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Misdiagnosed Hypomanic Symptoms in Patients with Treatment-Resistant Major Depressive Disorder in Italy: Results from the Improve Study

Moro Maria Francesca[1], Lecca Maria Efisia[1], Ghillani M. Alessandra[2], Alacqua Marianna[2] and Carta Mauro Giovanni[1,*]

[1]*Division of Psychiatry, Department of Public Health, University of Cagliari, Italy;*

[2]*Medical Department, AstraZeneca Italy SpA*

Abstract: *Background:* Undiagnosed and therefore inadequately treated hypomanic symptoms may be a leading cause of drug resistance in depression diagnosed as unipolar (major depressive disorder, MDD). The purpose of the IMPROVE study was to identify the rate of misdiagnoses in patients with treatment-resistant MDD by screening for the presence of previous hypomanic episodes, and to study the characteristics of those patients with a positive history of hypomania. *Methods:* Patients attending 29 psychiatric units throughout Italy with a diagnosis of MDD who were resistant to antidepressant treatment were included in this multicentre, observational single visit study. The Hypomania Checklist 32 (HCL-32) was administered to detect underlying bipolarity. *Results:* Among the 466 enrolled patients, 256 (57.40%) were positive at screening for a previous hypomanic episode (HCL-32 $\geq$12), therefore suggesting a misdiagnosis. These patients scored higher than those with a negative history in both the "active/elated hypomania" (11.27±3.11 vs 3.57±3.05; P<0.0001) and "irritable/risk-taking hypomania" (2.87±2.03 vs 2.06±1.73; P<0.001) HCL-32 sub-scales. Patients with a positive history of hypomania were younger, had a higher number of previous depressive episodes and a higher frequency of comorbid conditions compared to those with a negative history. *Conclusions:* This study suggests that screening for hypomania in MDD-resistant patients facilitates identification of a notable proportion of undiagnosed cases of bipolar spectrum disorder. Patients with a positive history of hypomania at screening had a demographic/clinical bipolar-like profile that included young age, higher number of previous depressive episodes and higher frequency of comorbid conditions. They also had both higher active and irritable hypomania symptom scores.

Keywords: Active hypomania, bipolar symptoms, HCL-32, irritable hypomania, resistant MDD, screening.

INTRODUCTION

Major depressive disorder (MDD) is a common chronic condition with a lifetime prevalence of around 13-17% in Europe and the USA [1-5]. MDD is the source of a substantial economic burden for both sufferers and society: in 1990 the treatment-related costs (direct costs) in the USA were estimated to be approximately US$ 19.9 billion, whereas the indirect costs were US$ 57.5 billion [4] for a total of US$ 77.4 billion, which rose to US$ 83.1 billion in 2000 (inflation-adjusted US dollars) [6]. In parallel, from 1990 to 2010, MDD increased from the 15th to 11th rank (37% increase) among the leading causes of disability worldwide [7].

Although several treatments have been found to be effective in the management of depressive episodes and patients may benefit from several classes of first-line antidepressant drugs, resistance to treatment is a major concern [3]. According to the STAR*D study, only 32.9% of patients achieved remission with first choice of antidepressant therapy, which was represented by selective serotonin reuptake inhibitors (SSRI) [8].

*Address correspondence to this author at the Center of Liaison Psychiatry and Psychosomatics, University Hospital, Via Ospedale 117, 09123 Cagliari, Italy; Tel: +39 335 499994; E-mail:mgcarta@tiscali.it

Treatment-resistant depression is defined as no response to at least two antidepressants from different pharmacological classes given at adequate doses for a sufficient duration [9-11].

One possible major determinant of resistance to antidepressants in diagnosed MDD is the misdiagnosis of bipolar disorder among patients with chronic depressive episodes [12].

Many patients with bipolar disorder remain undetected or are initially misdiagnosed as having unipolar depression [13, 14]. An important reason for this misdiagnosis is that depressed patients do not talk to their care provider spontaneously about their previous hypomanic symptoms [15]. A misdiagnosis of unipolar depression for bipolar depression can lead to inappropriate treatment, such as antidepressant monotherapy [16] which, in the absence of mood stabilisers, may be ineffective against depressive symptoms and lead to induction of chronicity, manic switching, mixed symptoms and rapid cycling [16, 17]. Furthermore, it has been suggested that treatment-resistant MDD increases medical costs and could be due to a missed underlying bipolar disorder [3, 12].

In a recent study, Dudek *et al.* compared patients with treatment-resistant MDD with those who had treatment-responsive MDD using the Hypomania/Mania Symptom

Checklist (HCL-32) as a tool to assess the presence of hypomanic symptoms [12]. They found that the proportion of patients with bipolarity features, detected by HCL-32, was significantly higher among patients with treatment-resistant MDD than among patients who responded to treatment [12].

The purpose of the IMPROVE study was to identify potential misdiagnoses among patients with treatment-resistant MDD in Italy by screening for the presence of previous hypomanic episodes. Factors associated with a hypomanic status were also investigated.

METHODS

Design

This was a multicentre, observational, single-visit study. (clinical trial.gov NCT01344733)

Objectives

The primary objective was to detect underlying bipolarity in patients with treatment-resistant MDD. Secondary objectives were to identify determinants of misdiagnosis, including demographics, medical history, clinical/symptomatic profile and medications.

Study Tools

The HCL-32, an instrument developed by Angst *et al.* and translated in several languages, is a simple, self-administered, 32-item questionnaire. The scale can provide important insights into unrecognised hypomanic symptoms [18, 19]. In an Italian validation study, a positive answer to at least 12 items was found to be the best cut-off for detecting a hypomanic condition [18].

Study Sample

All treatment-resistant MDD patients aged between 18 and 65 years consecutively evaluated in 29 Italian centres were included in the study. The planned enrolment period was from May 2011 to March 2012.

The diagnosis of treatment-resistant MDD was made according to DSM-IV TR (296.3 x); with treatment resistance defined as non-response to at least two antidepressants given at adequate doses for a sufficient period, with the last antidepressant treatment on-going. In accordance with the primary study objective, the estimation of sample size was based on the expected HCL-32 score in treatment-resistant patients in previous studies [10, 16]. Assuming 5% first type error and a power of 90% and conducting a two-tailed t-test, a total of 660 patients was sufficient for detecting as statistically significant an absolute difference in the HCL-32 score of 2.1 between the group of patients treatment resistant due to other causes and the group of patients treatment resistant due to bipolarity (expected 11.9±8.3).

From the first 202 patients enrolled in our study, it was noted that the proportion of HCL-32-positive subjects enrolled was greater than expected, namely 58.29%. The number of patients enrolled by the 29th February 2012 was sufficient for to detect a statistically significant absolute difference in the HCL-32 score of 2.1 with an α=0.05 and a power of almost 90%. For this reason, on the 14th March 2012 enrolment was prematurely closed with a total cohort of 446 patients enrolled.

Treatments

Neither the efficacy nor the tolerability of pharmacological treatments was assessed. However, information on antidepressant treatments and concomitant medications was collected for descriptive purposes. All subjects enrolled completed the HCL-32.

Statistical Analysis

Patients were divided into two groups according to the total HCL-32 score: a group with hypomanic symptoms (score $\geq$12) and a group without hypomanic symptoms (score <12). All the recorded data and derived variables were summarized by means of descriptive statistics.

The primary efficacy analysis was performed on patients without missing data in the 32 items of the scale used. The total score (complete case population) on the HCL-32 was computed as the sum of positive answers to the 32 items of the questionnaire.

The difference between the means in the two groups was estimated with a 95% confidence interval. A two-tailed t-test was also applied, to prove the hypothesis of a statistically significant difference between the two groups, with a 5% significance level. Two sub-scores addressing specific variants of hypomanic behaviour were also computed: "active/elated hypomania" and "irritable/risk-taking hypomania" sub-score.

A description of the demograpfics and anamnestic sample characteristics was provided. An explorative multivariate analysis was performed in order to investigate the effect of explicative factors (i.e. age, gender, family status, professional status, time elapsed from the onset of the current episode, number of previous episodes in the last year, relevant disease/pathology that could interfere with this pathology/treatment and treatment switch) on hypomanic condition status, identified by HCL-32 questionnaire. A logistic regression model including all the aforementioned variables was applied.

All the statistical analyses were performed using SAS System software, version 9.2.

Ethics

Informed consent to participation in the study was obtained from each subject. Patients unable to understand the meaning of the HCL-32 items were excluded.

Data were not nominal at source, and each subject was identified by a numerical code. The study was approved by the ethics committee of the University Hospital of Cagliari, Italy and by the local ethics committees of each collaborating centre. The research was conducted in compliance with the Helsinki Declaration.

RESULTS

Demographics and Baseline Characteristics

The study included 446 patients: 256 were positive at the screening (HCL-32 $\geq$12) and formed the hypomanic group,

while 185 were negative (HCL-32 ≤11) and constituted the non-hypomanic group. Only five patients (1.12%) had missing data making it impossible to allocate them to a group, thus the final study sample consisted of 441 (98.88%) subjects. As had already emerged during an interim analysis, the proportion of HCL-32-positive subjects was confirmed to be greater than expected (43.9% of the subjects examined).

The mean age (± standard deviation) was in the hypomanic group was statistically significantly lower than in the non-hypomanic group (47.66±10.41 years vs. 49.84±10.67 years, respectively; P = 0.0196) (Table **1**). Females were more prevalent in the overall population (female n=305, 68.39%, male n= 141, 31.61%), although no intergroup difference in gender was noted.

The most represented work-status categories were 'Employed' (32.06%), 'Homemaker' (30.94%), 'Unemployed' (17.49%) and 'Retired' (10.54%). The distribution was not homogeneous between hypomanic and non-hypomanic groups, with the proportion of employed or self-employed patients being higher in the hypomanic group and the proportion of homemakers being higher in the non- hypomanic group (P = 0.0216) (Table **1**).

Table 1. Demographics of the patients divided according to their HCL-32 score.

Characteristics	Hypomanic Group N=256	Non-Hypomanic Group N=185
Age, mean (SD), years	47.66 (10.41)	49.84 (10.67)
Gender, N (%)		
Male	80 (31.25)	59 (31.89)
Female	176 (68.75)	126 (68.11)
Family status, N (%)		
Never married	62 (24.22)	39 (21.08)
Married	151 (58.98)	110 (59.46)
Separated	23 (8.98)	14 (7.57)
Divorced	10 (3.91)	13 (7.03)
Widowed	10 (3.91)	9 (4.86)
Occupational status, N (%)		
Employed or self-employed	93 (36.33)	50 (27.03)
Unemployed	45 (17.58)	32 (17.30)
Homemaker	71 (27.73)	64 (34.59)
Retired	22 (8.59)	25 (13.51)
Student	10 (3.91)	12 (6.49)
Sick leave	8 (3.13)	1 (0.54)
Maternity leave or disability pension	7 (2.73)	1 (0.54)

Clinical History and Medications

In the overall population, patients had a mean of 3.58±13.50 depressive episodes in the year prior to the study evaluation. The mean number of prior depressive episodes was higher in the hypomanic group than in the non-hypomanic group (P = 0.0245). At least one relevant concomitant disorder was recorded for 97 patients (21.75%) in the overall population and this finding was more prevalent in the hypomanic group than in the non-hypomanic group (n=66; 25.78% vs. n=31; 16.76%; P = 0.0240).

The most frequently reported diseases among enrolled patients were hypertension, hypothyroidism and diabetes mellitus. Hypertension was present in 25 patients (5.61%), of whom 17 (6.64%) were in the hypomanic group and 8 (4.32%) in the non-hypomanic group; hypothyroidism was present in 13 patients (2.91%), 8 (3.13%) in the hypomanic group and 5 (2.70%) in the non- hypomanic group; and diabetes mellitus was present in 10 patients (2.24%), of whom 6 (2.34%) were in the hypomanic group and 4 (2.16%) in the non-hypomanic group.

Almost all patients in both groups reported the prior and current use of medications (97.98% and 99.33%, respectively) and almost 80% of patients had a change in therapy in the preceding year, with no significant difference between the two groups.

Primary End-Point

Overall, 420 patients (94.17%) completed the 32-item HCL-32 questionnaire; 242 (57.62%) of these 420 were in the hypomanic group. Among these 420 patients for whom complete information was available, the mean total HCL-32 score was 12.95±6.23; in particular, in the hypomanic group the mean was 17.34±3.87, while in the non-hypomanic group the mean total score was 6.99±3.05; (mean difference 10.35, 95% CI 9.69-11.01). Thus, hypomanic patients had a significantly higher total HCL-32 score than the patients without hypomania (P<0.0001). These data are summarised in (Table **2**).

The analysis of the HCL-32 sub-scores "active/elated hypomania" and "irritable/risk-taking hypomania" showed marked differences between the two groups. The scores for active/elated hypomania were 11.27±3.11 in the hypomanic group and 3.57±3.05 in the non-hypomanic group (P<0.0001). A statistically significant difference was also noted for the irritable/risk-taking hypomania score, which was 2.87±2.03 in the hypomanic group and 2.06±1.73 in the non-hypomanic group (P<0.0001). The items of the HCL-32 found to be more frequent in the hypomanic group than in the non-hypomanic group were inclinations to being more sociable (80.58% vs. 26.40%, respectively; P<0.0001), being more talkative (82.64% vs. 29.78%; P<0.0001), meeting more people (71.90% vs. 19.10%; P<0.0001), being physically more active (69.83% vs. 17.42%; P<0.0001), being more creative (76.86% vs. 24.72%; P<0.0001), making more jokes or puns (64.88% vs. 12.92%; P<0.0001), and doing things more quickly/easily (67.36% vs. 16.29%; P<0.0001).

In the hypomanic group more numerically "high" episodes were recorded than in the non-hypomanic group: 2.61±5.80 vs. 1.97±3.99 episodes in the preceding 12 months

Table 2. Total HCL-32 score and subscales scores: descriptive statistics.

	Total Sample N=420	Hypomanic Group N=242	Non-Hypomanic Group N=178
Total HCL-32 score			
Mean	12.95	17.34	6.99
Standard deviation	6.23	3.87	3.05
Active/Elated Hypomania Score			
Mean	8.01	11.27	3.57
Standard deviation	4.90	3.11	3.05
Irritable/Risk-Taking Hypomania Score			
Mean	2.53	2.87	2.06
Standard deviation	1.95	2.03	1.73
HCL-32 individual items, N (%)			
Item 1: Need less sleep	135 (32.14)	103 (42.56)	32 (17.98)
Item 2: More energetic and active	257 (61.19)	199 (82.23)	58 (32.58)
Item 3: More self-confident	264 (62.86)	202 (83.47)	62 (34.83)
Item 4: Enjoy the work more	225 (53.57)	179 (73.97)	46 (25.84)
Item 5: More sociable	242 (57.62)	195 (80.58)	47 (26.40)
Item 6: Want and/or do travel more	154 (36.67)	135 (55.79)	19 (10.67)
Item 7: Drive faster	58 (13.81)	46 (19.01)	12 (6.74)
Item 8: Spend too much money	90 (21.43)	80 (33.06)	10 (5.62)
Item 9: More risks in daily life	75 (17.86)	62 (25.62)	13 (7.30)
Item 10: Phisically more active	200 (47.62)	169 (69.83)	31 (17.42)
Item 11: Plan more activities or projects	222 (52.86)	177 (73.14)	45 (25.28)
Item 12: More creative	230 (54.76)	186 (76.86)	44 (24.72)
Item 13: Less shy	227 (54.05)	172 (71.07)	55 (30.90)
Item 14: More colorful clothes/make-up	96 (22.86)	90 (37.19)	6 (3.37)
Item 15: Meet more people	208 (49.52)	174 (71.90)	34 (19.10)
Item 16: More interested in sex/sexual desire	168 (40.00)	144 (59.50)	24 (13.48)
Item 17: More flirtatious and/or sexually active	113 (26.90)	107 (44.21)	6 (3.37)
Item 18: Talk more	253 (60.24)	200 (82.64)	53 (29.78)
Item 19: Think faster	226 (53.81)	173 (71.49)	53 (29.78)
Item 20: More jokes or puns	180 (42.86)	157 (64.88)	23 (12.92)
Item 21: More easily distracted	203 (48.33)	125 (51.65)	78 (43.82)
Item 22: Engaged in new things	112 (26.67)	106 (43.80)	6 (3.37)
Item 23: Thoughts jumping from topic to topic	175 (41.67)	108 (44.63)	67 (37.64)
Item 24: Do things more quickly/easy	192 (45.71)	163 (67.36)	29 (16.29)
Item 25: More impatient/irritable	218 (51.90)	123 (50.83)	95 (53.37)
Item 26: Exausting/irritating for others	168 (40.00)	101 (41.74)	67 (37.64)
Item 27: Get into more quarrels	102 (24.29)	68 (28.10)	34 (19.10)

(Table 2) contd….

	Total Sample N=420	**Hypomanic Group N=242**	**Non-Hypomanic Group N=178**
Item 28: More optimistic	257 (61.19)	197 (81.40)	60 (33.71)
Item 29: Drink more coffee	141 (33.57)	102 (42.15)	39 (21.91)
Item 30: Smoke more cigarettes	101 (24.05)	63 (26.03)	38 (21.35)
Item 31: Drink more alcohol	55 (13.10)	42 (17.36)	13 (7.30)
Item 32: Take more drugs	93 (22.14)	48 (19.83)	45 (25.28)

and 17.32±24.56 vs. 9.24±10.50 in the entire life (p=0.09 and p=0.10, respectively).

DISCUSSION

This is the first study conducted in Italy clearly showing that a large proportion (57.40%) of treatment-resistant MDD patients had a positive history of previous hypomanic episodes, as determined by the HCL-32. Compared with patients who did not have hypomania, those patients identified as having hypomanic features on the basis of the HCL-32 screening instrument had higher scores for both the "active/elated hypomania" and "irritable/risk-taking hypomania" subscales. Moreover, patients who were positive for hypomanic features according to the HCL-32 were younger, had more previous depressive episodes and had higher frequency of concomitant diseases.

The proportion of positive hypomanic patients in this study is higher than that reported in the aforementioned Polish study, in which the rate of treatment-resistant MDD patients with positive HCL-32 screening for hypomania was 43.9% [12]. One explanation for this difference could be the higher cut-off used in the Polish study (≥14 positive answers) compared to our investigation (≥12 positive answers). Of note, our cut-off was chosen in accordance with the findings of a validation study conducted in an Italian setting [18]. As a consequence, in our study about 10% more subjects were classified as positive for hypomania, their total score being between 12 and 13. However, the mean total HCL-32 score in our study (12.95) was slightly higher than that of the Polish cohort [12], suggesting some differences related to different settings and inclusion criteria.

Recent studies have raised some doubts about the accuracy of screening instruments in detecting bipolar disorders; in particular, the MDQ was shown have low sensitivity as a screening tool in US clinical settings [20]. Screening instruments with inadequate sensitivity, particularly in patients with bipolar type II disorders, have serious implications for the detection of these diseases [21]. The sensitivity is a key factor that depends on the frequency of false negatives and is, therefore, considered to be a critical element in all research on screening and particularly in case finding due to the possibility of classifying incorrectly as positive personality disorders [22] or disorders related to stress [23]. However, our research was designed using information from a preliminary validation of the HCL-32 performed in a clinical setting in Italy [18]. Based on this previous study, we chose the cut-off of 12 to increase the sensitivity of the instrument, which was excellent (0.85), while maintaining good specificity (0.61) [18]. At the same cut-off was also found that the performance of the HCL-32 specifically for screening for bipolar II disorders was good (sensitivity 0.80; specificity 0.54) [18]. The accuracy of the HCL-32 in identifying bipolar disorders according to DSM-IV criteria was determined using the SCID-IV interview, conducted by clinicians, as the gold standard [24]. Our results were similar to those found in another multicentre study in China (sensitivity 0.86, specificity 0.69) [25]. The high-quality performance of the screening tool and the integrity of our results were also indirectly confirmed by the profile of demographic and clinical factors associated with hypomania. Indeed, the factors associated with being positive for this status that is more frequently related in the literature [12] to bipolar disorder than to MDD were: younger age at symptom onset, higher number of previous depressive episodes worsening course of disease and higher frequency of concomitant conditions.

In our study, more patients than expected were found to have previous hypomanic features. However, in the BRIDGE study conducted in Germany [26] that included patients with a major depressive episode, a similar proportion of bipolar patients (58.7%) was found using the HCL-32. When DSM-IV criteria were used, the percentage of bipolar patients identified fell to only 11.6%. There was a lesser difference (40.6%) when the Bipolarity Specified Algorithm was used; this expands the DSM-IV criteria to patients with bipolar spectrum disorders. It is, therefore, possible that the large number of positive patients found in our study may be partially due to the wide range of sub-threshold bipolarity, as also described in the Chinese study [27]. Based on these data, we can tentatively hypothesize that the spectrum of bipolarity [28], including sub-threshold bipolar symptoms, could have a role in the management of treatment-resistant MDD.

Finally, the two sub-scales "active/elated hypomania" and "risk-taking/irritable hypomania" were able to detect those patients positive at the HCL-32 from among the treatment-resistant MDD patients. This could suggest a unique manic/dysphoric pattern profile in bipolar spectrum disorders, but, given the observational nature of the study, more robust information is needed to support this hypothesis.

A limit of the study is that the clinical assessment of fully diagnosed Bipolar Disorder in the sample by means of a semi-structured interview, would have allowed to separate

actual Bipolar Disorder patients from sub-threshold bipolar ones, adding information on the ratio between misdiagnosis and actual classification limits.

In conclusion, our study confirms the relevance of undiagnosed and therefore inadequately treated bipolarity in in depression with drug resistance diagnosed as being unipolar. Early identification of hypomanic symptoms may have a strategic role in the management of this disease.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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