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Clinical experience with venlafaxine in the treatment of hot flushes in women with a history of breast cancer

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ABSTRACT

Objective: To obtain practical experience with venlafaxine for hot flushes in breast cancer patients and incorporate this in a treatment protocol.

Method: Twenty-two women with a history of breast cancer (mean age 49.2 years, range 35-65) were referred for consideration of treatment with venlafaxine for hot flushes. Patients received extensive information on treatment with venlafaxine and were advised to self-monitor the frequency of their hot flushes.

Results: Eight women did not start venlafaxine because they had no postmenopausal complaints, were lost to follow-up, had too low a frequency of hot flushes, or refused treatment. Eventually 14 women started venlafaxine. Two of them did not tolerate venlafaxine, four reported some effect but stopped because of side effects, two women had no effect whatsoever. Six women observed a clear (>50%) reduction in their hot flush frequency that was maintained at a median follow-up of 13 months.

Conclusion: The group of patients referred for treatment was more heterogeneous and more patients dropped out because of side effects than expected. Extensive patient education, patient selection and evaluation of the treatment effect (by self-monitoring of hot flush frequency) are mandatory to avoid useless (continuation of) treatment and to prepare patients for side effects. Under these conditions, a substantial minority of patients benefit from venlafaxine.

KEYWORDS

Antidepressants, breast cancer, hormonal therapy, hot flushes, venlafaxine

INTRODUCTION

Hot flushes can be very bothersome postmenopausal symptoms. In this phase of life, about 75% of women experience hot flushes.[1-3] Most prominent are attacks of intense feelings of warmth, ascending from the chest to the head and neck region. A hot flush lasts several minutes and is accompanied by (often heavy and visible) transpiration and reddening of the skin of the head and neck. Hot flushes can also be accompanied by palpitations, dizziness, anxiety and irritability.[1]

Some women have a couple of hot flushes a week, others experience dozens a day. Also the intensity of hot flushes can vary considerably. Hot flushes can easily lead to avoidance of social contacts. Nightly hot flushes are especially troublesome, resulting in awakening due to profuse transpiration and having to change nightclothes and bed sheets. The consequent interference with sleep easily leads to daytime fatigue and diminished functioning.

In women with breast cancer, menopause can occur as a physiological phenomenon, but also as a side effect of the (systemic) oncology treatment. Chemotherapy can induce premature ovarian dysfunction, and in addition, hormonal treatment with drugs such as tamoxifen and LH-RH-agonists ('chemical castration') in hormone-sensitive breast cancer can lead to frequent and annoying hot flushes.[4] Bilateral oophorectomy, if performed, equally results in an irreversible postmenopausal state.

Temporary treatment with oestrogens is the most effective treatment for hot flushes. In women without a history of breast cancer, oestrogens provide a 50 to 100% reduction in hot flush frequency.[1,5] However, in patients with a history of breast cancer, oestrogens are relatively contraindicated. This is certainly the case for patients with hormone-sensitive tumours, because oestrogens can stimulate the growth of

'microscopic' tumour cells that might still be present after surgery, radiotherapy and/or chemotherapy.[6,7] In addition, specifically in hormone-sensitive tumours, hormonal manipulations aim to knock out the production of oestrogens or to block the stimulatory effects of oestrogens on the tumour cell.

Until recently, only moderately effective alternatives for treatment of hot flushes were available for this patient group. With clonidine (Catapresan®, Dixarit®), for instance, a drug that affects the central noradrenergic neurotransmission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a modest effect, taking into account the possible side effects as sedation, sleep disturbance, gastrointestinal symptoms and hypotension.[4,8]

Over the past years, however, favourable results have been reported with several modern antidepressants in women with a history of breast cancer, at first with venlafaxine (Efexor®), later on with fluoxetine (Prozac®) and paroxetine (Seroxat®).[9-11] In a randomised, placebo-controlled trial in 221 women with either a history of breast cancer or reluctance to take hormones because of fear of breast cancer, venlafaxine 75 mg daily resulted in a 61% reduction in the hot flush scores (number of hot flushes/24 hours x intensity), a response that was twice as high as in the placebo group.[9] A daily dose of 37.5 mg was somewhat less effective, a dose of 150 mg was as effective as 75 mg but induced more side effects.[9] Recently, paroxetine was also reported to be effective against hot flushes in healthy women.[12] The effects on hot flushes of these serotonergic drugs are thought to be mediated by an influence on a complex interaction of serotonin, noradrenaline, gonadotropic hormones and sex hormones in the thermoregulatory centres of the brain.[12,13]

After the publication by Loprinzi *et al.* in 2000, the oncology staff of our hospital decided to refer breast cancer patients with troublesome hot flushes to the psychiatry service in order to concentrate the experience with venlafaxine for this indication. At that time, we were unsure of the generalisability of the findings. In addition, the psychiatrists were familiar with venlafaxine and its side effects. The aim was to incorporate this clinical experience, finally, in a protocol or checklist.

PATIENTS AND METHODS

From January 2001 until July 2003, 22 women (mean age 49.2 years, range 35-65, SD 7.8) with a history of breast cancer were referred to the psychiatry department for possible treatment with venlafaxine for hot flushes. No strict referral criteria were established: obviously, patients had to be burdened significantly by hot flushes. Pretreatment with clonidine was advised. A semistructured history was taken and patient information was given according to *table 1*. For five days prior to starting venlafaxine, the patients monitored the frequency of troublesome hot flushes on a registration sheet (for each night, morning, afternoon, and evening). The decision to start venlafaxine

Table 1

Items to be addressed in breast cancer patients when prescribing venlafaxine for hot flushes

INFORMATION
No registration for this indication; few data on long-term efficacy
Most frequently occurring side effects: agitation, anxiety, gastric symptoms, constipation, dry mouth
May influence driving ability (warning on package)
Side effects manifest first, positive effects on hot flushes later
Venlafaxine only influences hot flushes, not other menopausal complaints as vaginal dryness or osteoporosis, nor does it have a direct positive effect on joint pains, fatigue, concentration difficulties
Effect to be expected is a reduction of 50% or more in hot flush frequency, according to literature data, intensity of flushes can also decrease
Explanation of rationale for self-monitoring of hot flush frequency: avoiding unnecessary treatment, enabling evaluation of the effect of therapy and of the ratio of benefits over side effects
INDICATION FOR PSYCHIATRIC REFERRAL, (RELATIVE) CONTRAINDICATIONS FOR VENLAFAXINE
Previous experience (side effects!) with serotonergic antidepressants (fluvoxamine-Fevarin®, fluoxetine-Prozac®, paroxetine-Seroxat®, sertraline-Zoloft®, citalopram-Cipram®)
Depressed now? Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks? In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?
History of manic episode(s)? Have you ever had a period of time when you were feeling, 'up' or 'high' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? Do not count times when you were intoxicated by drugs or alcohol. Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared with other people, even in situations that you felt were justified?
Anxiety disorder? Easily worried and tense? Sudden attacks of anxiety? Avoidance of places and situations in which you could become anxious or panicky? Compulsive behaviour as excessive checking or washing hands?

was made by the patient and the psychiatrist together; a threshold frequency of hot flushes for starting venlafaxine was not required. Follow-up visits were arranged after two to three weeks, four to six weeks and four to six months. Before each follow-up visit, the women monitored the frequency of troublesome hot flushes for a period of two to three days. Some of these follow-up appointments took place by telephone, e-mail or fax. The starting daily dose of venlafaxine was 75 mg, after two or three weeks, the dose could be increased to 150 mg in case of insufficient effect. We did not use predetermined criteria for response: the decision to stop or to continue venlafaxine after four to six weeks (or earlier in case of side effects) was taken after the patient and psychiatrist had discussed the costs and benefits.

RESULTS

At the first visit to the psychiatrist (AVG), one woman had complaints which could not be regarded as hot flushes and not even as postmenopausal. She was not prescribed venlafaxine. Of the remaining 21 patients, the hot flushes were attributed to the physiological menopause in two women, and in 19 to previous or ongoing treatment for breast cancer. Fourteen women had previously been treated with clonidine for hot flushes. For one woman, no reliable self-monitoring could be obtained; she was lost to follow-up. At self-monitoring, the frequencies of hot flushes turned out to be rather variable. In six cases it was decided not to start with venlafaxine. In three of these six women, to their own surprise, the hot flush frequency at self-monitoring was considerably lower than previously perceived by them. After receiving information, three women declined treatment, mainly because of a reluctance to use more drugs than they were already taking and a reluctance to take a 'psychiatric' drug. One patient had a depressive syndrome, of mild intensity (score on the Zung self-rating scale for depression: 49). Problems at work and sleep disturbance because of nightly hot flushes (with resulting daytime fatigue and irritability) were thought to be causal factors in this depression.

Eventually, 14 women (mean age 48.5 years, range 42-59, SD 6.0) started venlafaxine. In one of these women the hot flushes were attributed to the physiological menopause, in the other 13 to previous or ongoing treatment for breast cancer (hormonal therapy in eight, chemotherapy in one, combination of hormonal and chemotherapy in four). The reported duration of annoying hot flushes was more than two years in eight women, between six months and two years in four, and less than six months in two. On self-monitoring, ten women recorded between 10 and 25 hot flushes per 24 hours, while four women recorded more than 25. Ten women had been treated with clonidine. One patient insisted on continuing clonidine, and venlafaxine was added. Two women did not tolerate the starting dose of 75 mg venlafaxine because of severe agitation, anxiety and profound malaise occurring in the hours after taking the first dose. In four women, venlafaxine was effective to some extent (30 to 50% decrease in hot flush frequency), but they stopped taking venlafaxine because of troublesome side effects as constipation, weight gain and sleep disturbance. In two women, venlafaxine had no effect at all in doses of 75 and 150 mg respectively.

Six women took venlafaxine for three months or longer (four women in a daily dose of 75 mg, and two in a dose of 150 mg) and experienced a more than 50% reduction in hot flush frequency without significant side effects. In two of them, the hot flushes disappeared completely. Two women reported a definite psychic alteration: in the above-mentioned depressive patient, the depression went into remission; the other woman reported feeling less irritable and more able to cope emotionally with her difficulties. In these six women, the effect was maintained in the long term: dose increase was not necessary during a median follow-up of 13 months (range: 5-36 months).

DISCUSSION

The group of breast cancer patients referred for treatment of hot flushes was more heterogeneous than expected in terms of the frequency (and in one patient even the presence) of hot flushes and in terms of subjective burden. After self-monitoring, some women turned out to have far less flushes than had thought beforehand. Others decided against treatment after receiving information. Presumably, aside from their reluctance to take more or 'psychiatric' drugs, knowing that a form of treatment would be available if the symptoms became more intense satisfied these patients. Patient selection by giving extensive patient information, a standardised history (*table 1*) and self-monitoring of the hot flush frequency appears to prevent unnecessary treatment in majority of patients.

Of the treated patients, quite a lot dropped out because of side effects. Two patients even became severely agitated after the first dose. Patient education, in this way, is obviously also useful to prepare patients for annoying or even frightening side effects. Furthermore, evaluation of the treatment effect by means of self-monitoring is mandatory to avoid useless continuation of treatment. We noticed in several patients that clonidine had been prescribed for longer periods without much evidence of a positive effect. Evaluation of the treatment turned out to also be useful in enabling the patients to weigh the beneficial effects on the hot flushes against the side effects and the necessity to take another medication. In a context of extensive patient education, standardised history taking and self-monitoring,

more than one third of patients appear to derive a long-term benefit from venlafaxine.

The number of referrals was unexpectedly low. According to the oncology staff, women were mainly reluctant to take more drugs. In addition, a referral to a psychiatrist, for a possible treatment with a psychotropic drug, could have been an obstacle.

We realise that the procedure as presented here is relatively laborious. However, specialised oncology or psychiatry nurses could assist in patient education and self-monitoring. Moreover, as most oncologists will not be confronted frequently enough with this problem to build up experience, a standardised history as shown in *table 1* could be useful. In addition, it is important to obtain a short psychiatric history. For instance, in patients who went through a manic episode earlier in their life antidepressants might provoke a recurrent mania. Patients who had previously been treated with a serotonergic antidepressant should be asked about side effects: logically, they could experience the same side effects again. It is important to assess the presence of an ongoing mood or anxiety disorder. Questions on depression and a history of manic episodes can be asked directly or, as shown in *table 1*, with modules of the M.I.N.I.[14] Screening on depression and anxiety can also be done with self-report questionnaires as the Hospital Depression and Anxiety Scale.[15] If a mood or anxiety disorder is suspected, consulting with a psychiatrist or the general practitioner is self-evident.

Finally, we believe that our clinical experience in breast cancer patients is also relevant for the treatment of hot flushes in general (as part of the physiological menopause in otherwise healthy women), especially since long-term hormone replacement therapy in women with menopausal symptoms is under debate.[16]

According to the literature, venlafaxine is an effective therapy for hot flushes in breast cancer patients. Our experience indicates that matters are more complex and that the best results with this drug are obtained with extensive patient information, patient selection and repeated evaluation of the effects by self-monitoring of hot flush frequency.

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