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ORIGINAL RESEARCH

Prevalence and diagnostic distribution of medically unexplained painful somatic symptoms across 571 major depressed outpatients

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Objective: To assess the prevalence and distribution of medically unexplained painful somatic symptoms (PSSs) versus nonpainful somatic symptoms (NPSSs) in patients diagnosed with major depressive episode (MDE).

Method: A total of 571 outpatients diagnosed with MDE according to DSM-IV-TR criteria were consecutively enrolled into a cross-sectional, multicentric, observational study over a period of 7 months. Subjects were evaluated by means of the ad hoc validated 30-item Somatic Symptoms Checklist (SSCL-30) and Zung's questionnaires for depression and anxiety. The 32-item Hypomania Checklist (HCL-32) was also administered in order to explore any eventual association of PSSs or NPSSs with sub-threshold (DSM-IV-TR [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*] not recognized) bipolar disorder (BD).

Results: In our sample, just 183 patients (32%) did not report painful somatic symptoms (NPSSs). Of these, 90 patients (15.76%) had no somatic symptoms at all. The remaining 388 (68%) had at least one PSS being subdivided as follows: 248 (43%) had one or two PSSs, while 140 (25%) experienced two or more. Patients with at least one PSS also reported a greater number of nonpainful somatic symptoms than NPSS. Bipolar patients (associated with higher HCL-32 scores) were less represented across PSS cases than NPSS subjects. Conversely, females were more prone to having a higher number of total somatic symptoms (and bipolar features).

Conclusion: PSSs are common in patients with MDE, especially among those patients reporting fewer somatic symptoms in general as opposed to those patients who exhibit more somatic symptoms (both PSSs and NPSSs) with lower relative number of PSSs. A major therapeutic implication is that antidepressant monotherapy could be used with more confidence in unexplained PSS patients than in NPSS patients because of the latter group's lower frequency of (sub)-threshold bipolar features.

Keywords: major depressive episode, MDE, bipolar disorder, BD

Introduction

Major depressive episode (MDE) represents a multidimensional condition possibly exhibiting with a wide range of clinical pictures. Frequently, clinical presentations may include the presence of painful (PSSs) as well as nonpainful somatic symptoms (NPSSs).[1] Nonetheless, somatic symptoms in the course of MDE often go underestimated[2] despite their impact on the course of illness and treatment choices. In fact, when inappropriately recognized and treated, (medically unexplained) somatic symptoms – considered as symptoms otherwise not referable to nonpsychiatric disturbances – are associated with poor prognosis, higher risk for residual

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symptomatology, as well as increased risk for relapse and recurrence.[3–6] Hence, the need for their appreciation and proper recognition is unquestionable. Furthermore, MDE could frequently represent the main or even the only manifestation of bipolar disorder (BD) lasting for many years prior to the onset of frank (hypo)-mania. Thus, the importance of early appropriate recognition and management of depressive features, eventually pointing out a bipolar diathesis, should be considered mandatory in order to reduce the chance of iatrogenic effects as the antidepressant-induced resistance to treatment or cyclicity of the disorder.[7]

The aim of the present study is to assess the distribution of PSSs and NPSSs on MDE (including both single and recurrent episodes) and to explore their possible association with bipolarity assessed according to *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition, Text Revision* [DSM-IV-TR] criteria (full-threshold BD) and with the 32-item Hypomania Checklist (HCL-32) rating scale[8] (for sub-threshold bipolarity).

Methods

The present study is based on a post-hoc partial analysis of the database collected for a previous study, including 571 consecutive patients with a diagnosis of MDE, according to DSM-IV-TR, that were enrolled in a large cross-sectional, multicentre, observational study (COME TO ME).[9] The study involved 30 psychiatric outpatient facilities, distributed throughout Italy, investigating the prevalence of medically unexplained somatic symptoms in the course of MDE, which resulted in severe depressive symptomatology, high rates of misdiagnosis, and improper treatment and health resource utilization.

According to the observational nature of the protocol, routine medical procedures were not modified. The Ethics Committee of each center approved the study protocol in compliance with the Italian Ministerial Bulletin issued on September 2, 2002 regarding observational studies. All patients gave their informed consent concerning handling and use of the data collected during the course of the study. Finally, the study was sponsored by Boehringer Ingelheim, Italy.

Study population

Subjects referred to the selected centers between December 2006 and July 2007 were screened for inclusion in the study. Patients were recruited consecutively, according to the following inclusion criteria: 1) both genders, aged 18–75 years; 2) diagnosis of major depressive episode according to DSM-IV-TR (major depressive disorder, recurrent major depression, depressive episode in course of type I and II bipolar disorder, depression not otherwise specified (NOS); and 3) ability to complete the self- and hetero-administered questionnaires. The exclusion criteria were: 1) comorbidity with schizophrenia and other psychotic disturbances, and 2) current relevant physical illnesses.

The study included 571 depressed outpatients; 8 (1.4%) of them had incomplete information on demographic and clinical variables. The study population therefore consisted of 563 eligible subjects, with a mean number of patients of 18.7 (range 5–56) for each center; 376 subjects (66.8%) were females and 187 (33.2%) males; 251 subjects (44.5%) were aged 18–50 years, and 313 (55.5%) aged over 50, with mean age of 51 (standard deviation = 13). The level of education was higher than 11 years for 245 (43.5%) patients, and most of them (n = 331, 58.8%) were married.

Diagnostic procedure and symptom assessment

Individuals were assessed by psychiatrists with extensive clinical experience in the diagnosis and treatment of mood disorders. Diagnosis of MDE (major depressive disorder, recurrent major depression, depressive episode type I and II bipolar disorder; depression NOS) was made according to DSM-IV-TR criteria.

An anonymous datasheet was used to collect the following information: demographic status, lifestyle, surgical, pathological, and pharmacological case history, presence and characterization of somatic symptoms and related delay in major depression diagnosis and treatment, and consumption of health resources within the 6 months preceding enrollment. All of the information was gathered directly by the patient with the help of significant others and medical records.

HCL-32[8] was administered for the evaluation of lifetime manic or hypomanic features, and severity of depressive and anxious symptomatology was self-evaluated by means of the Zung's questionnaires for depression and anxiety.[10,11]

Statistical analysis

Comparative analysis for familial, epidemiological, clinical, and course characteristics of subgroups were conducted using the Student's *t*-test for the dimensional variables (Mann–Whitney *U*-test, when appropriate) and the chi-square analysis for those categories (Fisher exact-test, when appropriate). We used a Bonferroni's significance of $P = 0.001$ level corrected for multiple comparisons. Given the exploratory nature of the study, we set significance at level of 0.5, two

tailed, in order to detect potentially clinically meaningful associations.

Results

Among the 571 MDE outpatients of our sample, only 183 patients (32%) did not report unexplained PSS (NPSSs), including 90 subjects (15.76%) who reported no somatic symptoms at all. The other 388 (68%) patients had at least one PSS. Among this latter group, 248 (43%) had one or two, while 140 (25%) experienced two or more. The patients with at least one PSS who also reported associated NPSSs also showed a higher total number of NPSSs compared with the patients without PSSs, with a mean NPSSs number of 4.3 ± 3.3 versus 2.3 ± 1.7 ($t = 9.2$, $P = 0.0001$).

Headache was the most frequently reported PSS (n = 220, 38.5%), followed by osteo-articular pain (n = 200, 35%), and gastralgia (n = 102, 17.9%); concerning NPSSs, asthenia was the far more represented symptom (n = 368, 64.4%), followed by insomnia (n = 237, 41.5%), tenseness (n = 227, 39.8), palpitations (n = 190, 33.3%), dizziness (n = 114, 20%), decreased libido (n = 108, 19%), tremor (n = 108, 19%), decreased appetite (n = 105, 18.4%), constipation (n = 89, 15.6%), dyspnea (n = 89, 15.6%), and sweating (n = 86, 15.1) (Table 1).

Comparing the three groups (NPSS, one or two PSSs, and three or more PSSs), no differences were found concerning demographic features except for gender distribution. Females were more represented among patients with two or more PSSs, compared with groups with one PSS and NPSS (Table 2).

Concerning diagnostic distribution, bipolar depression was more frequent among patients with NPSS than in patients with PSSs ($P = 0.001$); also, the higher the number of PSSs, the lower the chance of bipolar diagnosis.

In contrast, depression NOS showed an inverse trend. As expected, Zung's depression and anxiety scores greater than 50 were more represented among the group of patients with three or more PSSs than in the other two groups. Remarkably, patients with three or more PSSs were less frequently represented among those having an HCL-32 total score greater than 14 (the cutoff diagnostic value), while a HCL-32 total score lower than 14 was more associated with NPSSs (Table 2).

Table 1 Medically unexplained somatic symptoms in 571 major depressed patients: frequency distribution

Symptom[a]	N	%
PSSs		
3. Headache	220	38.5
13. Osteoarticular pain	200	35.0
17. Gastralgia	102	17.9
9. Dyspepsia	83	14.5
12. Abdominal pain	75	13.1
15. Transient pain	68	11.9
7. Dysphagia	41	7.2
14. Chest pain	41	7.2
21. Itching	36	6.3
11. Dysuria	22	3.9
8. Dysmenorrhea	18	3.2
NPSSs		
2. Asthenia	368	64.4
19. Insomnia	237	41.5
25. Tenseness	227	39.8
20. Palpitations	190	33.3
30. Dizziness	114	20.0
6. Decreased libido	108	18.9
27. Tremor	108	18.9
18. Decreased appetite	105	18.4
4. Constipation	89	15.6
10. Dyspnea	89	15.6
24. Sweating	86	15.1
23. Drowsiness	78	13.7
29. Flushing	77	13.5
1. Aerophagia	61	10.7
28. Tenesmus	53	9.3
5. Diarrhea	37	6.5
16. Flatulence	35	6.1
26. Cough	26	4.6
22. Hiccups	10	1.9

Note: [a]The numbers refer to the items of the SSCL-30 scale.
Abbreviations: NPSS, painless somatic symptoms; PSS, painful somatic symptoms; SSCL-30, 30-item Somatic Symptoms Checklist.

Discussion

In interpreting our results, some methodological limitations must first be taken into account. Although recorded, pharmacological treatments were not considered as potentially influencing the perception of somatic pain. Yet, it must be noted that they might have influenced the pharmacological choices of the therapist. As expected, somatic symptoms were a frequent finding in the course of depression, especially for female patients. Nonetheless, avoidance of a systematic recording of the clinical history of the subjects might have further limited the validity of our results. This seems particularly true concerning the lack of information about the number and severity of previous episodes, if any, and the eventual presence of previous hospitalizations and/or suicidal attempts. Also, the anxiety/depression scores appear driven by endorsing the somatic items in the SSCL-30 scale, thus limiting the reliability of this finding, especially considering the absence of accurate records of anxious comorbidities (ie, somatoform disorder).

The fact that medically unexplained somatic complaints were essentially not associated with bipolarity is also a remarkable result since it was initially expected to be related

Table 2 Comparison between depressed patients with painless and painful somatic symptoms

	NPSSs N = 183	PSSs 1–2 N = 248	PSSs > 2 N = 140	Chi (df)	*P*
	N (%)	N (%)	N (%)		
Age, years					
≤45	66 (36.1)	82 (33.1)	39 (27.9)		
46–58	66 (36.1)	73 (29.4)	53 (37.9)	6.93 (4)	0.139
>58	51 (27.9)	93 (37.5)	48 (34.3)		
Gender					
Female	107 (58.5)	168 (67.7)	108 (77.1)	12.61 (2)	0.001
Male	76 (41.5)	80 (32.3)	32 (22.9)		
Diagnostic distribution					
Major depression	64 (35.0)	77 (31.0)	56 (40.0)		
Major recurrent depression	66 (36.1)	91 (36.7)	58 (41.4)	26.91 (6)	0.00015
Bipolar depression	50 (27.3)	56 (22.6)	13 (9.3)		
Depression NOS	3 (1.6)	24 (9.7)	13 (9.3)		
Zung depression					
<50	85 (46.4)	85 (34.3)	28 (20.0)	24.52 (2)	0.00000
≥50	98 (53.6)	163 (65.7)	112 (80.0)		
Zung anxiety					
<50	138 (75.4)	149 (60.1)	53 (37.9)	46.48 (2)	0.00000
≥50	45 (24.6)	99 (39.9)	87 (62.1)		
Hypomania checklist					
0–14	101 (62.2)	141 (67.1)	95 (77.2)	8.31 (2)	0.015
>14	64 (38.8)	69 (32.9)	28 (22.8)		

Abbreviations: NOS, not otherwise specified; NPSS, painless somatic symptoms; PSS, painful somatic symptoms.

to the "excitement" of mania. Rather, the total number of somatic symptoms (including both PSSs and NPSSs) was higher among those with a bipolar diagnosis. These findings indicate that PSSs could be less represented in "bipolar" (HCL-32 total score ≥ 14) MDEs rather than unipolar MDEs. A major therapeutic implication is that antidepressant monotherapy could be used with more confidence in unexplained PSS patients than in NPSS patients because of the latter group's lower frequency of (sub)-threshold bipolar features. Specifically, the use of SNRIs (serotonin norepinephrine reuptake inhibitors) or the choice of tricyclic antidepressants (TCAs), especially the more pro-norepinephrinergic secondary amines, may be preferred as hypothetically more somatic-symptoms-oriented therapies for those with PSSs (found to have also a higher total number of somatic symptoms in general). Furthermore, TCAs and SNRIs might be less prone to induce (hypo) manic switches in PSS patients compared with (bipolar) NPSSs.

Finally, stating the strong limits of our exploration, further longitudinal, more accurate investigations are needed in order to confirm this merely preliminary report.

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Disclosure

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