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Depressive syndrome in perimenopausal, menopausal and postmenopausal patients. An Italian multicentre observational study

Summary

Objectives

All women are at risk for developing somatic and psychiatric symptoms during their menopausal transitions, up to the occurrence of major depressive disorder. This study was aimed to evaluate and characterize the presence of a depressive status in a sample of perimenopausal, menopausal and postmenopausal women.

Materials and Methods

156 women with a diagnosis of depressive disorder under the DSM-IV-TR criteria, who spontaneously referred for a psychiatric evaluation during their perimenopausal, menopausal and postmenopausal stages, were enrolled in the study.

Results

Patients (51.9 ± 4.2 years) were diagnosed with unipolar disorder, dysthymia, bipolar disorder and cyclothymia in 67.9, 14.4, 14.1 and 4.5 % of the cases, respectively. Axis I and II co-morbidities were present in 14.1 and 7.7 % of the patients, respectively. No significant differences in the prevalence of disorders and co-morbidities during the different climacteric stages were observed. The HAM-D, HAM-A, and BDI-II rating scale scores were 17.4 ± 7.4, 19.8 ± 9.6, and 26.8 ± 13.2, respectively, with severe or very severe symptoms in 39.7, 28.8 and 35.9% of the patients, respectively. The GCS scale showed depression in 44.2% and anxiety in 38.5% of the patients, with general, somatic, and vasomotor scores of 27.5 ± 11.3, 8.0 ± 4.8, and 2.6 ± 2.2, respectively.

Conclusions

These results describe the psychopathological scenario of women who underwent a psychiatric evaluation during their different menopausal transitions. Although these results did not show any significant differences among those stages, they suggest a major psychiatric impairment, with several patients affected by severe disorders.

Keywords

Depression • Anxiety • Woman • Menopause • Transition

Introduction

Menopause is a normal, and for most women largely uneventful, part of life. For some women, however, the transition to menopause may represent a time of biological vulnerability, together with relevant somatic and psychiatric symptoms, up to the occurrence of a significant depressive disorder [1 2]. Specifically, the highest vulnerability for depressive disorders seems to be related to the periclimacteric period, with an increasing risk from early to late perimenopausal stage, and a subsequent decrease in the postmenopausal stage [2]. The results of recent cohort longitudinal

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studies demonstrate an approximatively 4-fold higher risk for depressive symptoms during this transition to menopause compared with premenopause, and a 2.5-fold higher risk for a major depressive episode [3 4]. Women with a history of previous depressive episodes are up to 5 times more likely to have a major depressive episode in perimenopause [2]. It's well known how the transition between women's menarche and menopause is characterized by monthly fluctuations of gonadal steroids (including estrogen and progesterone), in which neuromodulatory effects at the central nervous system are observed [5 6]. During the perimenopausal stage, these normally cyclic hormonal fluctuations become increasingly erratic followed by progressively longer periods of estrogen withdrawal [7 8]. It has been postulated that changes in these hormonally mediated neuromodulatory effects may heighten the risk for mood disorders in women with sensitivity to normal hormonal fluctuations (during the premenstrual period, puerperium, and perimenopause) [2 9]. The transition to menopause is often associated with somatic symptoms (pain, myalgia, fatigue, vasomotor symptoms, urogenital complaints and sexual disorders), psychological symptoms (irritability, anxiety, low libido) and sleep disturbances, all specific risk factors for developing depressive symptoms and a poorer patient's quality of life [10-12]. Notwithstanding their prevalence, all depressive disorders related to climacterium are often underdiagnosed and therefore not correctly managed, with subsequent psychiatric disorder worsening and chronicity. Several studies showed that general practitioners are unable to diagnose up to 30-50% of major depressive disorders, especially when associated with physical symptoms [13]. The acknowledgment and characterization of specific risk factors related to the occurrence of depressive disorders during climacterium could provide useful elements for both specialist and generic disease updating in order to establish an early treatment. The present observational study was aimed to evaluate the presence of a depressive status in a sample of perimenopausal, menopausal and postmenopausal women (age 45 to 65 years), describe their baseline demographics as well their clinical and psychopathological data and assess any possible differences, together with risk factors and predictors.

Materials and Methods

This observational study was carried out at ten outpatient- and inpatient-based Italian Psychiatric Centres, was approved by the Ethics Committee of each centre and conducted according to the Helsinki declaration. The study enrolled women who spontaneously referred for a psychiatric evaluation at the above-said centres between September 2012 and September 2014 according to the following inclusion criteria: age 45 to 65 years, a diagnosis of major depressive disorder under the DSM-IV TR criteria (Hamilton Depression scale score ≥ 8), a perimenopausal status (defined as almost 6 irregular menstrual cycles and less than one year of amenorrhoea) or a menopausal status (defined as 12 months of amenorrhoea following the last menstrual cycle) or a postmenopausal status (defined as the immediate subsequent period after menopause) not superior to 5 years, and a written informed consent for the observational study participation. Female patients of < 45 and > 65 years with menstrual abnormalities or not physiologically-induced amenorrhoea were excluded. Socio-demographical data, historical data of previous individual and familiar psychiatric disorders, data of current psychiatric and organic disorders and related drug therapies were collected in a single enrolling interview. The psychopathological scenario was evaluated by a psychiatrist after the administration of two clinical rating scales (Hamilton Rating Scale for Depression and Hamilton Anxiety Scale) and two self-administered scale for depressive symptoms (Beck Depression Inventory II) and menopause-related psychic and physical symptoms (Greene Climacteric Scale). During this observational period, 182 women with a diagnosis of depressive disorders referred to the above-said trial centres and were enrolled into this study. Among these patients, 26 were excluded during the first screening for missing data or inclusion criteria violations.

Statistical analysis

The variables were described using mean, standard deviation, median, standard error of the mean, 95% confidence interval and crosstabulation. Chi-square test for categorical data and ANOVA analysis of variance for continuous variables were applied. The differences were analyzed and assessed for significance testing through parametric tests – after checking the normality (Student t for independent data and ANOVA with Bonferroni correction) – and non-parametric tests (Mann Whitney and Kruskal-Wallis). The superiority of the depressive syndrome between phases was verified by dichotomous transformation (presence in the case of Ham-D > 14 and the absence in the event of Ham-D < 14) with chi-square test and relative risk factor estimates (OR). Predictors were tested by logistic regression. Statistical significance was considered for $p < 0.05$. All analyzes were performed with SPSS software (16.0, 2007).

Results

Table I shows the characteristics of the 156 women included in the study. In perimenopausal and postmeno-

TABLE I. *Baseline demographics and psychopathological features in the study population.*

	Total sample N = 156	Perimeno-pause N = 62	Menopause N = 22	Postmeno-pause N = 72	p
Mean age, years ± SD	51.9 ± 4.2	49.1 ± 3.1	50.7 ± 3.0	54.6 ± 3.5	< 0.0001
Age at stage onset, years ± SD	49.9 ± 3.6	48.3 ± 3.3	49.3 ± 2.3	51.4 ± 3.5	< 0.0001
Marital status (%)					NS
unmarried	17.3	19.4	13.6	16.7	
married	64.7	61.3	72.7	65.3	
legally separated/widow	17.9	19.4	13.6	18.1	
Smoking (%)					NS
no	61.5	66.1	72.7	54.1	
yes	34.0	32.3	22.7	38.9	
ex	4.5	1.6	4.5	6.9	
Alcohol abuse (%)	6.3	8.0	4.5	5.5	NS
Organic diseases (%)					NS
0	59.0	56.5	45.4	65.3	
1	24.4	29.0	36.4	16.7	
2	13.5	12.9	9.1	15.3	
≥ 3	3.2	1.6	9.0	2.8	
Unipolar disorder (%)	67.9	72.6	68.2	63.9	NS
Dysthymia (%)	14.4	9.7	13.6	18.1	NS
Bipolar disorder (%)	14.1	14.5	4.5	16.7	NS
Cyclothymia (%)	4.5	4.8	9.1	2.8	NS
Axis I co-morbidities (%)	14.1	11.3	18.2	15.3	NS
Axis II co-morbidities (%)	7.7	8.1	9.1	6.9	NS
Mean length of psychiatric disorder, years ± SD	9.6 ± 4.2	10.5 ± 10.1	3.5 ± 3.1	10.5 ± 9.5	0.042
Mean number of psychiatric episodes ± SD	1.7 ± 2.8	2.2 ± 3.2	1.4 ± 2.0	1.5 ± 2.7	NS
Depression during pregnancy (%)	7.7	8.1	9.1	6.9	NS
Post-partum depression (%)	21.2	22.6	18.2	20.8	NS
Premenstrual syndrome (%)	39.1	53.2	31.8	29.2	0.013
Psychiatric familiar history (%)	43.6	54.8	36.4	36.1	NS
Patients at their first psychiatric visit (%)	27.6	29.0	40.9	22.2	NS
Estrogen Replacement Therapy (%)	5.1	1.6	9.1	6.9	NS
Total number of received drugs (%)					NS
0	12.8	12.9	27.3	8.3	
1	32.1	27.4	36.4	34.7	
2	31.4	30.6	22.7	34.7	
3	14.7	19.4	4.5	13.9	
≥ 4	8.9	9.6	9.0	8.9	
Total number of psychotropic drugs (%)					0.052
0	16.7	16.1	36.4	11.1	
1	35.3	30.6	36.4	38.9	
2	30.1	30.6	13.6	34.7	
≥ 3	17.9	22.6	13.6	15.3	

(continued)

TABLE I (follows). *Baseline demographics and psychopathological features in the study population.*

	Total sample N = 156	Perimeno-pause N = 62	Menopause N = 22	Postmeno-pause N = 72	p
Number of benzodiazepines (%)					0.038
0	66.0	61.3	86.4	63.9	
1	26.9	29.0	9.1	30.6	
2	6.4	9.7	0.0	5.6	
≥3	0.6	0.0	4.5	0.0	
Number of antidepressant drugs (%)					NS
0	28.2	24.2	45.4	26.4	
1	66.0	66.1	54.4	69.4	
2	5.8	9.7	0.0	4.3	
Number of stabilizer drugs (%)					NS
0	85.3	85.5	81.8	86.1	
1	13.5	11.3	18.2	13.9	
2	1.3	3.2	0.0	0.0	
Number of antipsychotic drugs (%)					NS
0	79.5	83.9	81.8	75.0	
1	20.5	16.1	18.2	25.0	

SD: standard deviation; NS: non statistically significant.

pausal stages, the age at onset of women with smoking habit or ex-smokers was lower than the age at onset in women with no current or past smoking habit (47.7 *vs* 48.6 and 50.6 ***vs*** 52.1, respectively). This difference was not observed in the menopausal stage (49.2 ***vs*** 49.3). In this population, the age at onset of women in perimenopausal and postmenopausal stages is affected by alcohol abuse, being anticipated of about 12-15 months compared with no alcohol consumers. This was not observed in the menopausal stage (however, we must consider the limited sample size: in fact, only one case of menopausal woman with alcohol abuse was reported in the study). The most frequent organic diseases were: hypertension (15 cases) followed by endocrinological disorders (3 hyperthyroidism, 8 hypothyroidism), metabolic disorders (6 diabetes, 4 hypercholesterolemia) e gynaecological diseases (10). Multiple psychiatric diagnoses were possible. Psychotropic drugs: 26 women were not treated with a pharmacological therapy, 65% of the women were treated with one or two drugs, 18% with three or more drugs. Although this difference did not reached a significant level ($p = 0.052$), a trend toward an under-treatment of menopausal women compared with peri- and post-menopausal women has been observed. On average, a perimenopausal woman receives 1.9 drugs, of which 1.66 psychotropic drugs and 0.23 drugs for organic diseases; a menopausal woman receives 1.45 drugs, of which 1.14 psychotropic drugs and 0.32 drugs for organic diseases; ultimately, a postmenopausal woman receives 1.86 drugs, of which 1.58 psychotropic drugs and 0.28 drugs for organic diseases.

Table II shows the scores of psychiatric rating scales. The Greene scale scores demonstrate a significant correlation with the Hamilton-Depression scale ($r = 0.508$, $p < 0.001$), the Hamilton Anxiety scale ($r = 0.675$, $p < 0.001$) and the Beck Depression Inventory ($r = 0.609$, $p < 0.001$). The Greene subscale for vasomotor disorders does not show any correlation with the Greene subscale for depression ($r = 0.138$, $p = 0.067$), nor with the Hamilton-Depression scale ($r = 0.49$, $p = 0.547$) and the Beck Depression Inventory ($r = 0.57$, $p = 0.482$). Conversely, the Greene subscales for somatic disorders and for anxiety and depression show a positive correlation with the Hamilton Depression scale, the Hamilton Anxiety scale and the Beck Depression Inventory. The Hamilton Depression scale demonstrates a positive correlation with the Hamilton Anxiety scale ($r = 0.629$, $p = < 0.001$) and the Beck Depression Inventory ($r = 0.464$, $p < 0.001$). Postmenopausal *vs* menopausal stage was associated with a higher risk for severe depression (OR = 1.89 [IC 95%, 1.0-3.7]).

Discussion and Conclusions

We evaluated the psychopathological profiles of a women's sample with a diagnosis of depression, comparatively monitored during their three climacteric stages in order to identify any features and possible differences.

TABLE II. *Depression differentiation in the three climacteric stages.*

	Total sample N = 156	Perimenopause N = 62	Menopause N = 22	Postmenopause N = 72	p
HAM-D					NS
mean score ± SD	17.4 ± 7.4	17.5 ± 7.6	15.9 ± 6.5	17.8 ± 7.4	
mild (%)	35.9	38.7	45.5	30.6	
moderate (%)	24.4	17.7	18.2	31.9	
severe (%)	17.3	21.0	13.6	15.3	
very severe (%)	22.4	-22.6	22.7	22.2	
BDI					NS
mean score ± SD	26.8 ± 13.2	27.2 ± 13.2	27.6 ± 15.0	26.2 ± 12.8	
mild (%)	7.7	8.1	13.6	5.6	
moderate (%)	21.2	21.0	4.5	26.4	
severe (%)	35.3	30.6	45.5	36.1	
very severe (%)	35.9	40.3	36.4	31.9	
HAM-A					NS
mean score ± SD	19.8 ± 9.6	19.6 ± 9.3	18.9 ± 9.9	20.7 ± 9.8	
normal (%)	27.5	29.0	31.8	25.0	
mild (%)	16.0	14.5	13.6	18.1	
moderate (%)	27.6	27.4	31.8	26.4	
severe (%)	28.8	29.0	22.7	30.6	
GCS					NS
Depression, YES	44.2	50.0	27.3	44.4	
Anxiety, YES	38.5	41.9	31.8	37.5	
General score ± SD	27.5 ± 11.3	28.2 ± 10.9	27.5 ± 11.8	26.8 ± 11.5	
Somatic score ± SD	8.0 ± 4.8	8.2 ± 4.6	7.4 ± 4.6	7.9 ± 5.0	
Vasomotor score ± SD	2.6 ± 2.2	2.9 ± 2.0	3.1 ± 2.4	2.6 ± 2.2	

HAM-D: Hamilton rating scale for depression; HAM-A: Hamilton rating scale for anxiety; BDI: Beck depression inventory; GCS: Greene climacteric scale; SD: standard deviation; NS: non statistically significant.

Although data showed no difference of depressive syndrome during these three stages in the analytic sample, some findings must be clinically evaluated and furthermore investigated in order to assess the general validation of these reported data.

The analytic sample was made up by women referring for an outpatient psychiatric evaluation during the experimental period. 72.4% of this sample had been already visited at those Centres before the occurrence of their current depressive disorders.

The tested population showed a mean age at onset of 49.3 years for menopause, lower than the Italian mean age of 50.9 years [14]. The lowest mean age at onset for menopause was reported alcohol abuse and/or smoking habit, consistent with the findings of other studies, even if this gap is higher for the smoking category in the general female population (Parazzini et al. [15] reported a 0,2% anticipation; 3% in our sample).

In our study, the tested group of women experienced a relevant prevalence of premenstrual syndrome (almost 40% of the patients), post-partum depression (21.2%) and depression during pregnancy (7.7%), with significantly higher percentages than those reported in literature for the general female population: 13-26% premenstrual syndrome [16], 10-15% post-partum depression [17], and 2.2% depression during pregnancy [18].

Although not related to their depressive profile, interesting differences in these women's three stages were observed:

1. Three out of four **perimenopausal women** had been already visited at these Research Centres and their history shows 2-fold psychiatric episodes than the other two stages. More than half of perimenopausal women have a psychiatric familiar history and experience a premenstrual syndrome, 22.6% post-partum depression and 8% depression during pregnancy. In particular, these patients mostly complaint somatic disorders during their climacteric transitions.
2. Conversely, **menopausal women** are characterized by a significantly shorter disease than the other two stages, and a higher prevalence of first visits and vasomotor disorders. The latter symptoms are not significantly related with their depressive status (p = 0.547), but represent the rationale for their first

psychiatric visit ($p < 0.001$), apart from their menstrual cycle status. It may be postulated that this central stage of climacterium is associated with a psycho-physical suffering of the patients; therefore, these women are seeking for medical attention but they hardly find it in their primary care setting. Consequently, they ask for a previously not required specialist evaluation. Other differential features of menopausal women compared with the other two stages are represented by lower pharmacological treatment and higher self-reported complaints than those described by psychiatrists. In order to explain this discrepancy it may be suggested that, even if this distress can be objectively more severe in other climacteric stages, as reported by health professionals, it involves women with a history of previous psychiatric diseases who are more accustomed to this psychological distress and less prone to focus on a biunique equivalence between psychological distress and climacterium.

3. Postmenopausal women are the largest group in this study, with a long history of disease and visits at these centres (78% refers to these Centres for their follow-up visits). They exhibit the most severe depressive and anxious symptomatology and the highest risk for depression. They experience climacterium-related somatic disorders but a smaller number of organic diseases compared with other patients.
Individual history (disease length and number of previous psychiatric episodes) seems to explain some of depressive variations observed in postmenopausal women and not in perimenopausal women. Conversely, perimenopausal women's depression episodes seem to be related and partially explained by their own age and their age at onset in the perimenopausal stage through an inverse relationship (the lower patient's age, the higher chance of a depressive response), while age is not randomly related to a depressive syndrome in postmenopausal women.

Conclusions

Our results describe the psychopathological scenario of women who underwent a psychiatric evaluation during their different menopausal transitions, indicating a major psychiatric impairment, with several patients affected by severe disorders. Physicians who most commonly visit women going through the menopause, eg general practitioners and gynecologists medicine, should pay attention to and actively search for possible psychic symptoms.

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Conflictis of interest

A. Bellomo has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Janssen Cilag, Angelini e Lundbeck.
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