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Treatment-emergent mania/hypomania in unipolar patients

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Abstract

Objective—The aim of this study was to estimate the incidence of treatment-emergent mania/hypomania (TEMH) and to describe the clinical characteristics of patients with major depression experiencing this event during treatment with a selective serotonin reuptake inhibitor (SSRI) and/or interpersonal psychotherapy (IPT).

Methods—Following an algorithm-based protocol, 344 patients with major depression confirmed with the Structured Clinical Interview for DSM-IV disorders were treated with an SSRI, interpersonal psychotherapy, or their combination for nine months. The emergence of mania/hypomania was carefully monitored throughout the study using the Young Mania Rating Scale and clinical assessment.

Results—Overall, eight patients experienced TEMH. The incidence of this event was 3.0% in patients treated with an SSRI and 0.9% in patients treated with IPT alone. Among patients treated with an SSRI, the difference between sites was higher than expected by chance alone (6.8% at Pisa and 0% at Pittsburgh, $p = 0.002$). Despite the adoption of an identical protocol at the two sites, some demographic and clinical characteristics of participants may account for this unexpected result. Alternatively, the greater number of episodes and earlier age of onset at the Pittsburgh site suggests that the unipolar course of illness was more clearly established prior to study entry.

Conclusions—TEMH is an infrequent event, occurring in 2.3% of patients treated for major depression. Nevertheless, its consequences are clinically relevant and require prompt and appropriate therapeutic interventions. For this reason, recognising those patients at risk for such an event is of paramount clinical significance. The observed difference in the incidence of TEMH between the two sites requires further investigation.

Keywords

bipolar; hypomania; mania; treatment; unipolar

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The data for this report were drawn from the pilot and full-study phases of a study entitled: 'Depression: The Search for Treatment-Relevant Phenotypes.' The investigators were: PI: E. Frank (Pittsburgh), Co-PI: G.B. Cassano (Pisa). Pittsburgh Co-Investigators: B. Pollock, M.K. Shear, P. Pilkonis, A. Fagiolini, P. Rucci, H. Swartz, D. Kupfer, R. Bies. Pisa Co-Investigators: L. Dell'Osso, M. Mauri, S. Banti, A. Benvenuti, L. Maggi, M. Miniati, A. Papasogli, M. Sauttoni.

AB and AP have no reported conflict of interest.

The phenomenon of antidepressant-induced mania/hypomania in patients with unipolar depression has been described since the introduction of the first antidepressant agents. The hypothesis was that antidepressant agents triggered manic/hypomanic symptoms by influencing the central dopamine and serotonin systems (1). The first studies in this field (1, 2) described a relatively low prevalence of treatment-emergent mania/hypomania (TEMH), probably attributable to the heterogeneity of patients and to the relatively infrequent use of antidepressants prior to 1982. Subsequent studies reported TEMH rates of 1–17% (3–8), with the highest rates observed with tricyclic antidepressants and lower rates for bupropion, paroxetine, and moclobemide. Differences in the diagnostic assessment method (clinical diagnosis versus structured interview) may have resulted in a variable proportion of patients with bipolar disorders being misdiagnosed as unipolar across studies (9–12). Indeed, the percentage of correct diagnoses increases when structured interviews are conducted (13).

Recently, Goldberg and Truman (14) have tried to define a timeframe after beginning an antidepressant at a specific dose in which newly emergent mania or hypomania could be attributed to the effects of the antidepressant and not to the natural course of a bipolar disorder misdiagnosed as unipolar. They suggested that if mania or hypomania emerges after more than eight weeks of treatment, it should be considered drug induced only if a significant change in dosage preceded the switch. Of note, a recent study suggests that treatment-emergent hypomania can present in patients with chronic resistant depression even after different treatment trials (15), thus suggesting a longer time period at risk for TEMH.

Some clinical characteristics seem to be related to a higher risk of TEMH among patients with unipolar depression; these include early age at onset of affective illness, a family history for bipolar disorder and suicide, severity of current episode, hypersomnia, less anxiety and physical complaints, motor retardation, mood lability, and a high rate of recurrences (13, 16–22). The probability of (hypo)mania seems to be independent of the mean doses of antidepressants, whereas a switch seems to be more frequent between two and three weeks after a dose increase (8). In the attempt to characterize patients at risk of TEMH, some studies have focused on the subtype of depression (atypical versus typical depression), temperamental traits (23–25), and on specific psychopathological aspects such as mood lability, energy-activity, and daydreaming (26).

The identification of features that predict TEMH is of considerable clinical relevance as both misdiagnoses and subsequent mood destabilization induced by antidepressants may have a direct adverse impact on the course and outcome of an affective disorder. The aim of the present report is to estimate the incidence and describe the clinical characteristics of unipolar patients experiencing TEMH during treatment with a selective serotonin reuptake inhibitor (SSRI) (citalopram or escitalopram), a depression-specific psychotherapy [interpersonal psychotherapy (IPT)], or the combination. All patients were carefully diagnosed by experienced clinicians using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) interview for DSM-IV diagnoses.

Patients and methods

The study sample consisted of patients with unipolar depression recruited from February 2002 to March 2007 at the outpatient clinic of the Departments of Psychiatry of the Universities of Pisa and Pittsburgh in the framework of the study 'Depression: The Search for Treatment-relevant Phenotypes.' Between February 2002 and April 2003, 30 patients at Pisa and 35 patients at Pittsburgh participated in a pilot study phase. Between April 2003 and March 2007, 134 patients at Pisa and 145 patients at Pittsburgh entered the full study. Inclusion criteria were age between 18 and 66, being able and willing to give informed

consent, currently being in an episode of non-psychotic major depression as defined by the SCID, and by a rating of >15 on the 17-item Hamilton Rating Scale for Depression (HRSD-17) (27) and not currently receiving effective treatment. Females of childbearing potential had to practice an acceptable form of birth control. Subjects with suicidal ideation were eligible as long as outpatient treatment was deemed safe.

Exclusion criteria were a history of manic or hypomanic episodes, a history of schizophrenia or schizoaffective disorder, current primary diagnosis of eating disorders, drug and/or alcohol dependence or abuse, current psychosis, antisocial personality disorder, organic affective syndrome, kidney or liver disease, epilepsy, cardiovascular disease, and any uncontrolled illness. Patients with a well-documented history of an inability to tolerate one of the study treatments or currently receiving treatment with an effective antidepressant were also excluded.

Patients were diagnosed clinically by clinicians with 10–25 years of experience with mood disorders. Eligible subjects were then administered a research diagnostic interview, conducted by a trained research clinician different from the one who made the first interview, in order to confirm the diagnosis. The diagnostic assessment was conducted using the SCID-I for DSM-IV diagnoses by clinicians trained and certified to the use of the interviews when high levels (>0.90) of interrater reliability of their diagnoses with the trainer were achieved. All interviewers had longstanding experience in the administration of standardized interviews.

Subjects were randomly assigned to pharmacotherapeutic (citalopram or escitalopram) or psychotherapeutic intervention (IPT) for depression. If the initial treatment was not successful in bringing about stabilization, subjects received augmentation with the other treatment (pharmacotherapy or psychotherapy).

In the acute phase of treatment, subjects were randomly assigned to pharmacotherapy or IPT (28, 29). The acute treatment phase of the study involved three assessment and triage points, at Weeks 6, 12, and 20 (Fig. 1). During the pilot phase of the study, subjects randomized to pharmacotherapy received an initial dose of citalopram (20 mg) that was increased to a dose of 40 mg at Week 3 if they did not evidence a response, defined as a 50% reduction of baseline score on the HRSD. If patients were unable to tolerate an initial dose of 20 mg, the dose could temporarily be reduced to 10 mg and titrated up from that point. During the full study, patients randomly assigned to pharmacotherapy received an initial dose of escitalopram (10 mg) that was increased to a dose of 20 mg at Week 3 if they did not evidence a response. If patients could not tolerate an initial dose of 10 mg, the dose could temporarily be reduced to 5 mg and titrated up from that point. If patients did not evidence a response by Week 6, they were given psychotherapy in addition to pharmacotherapy. IPT was added by Week 12 if they did not meet stabilization criteria (as in the case of initial improvement followed by worsening). IPT could be added even if patients had not reached a dose of 40 mg of citalopram or 20 mg of escitalopram (as in the case of difficulties with side effects).

Pharmacotherapy was added to the treatment of patients assigned to IPT if they did not evidence a response at Week 6, if they worsened after Week 6, or if they had not achieved remission at Week 12. Patients who had not stabilized with combined IPT and pharmacotherapy at Week 20 continued IPT and were switched to a second antidepressant following the guidelines provided by the Texas Medication Algorithm Project (30). Subjects who did not meet stabilization criteria following an eight-week trial of this second antidepressant were offered an alternative treatment.

Measures

The diagnostic interview consisted of the administration of the SCID-I for DSM-IV Axis-I/ Patient version (SCID-I/P) (31) and Axis-II disorders (SCID-II) (32). The assessment was conducted by clinicians who were trained and certified in the use of the study instruments. The severity of the depressive episode was assessed at baseline and throughout the study using the interview-based HRSD and the Quick Inventory for Depressive Symptoms (QIDS) – self-report instrument (QIDS-SR) (33).

Determination of hypomania/mania

Anytime a patient exhibited hypomanic/manic symptoms or called to report such symptoms, the patient was observed and evaluated until the duration of the symptoms reached a four-day period. In the meantime, the treating clinician(s) reduced the dose of SSRI and, if necessary, added a benzodiazepine. If the independent clinical evaluator and the treating clinician(s) both judged that the patient still met DSM-IV criteria for hypomania or mania, and the independent evaluator rated the patient as having a score ≥ 10 on the Young Mania Rating Scale (YMRS) (34), the patient was seen by an independent senior psychiatrist not affiliated with the study who was blind to the patient's treatment condition. Hypomania/mania was confirmed only when the evaluations completed by the independent evaluator and the senior psychiatrist both indicated the presence of an episode of hypomania or mania according to the DSM-IV. Subjects with hypomania or mania were terminated from the study and offered appropriate treatment.

Results

Overall, 344 patients were recruited (249 female and 95 male; mean age 39.5, SD = 12.1). A total of 241 were treated with an SSRI (46 patients in the pilot phase and 195 patients in the full study phase) either at random assignment or following the addition of SSRI to IPT. A total of 103 received only IPT throughout the study. A higher proportion of patients (76.7% versus 62.8%, $\chi^2 = 7.86$, $p = 0.005$) were treated with an SSRI at Pittsburgh. Although the mean age and the severity of depression at baseline were similar between the two sites, patients at Pittsburgh were more frequently male (40.0% versus 14.0%, $\chi^2 = 28.96$, $p < 0.001$), had significantly more depressive episodes (median 3 versus 2 at Pisa, Mann-Whitney $Z = -4.51$, $p < 0.001$), a lower age at onset of depression [23.9 (SD=12.4) versus 31.14 (SD=11.6), $t = -5.54$, $p < 0.001$] and a higher body mass index (BMI) (28.26 versus 24.4, $t = 5.85$, $p < 0.001$) at baseline. The BMI was higher both among male (27.5 versus 25.4, $t = 2.35$, $p = 0.022$) and female subjects (28.7 versus 24.3, $t = 5.13$, $p < 0.001$).

During the study, 11 patients at the Pisa site and 6 at the Pittsburgh site were assessed with the YMRS for a suspected manic/hypomanic episode. Nine failed to meet the protocol criteria for hypomania because their YMRS scores were < 10 . Two had the dosage of escitalopram reduced, five remained at the same dosage, one was on IPT alone and no drug was added, and one had escitalopram added to psychotherapy, but treatment was subsequently discontinued because of intolerable gastrointestinal side effects. Seven patients treated with escitalopram and one patient treated with IPT alone were terminated from the study as a result of presenting a hypomanic (seven patients) or a manic episode (one patient), confirmed by a YMRS score of ≥ 10 (see Table 1). All the patients who experienced a TEMH were recruited during the full study.

The incidence of TEMH was 3.0% in patients treated with antidepressants and 0.9% in patients treated with IPT alone. Of note, all but one of the patients who experienced a TEMH were recruited at the Pisa site. Among patients treated with an SSRI, the incidence of TEMH was higher at the Pisa site than expected by chance alone (6.8% at Pisa and 0% at

Pittsburgh: Fisher exact test, $p = 0.002$), while no difference between sites was found among patients treated with IPT alone (0% at the Pisa site, 2.4% at the Pittsburgh site, Fisher exact test, $p = 0.408$).

A summary of the demographic and clinical characteristics of patients who experienced a TEMH (including the timing of the emergence of hypomania or mania) is presented in Table 1. Three of these patients also presented high scores on the HRSD.

Seven subjects with TEMH were female and one was male; mean age at onset of the first depressive episode was 33.2 (SD = 13.3), while mean age at baseline was 36.6 (SD = 11.6). The mean HRSD score at baseline was 20 (SD = 5.9). These subjects did not differ significantly in these characteristics from the rest of the sample. Five patients had recurrent depression, of whom two presented with atypical features; three patients were in their first depressive episode. Four patients with recurrent depression had been treated for the previous episodes with antidepressants and one with psychotherapy and St. John's wort without experiencing hypomanic, manic or mixed episodes.

Four patients were treated with SSRI alone; one began with IPT and had an SSRI added after seven weeks; two patients began with SSRI and then received IPT as adjunctive therapy.

All patients had required benzodiazepine treatment for sleep disturbance. As previously described, the study protocol allowed for reduction of the dose of SSRI whenever a patient presented with symptoms such as insomnia, agitation, or irritability. For this reason, the maximum dosage of escitalopram reached was different among these seven patients: four reached 20 mg, two remained at 10 mg, and one patient remained at 5 mg.

Two patients experienced TEMH (YMRS score = 10) at 20 mg of escitalopram, one patient at 10 mg, two patients at 5 mg, and one at 2.5 mg.

One patient experienced TEMH after changing treatment from 20 mg of escitalopram (no response) to 150 mg of venlafaxine. Among the patients with TEMH, three displayed these symptoms during the acute phase of treatment and four during the continuation phase, during which the dose of medication was required to remain stable.

Lifetime and cross-sectional comorbidity of patients is provided in Table 2. Three patients met criteria for current or lifetime anxiety disorders. Five patients met criteria for personality disorders. Among patients with at least one Axis II diagnosis, three patients did not show any Axis I comorbidity.

Discussion

During a protocol involving acute and continuation treatment of 344 patients with unipolar depression, we observed eight instances of treatment- emergent mania/hypomania. Our results suggest that the TEMH phenomenon is unrelated to specific demographic or clinical characteristics such as baseline severity of depression, change in dosage or comorbid diagnoses and that TEMH may occur even after many weeks of treatment with an SSRI or under conditions of non-pharmacologic treatment, suggesting that it reflects a course of illness phenomenon rather than a treatment- induced one. In the present study, the incidence of TEMH was related to site; all but one event occurred at Pisa, even though a higher proportion of patients were treated with an SSRI at Pittsburgh. Despite the adoption of an identical protocol at the two sites and the same mean age and severity of depression of the two samples at baseline, some characteristics may account for this unexpected result. Patients at Pittsburgh were more frequently male, had a median of three episodes (versus

two at Pisa), a lower age at onset, and a higher BMI. These characteristics may suggest a different tolerance to SSRI among subgroups of patients. Another possible explanation is differences in clinical management at the two sites. However, this is unlikely because, in keeping with the protocol, whenever a patient at either site experienced symptoms such as sleep problems, anxiety, and/or irritability, the escitalopram dosage was reduced and/or benzodiazepine added. A further possible explanation is that the diagnosis was more frequently inaccurate at Pisa. An *a posteriori* review of records suggests that two of the eight patients who switched might have received a clinical diagnosis of bipolar II disorder; however, they did not meet DSM-IV criteria for this diagnosis at study entry. These data are in line with previous studies which showed that, although research diagnostic criteria are carefully applied at initial assessment, bipolar I and II disorder can be subsequently diagnosed in apparently unipolar patients (26, 35, 36). Alternatively, the greater number of episodes and earlier age at onset at Pittsburgh may mean that the unipolar course of illness was more clearly established prior to study entry. Indeed, during the second half of the protocol, at the Pittsburgh site a recruitment of bipolar II patients was started for a separate study. It is possible that this had the effect of (i) increasing intensity of screening for bipolar II subjects and diverting them to the bipolar II protocol; or (ii) increasing Pittsburgh clinicians' awareness of the 'soft' symptoms of bipolarity, which may have made them more likely to probe for these symptoms when assessing patients and thereby more readily identify occult bipolar II disorder in individuals who previously may have been diagnosed as unipolar.

Of greatest interest is the fact that emergence of hypomania did not follow the time course suggested by Goldberg and Truman (14) or Wada et al. (8) for antidepressant-induced (hypo)mania.

Limitations

The small number of subjects who experienced TEMH does not permit statistical comparisons with the rest of the sample stratified by site. Family history was not included among the assessments. This could have provided additional information for patients at risk of a TEMH. Moreover, the practice of changing the dose both of SSRI and of benzodiazepines whenever a patient manifested symptoms such as insomnia, irritability, or motor agitation may have led to an underestimation of patients who may experience antidepressant-induced mania or hypomania.

Conclusions

TEMH was an infrequent event, occurring in 2.3% of a group of carefully diagnosed unipolar patients. Nevertheless, its consequences are clinically relevant and require prompt and appropriate therapeutic interventions. For this reason, recognizing those patients at risk for such an event is of paramount clinical significance. The observed difference in the incidence of TEMH between the two sites requires further investigation.

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Fig. 1.

Treatment protocol. Tx=treatment; ESCIT=escitalopram; MDE=major depressive episode; IPT=interpersonal psychotherapy.

Table 1

Demographic and clinical features of patients with treatment-emergent mania hypomania

Site	Sex	Age (years)	Age at onset (years)	Treatment at switch	Maximum dose of escitalopram (mg)	Dosage at switch	Baseline HRSD	HRSD at switch	YMRS score	Weeks of treatment at switch	Type of switch	Type of depressive episode	Previous exposure to drug
Pisa	F	46	44	SSRI	20	20	31	21	10	16	Hypomania	Recurrent	Reboxetine, fluoxetine, desipramine, trazodone, clomipramine
Pisa	M	46	43	SSRI + IPT	20	10	18	7	13	47	Hypomania	Recurrent/atypical	Paroxetine
Pisa	F	30	30	SSRI	10	5	15	6	16	14	Hypomania	First episode	–
Pisa	F	28	26	SSRI + IPT	20	20	27	23	11	10	Hypomania	Recurrent/melancholic	Sertraline
Pisa	F	37	37	SSRI	10	5	17	2	10	17	Hypomania	First episode	Levosulpiride
Pisa	F	27	17	IPT + SSRI	20	Venlafaxine 150 mg		20	15	8	Hypomania	Recurrent/atypical	Paroxetine
Pisa	F	56	53	SSRI	5	2.5	17	11	20	3	Mania	First episode/melancholic	Paroxetine
Pittsburgh	F	23	16	IPT	–	–	15	9	20	13	Hypomania	Recurrent	Psychotherapy + St. Johns wort

F = female; M = male; HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; SSRI = selective serotonin reuptake inhibitor; IPT = interpersonal psychotherapy.

Table 2

Axis I and Axis II comorbidity

Site	Axis I comorbidity	Axis II comorbidity
Pisa	–	–
Pisa	–	Obsessive-compulsive PD, passive-aggressive PD
Pisa	–	Obsessive-compulsive PD
Pisa	–	Depressive PD, schizoid PD
Pisa	GAD	–
Pisa	Dysthymia, GAD ^a , OCD ^a , panic disorder ^a	Obsessive-compulsive PD
Pisa	–	–
Pittsburgh	GAD, social phobia	Avoidant

^aCurrent disorder.

GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PD = personality disorder.