

Review of current treatment for hot flashes induced by androgen deprivation in prostate carcinoma

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Abstract

Considering the currently increased incidence, prevalence and survival of prostate cancer, the management of hot flashes associated with LH-RH analog treatment must be taken into account.

The most widely used and effective treatment is hormone replacement, though the latter is not without risks. It is presently possible to address hot flushes in these patients based on a broad range of treatment options in which hormone therapy may constitute a last option, due to the risk of tumour relapse or progression – since prostate cancer is hormone sensitive.

The present study reviews the currently used treatments and hygiene-dietary measures that may help reduce the symptoms.

A review is made of both hormonal and nonhormonal therapies, based on the existing scientific evidence.

Drugs such as the new antidepressants, gabapentin and clonidine may play an important role in the management of hot flashes. While the underlying mechanisms of action are varied, they are related to the complex feedback exerted by the sexual hormones upon the hypothalamic secretion of noradrenaline – this being the principal etiological factor of hot flashes.

Keywords: Prostate carcinoma, hot flashes/flushes, hormone deprivation, treatment, antidepressants, clonidine, gabapentin, hormone replacement therapy.

Because of the high incidence of prostate cancer in developed countries and the important role that androgen deprivation therapy will play in the treatment of many of these patients, correct management of the toxicity induced by treatment is increasingly important.

The most widely used mechanism at present for this deprivation are LH-RH analogs, either alone or combined with antiandrogens.

Previous studies showed their equal efficacy to surgical orchidectomy^{1,2}.

It should be noted that there was a higher prevalence of hot flashes in the group treated with analogs (60-75%)³⁻⁸. Hot flashes may occur during analog therapy for several months and may persist for years, although with less intensity and frequency.

Hot flashes were first described by Cabot who studied the effects of castration in the treatment of prostate cancer⁹.

Hot flashes may be accompanied by a multitude of other symptoms and signs, such as facial flushing, palpitations, anxiety, and feelings of loss of control, which cause great physical and emotional impact and largely determine the impairment in quality of life of these patients^{6,10,11}.

Their adequate control is of vital importance but stressing that hormone-sensitive tumors should not be treated with hormonal therapy, despite having shown superior efficacy, until controlled studies with adequate methodology and longer follow-ups demonstrate the absence of oncological risk^{12,13}.

The purpose of the present study is to review the extensive therapeutic armamentarium currently available for the management of these symptoms.

With the purpose and after an initial literature search in PubMed, the resulting articles are analyzed. The articles retrieved served in turn as a basis for expanding this search to obtain all the original articles of interest.

CURRENT TREATMENT OF HOT FLASHES

As could be expected, the large majority of published studies were carried out in menopausal women or in breast cancer survivors.

In view of their pathophysiology, the regulatory mechanisms on negative feedback should be taken into account as causes of these hot flashes¹³.

Abrupt hormonal deprivation with intervention of the hypothalamus is currently considered to be the main cause of these symptoms¹³. The proximity of the hypothalamic thermoregulatory center to LH-RH producing areas would play a role in the problem¹⁴⁻¹⁶.

Endogenous opiates would also be implicated in the process¹⁷. β -endorphins are increased by peripheral sex hormones, which in turn produce catecholestrogens, causing a reduction in hypothalamic synthesis of noradrenaline^{7,15,18-20}.

The abrupt fall in hormonal load will cause a decrease in endorphins and catecholestrogens, as a result of which hypothalamic noradrenaline (NA) levels will increase, which by activating the LH-RH producing center and by proximity stimulating the thermoregulatory center will cause a decrease in the response intervals to hot-cold stimuli^{18,21}. Other neurotransmitters such as serotonin and dopamine have an opposite effect, inhibiting hot flashes^{18,19,22-27}.

HORMONE REPLACEMENT

Hormone replacement with estrogens was the first treatment used in the 20th century. Other forms of replacement included progesterones and androgens, but because of the hormone sensitivity of prostate cancer, the latter would be contraindicated.

As for estrogens, it should be noted that despite their high efficacy even at low doses, they have negative side effects. These include thromboembolic phenomena, cardiovascular morbidity and painful gynecomastia²⁸⁻³⁰.

The most widely used estrogen, both orally and transdermally, is estradiol^{19,31}, which requires at least a month to obtain benefits. Higher doses provide better control of symptoms than lower doses but also have more side effects, though they are fewer when transdermal formulations are used.

The usual oral doses are ≥ 0.25 mg/day, whereas the daily amount required for patches is less than 0.05 mg/day.

In summary, estrogen therapy shows a dose-dependent response, with a balance in favor of transdermal therapy and an efficacy of 80-90%, reducing the number of hot flashes by 2.5 to 3 hot flashes daily^{14,28,32}, but with undesirable side effects that need to be considered^{13,14,33,34}.

Their effectiveness was confirmed in a 2002 meta-analysis from the Cochrane Library and in an extensive review published in JAMA in 2004³².

Progesterones, like estrogens, stimulate the production of hypothalamic β -endorphins. Their use is also not free from undesirable side effects^{21,35,36}. There is experience in both men and women, and the most used is megestrol acetate with starting doses of 20 mg twice daily and subsequent reduction to the lowest effective dose, with response rates of 80-90%^{3,13,21,28,35,37}.

As a second drug in use, cyproterone acetate is a steroidal antiandrogen with progestogenic action, with response rates comparable to megestrol acetate but with risk of hepatotoxicity, fatigue, painful gynecomastia and galactorrhea. Treatment for hot flashes should be started at 50 mg/day, and not exceed 300 mg/day^{13,38}.

Lastly, we need to mention medroxyprogesterone acetate³⁹⁻⁴¹ given in 20-40 mg oral doses daily with equal or superior efficacy to megestrol^{42,43} or a single 400 mg i.m. depot dose with an effect sustained over at least 6 months^{39,43}. Although some experts consider 400 mg to be a very high dose, it is a small dose if we compare it to the 500 mg intramuscular or oral doses used daily during months for the treatment of breast cancer^{39,43,44}. It was found to be correctly tolerated and weight gain was the only undesirable effect⁴⁴.

The use of progesterones in prostate cancer has some reservations because it has been reported in some articles to be related to increases in PSA levels⁴⁵⁻⁴⁷. Extrapolating these results to the use of low-dose progesterones in the treatment of prostate cancer remains to be clarified^{39,48}, although their antitumor activity has also been reported in breast⁴⁹, endometrium⁵⁰ and prostate cancer⁵¹.

The effect of estrogens and progesterones can persist for extended periods after their withdrawal^{21,52}.

The problems of the use of hormone replacement therapy in menopausal women have acquired a certain prominence as a result of the publication of the results of the *Women's Health Initiative randomized*

controlled trial, which reveal the increased risk of developing breast cancer^{53,54}, cognitive disorders, cardiovascular and thromboembolic disease^{33,34,39}, and therefore other alternative treatments are desirable. The absolute risks per 10,000 person-years were 7 more coronary events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. They also reduced vasomotor symptoms and vulvovaginal atrophy⁵⁴.

NONHORMONAL THERAPIES

It is interesting to point out that there are other nonhormonal therapies. This is of the utmost importance both for breast cancer survivors and men on hormone deprivation therapy for prostate cancer, where the use of hormone replacement therapy may be contraindicated because of its repercussions. (Table 1)

Table 1

List of drugs and % of control		
Estrogens:	Estradiol p.o. (0.25 mg/day) or transdermal (0.05 mg/day)	80-90 %
Progesterones:	Megestrol acetate 20 mg/12 h	80-90 %
	Cyproterone acetate 50 mg/day	
	Medroxyprogesterone acetate p.o. 20-40 mg/day or single 400 mg i.m. depot dose.	
Clonidine p.o.	25-400 mcg/day	20-55 %
Antidepressants:	Paroxetine 10-25 mg/day p.o.	60-65 %
	Venlafaxine 25-75 mg/day p.o.	55-65 %
	Fluoxetine 20 mg/day p.o.	50 %
	Sertraline 50 mg/day p.o.	36 %
	Trazodone 50-150 mg/day p.o.	
	Citalopram	
	Veralipride	
	Moclobemide	
Gabapentin	300 mg/8 h p.o. Even effective after failure of TAD	44-60 %
Placebo effect		20-40 %
Others that have not demonstrated their efficacy:	Bellegard	
	Isoflavones/phytoestrogens	
	Vitamin E	
	Cimifuga racemosa	
	Acupuncture	
	Methyldopa	
	Physical exercise	
	Relaxation techniques	

With regard to vasomotor symptoms, numerous drugs have been studied for this purpose. A recent meta-analysis from 2006⁵⁵ shows that the only effective therapies based on the existing literature, with valid methodological studies, are in decreasing order according to their effectiveness: gabapentin, selective serotonin reuptake inhibitors and clonidine.

We will describe them briefly below. Although they do not appear to be as effective as hormone replacement therapy, their effectiveness has been widely demonstrated^{14,39,56}.

Because noradrenaline is the neurotransmitter directly involved in control of the thermoregulatory center, blockade of both alpha and beta adrenoceptors can provide symptomatic relief. Based on this reasoning, clonidine, an α_2 -receptor agonist⁵⁷, has been used both in men^{8,27} and women⁵⁷⁻⁵⁹. These receptors (α_2) have been identified both in the hypothalamus and peripherally. Their presynaptic activation results in reduced release of NA⁶⁰. It also has peripheral action reducing vasodilatation and thus contributing to increased control of hot flashes¹³. The higher the dose, the better the symptom control, but also the greater the toxicity.

Transdermal administration^{61,62} is as effective as oral administration^{59,61-63} but it is frequently complicated by skin reactions. The recommended doses range from 25 to 400 µg. Clonidine treatment is inferior to hormone replacement therapy (20-55%) and has a high rate of undesirable side effects, although two recent double blind trials comparing it to venlafaxine, with disparate results, stress its good tolerance and even effectiveness in the control of hot flashes^{64,65}. It may have a role in patients in whom the use of other treatments is contraindicated¹³.

Gabapentin has been used at doses of 300 mg every 8 hours, with response rates of 44-60%, and the following reported side effects: somnolence, dizziness, fatigue, skin rash, palpitations and peripheral edema⁶⁶⁻⁶⁹. Gabapentin may reduce hot flashes by regulating the calcium channels, although its specific mechanism of action has not yet been clarified⁶⁹. A recent study showed its usefulness after an inadequate response to antidepressants⁶⁸.

Regarding the potential use of certain antidepressants and their effect on serotonin, these agents have emerged as drugs of interest. It is known that serotonin levels in postmenopausal women are decreased and that they apparently tend to normalize after replacement therapies. Based on this, an abrupt decrease in sex hormones would cause a reduction in the circulating serotonin level, with the consequent increase of its hypothalamic 5-HT_{2A} receptors^{22,24}, which would be implicated in the pathogenesis of hot flashes²².

The potency of blockade of 5-HT_{2A} serotonin receptors varies considerably among first-generation antidepressants (tricyclic). The importance of this effect on the therapeutic action of tricyclic antidepressants in general is not clear. However, there is another class of antidepressants, known as phenylpiperazines, which are more selective than tricyclic antidepressants and whose most potent pharmacological action is to block 5HT_{2A} receptors⁷⁰.

New antidepressants, especially venlafaxine, paroxetine, and to a less extent, fluoxetine, could play an important role in nonhormonal therapy of hot flashes^{48,64,65,71-74}, with response rates of around 50-65%, somewhat lower than hormonal therapies but with a superior safety profile in cancer survivors which makes them very interesting in this type of patients as an alternative²². Their side effects, although present, are not very significant because patients receive doses lower than those normally used for the treatment of depression and they have not experienced a previous withdrawal syndrome to such doses^{22,64,65}. (Table 2).

Table 2

Doses and response rates of some antidepressants

- Paroxetine, doses of 10 to 25 mg/day, with reductions of 60-65% ^{16,71,82} .
- Venlafaxine, doses of 25 or 37.5 mg/day increased to 75 mg/day after 1 week, with response rates of 50-65% ^{48,64,65,73,83-85} .
- Fluoxetine, doses of 20 mg/day, with an effectiveness of about 50% ^{72,74} .
- Citalopram ⁷² .
- Veralipride (antidopaminergic drug) ³³ .
- Sertraline, 50 mg/day, with a response rate of 36% ⁸⁶ .

We found few publications on the use of new generation antidepressants for the treatment of hot flashes in prostate cancer patients undergoing hormone deprivation therapy. A study with venlafaxine in 16 patients showed that the drug appears to alleviate symptoms⁴⁸. A pilot study with paroxetine that included 24 patients is also available, which noted relief of hot flash attacks in men⁷¹.

It is of interest to note that the placebo effect can control symptoms in 20-40% of patients, with individual perceptions of improvement of up to 50-75% over initial symptoms^{48,75-77}.

Many other products have been used that were much less effective, totally ineffective or discarded because of their high incidence of side effects. (Table 3)

Table 3

Some measures used to control hot flashes

- Bellergal (phenobarbital + ergotamine + belladonna alkaloids) with a 30% withdrawal rate from therapy due to toxicity⁸⁷.
- Dietary supplements⁷⁷.
- High-dose supplements of isoflavones/phytoestrogens with no effect (both estrogenic and antiestrogenic effects)⁸⁸.
- Medicinal plants⁷⁷.
- Vitamin E⁷⁷.
- Relaxation techniques⁸⁸.
- Physical exercise⁸⁸.
- Methyldopa^{89,90}.
- Acupuncture⁹¹⁻⁹³.

On the other hand, it is useful to recommend hygiene-dietary measures to prevent hot flashes such as: wash hands in cold water or apply cold, avoid eating or drinking foods that are too hot or remaining in very hot environments, restrict intake of spices, coffee and alcohol, eat a diet rich in products containing soy proteins (and not phytoestrogens as recommended)^{77,78}, reduce stress by relaxation techniques, do nonstrenuous exercise to maintain an adequate weight (excess weight may increase the frequency and intensity of hot flashes)¹⁸ and quit smoking⁷⁶. (Table 3).

Recent investigations have shown a correlation between body mass index and hot flash frequency, which would be due to the effect of insulin metabolism in fat and an increase in body temperature^{18,78,79}. Hot flashes have also been related to smoking, possibly through the effect on estrogen metabolism or through the thermogenic effect of nicotine^{18,80,81}.

CONCLUSION

Hot flashes are frequent in men undergoing androgen deprivation therapy for prostate carcinoma. There is a clear association between prostate cancer, androgen deprivation and hot flashes, which severely impair the quality of life of these patients.

The use of hormone replacement therapy, both with estrogens and progesterones, is complicated by the hormone dependency of prostate cancer, making it necessary to look for alternative treatments that may be useful in these patients.

Nonhormonal therapies do not appear to have similar efficacy to hormonal therapy. Hygiene-dietary measures have been recommended to reduce hot flashes and they have also been related to obesity due to its effect on insulin metabolism.

Clonidine, with an efficacy of 20-55% compared to hormone therapy, has been proposed as an effective reducer of NA release. The regulatory effect of gabapentin on calcium channels appears to exert positive effects on symptoms, although the mechanism of action is still not well understood.

It is known that the abrupt reduction in sex hormone plasma levels reduces serotonin levels, resulting in an increase in the number of hypothalamic 5-HT_{2A} receptors implicated in the pathogenesis of hot flashes.

Serotonergic antidepressants may play an important role by increasing serotonin centrally, as a result of which they may cause a shift in the balance of NA in the thermoregulatory center.

Serotonergic antidepressants such as venlafaxine, paroxetine and fluoxetine have been tested in male patients receiving hormone deprivation therapy with positive results. Although response rates were somewhat lower than those obtained with hormone replacement therapies at around 50-65%, they showed a much better safety profile.

Further clinical trials along these lines will be needed to clarify the role that all these therapies can play in the treatment of hot flashes induced by androgen deprivation with LH-RH analogs in prostate carcinoma. It is highly relevant and current topic because of the increased incidence of this disease in our contemporary society, and the significant impairment it causes in the quality of life of our patients and their social environment.

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