A Bit More about ADT (Androgen Deprivation Therapy) That You and Your Partner Might Want to Know

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General Background

With increased awareness of prostate cancer (PCa) and PSA screening, men are increasingly diagnosed, treated (and cured) of the disease when they are largely asymptomatic. As such, any long term suffering they experience is more likely from the side effects of treatment rather than from the disease itself.

Approximately half of all men treated for PCa will be on androgen deprivation therapy (ADT) at some time in their life.

Prevalence of ADT

Between short- and long-term use ~600,000 men in North America are on ADT at any one time. The numbers are comparable for Europe.

Pre-COVID there was a push toward active surveillance and intermittent ADT administration leading to a slight decline in ADT use (at least in Canada). However, because of earlier detection, PCa patients are now starting on ADT at a younger age than in previous years. Some PCa patients, diagnosed early, may now be on and off ADT for 20+ years.

Primary forms of ADT

Chemical Castration

- luteinizing hormone releasing hormone <u>agonist</u> (LHRHa); e.g., leuprolide (= Lupron/Eligard), goserelin (= Zoladex)
- luteinizing hormone releasing hormone <u>antagonist</u>; e.g., degarelix (= Firmagon) or relugolix (Orgovyx).
- anti-androgen monotherapy; e.g., bicalutimide (= Casodex).
- Non-oral estrogens (e.g., dermal patches).

Orchidectomy (= surgical castration)

New Agents and New Combinations

Hormonal intensification is increasingly common by added to standard ADT:

An androgen-receptor targeted agents (ARTAs; also called androgen-receptor signaling inhibitors (ARSI). These are:

- abiraterone (=Zytiga)
- second generation anti-androgens—i.e., enzalutamide (=Xtandi), apalutamide (=Erleada), and darolutamide (=Nubeqa)

"Androgen annihilation" (Standard ADT + abiraterone)

Leading to Double and triple therapy

Erectile dysfunction
Osteoporosis
Hot flashes
Loss of sexual interest
Genital shrinkage
Gynecomastia
Impaired memory and attention
Weight gain/body fat redistribution
Loss of muscle mass

Anemia
Fatigue
Increased risk of:
- diabetes
- cardiovascular disease

Increased emotionality and tearfulness
Distress at loss of identifiers of masculinity (e.g., loss of body hair)

Topics to cover include:

1. The barriers to PCa patients being able to recognize, accept, and adapt to the side effects of androgen-deprivation therapy (ADT).
2. Areas where PCa patients and their partners need more information and skills in managing side effects.
3. The best strategies dealing with both the most serious and the most bothersome adverse effects of ADT on the lives.

Objectives

1. What are the barriers to PCa patients (and their partners) being able to recognize, accept, and adapt to the side effects of androgen-deprivation therapy (ADT)?

Hormonal therapy = androgen deprivation therapy = chemical castration

However both MDs and patients tend to avoid the word “castration” because of the stigma associated with it. Although the terms above mean the same thing, patients understand them differently. In an online survey of men, significantly fewer would accept “chemical castration” than “hormonal therapy” to treat PCa, if recommended by their physicians.

Rot, I., I. Ogah & R. J. Wassersug (2012) The language of prostate cancer treatments and implications for informed decision making by patients and their partners. *Eur. J. Cancer Care*, **21**:766-775.

Beyond the more serious physiological effects, such as metabolic syndrome and osteoporosis, which patients may not notice, what are the ADT side effects that they are likely to notice and, along with their partners, should be aware of?

Side effects of ADT

Side effects identified as particularly challenging—as summarized in Elliott et al. (2010) *Androgen deprivation therapy for prostate cancer: recommendations to improve patient and partner quality of life*. (*J. Sex Medicine* **7**: 2996–3010)—are:

1. body feminization
2. changes in sexual performance
3. cognitive and affective (=mood) changes
4. relationship changes
5. fatigue, sleep disturbance, and depression.

1. feminization of the body

- Loss of body hair
- Loss of muscle mass (~ 4%)
- Increase in weight (~ 10%) largely as cutaneous body fat.
- Some gynecomastia (and mastalgia) depending on the drugs used.

Altered or reduced body odour? Documented in one small paper…and could have social/sexual implications.

2. sexual side effects

With long term ADT there is:

- Testicles and penile shrinkage
- Impotence (in >80%)
- Reduced libido (in >80%)

More than 60% of men treated for localized prostate cancer by surgery, radiation therapy, or brachytherapy have substantial residual erectile dysfunction (ED).

3. cognitive and affective symptoms

Cognitive effects—One study reported that "verbal memory…[is]…significantly worse in patients on ADT" (Beer *et al*., 2006). As an aside, there is some evidence that this can be reduced or reversed with transdermal estradiol, but this has not been replicated in a larger study.

A recent meta-analysis suggested that the biggest cognitive effect is the areas of visuospatial and visual motor processing. Skills in this area help us to order an organize our lives.

ADT and depression

Depression is often associated with low testosterone. In cancer patients it may be linked as well to anxiety associated with disease progression.

DiBlasio *et al.* (2008) reported "a three-fold increase… between rates of pre-ADT psychiatric illness and development of *de novo* illness [after starting ADT]" (9% vs. 29%). Most common was **depression**, reported in 56% of those patients.

DiBlasio C.J. *et al*. (2008) Prevalence and predictive factors for the development of *de novo* psychiatric illness in patients receiving androgen deprivation therapy for prostate cancer. *Can. J. Urol*., **15**:4249-4256.

The bottom line on cognitive decline:

"Between 47% and 69% of men on ADT …[experience a decline]… in at least one cognitive area, most commonly in visuospatial abilities and executive functioning." ADT "is linked to subtle but significant cognitive declines in men with prostate cancer."

"The authors believe that clinicians should… inform and monitor patients for this possible side effect of treatment."

Nelson C. J. *et al.* (2008) Cognitive effects of hormone therapy in men with prostate cancer: A review. *Cancer,* **113**:1097-1106.

Emotionality

- Changes in emotionality have been repeatedly reported for androgen-deprived prostate cancer patients (as well as male-to-female transsexuals)…most conspicuously as an increase in tearfulness.

- In our society women may cry, but "*real men don't cry.*"

- Increased tearfulness can thus be embarrassing to men on ADT.

4. relationship changes

Faced with such changes in their lives, many men:

→ withdraw their affection from, and physical contact with, their partners.

→ are embarrassed by the changes they've experienced and are reluctant to discuss them with their partners.

… which leads to depression & frustration in their partners.

Soloway C.T. *et al*. (2005) Sexual, psychological and dyadic qualities of the prostate cancer 'couple'. *BJU International*, **95**:780-785.

Cost to the partner

Studies going back to 1994 show that the psychological distress on the partners of PCa patients on ADT is even <u>greater</u> than that on the patients themselves. Withdrawal of intimacy in general—not necessarily loss of coital sex—seems to be the biggest problem.

Hagedoorn M. *et al.* (2008) Distress in couples coping with cancer: A meta-analysis and critical review of role and gender effects. *Psychological Bulletin*, **134**:1-30.

Kim Y. *et al*. (2008) Quality of life of couples dealing with cancer: Dyadic and individual adjustment among breast and prostate cancer survivors and their spousal caregivers. *Annals of Behavioral Medicine*, **35**:230-238.

Loss of intimacy harms <u>both</u> the patient and the partner

ADT causes a "communicable iatrogenic psychiatric disorder" → i.e., he's chemically castrated…and she's now depressed.

Distress in the partners correlates with distress in patients. Namely there is "evidence of partner effects, at least for women. That is, women's distress predict[s] men's physical health, over and above the men's distress, …age, and cancer stage." (Kim *et al*., 2008)

5. fatigue, sleep disturbance & depression

Depression has already been discussed. Sleep disturbance can be associated with insomnia leading to daytime fatigue. Insomnia itself can result from nocturnal hot flashes, which may not be remembered, but disrupt sleep and lead to daytime fatigue.

The trio of symptoms—depression, insomnia and fatigue—are common in many cancer patients.

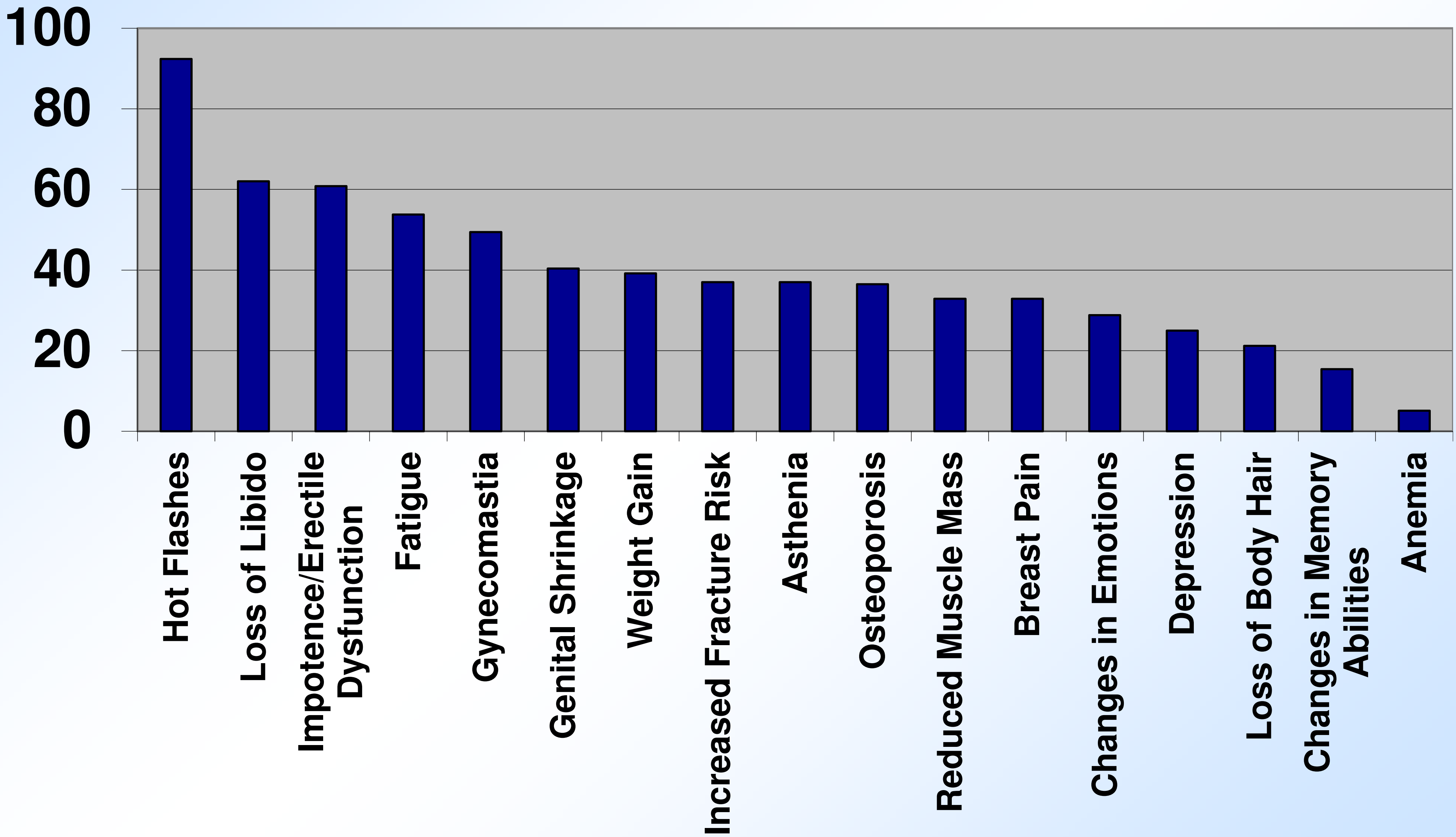
In order to manage the side effects of ADT, patients and their partners need to know what the adverse effects are of these drugs.

So how well informed are they about the side effects of ADT?

Objectives:

2. What are the areas where PCa patients and their partners most need information and skills in managing ADT side effects?

Percentage of patients who were aware of specific ADT side effects



The patients were significantly more aware than their partners of the sexual side effects of ADT (such as its impact on genital size).

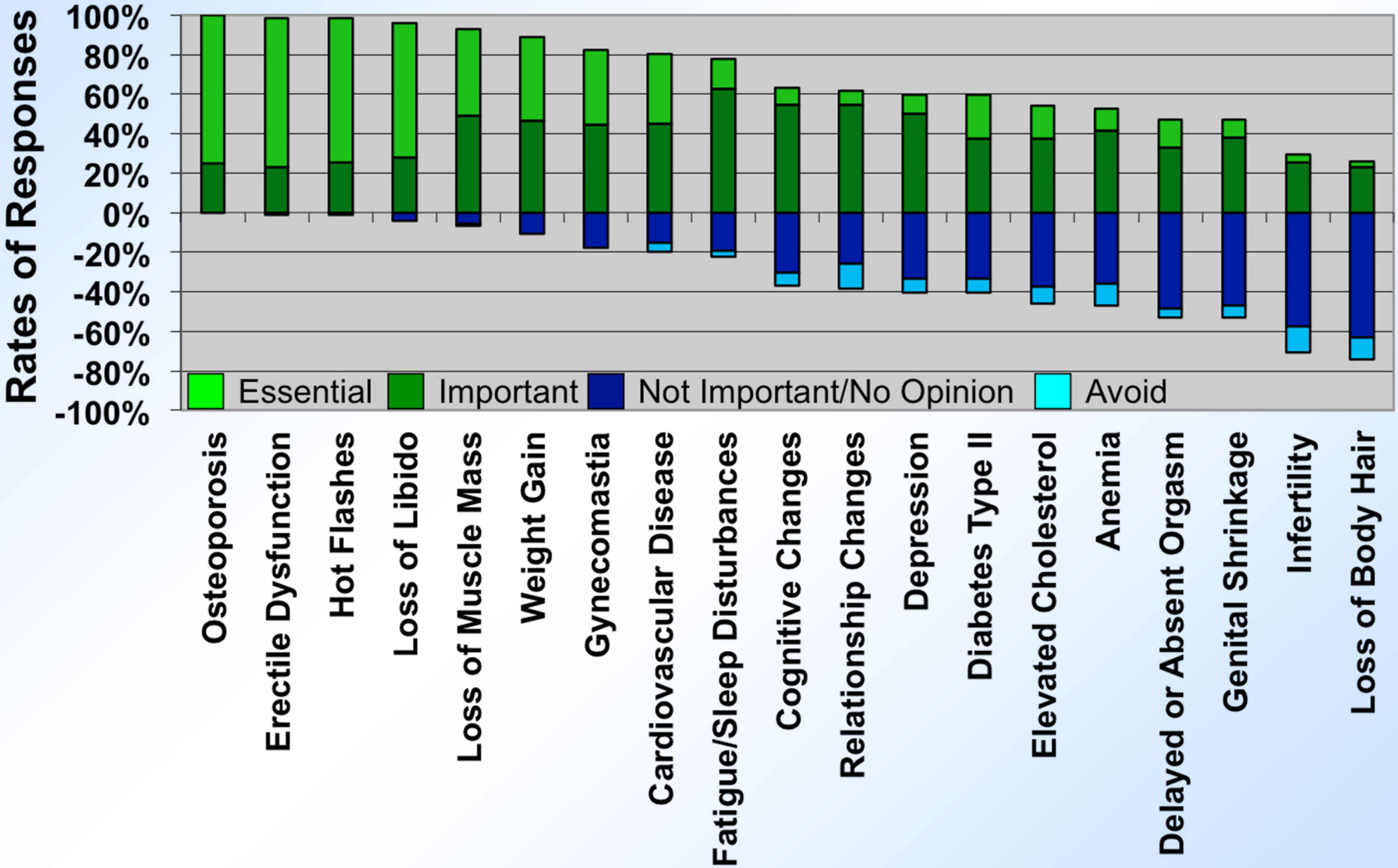
The partners were significantly more aware of the impact of the drugs on the patients' mood and affect.

This is despite the fact that they had attended the same information session with the prescribing physicians!

Walker, L., Tran S, Wassersug, RJ ThomasB & Robinson J 2013 Patients and partners lack knowledge of androgen deprivation therapy side effects. *Urol. Oncol*., **31**:1098-1105.

So, are the patients and their partners simply not hearing what the physicians are telling them, or are the physicians not telling the patients about all the side effects?

Percentage of uro-oncologists who judged specific ADT effects as important



Tran, S, Walker L, Wassersug RJ , Matthew AG , McLeod DL & Robinson JW (2014) What do Canadian uro-oncologists believe patients should know about androgen deprivation therapy? *J. Oncol. Pharm. Pract*. 20:199-209.

So, maybe the healthcare providers themselves are not well informed about the breadth of side effects of LHRH agonist drugs?

Two studies have explored this topic in quite different ways:

1. Soeyonggo T, Locke JA, Del Guidice L, Alibhai S, Fleshner N, Warde P. (2014) National survey addressing the information needs of primary care physicians: side effect management of patients on androgen deprivation therapy. *Canad. Urol. Assoc. J.* **8**(3-4):e227-234.

2. Phillips, JL , Wassersug RJ & McLeod, DL (2012) Bias and redundancy in oncological literature: The case of androgen deprivation therapy and its side effects. *Int. J. Clin. Practice,* **66**:1189-1196.

Soeyonggo et al. (2014)

They surveyed 92 primary care physicians in Canada, who had patients on ADT; >50% of whom administered ADT annually.

They found that:

"38% of the primary care physicians felt their knowledge of ADT side effects was inadequate and 50% felt uncomfortable counseling patients on ADT."

Many of the physicians were not well-informed about incidence of hot flashes, fatigue, and ED from ADT. <u>The</u> <u>majority</u> "expected their specialist colleagues to monitor [their patients'] ADT side effects."

Phillips et al. (2012)

They explored the medical literature to see how comprehensive and objective it was in informing healthcare providers about ADT side effect and side effect management strategies.

Specifically Phillips et al. reviewed 155 papers in the English language, peer-reviewed literature published between ~2000-2010 related to the side effects of ADT and their management.

Phillips et al. (2012)

Of the papers in the peer-reviewed medical literature, only 1/5 mentioned ADT's impact on partners and just over a 1/3 mentioned depression as a side effect of ADT.

However 1/4 of the medical papers had drug company support indicative of a conflict of interest. Not surprisingly, less than a third of those papers mentioned less expensive alternatives to the LHRH agonists that dominate the market.

Approximately half of the papers had no new information!

Objectives:

3. What are best strategies dealing with both the most serious and the most bothersome adverse effects of ADT on the lives

WHAT SIDE EFFECTS ARE YOU MOST CONCERNED ABOUT?

Some patients experience a lot of these side effects and some experience few, if any.

The side effects you might experience are not necessarily the ones that you should be most concerned about.

Some side effects are common and obvious, but not of great medical concern. Others are inconspicuous, but potentially serious.

HOT FLASHES

What to do about it?

- Medications
  (e.g. Estradiol, Effexor)

- Abdominal breathing exercises

- Hot flash diary

FATIGUE

- Mild anemia is common with ADT, but it is not due to low iron.

- You may not feel that you have the energy to exercise…

What to do about it?

- Physical exercise works!

  - If you haven't been exercising commit yourself to start, and see how you feel after 10 minutes.

  - If just starting, exercise in small chunks—e.g., 3-10 minute periods.

WEIGHT GAIN, MUSCLE LOSS

- These are associated with increased risk for diabetes & cardiovascular disease ("Metabolic syndrome")— A serious concern.

What to do about it?

Exercise

- ➢ Men who engage in regular exercise while on ADT show less significant declines in muscle mass (but still show some declines).
- ➢ Balance—even a 20% loss of the small muscles in your core can lead to increased falls.

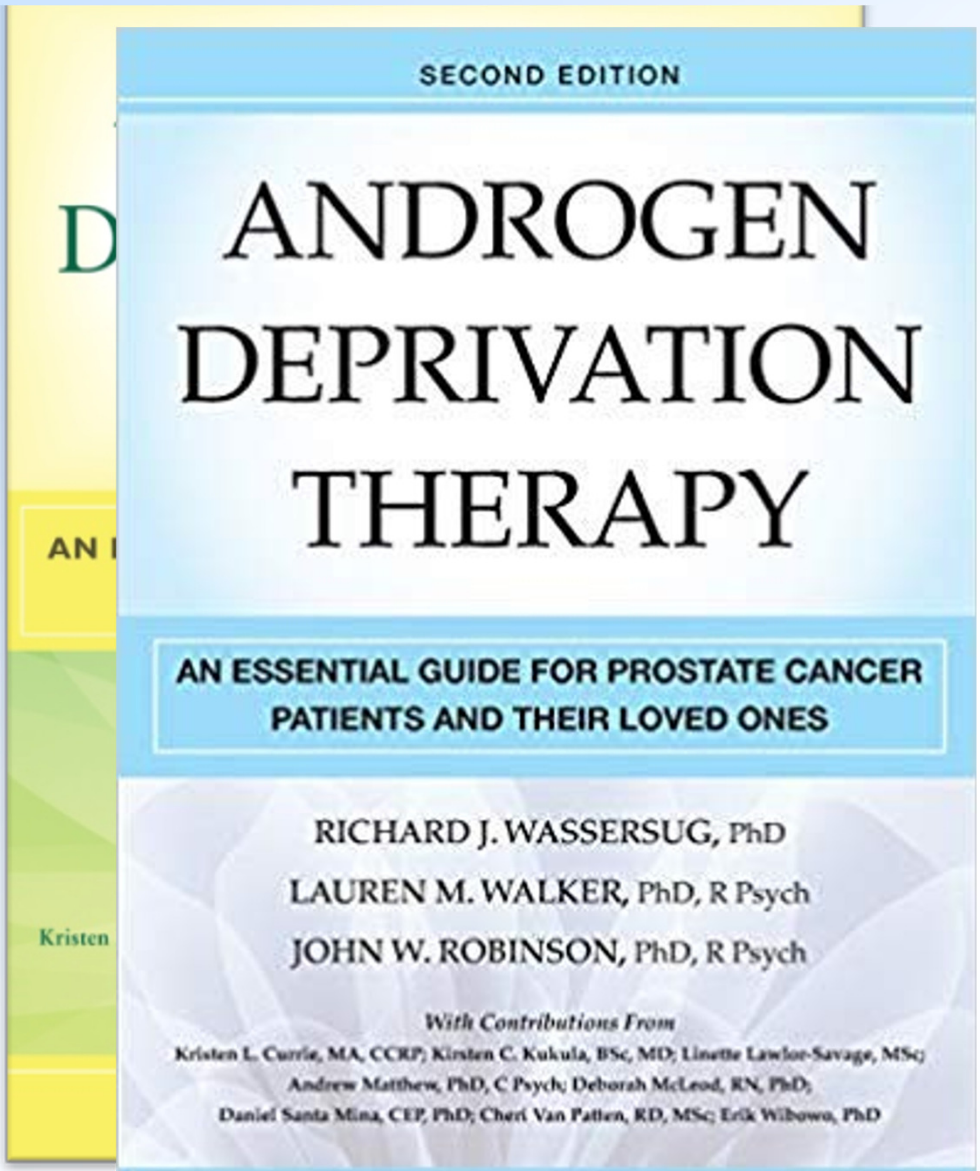
Exercise

Helps—

- ✓ Maintain muscle strength
- ✓ Keep weight properly controlled
- ✓ Helps reduce risk of depression
- ✓ Helps preserve bone
- ✓ Helps reduce falling and breaking bones
- ✓ Improves sleep
- ✓ Reduces daytime fatigue
- ✓ May help maintain cognitive function
- ✓ Can even help maintain some sexual interest above

Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones

- Produced by the “ADT Working Group” and first published in 2014 by Springer DEMOS Health. New 2021 European edition sponsored and endorsed by the European Association of Urology.
- Core to an online 1.5 hour ADT educational classes for those starting on ADT and their partners. Offered once a month for free across Canada.
- Now piloting classes in Europe in partnership with the European Association of Urology.



Endorsed by the Canadian Urological Association and
the European Association of Urology

- How ADT works.
- How to monitor side effects.
- Physiological side effects.
- Exercise.
- Nutrition.
- Sexual changes.
- Relationship changes.
- Self-management strategies.

Thank you!

Any questions?

For more information contact:

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