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Review article

First manic/hypomanic episode in obsessive-compulsive disorder patients treated with antidepressants: A systematic review

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ABSTRACT

High doses of antidepressants, particularly clomipramine and selective serotonin reuptake inhibitors (SSRIs), are the well-established treatment for obsessive-compulsive disorder (OCD), but manic/hypomanic episodes are potential adverse events associated with this treatment. A systematic literature review was performed on manic/hypomanic episodes in non-bipolar OCD patients. Clinical, sociodemographic and antidepressant characteristics during the manic/hypomanic switch were extracted using descriptive statistics. Data were obtained from 20 case reports and case series. Switching episodes mostly appeared in the first 12 weeks after antidepressant initiation and took place more frequently during SSRI use (mostly fluoxetine) in 64.3% of cases. Clomipramine and SSRI use differed non-significantly between the switching episodes that appeared during the first 12 weeks of antidepressant treatment and the episodes that appeared beyond 12 weeks. Switching episodes emerging before 12 weeks were associated with a lower defined daily dose of antidepressants than episodes emerging after 12 weeks. These findings suggest that there are two independent characteristics involved in manic/hypomanic switch in OCD: a) they appeared most frequently with SSRI use (fluoxetine) regardless of the time of it use, and b) episodes appeared in the first 12 weeks after SSRI or clomipramine initiation had a lower dose of antidepressant than episodes appeared after 12 weeks.

Introduction

Obsessive-compulsive disorder (OCD) is usually a chronic disorder that may lead to significant suffering and functional impairment. The lifelong prevalence is around 2.3% in the general population. Although in a small percentage of patients the course may be episodic, in most of them symptoms are chronic and debilitating, with more than half of these cases being of high severity (Kessler et al., 2005; Ravizza et al., 1997; Ruscio et al., 2010). Both cognitive-behavioural therapy and antidepressants (ADs) such as serotonin reuptake inhibitors (SRIs, e.g. clomipramine) and selective serotonin reuptake inhibitors (SSRIs) are used for the treatment of OCD due to their proven efficacy. High doses of ADs are used to treat OCD (Baldwin et al., 2014; Bloch et al., 2010; Hirschtritt et al., 2017; Montgomery et al., 1993, 2001; Tollefson et al., 1994).

Manic and hypomanic episodes are an adverse event reported in the AD premarketing studies and is reported in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for each AD as having a mean prevalence of <1%. The only individual data is for fluvoxamine, showing a switching rate of 4% for OCD patients and 0.2% for major depressive disorder patients (U. S. Food and Drug Administration - Medication Guide, 2017).

Switching to manic episodes has been described in patients with unipolar depression treated with ADs but differences have been observed according to the different classes of antidepressants (Vallejo et al., 1991). A post-marketing review about the prescription of citalopram in depressive disorder reported fewer than 1% of manic episodes during treatment. Furthermore, these episodes occurred more

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Table 1
Synthesis of clinical characteristics of papers included in the review.

Citation	Design and sample size	Dx and criteria	Demographics	Symptomatic dimension	Personal psychiatric history	Family history
Insel (1983)	*Double-blind trial *1 case included (total sample: 13)	(DSM-III) OCD	*32 years (mean) *Our case: no data *8 males and 5 females	Washing	Secondary depression not excluded. No data of the case.	No data
Turner (1985)	*Letter to the editor *1	OCD	39-year-old male	No data	No data	No data
White (1986)	*Case report *1 (2 manic episodes)	OCD	31-year-old male	Fears, internal routine, count, check, clean and order	14-year history of waxing and waning behavioural disorder	Suicides and alcohol abuse
Bernardo 1989	*Case report *1	(DSM–III–R) OCD	35-year-old female	No data	Postpartum hypothymia	No
Steiner (1991)	*Letter to the editor *1	OCD	42-year-old male	Cleaning and washing	No	No
Christensen (1995)	*Letter to the editor *1	OCD	32-year-old male	No data	Dysthymia	No data
Berk (1996)	*Case series *5 (2/5 patients had 2 manic episodes)	OCD	*19–60 years old *2 females and 3 males	*1/5: "right" thought *1/5: fear of contamination with washing rituals	*1/5: Symptoms of depression *1/5: Postpartum depressions *1/5: Borderline intellectual functioning	1/5 unipolar depression
Rihmer (1996)	*Observational *3 cases included (total sample: 10)	(DSM–III–R) OCD and secondary major depression in 4/10 (1 of the 3 patients who developed hypomania)	*29 years (mean); range: 17–45 *2 females and 1 male (3 hypomanic episodes)	No data	No	No data
Figueroa (1998)	*Case series *1 case included (total sample: 7)	OCD	18-year-old male	Check, wash, fears of contamination, indecisiveness	Mild facial tic	No data
Levy (1998)	*Retrospective *1 case included (total sample: 167)	(DSM–III–R) 122 PD and 44 OCD Our case: OCD	*32.8 (mean) SD: 14.8 *Our case: 38-year-old female	No data	Borderline personality	No
Perugi (2002)	*Exploratory analysis *1 case included (total sample: 68)	(DSM-IV) OCD + major depressive episode	*34.2 years (mean) SD: 12.5 *32 (41.7%) males	No data	*38 patients (55.8%) comorbid BD *30 patients (44.2%) non-BD	No data
Matur (2003)	*Case report *1	(DSM-IV) OCD and Tourette Syndrome	20-year-old female	No data	Tics and stereotypic behaviour	Stereotypic behaviours
Ramasubbu (2004)	*Case series * 1 case included (only 1 of 5 case have an OCD)	OCD and depression	37-year-old female	No data	Chronic depression	No
Wickham (2007)	*Case report, letter *1	(DSM-IV) OCD	60-year-old male	Contamination and cleaning rituals	GAD	OCD and anxiety
Yalug (2007)	*Case report *1	(DSM-IV) OCD	34-year-old female	Obsessions of cleanliness and compulsions of washing	No	GAD and MDD
Rabinowitza (2008)	*Open label, prospective study *1 case included (total sample: 67)	(DSM-IV) OCD (Mean YBOCS: 29,6. Mean MADRS: 28,3)	*34.8 years (mean) SD: 13.3 *34 male and 33 females	No data	Mania/bipolar as an exclusion criteria	No data
Shim 2008	*Case series *1 case included (total sample: 21)	OCD (not excluded other Axis I diagnosis) CGI-S≥4	*27.6 years (mean) SD: 9.7 *17 male and 4 females	No data	No data	No data
Philip (2012)	*Case report *1	OCD and depression	48-year-old female	Contamination	Recurrent depressive episodes	No data
Tikka (2013)	*Case report *1	(ICD-10) OCD, YBOCS: 17 Moderate depressive episode, HAMD-17: 15	21-year-old male	Intrusive thoughts about symmetry and arranging objects	No	BD
Amerio (2014)	*Case report *1	(DSM-IV) OCD and depressed mood	54-year-old female	Contamination-cleaning	No	MDD

Abbreviations: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-III: Diagnostic and Statistical Manual of Mental Disorders Third Edition; DSM–III–R: Diagnostic and Statistical Manual of Mental Disorders Third Edition revised; ICD-10: International Classification of Diseases Tenth Revision; HAMD-17: Hamilton Depression Rating Scale of 17 items; MADRS: Montgomery-Asberg Depression Rating Scale; YBOCS: Yale-Brown obsessive-compulsive scale; CGI-S: Clinical Global Impression scale-Severity score; OCD: Obsessive-Compulsive Disorder; PD: panic disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder; BD: bipolar disorder; SD: standard deviation.

frequently when patients were treated with noradrenergic tetracyclic antidepressants (maprotiline and mianserin) compared with citalopram (Barak et al., 2000).

According to a large pharmacoepidemiological study, SSRIs are the most prescribed ADs in medicated OCD patients (88%), being the ranking as follows: sertraline (45%), fluoxetine (21%) and citalopram (20%). Clomipramine was prescribed in nearly 11% of the cases (Isomura et al., 2016). Given that higher doses of ADs are used to treat OCD compared with other disorders, it seems predictable that manic/hypomanic episodes might occur more frequently than in major depressive disorder (MDD) (Rihmer et al., 1996).

In 1984 Turner first described the emergence of manic/hypomanic episodes in a patient with a history of OCD who was being treated with fluoxetine (Turner et al., 1985). Since then, other clinical cases have

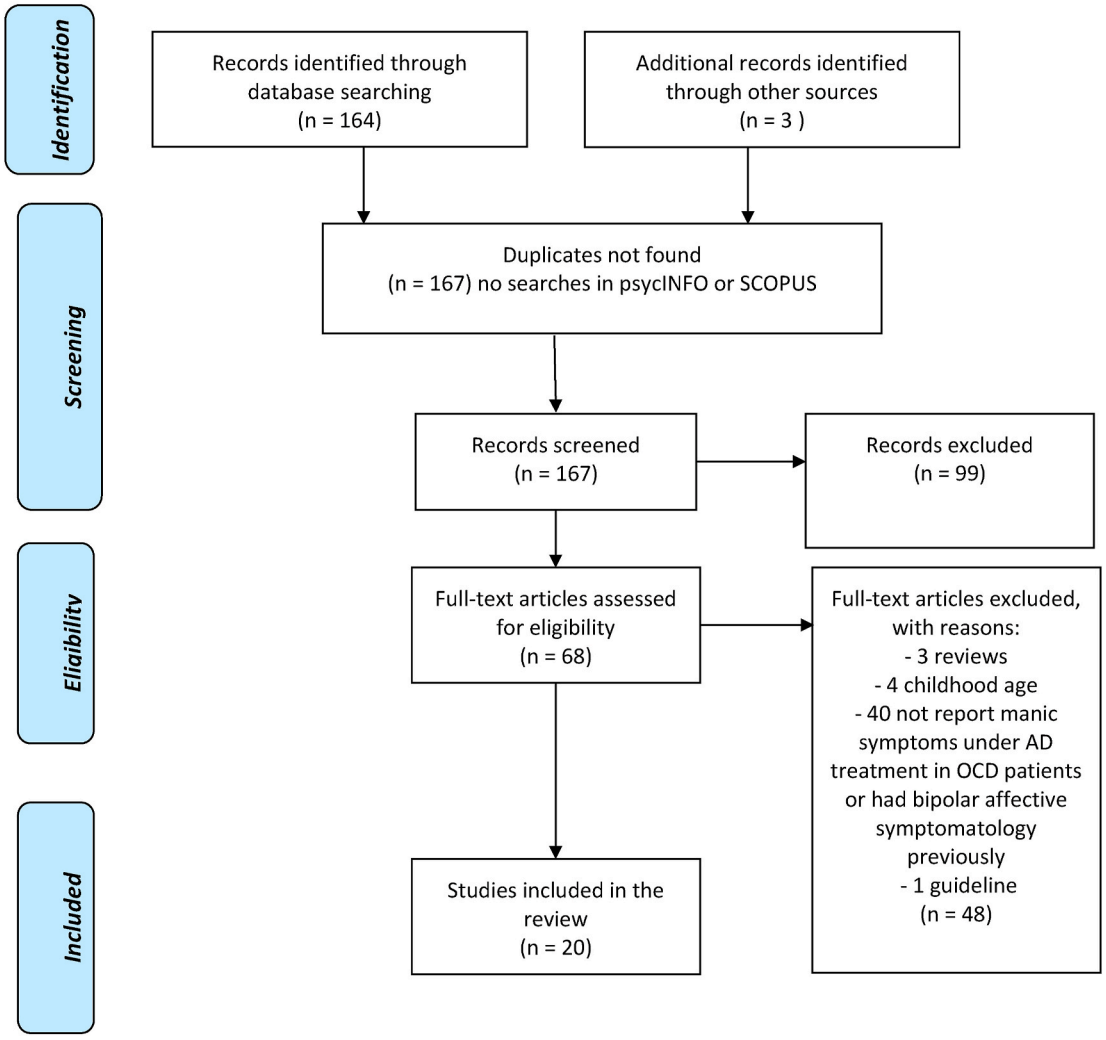

Fig. 1. Study selection flowchart.

appeared in the literature, although no studies with a good evidence-based design have been carried out.

It is difficult to determine whether ADs (especially at the high doses used in OCD) act as a trigger for manic episodes in vulnerable patients who are in fact bipolar patients, or whether the development of manic episodes depends exclusively on the class, type and dose of the AD. According to a large meta-analysis, the presence of bipolar disorder (BD) in patients previously diagnosed with OCD is 18.47% (Amerio et al., 2015). Moreover, there is no conclusive information about the dose and class of AD most likely to be associated with the manic/hypomanic switch. The relevance of studying the BD-OCD comorbidity is based on the worse outcomes, higher severity, higher comorbidity rates, greater overall impairment and a need of a more complex treatment strategy (Magalhães et al., 2010; Timpano et al., 2012).

The primary objective of this systematic review was to determine whether there is a relationship between the occurrence of first manic or hypomanic episodes and the pattern of use of ADs in OCD patients with no history of bipolarity. The secondary objective was to investigate whether there are specific clinical characteristics in OCD patients that may be associated to the emergence of these manic or hypomanic episodes. A better understanding of this phenomenon may have relevant clinical implications in terms of pharmacological management and preventive strategies in the follow-up of those cases that may be at risk to develop a comorbid bipolar disorder.

Methods

We conducted a systematic review of all reported cases and studies in the literature to summarize the existing evidence about the development of mania/hypomania in OCD patients under AD treatment. Although a systematic review of case reports cannot support causality between ADs and mania/hypomania in OCD patients, results can lead to generate hypotheses for subsequent studies. Our objective was to identify ADs putatively reported in the literature as being associated with manic/hypomanic episodes in these patients, and to describe related clinical features. The focus of our review was primary OCD. Studies focusing on episodic obsessive-compulsive symptomatology that emerged during an affective episode were not included. Studies including patients with BD and OCD as comorbid conditions were excluded. The evidence level of the selected items precluded a meta-analysis.

Search strategy

A systematic review was conducted following PRISMA guidelines for

systematic reviews (Moher et al., 2009). An electronic search was carried out in PubMed database and PsycINFO using the following MeSH terms by themselves and in combination: 'manic', 'manic depressive', 'BD', 'bipolar', 'Bipolar Disorder' AND 'obsessive-compulsive', obsessive-compulsive disorder', 'OCD', 'obsessive behaviour' AND 'antidepressants', 'antidepressive drugs', 'antidepressive agents'. We also searched for efficacy and safety references for the following antidepressants in the same databases: 'fluoxetine', 'escitalopram', 'citalopram', 'sertraline', 'fluvoxamine', 'clomipramine' and 'paroxetine' combined with the keywords 'OCD' AND 'adverse effects' OR 'mania' OR 'hypomania'. We also examined other references found in the literature reviewed. The search was conducted up to January 2020.

Eligibility criteria

Studies included in the review are summarized in Table 1. The inclusion criteria were as follows: 1) reports published in English and Spanish language, 2) patients aged 18–65 years (due to the high prevalence of other psychiatric diagnoses made in the follow up of paediatric OCD patients (Carballo et al., 2010), 3) OCD as the main psychiatric diagnosis, 4) all types of study design, 5) treatment of OCD with AD agent (first line serotoninergic agent such as SSRI or clomipramine as APA OCD guideline recommend) (American Psychiatric Association, 2007), 6) onset of manic or hypomanic symptoms under treatment with an AD. Studies with the following criteria were excluded: 1) previous diagnosis of bipolar disorder or patients with symptoms categorized as manic or hypomanic, 2) guidelines and reviews.

Data collection and extraction

The literature search, data collection and extraction were conducted independently by two authors (SB and CS). Disagreements were solved by consensus.

For each study, the following data were extracted systematically:

- Patient characteristics: age, gender and comorbidities.
- Size of population studied.
- Family psychiatric history.
- Characteristics of the AD that patient was taking for OCD: type, dose and time of exposure prior to the manic/hypomanic episode.
- Response of obsessive-compulsive symptoms after AD was initiated (also clinical response for comorbidities).
- Response of manic symptoms.

Results

Search results

The initial database search found 164 papers and three additional papers were added from other sources. There were no duplicated reports, so all 167 papers were selected for title and abstract screening. After this initial screening, 68 citations were evaluated for eligibility by full-text reading. Twenty articles satisfied the inclusion criteria: 15 were single reports or case series (Amerio et al., 2014a; Berk et al., 1996; Bernardo et al., 1989; Christensen, 1995; Figueroa et al., 1998; Matur et al., 2003; Philip et al., 2012; Ramasubbu, 2004; Shim et al., 2008; Steiner, 1991; Tikka et al., 2013; Turner et al., 1985; White et al., 1986; Wickham et al., 2007; Yalug et al., 2007) and five of them used a different methodology. The first one was an exploratory analysis studying clinical features and treatment outcomes in OCD patients with and without bipolar disorder (BD) (Perugi et al., 2002), in which a hypomanic episode was reported to have occurred in one non-BD patient. The second one was a prospective open-label study evaluating the efficacy of high doses of escitalopram in 67 patients, reporting one episode of hypomania (Rabinowitz et al., 2008). The third one was a retrospective study analyzing manic episodes in patients with anxiety disorders, in which a single manic episode was reported in an OCD patient (Levy et al., 1998). The fourth one was an observational study reporting three hypomanic episodes in a case series of 10 OCD patients (Rihmer et al., 1996). And the fifth one was a double-blind placebo--controlled study of clomipramine and clorgyline in patients with OCD (Insel et al., 1983) (Fig. 1). Altogether, 26 OCD patients were reported to have developed 29 manic/hypomanic episodes under antidepressant treatment: three of them had suffered from two episodes with different types of AD (clomipramine first and a SSRI later). These cases developing a second manic episode were not excluded because they had no history of bipolar disorder prior to inclusion. Moreover, results did not change when they were excluded from the analysis.

Assessment of bias

The overall quality of the cases was considered good to moderate. Cases were described adequately, and convincing evidence in support of the diagnosis and course of the illness was presented. Accurate details of antidepressant treatment (class, dose and time of exposure) were given in all the selected articles. Most cases reported personal psychiatric history and comorbid psychopathology.

Demographic characteristics

The mean age from single case reports developing manic or hypomanic episodes (data from 20 cases reviewed) was 34 years (S.D. 13.42). The mean age of participants in papers that reported sample data (not an individual case report) was 31.2 years (S.D. 3.02). There were no gender differences in the reports included in the review (42.3% of males and 46.2% of females; no reported data from three cases).

Clinical characteristics

Table 1 shows the most common features of OCD patients who developed mania/hypomania under AD treatment. Seven papers (35%) reported comorbid depressive episodes or symptoms in addition to the main OCD diagnosis. Five papers (25%) reported a depressive personal past history in the patients included. Overall, 11 patients (42.3%) had past or current depressive symptomatology. All patients with depression comorbidity also had a clinical response or improvement of the mood disorder.

In the papers included, 53.6% of patients with OCD showed improvement of symptoms with AD treatment.

Regarding the symptomatic dimension, when data were available (10 out of 20 papers), contamination worries and cleaning was the most prevalent symptomatology, being found in 9 patients.

Characteristics of antidepressants involved in manic/hypomanic episodes in OCD patients (Table 2)

CLASS OF ANTIDEPRESSANT: During the 29 manic/hypomanic episodes, 62.1% of patients were taking SSRIs and 37.9% were taking clomipramine. Three out of all the patients that initially switched to mania while taking clomipramine developed a subsequent manic episode when under SSRI treatment. Fluoxetine was the most frequently reported SSRI in association with emerging manic/hypomanic episodes (21.4%), followed by fluvoxamine, escitalopram and citalopram (10.7% each).

TIME TO SWITCH: The mean time of exposure to the serotonergic agent before the emergence of the manic/hypomanic episode was 9.08 weeks (S.D. 7.65). The APA OCD guideline (American Psychiatric Association, 2007) recommends evaluating the efficacy of an AD until week 12, and therefore two patient groups (under treatment for less than 12 weeks and under treatment for more than 12 weeks) were formed based on the duration of the treatment before the manic/hypomanic episode appeared. The majority of the patients developed

Table 2
Switch and treatment characteristics of papers included in the review.

Citation	Treatment involved in hypo/manic episode	Outcome of OCD and comorbidities	Exposure before manic/hypomanic episode	Manic or hypomanic episode	Mania outcome (pharmacological strategies and time)	Follow up	Concurrent OC and manic Sx
Insel (1983)	CLMP up to 300 mg	No data	No data	Hypomania	*Decrease dose of CLMP *Resolve quickly	Recurrence of OCD symptoms	No
Turner (1985)	FLX 80 mg	Improved obsessive symptoms in 9 weeks	13 weeks	Mania + pharmacological overdose	*Discontinuation of FLX and add LI 300 mg and HLP *four weeks	Several relapses of depressed mood and obsessional thinking and rituals (ECT)	No
White (1986)	*1st episode: CLMP 250 mg *2nd episode: CIT 80 mg	*1st: remission of obsessions *2nd: remission of obsessions	*1st: five weeks *2nd: five weeks	*1st: mania *2nd: mania	*1st: decrease CLMP dose to 200 mg add LI + CLNZ + pimozide *2nd: discontinuation of CIT add LI + chlorpromazine + clonazepam	OCD recurred after mania resolved	No
Bernardo 1989	CLMP up to 300 mg	No data	Three months (four days with 300 mg)	Mania	*Discontinuation of CLMP and add LI 800 mg *One week	Recurrence of OCD symptoms and maintaining euthymia	OCD disappeared when mania started
Steiner (1991)	FLX 20 mg	Improved obsessive symptoms in 4 weeks	Six weeks	Mania	*Decrease dose of FLX *Two weeks	Four weeks: recurrence of OCD Sx - > increase FLX + add Clonazepam (remission of OCD, no hypomania)	No
Christensen (1995)	PXT 60 mg	No data	Six weeks	Psychotic mania	*Discontinuation of PXT and add HLP *Six days	No data	No data
Berk (1996)	*4/5: 1st episode: CLMP 150–300 mg (2/4) 2nd episode: FLX 20–60 mg *1/5: + zuclopenthixol 50 mg *1/5: CIT 20 mg + pimozide 4 mg	1/5: improved obsessive symptoms in 4 weeks	2–6 weeks	Seven manic episodes	*Discontinuation of AD *4/5: add LI/VLP±HLP/psychotherapy … … … … … …. 1/5: 1st mania: discontinuation of AD and remained OCD stable for 1 year. OCD relapse: FLX trial. 2nd mania: discontinuation of FLX 1/5: 1st mania: discontinuation of AD and add LI: mania resolution but OCD re-emerged: add FLX 60. 2nd mania: discontinuation of FLX and add VLP to the LI: controlled mood but OCD was impairing function.	*2/5: no data *1/5: psychotic depression (treated with ECT and developed hypomania) *2/5: remained OCD	3/5: no 1/5: yes 1/5: no data
Rihmer (1996)	*1/3: CLMP 200 mg *1/3: FLVX 200 mg *1/3: FLVX 250 mg	*Responders: 4/10 (2 with depression; one of the three patients who developed hypomania) *Partial: 4/10 (1 with depression) *No responders: 2/10	5–8 weeks	Three hypomanic episodes	*Decrease dose 50 CE% *2/3: + LI *3–5 weeks	No data	No data
Figueroa (1998)	FLX 80 mg	Improved obsessive symptoms	Four months	Mania	*Decrease FLX to 40 mg *Add LI 900 mg	Five years later: comorbid GAD and alcohol abuse BD could not be diagnosed	No
Levy (1998)	CLMP 250 mg	No data	At least three months	Mania	*Discontinuation of CLMP *Two weeks	No data	No data
Perugi (2002)	*OCD-noBD 1 patient had a hypomania with CLMP	Clinical course featured differences between OCD-BD and OCD-noBD	No data *follow-up: 23.2 weeks (mean) SD: 24.3	Hypomania	No data	No data	No data
Matur (2003)	CLMP 225 + RI 2 mg (initiated two	Whereas tics and obsessive complaints	Few days	Mania (B-RMS: 25. YBOCS: 28)	*Discontinuation of CLMP and RI *Add QT	Two months later: no tics, OCD was	No

(*continued on next page*)

Table 2 (*continued*)

Citation	Treatment involved in hypo/manic episode	Outcome of OCD and comorbidities	Exposure before manic/hypomanic episode	Manic or hypomanic episode	Mania outcome (pharmacological strategies and time)	Follow up	Concurrent OC and manic Sx
	days before hospital admission)	regressed, manic symptoms started			up to 600 mg *12 days (B-RMS: 1, YBOCS: 7)	better, social-life normalized	
Ramasubbu (2004)	PXT up to 80 mg	Remission of depression and partial recovery of OCD symptoms up to nine months	Nine months	Hypomania	*Decrease PXT to 40 mg *Two weeks	No data	No data
Wickham (2007)	CIT 80 mg + Ziprasidone 20 mg + CLONA 1.5 mg	With CIT 80 mg monotherapy: partial response to OCD symptomatology	Seven days (after association of ziprasidone and CLONA)	Mania	*Discontinuation of ziprasidone *Decrease CIT to 20 mg *Three days	Four years with no manias. But had had one major depressive episode	No data
Yalug (2007)	ESCIT 20 mg	*Decreased OCD symptoms	One month	Dysphoric mania	*Discontinuation of ESCIT *Add VLP 1000 mg + QT 600 mg	No data	OCD Sx increased during mania
Rabinowitza (2008)	ESCIT up to 50 mg	*2/67: response (≥25% reduction YBOCS) at 4 weeks *53/66 response (≥25% reduction YBOCS) and MADRS: 12 (mean) over the study	Seven weeks (1/67 hypomania)	Hypomania (1/67 with ESCIT 45 mg)	*Decrease ESCIT to 30 mg *10 days	Patient continued in the study	No data
Shim 2008	ESCIT 30 mg	CGI-I: 2.6 (mean) SD: 1.1	*38.8 days (mean) SD: 43.1 with 20 mg *four days with ESCIT 30 mg	Mood elation	Elated mood was not aggravated with a further dose increase	Patient was more stabilized at the end point	No data
Philip (2012)	FLX 60 mg	*Improved depression *Persistent OCD symptoms	Five months	Mania	*Discontinuation of FLX *Add VLP 1000 mg + OLZ 10 mg *One week	No data	No data
Tikka (2013)	FLVX up to 250 mg	Improved depressive (HAMD-17: 4) and obsessive (YBOCS: 14) symptoms	27 days with FLVX (2 days with 250 mg)	Mania (YMRS: 16)	*Decrease FLVX to 150 mg *Add LI to 1050 g (blood level: 0.72 mEq/L) *10 days	No data	No
Amerio (2014)	SER 250 mg	OCD and affective symptoms were controlled	Eight months	Mania	*VLP 1000 mg + OLZ 10 mg *No time data	Five months' stabilization with SER 75 mg + VLP	No

Abbreviations: HAMD-17: Hamilton Depression Rating Scale of 17 items; MADRS: Montgomery-Asberg Depression Rating Scale; YBOCS: Yale-Brown obsessive-compulsive scale; YMRS: Young Mania Rating Scale; CGI-I: Clinical Global Impression Scale-Improvement score; OCD: obsessive-compulsive disorder; BD: bipolar disorder; AD: antidepressant; SER: sertraline; FLVX: fluvoxamine; FLX: fluoxetine; ESCIT: escitalopram; CIT: citalopram; CLMP: clomipramine; PXT: paroxetine; CLNZ: clonazepam; LI: lithium; VLP: valproate; OLZ: olanzapine; QT: quetiapine; RI: risperidone. HLP: haloperidol; ECT: electroconvulsive therapy; SD: standard deviation; mEq/L: milliequivalents per litre; Sx: symptoms.

manic/hypomanic episodes soon after the AD was added (within 12 weeks of initiation), accounting for 65.5% of the total number of manic/hypomanic episodes (Table 3). Clomipramine was associated with 42.1% (N = 8) of all manic/hypomanic episodes in this group of patients but only in 14.3% (N = 1) of manias when the treatment had been underway for more than 12 weeks. On the other hand, SSRIs were associated with 57.9% (N = 11) of manic/hypomanic episodes that appeared before the end of 12 weeks of treatment and with 85.7% (N = 6) of manic/hypomanic episodes that appeared more than 12 weeks after drug initiation. No statistically significant differences were found between different period times of any antidepressant use (a chi-square test was used).

ANTIDEPRESSANT DOSE: The defined daily dose (DDD) (WHO, 2020) is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDD was used as an operational term to compare the effects of different AD interventions (i.e., adverse events, therapeutic effects). The 28 reported switches to manic/hypomanic episodes had a mean of 2.7 (S.D. 0.99) DDD. Four of these episodes appeared after initiation and/or up-titration of the dose. Significant differences were found between the two subgroups: manic/hypomanic episodes that appeared before 12 weeks of treatment had a lower mean DDD (2.4, S.D. 0.85) than episodes that appeared after 12 weeks (3.4, S.D. 0.73) ($t = -2.593$, $p = 0.016$).

MANIA/HYPOMANIA EPISODE RESPONSE: The AD involved in mania or hypomania was discontinued or its dose was reduced in the majority of emerging manic/hypomanic episodes (71.4%, n = 20), and in 55.2% of cases (n = 16) a mood stabilizer or a neuroleptic treatment was initiated (see Table 2). In those cases for which long-term data on OCD evolution were available, 13.8% of patients stabilized with the treatment prescribed, 13.8% had other recurrences (depression and anxiety), and 10.3% had a second manic or hypomanic episode that was treated as described above. The assessment of these results should be done with caution because there are a 48% of missing data regarding the follow-up of each case. None of the reported outcomes significantly changed when the second manic episode was excluded from the analysis.

Discussion

To our knowledge, this is the first systematic review about the role of antidepressant agents in manic/hypomanic episodes emerging in OCD patients with no history of bipolarity. Our review identified 26 cases of patients developing 29 manic/hypomanic episodes under AD treatment. SSRIs (especially fluoxetine) were the most associated AD to manic/

Table 3
Time to switch, class and dose of serotonergic agent involved in switching to hypo/mania episode[a].

<12 weeks antidepressant, dose (mg/DDD), reference (N, episode type)	≥12 weeks antidepressant, dose (mg/DDD), reference (N, episode type)	2nd manic episode in patients previously switched to CLMP antidepressant, dose (mg/DDD), reference (N, episode type)
FLX	**FLX**	**FLX**
20/1 Steiner (1991) (N = 1, 1 m)	60/3 Philip (2012) (N = 1, 1 m)	20-60/1–3 few weeks Berk (1996) (N = 2, 2 m)
ESCIT	80/4 Figueroa (1998) (N = 1, 1 m)	**CIT**
45/4.5 Rabinowitz (2008) (N = 1, 1 h)		80/4 5w White (1986) (N = 1, 1 m)
20/2 Yalug (2007) (N = 1, 1 m)	80/4 Turner (1985) (N = 1, 1 m)	
30/3 Shim, 2008 (N = 1, n/a)	**SER**	
	250/2.5 Amerio (2014) (N = 1, 1 m)	
FLVX	**PXT**	
250/2.5 Tikka (2013) (N = 1, 1 m)	80/4 Ramasubbu (2004) (N = 1, 1 h)	
200-250/2–2.5 Rihmer (1996) (N = 2, 2 h)	**CIT**	
	80/4 Wickham (2007) (N = 1, 1 m)	
PXT	**CLMP**	
60/3 Christensen (1995) (N = 1, 1 m)	250/2.5 Levy (1998) (N = 1, 1 m)	
CIT		
20/1 White (1986) (N = 1, 1 m)		
20/1 Berk (1996) (N = 1, 1 m)		
CLMP		
225/2.3 Matur (2003) (N = 1, 1 m)		
200/2 Rihmer (1996) (N = 1, 1 h)		
150-300/1.5–3 Berk (1996) (N = 4, 4 m)		
300/3 Bernardo (1992) (N = 1, 1 m)		
250/2.5 White (1986) (N = 1, 1 m)		

Abbreviations: FLX: Fluoxetine; SRT: Sertraline; PXT: Paroxetine; CIT: Citalopram; ESCIT: Escitalopram; FLVX: Fluovoxamine; CLMP: Clomipramine; N = number of cases, m: mania; h: hypomania.

[a] This table does not report the hypomanic episodes described by Insel et al. and Perugi et al. because the dose and the time of exposure were not given.

hypomanic episodes in the whole sample, but no significant differences were found to clomipramine. Most of the episodes occurred in the first 12 weeks of AD treatment. Interestingly, these episodes emerging in the first 12 weeks of treatment were associated with a lower defined daily dose (DDD) of ADs when compared to episodes emerging after 12 weeks of treatment. The fact that manic/hypomanic episodes emerged during dose escalation aimed to reach full doses suggest that the risk of developing them could be dose-dependent, as reported by previous authors (Goldberg and Truman, 2003; Ramasubbu, 2001; Yamaguchi et al., 2018). These results, together with the fact that mood stabilizers were added to treat manic/hypomanic episodes in a substantial number of cases in the study sample, seems to support the fact that an underlying bipolar disorder could be present.

While the majority of the patients reported no current or past comorbidity, depression was the most common pre-existing feature in patients with a psychiatric history other than OCD. All patients experienced improvement in depressive symptoms with treatment, while only half of them perceived improvement in obsessive-compulsive symptoms.

Data regarding on clinical predictors and on treatment of manic/hypomanic episodes are scarce and heterogeneous in the literature. Some studies have assessed the efficacy, tolerability and safety of ADs in patients with OCD and they mostly report adverse events in the form of anxiety, irritability or insomnia without mania/hypomania (Alderman et al., 2006; Montgomery, 1993; Tollefson, 1994). We only found one open-label prospective study reporting a hypomanic episode while assessing the efficacy of escitalopram at high doses in OCD (Rabinowitz et al., 2008). More studies have investigated the development of manic/hypomanic episodes in patients with anxiety or affective disorders. The co-occurrence of manic episodes under AD treatment in patients with no history of bipolarity dates back to 1979 (van Scheyen et al., 1979). The authors reported the emergence of manic episodes in a group of inpatients suffering from unipolar depression who were being treated with clomipramine or amitriptyline. In the same year, Bunney and colleagues reported a potential association between the onset of mania to dopamine and to supersensitivity of catecholamine receptors (Bunney et al., 1979).

The frequency of switching to mania or hypomania in patients with anxiety disorders and with no history of bipolar disorder is reported to be less than 3% (Levy et al., 1998). There are no conclusive data about the rate of hypo/mania in OCD patients treated with ADs.

In many of the papers that were excluded from this review, the investigators reported behaviour activation related to AD treatment involving symptoms such as irritability, anxiety or insomnia. These cases were not included because they were not identified as involving manic or hypomanic episodes and these symptoms are also reflected in the datasheets of the drugs and are reported as a side effect. However, activation was added as a symptom in the diagnosis of manic/hypomanic state in DSM-5 (reviewed by Scott et al., 2017).

Different theories about switching have been proposed, but no specific data about mechanisms of this phenomenon in depressive or obsessive-compulsive disorders have been published. One of the main hypotheses is that developing mania while under treatment with an antidepressant is a predictor of bipolarity. One of the reasons we excluded episodic OCD from our review is that this clinical course is more associated with this mood condition. The lifetime comorbidity of bipolar disorder in OCD patients is around 6–10% (Amerio et al., 2014b).

One of the most accepted theories about how manic symptoms are triggered by AD is based on their serotoninergic and noradrenergic effect, predominantly in bipolar disorder (Leverich et al., 2006; Peet, 1994; Vieta et al., 2002). Neuroimaging studies add further evidence for this hypothesis. In this line, lower serotonin transporter binding in the thalamus and midbrain has been described in both bipolar and obsessive patients, when compared with healthy controls (reviewed by Spies et al., 2015). Moreover, similar neuroimaging findings have been reported for both disorders in areas involved in emotional regulation (van den Heuvel et al., 2016).

The limitations of this review derive from the difficulty in extracting conclusions based on articles using different methodologies, especially case reports. However, most of them were focused specifically on detecting manic episodes. No systematic rating scales were used to assess the manic/hypomanic episodes. Moreover, no randomized designs were used to study the main topic of these papers due to the low prevalence of manic episodes and the difficulty in controlling all the clinical factors. Related to the class of AD, SSRIs were the most frequently reported drugs involved in manias/hypomanias, but the higher prevalence of use of such ADs could be a source of bias. In addition, dual-action ADs are used less frequently in OCD than SSRIs or clomipramine. Methodological limitations preclude establishing whether comorbid depressive symptoms might already be part of a bipolar disorder.

Conclusions

Based on our review, we can conclude that the emergence of manic/hypomanic episodes while treating OCD patients might be influenced by several factors. SSRIs (especially fluoxetine) were the most associated

AD to manic/hypomanic episodes in the whole sample, but no significant differences were found to clomipramine. Most of the episodes occurred in the first 12 weeks of AD treatment and these were associated with a lower defined daily dose (DDD) of ADs when compared to episodes emerging after 12 weeks of treatment. There would be some common factors in OCD patients with more vulnerability to develop manic/hypomanic episodes under AD treatment: depressive history, patient in their 30s, patients taking fluoxetine, and being in the first 12 weeks of AD treatment. This information may be of clinical relevance, as it highlights the need for close monitoring in patients with these characteristics, especially in the first 12 weeks of treatment (when therapeutic doses have not yet been reached).

The emergence of manic/hipomanic episodes while treating OCD patients is a rare phenomenom and should not prevent treating them according to OCD clinical practice guidelines (SRIs at high doses). However, it seems useful to keep in mind that they may occur, especially in patients sharing common characteristics like the ones exposed before, and that additional treatment and close monitoring may be needed.

Declaration of competing interest

All the authors declare that they have no conflict of interest associated with this article.

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References

Alderman, J., Wolkow, R., Fogel, I.M., 2006. Drug concentration monitoring with tolerability and efficacy assessments during open-label, long-term sertraline treatment of children and adolescents. J. Child Adolesc. Psychopharmacol. 16, 117–129. https://doi.org/10.1089/cap.2006.16.117.

American Psychiatric Association, 2007. Practice Guideline for the treatment of patients with obsessive-compulsive disorder. Am. J. Psychiatr. 64, 5–53. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd.pdf.

Amerio, A., Odone, A., Liapis, C., Ghaemi, S., 2014. Diagnostic validity of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. Acta Psychiatr. Scand. 129, 343–358. https://doi.org/10.1111/acps.12250.

Amerio, Andrea, Odone, A., Marchesi, C., Ghaemi, S.N., 2014. Do antidepressant-induced manic episodes in obsessive-compulsive disorder patients represent the clinical expression of an underlying bipolarity? Aust. N. Z. J. Psychiatr. 48 https://doi.org/10.1177/0004867414530006, 957–957.

Amerio, A., Stubbs, B., Odone, A., Tonna, M., Marchesi, C., Ghaemi, S.N., 2015. The prevalence and predictors of comorbid bipolar disorder and obsessive – compulsive disorder : a systematic review and meta-analysis. J. Affect. Disord. 186, 99–109. https://doi.org/10.1016/j.jad.2015.06.005.

Baldwin, D.S., Anderson, I.M., Nutt, D.J., Allgulander, C., Bandelow, B., Den Boer, J.A., Christmas, D.M., Davies, S., Fineberg, N., Lidbetter, N., Malizia, A., McCrone, P., Nabarro, D., O'Neill, C., Scott, J., Van Der Wee, N., Wittchen, H.U., 2014. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J. Psychopharmacol. 28, 403–439. https://doi.org/10.1177/0269881114525674.

Barak, Y., et al., 2000. Is selectivity for serotonin uptake associated with a reduced emergence of manic episodes in depressed patients? Int. Clin. Psychopharmacol. 15, 53–56.

Berk, M., Koopowitz, L.F., Szabo, C.E., 1996. Antidepressant induced mania in obsessive compulsive disorder. Eur. Neurospychopharmacology 6, 9–11.

Bernardo, M., Vieta, E., Vallejo, J., 1992. Episodio maniaco en una paciente con trastorno obsesivo-compulsivo tratado con clomipramina. Med Clin (Barc). 7 93 (10), 395.

Bloch, M., et al., 2010. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Mol. Psychiatr. 15, 850–855. https://doi.org/10.1038/mp.2009.50.

Bunney, W.E., Pert, A., Rosenblatt, J., Pert, C.B., Gallapert, D., 1979. Mode of action of lithium: some biological considerations. Arch. Gen. Psychiatr. 36, 898–901.

Carballo, J., et al., 2010. Stability of childhood anxiety disorder diagnoses: a follow-up naturalistic study in psychiatric care. Eur. Child Adolesc. Psychiatr. 19, 395–403. https://doi.org/10.1007/s00787-009-0064-1.

Christensen, R., 1995. Paroxetine-Induced psychotic mania. Am. J. Psychiatr. 152, 1399–1400.

Figueroa, Y., Rosenberg, D.R., Birmaher, B., Keshavan, M.S., 1998. Combination treatment with clomipramine and obsessi. J. Child Adolesc. Psychopharmacol. 8, 61–67.

Goldberg, J.F., Truman, C.J., 2003. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord. 5, 407–420. https://doi.org/10.1046/j.1399-5618.2003.00067.x.

Hirschtritt, M.E., Bloch, M.H., Mathews, C.A., 2017. Obsessive-compulsive disorder advances in diagnosis and treatment. JAMA, J. Am. Med. Assoc. 317, 1358–1367. https://doi.org/10.1001/jama.2017.2200.

Insel, T.R., Murphy, D.L., Cohen, R.M., Alterman, I., Kilts, C., Linnoila, M., 1983. Obsessive-compulsive disorder. A double-blind trial of clomipramine and clorgyline. Arch. Gen. Psychiatr. 40, 605–612. https://doi.org/10.1001/archpsyc.1983.04390010015002, 1983.

Isomura, K., Nordsletten, A.E., Rück, C., Ljung, R., Ivarsson, T., Larsson, H., Mataix-cols, D., 2016. Pharmacoepidemiology of obsessive – compulsive disorder : a Swedish nationwide cohort study. Eur. Neuropsychopharmacol 1–12. https://doi.org/10.1016/j.euroneuro.2016.02.004.

Kessler, R., et al., 2005. Prevalence, severity, and comorbidity of. Arch. Gen. Psychiatr. 62, 617–627. https://doi.org/10.1001/archpsyc.62.6.617.

Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T., McElroy, S.L., Keck, F.E., Kupka, R. W., Denicoff, K.D., Holen, W.A., Grunze, H., Martinez, M.I., Post, R.M., 2006. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am. J. Psychiatr. 163, 232–239. https://doi.org/10.1176/appi.ajp.163.2.232.

Levy, D., Kimhi, R., Barak, Y., Aviv, a, Elizur, a, 1998. Antidepressant-associated mania: a study of anxiety disorders patients. Psychopharmacology (Berlin) 136, 243–246. https://doi.org/10.1007/s002130050562.

Magalhães, P.V.S., Kapczinski, N.S., Kapczinski, F., 2010. Correlates and impact of obsessive-compulsive comorbidity in bipolar disorder. Compr. Psychiatr. 51, 353–356. https://doi.org/10.1016/j.comppsych.2009.11.001.

Matur, Z., Üçok, A., 2003. Quetiapine treatment in a patient with tourette ' s syndrome, obsessive-compulsive disorder and drug-induced mania. Isr. J. Psychiatry Relat. Sci. 40, 150–152.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D., The PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 https://doi.org/10.1371/journal.pmed1000097.

Montgomery, S., et al., 2001. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int. Clin. Psychopharmacol. Psychopharmacol 16, 75–86.

Montgomery, S., et al., 1993. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. Eur. Neuropsychopharmacol 3, 143–152. https://doi.org/10.1016/0924-977X(93)90266-O.

Peet, M., 1994. Induction of mania with selective serotonin Re-uptake inhibitors and tricyclic antidepressants. Br. J. Psychiatry 164, 549–550. https://doi.org/10.1192/bjp.164.4.549.

Perugi, G., Toni, C., Frare, F., Travierso, M.C., Hantouche, E., Akiskal, H.S., 2002. Obsessive-compulsive–bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. J. Clin. Psychiatr. 63 (12), 1129–1134.

Philip, J., Janaki, R., 2012. Antidepressant-induced mania in obsessive compulsive disorder. Indian J. Psychiatr. 54, 194–196. https://doi.org/10.4103/0019-5545.99543.

Rabinowitz, I., Baruch, Y., Barak, Y., 2008. High-dose escitalopram for the treatment of obsessive – compulsive disorder. Int. Clin. Psychopharmacol. 23, 49–53.

Ramasubbu, R., 2004. Antidepressant treatment-associated behavioural expression of hypomania: a case series. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 28, 1201–1207. https://doi.org/10.1016/j.pnpbp.2004.06.015.

Ramasubbu, R., 2001. Dose - response relationship of selective serotonin reuptake inhibitors treatment-emergent hypomania in depressive disorders. Acta Psychiatr. Scand. 104, 236–239. https://doi.org/10.1034/j.1600-0447.2001.00383.x.

Ravizza, L., Maina, G., Bogetto, F., 1997. Episodic and chronic obsessive-compulsive disorder. Depress. Anxiety 6 (4), 154–158.

Rihmer, Z., Barsi, J., Belsō, N., Pestality, P., György, S., 1996. Antidepressant-induced hypomania in obsessive-compulsive disorder. Int. Clin. Psychopharmacol. 11, 203–205. https://doi.org/10.1097/00004850-199609000-00008.

Ruscio, A., Stein, D., Chiu, W., Kessler, R., 2010. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol. Psychiatr. 15, 53–63. https://doi.org/10.1038/mp.2008.94.

Scott, J., Murray, G., Henry, C., Morken, G., Scott, E., Angst, J., Merikangas, K.R., Hickie, I.B., 2017. Activation in bipolar disorders a systematic review. JAMA Psychiatry 74, 189–196. https://doi.org/10.1001/jamapsychiatry.2016.3459.

Spies, M., Knudsen, G.M., Lanzenberger, R., Kasper, S., 2015. The serotonin transporter in psychiatric disorders: insights from PET imaging. The Lancet Psychiatry 2, 743–755. https://doi.org/10.1016/S2215-0366(15)00232-1.

Steiner, W., 1991. Fluoxetine induced mania in patients with obsessive-compulsive disorder. Am. J. Psychiatr. 148, 1403–1404. https://doi.org/10.1176/appi.ajp.2010.10040606.

Tikka, S.K., Garg, S., Das, B., 2013. Fluvoxamine induced oculogyric dystonia and manic switch in a patient with obsessive compulsive disorder. Indian J. Pharmacol. 45, 532–533. https://doi.org/10.4103/0253-7613.117760.

Timpano, K.R., Rubenstein, L.M., Murphy, D.L., 2012. Phenomenological features and clinical impact of affective disorders in OCD: a focus on the bipolar disorder and ocd connection. Depress. Anxiety 29, 226–233. https://doi.org/10.1002/da.20908.

Tollefson, G.D., et al., 1994. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch. Gen. Psychiatr. 51, 559–567.

Turner, S.M., 1985. A second case of mania associated with fluoxetine. Am. J. Psychiatr. 142, 274–275.

U. S. Food and Drug Administration - Medication Guide, 2017. Prozac (Fluoxetine Hydrochloride). Indianapolis, IN 46285, USA.

Vallejo, J., Gasto, C., Catalan, R., Bulbena, A., Menchon, J.M., 1991. Predictors of antidepressant treatment outcome in melancholia: psychosocial, clinical and biological indicators. J. Affect. Disord. 21, 151–162. https://doi.org/10.1016/0165-0327(91)90036-R.

van den Heuvel, O.A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S.R., Nakamae, T., Denys, D., Goudriaan, A.E., Veltman, D.J., 2016. Brain circuitry of compulsivity. Eur. Neuropsychopharmacol 26, 810–827. https://doi.org/10.1016/j.euroneuro.2015.12.005.

van Scheyen, J.D., van Kammen, D.T., 1979. Clomipramine-induced mania in unipolar depression. Arch. Gen. Psychiatr. 36 (5), 560–565. https://doi.org/10.1001/archpsyc.1979.01780050070008.

Vieta, E., Martinez-Arán, A., Goikolea, J.M., Torrent, C., Colom, F., Benabarre, A., Reinares, M., 2002. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J. Clin. Psychiatr. 63, 508–512. https://doi.org/10.4088/JCP.v63n0607.

White, K., Keck, P.E., Lipinski, J., 1986. Serotonin-Uptake inhibitors in obsessive-compulsive disorder: a case report. Compr. Psychiatr. 27, 211–214.

Wickham, R., Varma, A., 2007. Ziprasidone-associated mania in a case of obssessive-compulsive disorder. CNS Spectr. 12, 578–579.

World Health Organization, n.d. Defined daily dose (DDD). https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/.

Yalug, Özten E., 2007. Manic episode due to escitalopram in a patient with episodic obsessive compulsive Disorder : a case report. Bull. Clin. Psychopharmacol. 17, 80–83.

Yamaguchi, Y., Kimoto, S., Nagahama, T., Kishimoto, T., 2018. Dosage-related nature of escitalopram treatment-emergent mania/hypomania: a case series. Neuropsychiatric Dis. Treat. 14, 2099–2104. https://doi.org/10.2147/NDT.S168078.