final review, Mohile et al. (2009) reviewed the management of androgen deprivation complications in men with prostate cancer. This review provides a detailed background regarding prostate cancer and ADT as well as detailed summary of common side effects to ADT such as anemia, hot flashes, depression, sexual dysfunction, cognitive changes, physical function, metabolic syndrome, cardiovascular disease and bone mineral density impairments. Suggestions for screening and management are provided for a select group of side effects. However the screening recommendations presented are relatively ambiguous, nonetheless an emphasis on screening for depression, cognitive changes, physical function, metabolic syndrome, cardiovascular disease and bone mineral density are included. For example, recommendations included in this review simply state men receiving ADT should be screened for depression and other mental health problems, however fail to provide guidance on methods or intervals for screening. Slightly more specific are recommendations for cognitive impairment screening, which is suggested prior to the initiation of ADT and throughout treatment. Although methods of screening are not provided for cognitive assessment, rationale for screening is highlighted, suggesting regular screening can provide valuable information regarding underlying deficits which can negatively impact cancer care, outcomes, treatment tolerability and patient decision making (Mohile et al., 2009).

For those with pre-existing metabolic or cardiovascular disease or risk factors for cardiovascular disease, Mohile et al. (2009) suggests patients be assessed prior to the initiation of ADT as well as consider referring such patients to a cardiologist. Moreover, for those with cardiovascular disease, routine testing is suggested to evaluate worsening of underlying disease. Means or intervals for assessment are not included in the review.

The most detailed recommendation in this review is for osteoporosis screening (Mohile et al., 2009). Recommendations include a full history and physical examination prior to starting ADT to assess for risk factors for osteoporosis, falls and fractures. Further, screening for bone mineral density via a DEXA scan is recommended prior to ADT initiation and then every 6-24 months depending on risk factors and baseline bone mineral density. It also appears a careful assessment of overall health status is recommended prior to the initiation of ADT and throughout treatment to "include examination of domains that could exacerbate pre-existing conditions and accelerate mortality" (p. 15), however details regarding methods of exam, tools or frequency are not included (Mohile et al., 2009).

In summary, the available clinical reviews provide an array of information regarding prostate cancer incidence, prevalence, side effects to ADT and suggested management of effects but do not lend themselves to comprehensive screening recommendations for adverse effects of ADT. Similar to clinical practice guidelines, some of the above clinical reviews are more comprehensive than others, although none of the reviews provide inclusive recommendations for screening of all ADT related side effects. Although frequency and intervals of screening were variable in the recommendations, half of the reviews adapted their recommendations from clinical guidelines such as the ADA and the NCEP ATP III. The most consistent screening recommendations were related to bone mineral density, metabolic syndrome and cardiovascular disease, all of which were emphasized to some degree in three out of the four reviews. Moreover, only one review proposed screening recommendations for depression, one discussed cognitive impairment screening and one addressed diabetes screening. The final component of this chapter will present recommendations for screening from an editorial identified during the literature search.

Editorials

Medical journal editorials are short articles or essays that express the views and opinions of the authors. Editorials provide perspective on a specific topic of interest, often related to a research or review article published in the same journal issue (Stevens, 2006). In this case, Jones (2011), a consultant physician and endocrinologist released an editorial in the British Medical Journal discussing the cardiovascular risk factors associated with ADT. This editorial further highlights the accumulating evidence to suggest ADT is associated with adverse effects on cardiovascular risk factors, cardiovascular events and possible mortality. However it is noted that not all study results concur with these findings of increased risk of morbidity and mortality. It is believed that the association and risks of ADT and cardiovascular disease will become more apparent with time. Despite the inconclusive findings, an advisory statement from the American Heart Association, American Cancer Society and the American Urological Association has been released with recommendations that all patients receiving treatment with ADT be seen periodically for follow up assessment of cardiovascular risk factors, and ensure those with pre-existing cardiovascular disease have their secondary prevention treatment optimized. Furthermore, on the basis of the current evidence and potential for risks the US Food and Drug Administration have made changes to the label on gonadotropin releasing hormone agonists. Recommendations advocate for PCPs to monitor patients for signs and symptoms suggestive of cardiovascular disease as well as the periodic monitoring of blood glucose or glycosylated hemoglobin (U.S Food and Drug Association, 2013).

The increased prevalence of metabolic syndrome and metabolic effects of ADT are also noted, therefore, patients are recommended periodic follow up with their PCPs. Suggestions include a review of cardiovascular risk factors after three to six months and then at least

annually. Further, review of lipid lowering treatment, anti-hypertensive medications, glucose lowering treatment and antiplatelet therapy is indicated when appropriate. Extra vigilance is also recommended for those being treated with insulin for diabetes, as a study by Haider, Yassin, Saad and Shabsigh (2007) as cited in Jones (2011) identified ADT may negatively affect glycemic controls.

In summary, the research has demonstrated a lack of clear, consistent, comprehensive recommendations and guidelines. Available guidelines and reviews have attempted to address screening for adverse effects of ADT however recommendations for screening do not materialize into a comprehensive guide for PCPs. Recommendations are vague in nature, as specifics regarding methods of screening or frequency are either inconsistently provided or not provided at all. Furthermore, all guidelines and reviews fail to address all side effects including a blatant lack of recommendations for common adverse effects. This variability in recommendations likely reflects the lack of definitive evidence available on this topic (McIntosh et al., 2009). What is also apparent from the findings is a lack of uptake or adherence to the few screening recommendations that are available. Finally, it is identified that although individual research studies are focusing on ADT related side effects, very few provide implications for practice with regard to screening which explains the exclusion of a significant number of studies in the literature search. The following chapter will discuss the research findings previously analyzed combined with supplementary research to inform evidence based recommendations for screening of ADT related side effects.

Chapter Four

Discussion

The research described in the Findings Chapter has afforded insight into the research question regarding screening for men receiving ADT for prostate cancer. This chapter will synthesize the research findings in terms of current recommendations for screening practices in those receiving ADT as to what should be screened, how to screen, and intervals for screening. Recommendations for practice will then be presented based on a consolidation of the literature and supplemented with evidence based guidelines to inform suggestions for screening and care. Recommendations will be organized according to each side effect identified under the physical, cognitive and psychological health domain. Specific screening strategies and intervals of assessment will be proposed. Furthermore, an overview of recommendations will be presented in order to provide PCPs with a quick reference for screening for this patient population. The chapter will finish with a brief discussion on recommendations for education and research. The recommendations below are not intended to replace clinical judgement but rather inform practice. Therefore, recommendations should be considered in conjunction with individual patient circumstances.

Clinical Practice Recommendations

To begin, general follow up recommendations will be proposed. Clinical practice recommendations for each physical, cognitive and psychological side effect will then be presented to include both methods and intervals for screening.

Follow up. Clinical follow up is an important aspect of managing patients with cancer. With respect to monitoring men with prostate cancer receiving ADT, common objectives for follow up include monitoring response to treatment, ensuring compliance with treatment,

detecting complications of therapy, and assessing and managing palliative symptoms (Mottet et al., 2015). However, the literature reveals recommendations for follow up in this patient population are limited and inconsistent. Very few research studies, clinical practice guidelines or reviews stress the importance of providers regularly assessing patients or propose recommendations for methods or frequency of follow up. The EAU (2015) illustrate the most detailed recommendations and stress clinical follow up is absolutely mandatory for those prescribing and or managing those receiving ADT for prostate cancer. It is emphasized that regular follow up allows the provider to assess the patient's current condition, check for possible troublesome side effects to treatment as well as symptoms of disease, as 'neither biology nor imaging modalities can replace face to face clinic visits' (EAU, 2015, p. 100).

Although some authors, such as Wilkinson et al. (2008) and the EAU (2015) suggest specific screening tests to occur during follow up, such as a digital rectal examinations and laboratory tests, the majority of findings demonstrate broad and vague recommendations, such as statements that encourage evaluation of symptoms and side effects of treatment without providing specifics (EAU, 2015; Mohile et al., 2009; Wilkinson et al., 2008). Vague recommendations such as these require PCPs to have in depth knowledge of screening for ADT related side effects and health risks in order to assess the patient properly. This limitation leaves PCPs guessing as to which side effects to address and how to best screen for these issues.

As always screening should be individualized, based on age, symptoms, co-morbidities, treatment modality and prognosis (EAU, 2015). Although optimal levels for follow up are variable in the literature, ranging from three to six months, based on the above findings it is recommended patients be reviewed within three months of initiating ADT, and then every three to six months (Alberta Provincial Genitourinary Tumor Team, 2013; EAU, 2015; Wilkinson et

al., 2008). During these follow up appointments it is critical that patients be reviewed thoroughly to monitor for disease and treatment related issues. Specifically, follow up should include a physical examination, screening of symptoms and side effects as well as laboratory measurements, all of which are described below with detailed recommendations.

Physical function. Screening of physical functioning is only briefly mentioned in the literature findings. It is proposed by this paper that this may be due to the assumption that PCPs frequently screen patient functioning as a basic aspect of appropriate primary care. Nonetheless, it is difficult to infer from blanket statements such as 'careful assessment of overall health status' used in Mohile et al.'s (2009) clinical review, whether this includes screening of physical functioning. Mohile et al. (2009) does however provide slightly more specific recommendations, suggesting patients be assessed prior to ADT initiation for risks for falls, which one could assume would include measures of functional status such as balance and mobility. Regardless, the mention of physical assessment without specific recommendations related to intervals or screening methods does not provide PCPs with clear guidance. Interestingly, Bylow et al.'s (2008) study was the only study to investigate the impact of ADT on physical function with a variety of validated and reliable tools; however the study recommendations, did not recommend any of the tools used in the study for the screening of physical functioning in patients on ADT.

A functional status assessment, a component of a comprehensive geriatric assessment, is commonly utilized in a variety of settings, including the Bylow et al.'s (2008) study as well as the NCCN (2015b) clinical practice guidelines in oncology for older adults. This tool will be proposed by this paper as a tool for physical function screening in those receiving ADT. The assessment can be completed via self-reported measures, such as one's ability to carry out activities of daily living (ADLs) and instrumental activities of daily living (IADLs) or through

physical performance measures, such as the Timed Up and Go (TUG) test (NCCN, 2015b). The following components should be included in the functional status assessment:

Table 3 *Functional Assessment*

Ability to perform activities of daily living (ADLs): eating, getting dressed, grooming, mobility, ability to use bathroom facilities independently and continence. Ability to perform instrumental activities of daily living (IADLs): preparing meals, doing housework, shopping, managing money and using the telephone. Performance Status: via Karnofsky or ECOG (http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales) Falls: Assess for falls in the last 6 months or fear of falling. For those who have experienced a recent fall (within 6 months) or have a fear of falling, consider additional evaluation with: • Physiotherapy or occupational therapy assessment • Assess Gait using the TUG test (see NCCN, 2015b for test specifics) • Checking and replacing Vitamin D levels when appropriate • Refer to geriatrics physician if appropriate

(NCCN, 2015b).

Ideally a functional status assessment would be done by the oncologist or urologist during the diagnostic and treatment planning process, regardless PCPs should consider a baseline functional status assessment and repeat this assessment throughout treatment in order to identify changes to physical status or functioning. Intervals of screening should be based on the patients' age, co-morbidities and overall health status, ideally occurring at least every 6-12 months. Moreover, a full functional assessment is not always required as a brief screening of physical and

functional abilities can occur during regular follow up visits by observing mobility and gait as the patients' moves throughout the clinic exam room.

Metabolic disease and diabetes. Screening for insulin resistance and diabetes is included as a recommendation in many clinical practice guidelines, clinical reviews and independent research studies based on significant evidence that ADT increases insulin resistance and therefore incidence of diabetes. Tsai et al. (2015), Saylor et al. (2013), and Saylor and Smith (2013) all refer to the American Diabetes Association (ADA) guidelines for their recommendations with regard to methods of screening, however intervals proposed by these authors differ from ADA guidelines and from each other. ADA guidelines suggest screening intervals based on level of risk, for example those without risk factors be screened every three years and those with risk factors should be screened more frequently. Currently, ADT or hypogonadism is not noted to be a risk factor for diabetes in the ADA guidelines, but it appears the majority of study authors, including Tsai et al. (2015), Saylor et al. (2013), and Saylor and Smith (2013) consider the risk to be high enough to pursue more frequent screening. Moreover, the majority of studies anticipate diabetes or insulin resistance as a potential issue by recommending baseline screening in the form of laboratory work be considered in all patients prior to ADT initiation.

As noted above, the majority of research articles on this topic adapt their screening recommendations from the ADA, however, as this paper serves to inform care delivered by PCPs within Canada, Canadian guidelines from the Canadian Diabetes Association (CDA) will be presented. Based on the increased risk demonstrated in the literature, those undergoing ADT for prostate cancer with or without other risk factors should undergo screening prior to ADT initiation and repeated annually. Methods of screening should include a fasting plasma glucose

(FPG) or hemoglobin A1C (Ekoe, Punthakee, Ransom, Prebtani, & Goldenberg, 2013). Additionally, risk factors for diabetes should be assessed prior to ADT and repeated annually, please see the CDA guidelines from Ekoe et al. (2013) for specific risk factors.

The assessment for metabolic syndrome is simply based on the diagnostic criteria noted by Goldenberg and Punthakee (2013) above. Measurements such as blood pressure should be obtained at baseline and repeated with each follow up assessment. Other measurements such as waist circumference should be obtained ideally at baseline and at least annually in order to monitor changes and adequately assess risk. Furthermore, intervals for screening should follow the above recommendations for insulin resistance that recommends yearly screening with either a FPG and/or A1C. Fasting lipid screening recommendations will be discussed below and should be implemented for this patient population.

Cardiovascular disease. There is accumulating evidence to suggest ADT can negatively impact ones cardiovascular health. The correlation between ADT and cardiovascular disease is suggested to be related to effects on varying cardiovascular risk factors impacting the likelihood of cardiovascular events and possible mortality (Jones, 2011). As Jones (2011) highlights however, there is no consensus that this association truly exists, however in light of the potential for increased morbidity and mortality, consideration of cardiovascular health is recommended in a small minority of clinical practice guidelines and reviews (EAU, 2015, Jones, 2011; Mohile et al., 2009; Saylor et al., 2009; Saylor & Smith, 2013). Otherwise, screening recommendations with regard to ADT and its association with cardiovascular health are somewhat limited in the literature, particularly in individual research studies.

Potential strategies to minimizing morbidity and mortality include a shared care approach between PCPs and specialists. For example, PCPs should routinely assess patients for

cardiovascular risk factors, monitor for signs and symptoms of cardiovascular disease, review current cardiovascular treatments, and refer or consult when pre-existing disease or concerns are identified (EAU, 2015; Jones, 2011; Mohile et al., 2009). It is anticipated that with time and further research, new data will guide cardiovascular screening recommendations for those receiving ADT. In the meantime, the literature is not conclusive as to whether screening strategies for the prostate cancer population receiving ADT should differ for the general population (NCCN, 2015a). As such the premise of the majority of available recommendations stem from the NCEP ATP III guidelines which are discussed in detail in the findings, which focuses on identifying and categorizing risk and dyslipidemia screening and management (Saylor et al., 2009; Saylor and Smith, 2013). What remains unclear is how often screening should occur, as this varies between study recommendations.

Anderson et al. (2013), authors of the most recent Canadian Cardiovascular Society (CCS) guidelines provide recommendations that are closely aligned with the NCEP ATP III guidelines referenced by many of the research findings in the literature. As such, the CCS guidelines will provide the basis for cardiovascular screening recommendations in this paper. Screening should begin with a history and physical examination, ideally completed prior to ADT initiation and then routinely assessed during follow up as previously described. The history should include screening for cardiovascular risk factors such as: smoking, diabetes, hypertension, family history of hyperlipidemia or premature cardiovascular disease, chronic kidney disease, inflammatory bowel disease, HIV, COPD, abdominal aneurysm, erectile dysfunction and obesity (BMI >27) (Anderson et al., 2013). Physical examinations should aim to identify clinical evidence of atherosclerosis and or hyperlipidemia and include an ocular, cardiovascular, carotid, respiratory and abdominal examination (Anderson et al., 2013).

Next, obtaining baseline laboratory measurements, such as LDL, HDL, triglycerides, glucose and renal function (GFR) is recommended. Once this data is obtained, the PCP can calculate the patients cardiovascular risk score via the Framingham risk score calculator, which determines the patients level of risk into three categories, low, intermediate and high risk for CV disease (http://www.ccs.ca/images/Guidelines/Tools_and_Calculators_En/Lipids_Gui_2012_FRS_Col_EN.pdf#page=1&zoom=auto,-139,540). This risk assessment helps to illustrate which patients would most likely benefit from primary prevention strategies such as pharmacological treatment of hypertension and dyslipidemia (Anderson et al., 2013). Intervals for screening are proposed based on Framingham risk score, and include screening as above every three to five years if Framingham risk score is under 5% and annually if score is above 5% (Anderson et al., 2013).

Andropause. The findings demonstrate the symptoms of andropause, such as hot flashes, night sweats, gynecomastia, loss of libido and sexual dysfunction are common, immediate and bothersome side effects to ADT. However, screening recommendations are infrequently emphasized in the literature. For example, literature findings failed to present any screening recommendations for hot flashes or night sweats. Moreover, gynecomastia was briefly mentioned in one of the five clinical practice guidelines, with a focus on early assessment and treatment with radiation therapy if necessary and desired (NICE, 2014). This suggests to the reader that this group of side effects is either entirely known to PCPs and therefore requires little attention in screening recommendations or these side effects are simply common and assumed outcomes of treatment therefore require little focus by PCPs. Surprisingly, only four of the twenty-two papers from the literature review acknowledged andropause symptoms with supplemental recommendations. Of these four papers, the most commonly defined symptom is sexual dysfunction. Interestingly, men infrequently disclosed sexual side effects with PCPs that

likely contributes to the large group of men that were left untreated for this side effect despite desire to resume sexual activity (Grunfeld et al., 2012). Although anticipated changes to sexual function are most commonly related to depletion of testosterone, it is also essential to anticipate changes to libido, sexual response and intimate relationships due to impaired perception of body image, masculinity and sexual attractiveness (Harrington et al., 2009). Based on these findings it becomes evident that PCPs play an essential role in ensuring patients who desire sexual activity and intimacy are screened appropriately and provided the necessary treatment options such as pharmacological agents and counselling (Grunfeld et al., 2012).

As specific side effects and their treatment are expected to occur at specific points in ADT treatment, PCPs must ensure the appropriate side effects are being routinely screened. For example, treatment with radiation therapy or Tamoxifen may be offered for gynecomastia which occurs within one to three months of treatment initiation, therefore screening for this condition must occur at the first follow up appointment after starting ADT (NICE, 2014).

Similarly, sexual function should be screened regularly in order to identify the issue as early as possible to ensure the appropriate support and treatment is offered. Thus screening is recommended at regular intervals throughout treatment, beginning at the first follow up appointment after ADT initiation (NCCN, 2015c). Those with identified issues should then undergo a more thorough evaluation, which should include psychosocial issues, such as depression, impaired body image, relationship problems, or other contributing factors such as drugs or alcohol (NCCN, 2015a; NCCN, 2015c). Lastly, a physical examination should be considered in those with sexual dysfunction, with a focus on the chest for gynecomastia, abdomen, phallus, scrotum and testicles, and the cardiovascular system (NCCN, 2015c).

This paper recommends the use of validated tools to assess for andropause symptoms,

such as the Distress Thermometer (DT) (http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf) and the Sexual Inventory for Men (SHIM) (http://www.auanet.org/education/erectile-dysfunction.cfm). Neither tool were included or recommended in the study findings for screening, however both have demonstrated validity and reliability for screening in cancer patients (Cappelleri & Rosen, 2005; NCCN, 2015c). The DT tool is quite inclusive and addresses many of the common side effects to ADT, including sexual dysfunction. This tool can be completed prior to appointments, saving time as PCPs can simply refer to the identified issues, or can be used to prompt PCPs to assess specific side effects. More specific to sexual health is the SHIM, which is recommended by the NCCN (2015c) and subsequently this paper. This short screening tool screens for erectile dysfunction and those who may benefit from treatment for this condition (NCCN, 2015c).

Anemia. The correlation between anemia and both cancer and ADT is well established in the literature (Curtis et al., 2008; Dicatol et al., 2010). Despite this association, very little information was found in the literature with regard to screening or symptom assessment. This is an important gap as symptoms associated with anemia, such as fatigue and dyspnea (Curtis et al., 2008), should be a consideration when it comes to symptom assessment and management. Nonetheless, screening is only recommended by two studies via a hemoglobin measurement (Curtis et al., 2008; EAU, 2015). Consequently, baseline laboratory investigations via a hemoglobin or hematology panel should be considered in order to trend hemoglobin values with the initiation and or long term treatment with ADT. As the literature demonstrates anemia can occur within three to six months of ADT initiation, therefore repeating screening via a hemoglobin would be appropriate at that time or sooner if clinically indicated. Screening intervals should depend on clinical presentation and symptoms as well as consideration of co-

morbidities. Co-morbidities, such as impaired kidney function, coagulation disorders, nutritional insufficiencies and inflammatory disease should be considered as a contributing factor to anemia and may change intervals for screening (Dicatol et al., 2010).

Cataracts. Regrettably, research findings failed to produce any literature with recommendations related to cataract screening or eye examinations in general. This limitation is likely related to cataracts being a new defined side effect to ADT. However, for the sake of comprehensiveness, general recommendations derived from the Canadian Ophthalmic Society (COS) are provided to help guide PCPs in providing care. COS (2007) recommend regular ocular exams in the adult population, with intervals depending on risk and age. High risk patients include those with diabetes, and family history of ocular conditions such as cataracts. Although ADT is not currently a documented risk factors identified by the COS, given the potential for increased risk of cataracts with this treatment regimen it is suggested that those receiving ADT be considered to be at higher risk and therefore pursue screening more frequently. Therefore, as recommended by the COS (2007), those who are asymptomatic and receiving ADT should undergo screening at least every two years for those over the age of 50 and annually for those over the age of 60. Patients who identify visual changes such as impaired visual acuity, visual fields, color visions or physical changes to the eye should be examined as soon as possible by an eye specialist (COS, 2007).

Bone mineral density impairment. The most consistent recommendation for screening in men with prostate cancer receiving ADT appears to be bone mineral density testing. All five clinical practice guidelines provide some form of recommendation as do the majority of the clinical reviews, however there are inconsistencies noted in initiation of screening, frequency and intervals. For the most part, the majority of recommendations uniformly propose baseline bone

mineral density screening prior to the initiation of ADT (Australian Cancer Network, 2010; Mohile et al., 2009; Wilkinson et al., 2008). While intervals and frequency of screening are variable, with recommendations varying from no suggestions on frequency, to annually, to every two years or every 6-24 months respectively (Australian Cancer Network, 2010; Mohile et al., 2009; Saylor et al., 2009, Wilkinson et al., 2008). What remains consistent however is the suggested method of assessment for bone mineral density, with the use of the World Health Organization FRAX tool alongside a DEXA scan. Although small variations do exists as some authors suggest FRAX in conjunction with DEXA scan (Alberta Provincial Genitourinary Tumor Team, 2013; Al-Shamsi et al., 2012) while others suggest a step wise approach to screening which starts with the less invasive FRAX and proposes DEXA if risk is identified by the FRAX (NCCN, 2014).

Interestingly only one study with a focus on impaired bone mineral density recommended a history and physical assessment for those on ADT in order to identify risk factors for osteoporosis. Although the FRAX assessment does require data gathering through a focused history in order to obtain information for osteoporosis risk, it does not cover other avenues that would suggest risk, such as physical and functional decline. As such, what then becomes glaringly absent in many of the osteoporosis and fracture risk assessment recommendations is an assessment of physical function, such as mobility, balance and gait as impairment in these areas may increase ones susceptibility for falls and thus fractures. Other studies however, such as Bylow et al. (2008) and Mohile et al. (2009) link altered physical function such as impaired balance and strength with risk for falls and fracture and use this information to premise screening recommendations.

Nonetheless, the literature supports screening bone mineral density. Inconsistencies

however do not lend for straightforward recommendations, therefore clinical practice guidelines from Osteoporosis Canada, by Papaioannou et al. (2010) will be proposed for osteoporosis and fracture risk screening in this paper. As such, recommendations will begin with emphasis on screening all men undergoing ADT, regardless of age. This should include an initial bone mineral density assessment via a DEXA scan and an assessment of fracture risk based on a focused history, physical examination and FRAX assessment (http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Fracture-Risk-Assessment-Tool-FRAX) (Papaioannou et al., 2010). Bone mineral density testing should be repeated annually while undergoing ADT, particularly if treatment for osteoporosis would be acceptable to the patient. However, if the patient would not consider pharmacological treatment for osteoporosis one should consider the necessity for bone mineral density testing.

Acute kidney injury. Similar to cataracts, acute kidney injury appears to be a relatively newly defined side effect to ADT as there is very little data available describing this issue. The studies that are currently available propose further research to investigate the clinical importance of this side effect (Lapi et al., 2013). Consequently, of the available research studies identifying this side effect, screening recommendations are not provided, therefore this side effect was not defined in this paper's findings.

In light of the suggested association between ADT and acute injury and the impact prostate cancer itself can have on renal function, it is reasonable to screen for kidney function periodically throughout treatment. Intervals for screening should depend on patient's age, condition, presence of co-morbidities and pharmacological agents prescribed. Screening for kidney function via a creatinine and or glomerular filtration rate (GFR) should be added to other regular screening laboratory work such as hematology panel, fasting glucose or lipids and be

done at least annually. For those receiving specific medications that are potentially nephrotoxic or have comorbid conditions that increase ones risk of renal issues, screening should be considered more frequently such as every three to six months.

Cognitive impairment. Mohile et al. (2009) acknowledges the impact cognitive impairment can have on cancer patients, potentially negatively impacting cancer care, outcomes, treatment tolerability and patient decision-making. Despite this identified value in screening and potential for identifying underlying cognitive issues, very few findings recommended such screening. Mohile et al. (2009) and Mohile et al. (2010) both advocate for screening for cognitive impairments prior to the initiation of ADT in order to identify those with underlying cognitive deficits in which treatment may be offered or require further monitoring. Moreover, cognitive screening was particularly emphasized for those at higher risk of developing conditions such as dementia (Mohile et al., 2010). Unfortunately, a guide or tool was not provided in the literature findings.

Although study findings present evidence to support screening for cognitive impairment in some patients with prostate cancer receiving ADT, very little evidence was available to support initiation, methods or intervals of cognitive impairment screening. Consequently, further evidence was sought from the literature in order to provide concrete recommendations. While Mohile et al. (2009) and Mohile et al. (2010) recommend all patients be screened for cognitive impairment, current evidence suggests that screening for cognitive issues in those without symptoms of impairments in insufficient (U.S Preventative Services Task Force, 2014). However, cognitive screening is supported if patients, family or PCPs identify signs and symptoms of impairment (NCCN, 2015b; U.S Preventative Services Task Force, 2014). Those with identified impairments should be screened for potentially reversible or contributing factors

to cognitive impairment, such as medications, emotional disturbances, co-morbidities, substance use, and symptoms burden should be done by the PCP (NCCC, 2015b). Additionally, specific questioning clarifying the nature of impairment is recommended. Examples provided by the NCCN (2015b) include:

Table 4 *Screening Questions to Assess Cognitive Impairment in Cancer Patients*

Do you have difficulty paying attention?
Do you have difficulty multitasking?
Do you frequently leave tasks incomplete?
Do you have difficulty finding words?
Do you have difficulty remembering things?
Do you need to use more prompts to remember things?
Does it take you longer to think through problems?
Do you notice an impact on functional performance? Job performance?

If cognitive screening is required due to identified impairments, PCPs should continue to monitor signs and symptoms throughout treatment to monitor for progression and or offer appropriate treatment. Finally, a neurological examination may also be indicated, in which additional assessment or imaging may be indicated if focal neurology defects are noted (NCCN, 2015b). A referral to neuropsychology may also be considered (NCCN, 2015b).

Depression and distress. Based on overall prevalence of depression in the general cancer population in conjunction with risks associated with ADT it seems practical to screen for depression in this patient population, however the literature provides little recommendation. For example, Mohile et al. (2009) emphasizes screening for depression and other mental health issues, while Pirl et al. (2002) suggests 'appropriate and regular' assessment of mood, and Lee et al. (2014) advises the identification and treatment of depression should be a priority. The Australian Cancer Network (2010) provide equally ambiguous counsel, suggesting health

professionals be aware of the risk factors for anxiety and depression and be prepared to treat appropriately. Methods for screening and tools are not suggested by any of the findings.

In order to support patients with appropriate mental health services for distress the PCP needs to identify the issue. Ideally, patients notify their PCPs of issues and concerns or PCPs ask about mental health issues regularly, however, stigma and time constraints often stifle discussion regarding mental health issues (NCCN, 2015d). Several studies have identified low concordance rates between patients self-reports of distress or mood alterations with that of physicians clinical impressions, which supports the use of standardized validated tools for measuring psychological issues in those with cancer (Litofsky et al., 2004; Sollner, Devries, & Steixner, 2001 as cited in NCCN, 2015d).

What becomes more complicated is recommendations for what specific tools to use. There are a variety of systematic reviews and individual research studies examining the use of the varied validated screening tools available with very little consensus on the ideal tool but an overall consensus does exist for the need and importance of screening (Australian Cancer Network, 2010; Lee et al., 2014; Mohile et al., 2009; Pirl et al., 2002). Therefore, this paper recommends the adoption of current psychological screening tools recommended by ones current facility or as follows.

The NCCN (2015d) guidelines for survivorship, which focuses on the late effects and long term psychosocial and physical problems associated with cancer and its treatments recommend either the PHQ9 or PHQ2 as validated assessment tools for depression in the cancer survivor population (doi: 10.1046/j.1525-1497.2001.016009606.x). The patient health questionnaire (PHQ) is a self-administered diagnostic instrument for criteria based diagnosis of mental health disorders such as depression (Kroenke, Spitzer, & Williams, 2001). The PHQ9

consists of nine criteria upon which depression is diagnosed based on the DSM-IV depressive disorders (Kroenke et al., 2001). Similarly, the PHQ2 consists of 2 questions to screen for depression, in which if scores are high for depression, additional questions must be asked to establish diagnostic criteria (Kroenke et al., 2001). The benefits of these tools is diagnostic validity, with the ability to both diagnose and grade the severity of depression (Kroenke et al., 2001). Its application to the ADT population relates to parallel issues faced by the ADT and survivorship population, such as depression, body image issues, sexual dysfunction and cognitive impairment. Therefore these tools may prove helpful when assessing for mood in the prostate cancer population receiving ADT.

The NCCN (2015d) also recommends using the Distress Thermometer (DT) and accompanying 36 item problem list as an initial screening tool for cancer related distress. This tool identifies the presence and level of distress as well as sources such as practical, family, emotional, spiritual and physical issues related to cancer and its treatments (http://www.nccn.org /professionals/physician_gls/pdf/senior.pdf). This validated screening tool was developed specifically for cancer patients and has demonstrated good sensitivity and specificity, as well as good correlation with other psychological tools such as the Hospital Anxiety and Depression scale (NCCN, 2015d). Mitchell, Kaar, Coggan and Herdman (2008) notes it was deemed acceptable to 75% of clinicians when used (as cited in NCCN, 2015d). Although this tool does not singularly screen for psychological conditions such as depression, it allows for a broad screen for cancer treatment related effects that can influence psychological health. Moreover, as this tool screens for a variety of side effects, its use may eliminate the need to complete a variety of screening tools for each component of health, such as physical, cognitive and psychological.

Altered body image and loss of masculinity. For a large majority of men receiving ADT for prostate cancer, side effects do not occur in isolation. Many of the above side effects can directly or indirectly impact other areas of health and well-being. For example, ADT related changes to physical appearance, such as gynecomastia, and sexual dysfunction were identified to significantly impact men's perception of masculinity, attractiveness and body image (Grunfeld et al., 2012; Harrington et al., 2009). Moreover, in order to provide patient centered, holistic care, PCPs need to consider the impact these changes to body image and masculinity may have on men and their quality of life. The literature has suggested a possible connection between changes to physical appearance with depressive symptomology, which may be related to alterations in self-esteem and the impact of side effects on intimate relationships (Harrington et al., 2009; Lee et al., 2014). Therefore, PCPs must anticipate changes to psychological health and thus screen early and frequently, starting at the first follow up appointment in order to support, educate and treat appropriately. As identified in study findings, patient and PCPs may be reluctant to openly discuss these issues due to embarrassment or discomfort, therefore the use of a screening tool, such as the Body Image Scale (http://tools.farmacologiaclinica.info/index.php), which is specific to body image changes related to cancer, or the DT may be indicated to identify those with altered body image (http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf) (Harrington et al., 2009; NCCN, 2015d).

Comprehensive recommendations have been developed to support PCPs with screening men with prostate cancer receiving ADT. Proposed screening recommendations were developed based on the above research findings and supplemental evidence described in the literature. Recommendations included both methods and intervals for screening a variety of physical, cognitive and psychological side effects to ADT. In light of time constraints noted in primary

care, a one page summary of screening recommendations was developed to provide a quick reference for PCPs providing care to this patient population, which is provided below. The final component of this chapter will discuss implications for practice, such as patient and PCP education needs and further research requirements.

Table 5 *Summary of Clinical Practice Recommendations*

Health Domain	Recommendation	Interval
Physical		
Impaired physical function	-Functional status assessment	-Every 6-12 months.
Metabolic syndrome and Diabetes	-Assess for metabolic disease criteria, diabetic risk factors and laboratory assessment (FPG/A1C)	-Prior to ADT initiation and then annually. -BP every 3-6 months.
Cardiovascular disease	-Calculate Framingham risk score. -Laboratory screening: LDL, HDL, triglycerides, glucose and GFR -Physical examination	-Baseline labs prior to ADT and then at least annually if Framingham risk score >5% -Physical examination every 3-6 months.
Andropause	-Physical exam patient for gynecomastia -Inquire about hot flashes and night sweats. -Sexual dysfunction screen through inquiry or use of a screening tool such as the DT or SHIM. -If sexual dysfunction, exam phallus, scrotum and testicles, and the cardiovascular system (NCCN, 2015b).	-Gynecomastia assessment within 1-3 months of ADT initiation. -Hot flashes, night sweats and sexual dysfunction should be assessed at first follow up appointment after ADT initiation (within 3 months) and then every 3-6 months).
Anemia	-Laboratory studies to include a hematology panel or hemoglobin.	-Prior to ADT, repeat within 3-6 months, then at least annually.
Cataracts	-General eye examination by an ophthalmologist.	-Every 2 years >50 and annually for those >60 years old.
Impaired bone mineral density	-DEXA scan and fracture risk assessment based on a history, physical and FRAX assessment tool.	-Baseline DEXA/FRAX and repeat annually.
Acute kidney injury	-Laboratory assessment (creatinine, GFR).	-At least annually.
Cognitive		
Cognitive impairment	-Screen for potentially reversible/contributing factors. Consider neurological examination or referral to neuropsychology.	-Assess if patients, family or PCP identify signs and symptoms of impairment.
Psychological		
Depression and distress	-PHQ9/PHQ2 or the DT	-Every 3-6 months.
Body image and loss of masculinity	-Body Image Scale (BIS) or DT	-Assess within 3 months of ADT initiation and repeat every 3-6 months.

Recommendations for Education

Findings have also demonstrated gaps in both patient and PCP knowledge and education regarding side effects and screening requirements for ADT, both of which impact care. For example, several studies have demonstrated that awareness of common ADT side effects varied significantly amongst patients, as some patients attributed effects to either age or unknown causes or described surprise when symptoms arose (Grunfeld et al., 2012; Mohile et al., 2010). Furthermore, despite guidelines and information regarding specific adverse effects, such as bone loss and ADT, overall knowledge, perception of susceptibility and engagement in preventative behaviours was demonstrated to be low overall (Nadler et al., 2013). In addition to gaps in patient education identified in the literature, it is also noted that patients are frequently dissatisfied with the education they received from health care providers (Chapman & Rush, 2003 as cited in Institute of Medicine, 2008). Based on these findings it is evident that patients would benefit from an open discussion with specific and clear evidence based education regarding ADT and its side effects (Nadler et al., 2013). Further, through providing this education patients will better understand reasoning for screening which may influence uptake.

Screening itself provides an important opportunity as it may lead to patients seeking further knowledge regarding side effects and provides an entry point for discussion and education from PCPs (Nadler et al., 2013). In order to increase the uptake of information, two things should be considered. First, adequately managing side effects to illness, such as anxiety or pain may be useful with comprehension and satisfaction with information provided (Chapman & Rush, 2003 as cited in Institute of Medicine, 2008). Secondly, information should be tailored to each individual, based on education, clinical situation, diagnosis, expectations and preferences (Institute of Medicine, 2008). For example, some prefer very detailed information while others

prefer less detail but prefer information be provided on an as needed basis (Institute of Medicine, 2008). Finally, information needs change through the disease trajectory, therefore information should be offered regularly (Institute of Medicine, 2008).

Similarly, PCP's also require more education regarding screening requirements for those receiving ADT for prostate cancer. This is demonstrated by the poor uptake of screening for commonly defined side effects to ADT such as impaired bone mineral density as well as patient uncertainty of side effects (Al-Shamsi et al., 2012; Chapman & Rush, 2003 as cited in Institute of Medicine, 2008). Poor uptake in screening practices and patient education is likely multifaceted, including limited clinical practice guidelines, PCPs uncertainty about current practice and guidelines, a lack of education regarding the usefulness and application of screening tools, and an overall lack of education of the impact of side effects and their consequences on overall health and well-being (Al-Shamsi et al., 2012). Thus, it stands to reason that the development and distribution of comprehensive guidelines would provide PCPs with the support and education required to provide appropriate care for those with prostate cancer receiving ADT. Consequently, consolidating current evidence and pursuing gaps in research to develop one comprehensive document should remain a focus for researchers and professional organizations.

Consequently, education, further research and guideline development is required. Education must be targeted to those prescribing and managing the care of those on ADT, such as PCPs in order to increase screening and reduce ADT associated morbidity (Alibhai et al., 2012). Ideally, this education would be in the form of comprehensive guidelines, however in the interim regular education sessions and appropriate dissemination of information that focuses on current evidence and clinical practice guidelines related to screening may be useful (Tomasone et al., 2015). Al-Shamsi et al. (2012) noted some success with professional group workshops in

increasing PCP knowledge of screening for osteoporosis and the identification of risk factors in a 2008 study, and suggest implementation of similar education initiatives for GP and NP's. The goal of these initiatives would be to increase PCP's knowledge regarding side effects of ADT, the benefits and recommendations for screening, and the importance of disseminating this information to patients. Moreover, encouraging coordinated and shared care between PCPs and oncologists should be considered, as this would allow for PCPs to use the oncologists as a supportive resource and consult as needed with regard to ADT screening recommendations or side effects management (NCCN, 2015b).

Recommendations for Research

Finally, as Saylor et al. (2009) indicate some of the ADT related side effects are newly identified and therefore not fully defined. This suggests further research into the side effects of ADT in order to adequately develop evidence based screening recommendations and guidelines. Moreover, it may be beneficial to focus research on the younger prostate cancer population as this may potentially identify new themes or highlight side effects that may be more likely to occur or cause distress compared to men in an older cohort. Similar issues were validated in previous breast cancer studies which demonstrated significantly more distress regarding body perception in younger populations (Harrington et al., 2009). Such findings will allow for greater support to this patient population.

Conclusions

The research question, for NPs practicing in a primary care setting, what screening is required to identify side effects in men with prostate cancer receiving ADT was explored in this literature review. In order to answer this question the literature was search through a variety of databases, such as the Cochrane library, CINAHL, Pubmed and Joanna Briggs Institute Library as well as the grey literature. Through various combinations of search terms and the application of inclusion and exclusion criteria, a total of 22 articles were selected that were pertinent to the research question.

The research findings demonstrated few clinical practice guidelines that present recommendations for screening for ADT related side effects. Moreover, the guidelines that are available lack consistent and comprehensive recommendations for screening. Consequently, without guidelines to support primary care practice and aid decision making, PCPs do not have the means to adequately support this patient population. A variety of other issues has presented barriers to PCPs screening patients appropriately, such as a lack of knowledge, time constraints and provider discomfort addressing specific adverse effects. Patients too have demonstrated a lack of awareness of ADT side effects which may limit their probability to report side effects to their PCPs. Finally, although there is an abundance of literature regarding side effects to ADT, new adverse effects are being identified in the literature, calling for further research into specific risks of treatment.

Through an integrative review of the literature, current recommendations, methods and intervals of screening were reviewed. Recommendations for practice have been presented based on a consolidation of these findings in conjunction with other evidence based guidelines. Specific recommendations include regular clinical follow up, starting within three months of

treatment initiation, followed by a review every three to six months. During each follow up appointment, patients may be offered a variety of validated screening tools or simply undergo inquiry of side effects from their PCPs in order to identify adverse effects to ADT and provide the appropriate support and treatment. Follow up appointments must also include a physical assessment as well as intermittent laboratory studies which were identified in detail based on individual side effects of ADT. In any event, patients are to be screened for physical, cognitive and psychological issues prior to initiating treatment and throughout the treatment regimen. Additionally, patients and PCP's require further education regarding ADT side effects and their potential impact on overall health and well-being, while PCP's must ensure they engage in appropriate knowledge translation and regular screening. Finally, further research is required to fully define the adverse effects of ADT in order to incorporate evidence based recommendations and develop comprehensive guidelines.

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Appendix A

Pharmacological ADT

Medication	Mechanism of Action	Indications	Administration and Dosage
Luteinizing hormone releasing hormone agonists • Leuprolide • Goserelin • Buserelin	These medications stimulate the release of luteinizing hormone causing an initial elevation in serum androgen. Chronic administration causes a reduction in the secretion of luteinizing hormone and androgens through down regulation of LHRH receptors.	Indicated for localized, locally advanced disease, biochemically recurrent disease (increasing PSA) and metastatic prostate cancer	Leuprolide: 1 month depot 7.5 mg IM, 3 month depot 22.5 mg IM or 4 month depot 30 mg IM OR 3 month depot 22.5 mg SC or 6 month depot 45 mg SC. Goserelin: 3.6 mg SC monthly or 10.8 mg SC every 3 months. Buserelin: 6.3 mg SC every 8 weeks or 9.45 mg SC every 12 weeks.
GnRH antagonists • Degarelix	Competitively binds to the GnRH receptors in the pituitary, which reduces the release of follicle stimulating hormone and luteinizing hormone which reduces the release of testosterone.	Used in metastatic prostate cancer, as an alternative to GnRH agonists.	Two 120 mg injections (240 mg total) SC on day 1 followed by 80 mg SC monthly.
Anti-androgens • Flutamide • Bicalutamide • Nilutamide	Binds to androgen receptors, inhibiting the binding of testosterone and dihydrotestosterone.	Can be used as first line monotherapy for advanced prostate cancer, in combination with GnRH agonists for advanced prostate cancer	Flutamide: 250 mg PO three times daily Bicalutamide: 50 mg PO once daily Nilutamide: 300 mg PO once daily for 30 days or less,

		or as second line therapy after progression on GnRH agonist or antagonist monotherapy.	then 150 mg PO daily.
CYP17 inhibitors • Ketoconazole • Abiraterone	Inhibition of CYP17 in the adrenal gland results in a reduction in the production of androgens.	Second line therapy for advanced prostate cancer after chemotherapy treatment failure.	Ketoconazole Abiraterone: 1 gram once daily PO

(BCCA, 2012a; BCCA, 2012b; BCCA, 2012c; BCCA, 2013; Perlmutter & Lepor, 2007).

Appendix B

Literature Search Flow Chart