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BRIEF REPORT

SERTRALINE RELIEVES HOT FLASHES SECONDARY TO MEDICAL CASTRATION AS TREATMENT OF ADVANCED PROSTATE CANCER

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Gonadotropin releasing hormones are the mainstay of treatment for metastatic prostate cancer. They prevent progression of the illness and effectively reduce the pain caused by bony metastases. Unfortunately, they are not innocuous in the asymptomatic individual. In addition to loss of libido, loss of erectile function, muscle weakness and fatigue, nearly two-thirds of men with prostate cancer treated with gonadotropin releasing hormone therapy and over 50% treated by orchiectomy, develop hot flashes severe enough to warrant treatment (The Leuprolide Study Group, 1984; Charig and Rundle, 1989). Hot flashes, also called hot flushes, are due to vasomotor instability, that ultimately lead to thermoregulatory changes. Symptoms are described as episodes of increased warmth of the face and upper body; flushing of the skin; profuse sweating requiring change of clothes and bed sheets; chills; and fatigue. Patients report difficulty coping with these symptoms when they interfere with sleep, energy, and mood. These episodes may occur spontaneously or may be brought on by external factors such as hot drinks and changes in outside temperature. They may occur many times during the day or night or only infrequently. However, some men have stopped their hormonal treatment, or have gone onto intermittent hormonal therapy, because they could not cope with the side effects.

Presently, there is no reliable treatment for hot flashes in men. One small study using clonidine noted partial response of hot flashes secondary to leuprolide or goserelin (Bressler *et al*., 1993). This led to a proposed mechanism for the flashes involving the interaction of sex steroids, opioids and norepinephrine. Hormonal replacement therapy has been used with some success in women (Frishman, 1995). Recently, there have been studies of diethylstilbestrol and megestrol acetate in controlling hot flashes in some men (Loprinzi *et al*., 1994; Smith, 1994). However, there are some men who either have uncomfortable side effects with these therapies, or have not experienced sufficient relief from their hot flashes. There is also a question about whether megestrol acetate poses a risk for recurrence of prostatic disease (Kelly and Scher, 1993).

Anecdotal reports from men on hormonal therapy for prostate cancer who were treated for depression with the antidepressant sertraline (Zoloft) noted that some experienced fewer and less severe hot flashes. We have monitored the clinical effects of sertraline in several men treated for psychological distress (depressed mood, irritability, middle insomnia, anxiety) who also had hot flashes. At the time of their regular oncology clinic visit, the consulting psychiatrist reviewed

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the patients' charts, then examined the patients, with special attention to autonomic symptoms and mood. Psychological symptoms including depression, irritability, sleep disturbance and anxiety, as well as a description of precipitants and quality of hot flashes were noted. Patients reported to what extent these symptoms changed over the next 1 or 2 months.

We report five cases that illustrate a possible use of sertraline in the management of hot flashes in men with prostatic cancer.

CASE REPORTS

Case 1

AA was a 64-year-old businessman with prostate cancer who had been treated with leuprolide and flutamide for 3 years. He noted that after his hormonal therapy began, his mood became depressed and his energy decreased. Though never a good sleeper, he had insomnia and mild anhedonia. He described mild, intermittent periods of anxiety related to his work. He had significant distress from hot flashes five to ten times per day and night. He had no past family or personal history of a psychiatric disorder. His medical history was significant for hypertension for which he took nifedipine. The patient was started on sertraline 25 mg per day and titrated to 100 mg over 6 weeks. His mood improved as did his energy by week 4 at 75 mg per day. He felt much more productive at work. The patient noted a significant decrease in the frequency and intensity of his hot flashes to three to five times per day with decreased duration of each episode.

Case 2

BB was a 62-year-old retired engineer with D2 prostate cancer treated initially with radiation therapy, now on leuprolide and flutamide. He stated he had been depressed for 'a long time', for which he had long term psychotherapy. His depression had worsened after his father's death 4 months earlier. Past medical history was significant for peptic ulcer disease. Other medications included atenolol which had been prescribed for palpitations 8 years ago. The patient was experiencing hot flashes a few times per day and was awakened once to twice nightly by the flashes. The patient was diagnosed as having a depressive disorder secondary to medical factors. Sertraline was prescribed for the depression. The depression improved in 3 weeks and the patient noted that his hot flashes subsided considerably when the sertraline dose reached 100 mg per day. He experienced nausea and other GI symptoms at 150 mg per day, at which time the dose needed to be decreased. He continued to feel better on a daily dose of 100 mg, over several months.

Case 3

CC was a 62-year-old factory worker who had been diagnosed with prostate cancer 3 years earlier, and was being treated with depot leuprolide. He was seen in the prostate clinic for progression of this disease in the pelvis. The patient had been getting increasingly depressed over the previous 3–4 months with worsening mood, increased fatigue, decreased appetite, and concern about his illness and its outcome. Though being awakened by hot flashes about twice per night, he felt he got 'enough sleep.' The patient had a history of depression a few years earlier requiring a psychiatric hospitalization for suicidal ideation while going through a divorce. He was seeing a psychotherapist intermittently. He was without suicidal ideation when seen in our clinic, but was feeling hopeless about his future. He had pelvic pain that was relieved by oxycodone. The patient was started on sertraline and titrated to 75 mg per day. He stated his mood improved, and his hot flashes became less frequent and more tolerable. Though the patient began to feel more anxious and depressed when his medical condition worsened, he did not want to increase the medication. In fact he decided to reduce it to 50 mg per day, inappropriately fearing reliance on a psychotropic medication. He stated that his flashes did not worsen again or 'at least I'm not so bothered by them'.

Case 4

DD was a 63-year-old salesman with metastatic prostate cancer who was treated with leuprolide about 2 years ago. The patient became quite depressed with irritable mood, decreased energy, decreased motivation, and loss of pleasure in doing activities he usually enjoyed. He also developed hot flashes consisting of drenching sweats,

occurring several times per day and without warning. Around the same time the patient was placed on sertraline for depression by an outside psychiatrist. The patient's mood symptoms and hot flashes improved when the dosage reached 100 mg per day. As the patient was quite bothered by the continual loss of sexual libido, his hormonal therapy was interrupted and he was placed on intermittent therapy. When the patient's PSA began to rise, he was placed on bicalutamide and sertraline was eventually tapered as the patient's mood and hot flashes were no longer problematic. When the patient's PSA continued to rise, he was placed on goserelin depot. Within 4 weeks, the patient's mood became depressed and irritable; his energy level dropped considerably, hot flashes returned, and he developed middle insomnia. He also had passive suicidal ideation. The patient was restarted on sertraline and titrated on 100 mg per day. Within 1 week of being at the 100 mg per day dosage, the patient's mood began to improve and his irritability decreased. One month later he was euthymic. The hot flashes decreased from eight episodes per 24 h period to two, with decreasing intervals of each flash from about 2–3 min to less than 1 min. There was equal intensity of sweating, warmth and subsequent chills, but they were now much more tolerable.

Case 5

EE was a 72-year-old man who had been diagnosed with prostate cancer in June 1991 for which he was treated with radiation therapy. He was started on leuprolide and flutamide 6 months before the present consultation. Though he described his mood as 'okay', he complained of extreme fatigue, frustration with his condition, irritability, and distressing hot flashes several times per day. He was awakened several times per night with them. He described the night time as the most distressing for him, a time when he worried most about his disease. The patient was diagnosed as having an adjustment disorder related to the new status of his cancer and treatment. He was started on sertraline 25 mg per day and titrated to 125 mg per day. The patient's wife noted considerable improvement in the patient's irritability and ability to cope with stressors. He reported no decrease in the frequency or intensity of his hot flashes, though he and his family felt he did not complain about them as much. He wanted to taper the sertraline, for concern about being on a psychotropic medication, and noted a significant increase in his hot flashes and subsequent distress. He restarted sertraline at 50 mg per day, and found improvement in both.

Five additional patients with mood or anxiety disturbances as well as distressing hot flashes were started on sertraline; however, they were either noncompliant with the medication or developed side effects to the medication which precluded continuation of the therapy.

COMMENT

Antidepressants are particularly useful for relief of depressive, panic, and obsessive-compulsive symptoms. The new antidepressants, the serotonin reuptake inhibitors have become popular in the last few years, particularly in the medically ill, because of their minimal distressing or complicating side effects. Antidepressants are also used for purposes other than psychiatric disorders, such as the use of tricyclic antidepressants for neuropathic pain syndromes and as an adjunct to pain therapies. The mechanism for this anesthetic action is not fully understood, though it is hypothesized that drugs which potentiate the serotonergic system are central to the anesthetic properties (Breitbart, 1989). There have also been reports of the SSRI's alleviating some symptoms of pre-menstrual syndrome (PMS) (Eriksson *et al.*, 1995). Unfortunately, there is a stigma attached to taking psychotropic medication. This is particularly felt by older men, who also shun psychotherapy.

The cases described above illustrate improvement of hot flashes during treatment with sertraline, a serotonergic modulator, for depressive and anxiety symptoms in men with prostate cancer. Though the exact mechanism for the effect of sertraline in relieving hot flashes is unclear, a stabilizing effect upon the autonomic nervous system is surmised. It is uncertain why some men experience relief while others do not. An interesting study in women (Hunter and Liao, 1995) noted that those seeking treatment for their hot flashes were more anxious and had lower self-esteem compared with those not seeking treatment, indicating there may be a psychological component in those experiencing more significant hot flashes or in their ability to cope with the flashes. It is not clear whether sertraline was indirectly

effective by improving the patient's mood or whether a direct effect of sertraline on the autonomic nervous system and vascular stability may be the explanation for relief. A larger study with randomization is warranted.

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