Trazodone: a non-hormonal alternative for neurovegetative climacteric symptoms

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Summary: Hormone replacement therapy (HRT) is the treatment of choice for neurovegetative climacteric symptoms. In some women, however, HRT may either be contraindicated, or the patients themselves may prefer a non-hormonal form of treatment. Trazodone is a drug that acts as a weak, but specific, inhibitor of the uptake of ^{3}H-serotonin and is generally used for its antidepressant effects. In this study we have observed the efficacy of oral Trazodone (75 mg/day) in the treatment of the climacteric symptoms in 25 menopausal patients recruited at the Menopause Clinic of Ferrara University Hospital. The symptoms were scored from 0 to 3 according to presence and intensity. The patients were all complaining of climacteric neurovegetative symptoms (average symptom score 2.43).

Symptoms scores were recorded before starting treatment and then again after 3 months. The drug appeared to be particularly effective on the intensity of anxiety (OR: 0.08, CI: 0-0.080), insomnia (OR: 0.15, CI: 0.02-0.71), and irritability (OR: 0.29, CI: 0.04-1.48). The intensity of hot flushes appeared reduced but was not statistically significant (OR: 0.52, CI: 0.08-1.87). However, the average total score of symptoms appearing in the Kupperman scale was reduced (−14%) after treatment. Trazodone should be kept in mind as a possible alternative to HRT. This drug can be particularly useful for those patients whose climacteric symptoms have a marked connotation of anxiety rather than for hot flushes or when HRT are contraindicated.

Key words: Climacteric syndrome; Trazodone; Non-hormonal treatment.

INTRODUCTION

Hormone replacement therapy (HRT) is the treatment of choice for climacteric symptoms such as hot flushes, depression, anxiety, palpitations and so on. HRT may, however, be contraindicated in some women, or the patients may wish to have some form of alternative treatment. Moreover, there are several climacteric patients who complain chiefly of symptoms that are not strictly estrogen-dependent, such as depression, anxiety, insomnia and irritability.

Trazodone is in a new class of triazolopyridine antidepressant drugs. It acts as a weak, but specific inhibitor of the synaptosomal uptake of ^{3}H- serotonin (^{3}H-5 hydroxytriptammine) ([1]). It offers the therapeutic benefits of tricyclic antidepressant agents ([2]) but produces fewer of the untoward side effects associated with these drugs, such as anticholinergic effects, cardiovascular disturbances, impairment of cognitive skills, lethargy, diz-

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ziness and confusion ([3]). Oral trazodone at a dosage of 75 mg daily was shown to be superior to a placebo in the treatment of depression with associated anxiety and, at a mean dosage of 151 mg daily, tended to be more effective than amitriptyline as indicated by Goldberg and Finnerty in their study ([4]).

In this study we evaluated the efficacy of trazodone on the 11 Kupperman neurovegetative symptoms of 25 climacteric women.

MATERIALS AND METHODS

Twenty-five menopausal patients, complaining of climacteric neurovegetative symptoms (average symptom score: 2.43), were recruited at the Menopause Clinic of Ferrara University Hospital. Their median age was 50 (range 43-61). Four patients were premenopausal and therefore still regularly menstruating, 9 patients were perimenopausal, 8 patients had more than 11 months of amenorrhea (spontaneous menopause), 3 patients had a surgical menopause (hysterectomy with bilateral oophorectomy) and one patient had become menopausal after chemotherapy for breast cancer. The patients were chosen either because they themselves refused HRT or because there were absolute contraindications to hormonal replacement therapy.

The patients scored the 11 Kupperman climacteric symptoms scale, vaginal dryness and dyspareunia from 0 to 3, according to the presence and intensity of their complaints. The scoring was performed twice; once at the first visit, then again after 3 months of therapy or earlier if the patient decided autonomously to stop treatment before 3 months. The patients were then all instructed to take one tablet of 75 mg of trazodone daily in two divided doses. The final daily dose was, however, built up gradually over a week, in the attempt to avoid side effects.

The Wilcoxon paired test was used to evaluate differences between mean scores before and after therapy. Odds Ratios (OR) and their confidence intervals (CI) were calculated by logistic regression analysis for comparison of observed proportions of symptoms in the treated versus non treated group.

RESULTS

The whole 3 months of treatment was completed by 14 women. One patient discontinued the medication after two months and 10 patients discontinued after less than 30 days. The causes for the drop out are summarised in Table 1. However, none of the causes of drop out were severe enough to require treatment.

Table 1. – *Causes of drop out.*

	No.	%
Drowsiness	3	27.3
Unbearable hot flushes	2	18.2
Erythema	1	9.1
Headache	1	91.1
Poor compliance	4	36.3
Total	11	100

Table 2 reports the intensity of climacteric symptoms before and after treatment with trazodone. The intensity of anxiety, insomnia and irritability appeared significantly reduced ($p=0.003$, $p=0.005$ and $p=0.01$ respectively), while the intensity of depression, palpitations and hot flushes was reduced (−17%) but this reduction was not statistically significant. The total average score of the symptoms appearing in the Kupperman scale had, however, decreased (−14%) after treatment.

Table 3 shows the observed proportions of presence/absence of climacteric symptoms after 3 months versus before treatment with trazodone. The drug appeared to be particularly effective on anxiety (OR: 0.08, CI: 0-0.080), insomnia (OR: 0.15, CI: 0.02-0.71), and irritability (OR: 0.29, CI: 0.04-1.48). The incidence of hot flushes appeared reduced after therapy, but again this was not statistically significant (OR: 0.52, CI: 0.08-1.87).

DISCUSSION

The climacteric is characterised by a variety of distressing symptoms some of which, such as hot flushes, vaginal dryness and dyspareunia are clearly estrogen dependent while others, such as depression, anxiety and insomnia, may have a more phychological connotation. Hot flushes,

Table 2. – *Intensity of climacteric symptoms (as mean score ± ES) before and after treatment with trazodone.*

Symptoms	Trazodone		Δ%	p
	Before	After		
Anxiety	3.48±0.15	2.56±0.24	−26	0.003
Depression	3.04±0.21	2.50±0.24	−18	0.02
Hot flushes	2.40±0.25	2.00±0.24	−17	0.23
Insomnia	2.16±0.20	2.04±0.23	−5	0.005
Irritability	3.16±0.18	2.52±0.23	−20	0.01
Memory loss	2.32±0.25	2.20±0.24	−5.2	0.31
Palpitations	2.09±0.24	2.60±0.25	−8	0.17
Paresthesia	2.56±0.23	2.24±0.24	−1	0.24
Reduced libido	2.20±0.24	2.08±0.23	−5	0.18
Sweats	2.36±0.23	1.96±0.22	−17	0.14
Tireness	3.08±0.24	2.64±0.26	−14	0.02
Dispareunia	*1.32±0.17*	*1.32±0.17*	*0*	*1.00*
Vaginal Dryness	*1.40±1.73*	*1.40±1.73*	*0*	*1.00*
Total	2.43	2.08	−14	

p: probability level by Wilcoxon paired test. In *italic* are the two symptoms that are not part of the 11 Kupperman's symptoms scale.

however, have been shown to act as an amplifying factor on the intensity of those symptoms not traditionally considered strictly hormone dependent ([5]).

Hormone replacement therapy is thus to be considered the treatment of choice for climacteric symptoms and is widely used for this purpose. However, debate on the safety of HRT is also increasing, and while its benefits have been shown to far outweigh the risks, some women and their doctors remain concerned about the

Table 3. – *Odds Ratio (OR) of climacteric symptoms after vs before treatment with trazadone.*

Symptoms	OR	CI	chi-square	p
Anxiety	0.08	0-0.080	6.84	0.008
Depression	0.40	0.08-1.86	1.75	0.18
Hot flushes	0.52	0.14-0.85	1.30	0.25
Insomnia	0.15	0.02-0.71	7.71	0.005
Irritability	0.29	0.04-1.48	2.91	0.08
Memory loss	0.85	0.24-3.01	0.08	0.77
Palpitations	0.64	0.14-2.87	0.44	0.50
Paresthesia	0.60	0.16-2.19	0.76	0.38
Reduced libido	0.85	0.24-2.98	0.08	0.77
Sweats	0.43	0.12-1.58	2.05	1.15
Tireness	0.44	0.10-1.87	1.59	0.20
Dispareunia	*1.00*	*0.16-6.14*	*0.00*	*1.00*
Vaginal dryness	*1.00*	*0.20-5.10*	*0.00*	*1.00*

In *italic* are the two symptoms that are not part of the 11 Kupperman symptoms scale.
C: 95% confidence interval; p: probability level.

side effects of hormone replacement and want to avoid such a treatment whenever possible. Moreover, an alternative form of treatment would be welcome for those women who have only neurovegetative complaints or for whom estrogen is contraindicated.

Various drugs, namely clonidine, β-blockers, gamolenic acid, veralipride have been used in the past in the attempt to relieve climacteric symptoms without using hormonal therapy. In the vast majority of cases, however, despite supporting data, beneficial results are rarely seen with these agents in clinical practice ([6-8]).

It has been stated that most menopausal symptoms are also symptoms of stress. For example, flushing is a common symtom of anxiety, and feeling anxious will often exacerbate hot flushes at menopause ([9]). We have therefore performed a pilot study on the effect of a small dose of a commonly used antidepressant drug (trazodone) on climacteric symptoms.

Controlled trials indicate that, while oral trazodone at 150 to 800 mg daily is an effective antidepressant comparable with tricyclic antidepressants agents ([2]), the same drug given at lower doses appears to be useful in patients with predominantly anxious symptoms ([10]). This found confirmation in our data where we had used oral trazodone in a small dose (75 mg/day). This dose was shown to be generally effective on climacteric complaints and symptoms scores appeared decreased by 14% after treatment. Trazodone was particularly effective on three out of the eleven Kupperman climacteric symptoms namely anxiety, insomnia and irritability. However, while the intensity of hot flushes and depression appeared reduced, this result was not statistically significant. Moreover, none of the estrogen dependent symptoms such as vaginal dryness and dyspareunia were relieved. This data was obviously expected, as trazodone is not an estrogen related drug.

Although larger studies are required, trazodone should be kept in mind as a possible alternative to HRT. This drug can be particularly useful for those patients whose climacteric symptoms have a marked connotation of anxiety rather than hot flushes, or when HRT are contraindicated.

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