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Case report

Antidepressant treatment-associated behavioural expression of hypomania: a case series

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Abstract

Objective: Emerging literature suggests that hypomanic behaviour may be clinically more important than elated mood in spontaneous hypomania. This report describes dysfunctional behavioural activation as a milder expression of antidepressant-associated hypomania.
Method: Five outpatients with mood disorders developed problem behaviours following antidepressant treatment. These behaviours include gambling, excessive spending, increased sexual activity, excessive shopping and socially inappropriate verbal aggression. These behaviours were not accompanied with noticeable euphoria or persistent dysphoria and were not characteristics of the individual's personality functioning. They were reported by significant others and patients had no history of primary impulsive, substance abuse or personality disorders.
Results: The observed antidepressant-associated behavioural activation was suggestive of hypomanic behaviours not of impulse control disorders because of; (a) absence of other accountable mental or medical disorders characterized by impulsivity, (b) the evidence of close association between impulsivity and hypomanic/manic states, (c) increasing awareness of the diagnostic importance of behavioural disturbances in hypomania, (d) the substantial evidence relating antidepressant treatment to the emergence of hypomania, but not to impulse control disorders, (e) the well documented therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) in impulse control disorders.
Conclusions: In accordance with the recent proposed revision in the diagnostic criteria of hypomania, the observed dysfunctional behavioural activation during antidepressant treatment may represent milder expression of antidepressant-associated hypomania. More research is warranted to study the behavioural expression of hypomania secondary to antidepressants.

Keywords: Antidepressants; Hypomanic behaviour; Adverse effects

1. Introduction

The development of hypomania during antidepressant treatment has been well documented. Studies have shown higher incidence rates of hypomania or mania with antidepressant treatments than with placebo in unipolar (1.4–11 % vs. 1.21–0.91%) and in bipolar depression (2.2–70% vs. 4.2%) (Akiskal et al., 1995; Coryell et al., 1995; Kupfer et al., 1998; Nasarallah et al., 1982; Peet, 1994; Rouillon et al., 1992). These findings from placebo-controlled studies suggest that dysfunctional mood activation occurring during antidepressants may be related to the pharmacological effects of antidepressants.

The clinical phenomenon of antidepressants-associated hypomania or mania has been increasingly the focus of research in recent times for several reasons. First, treatment-associated hypomania has been reported with essentially every class of antidepressants including with newer and safer antidepressants, although SSRIs seem to have lower risk of hypomania or mania than tricyclics and tetracyclic noradrenergic antidepressants, in bipolar and unipolar depression, respectively (Barak et al., 2000; Rouillon et al., 1992). Second, hypomanic reactions have been observed not only in patients with affective disorders (unipolar and bipolar

Abbreviations: APA, American Psychiatric Association; BSD, bipolar spectrum disorder; CT, computerized tomography; DSM, Diagnostic Statistical Manual; EEG, electroencephalogram; ICD, International Classification of Diseases; MRI, magnetic resonance imaging; OCD, obsessive compulsive disorder; SSRI, selective serotonin reuptake inhibitor; WHO, World Health Organization.

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depression) but also in patients with anxiety and non-mood disorders (Diler and Avei, 1999; Levy et al., 1998). This is noteworthy given the fact that antidepressants are widely prescribed for many conditions other than depression, such as anxiety disorders, premenstrual dysphoric disorder, pain syndromes, impulse control disorders, and personality disorders. Third, the utilization of antidepressants has increased drastically in most developed countries over the last 10 years due probably to broadening of indications, increased awareness and understanding of depression and decreased stigma toward seeking treatments for mood disorder (Freeman et al., 2000; Hemels et al., 2002; McManus et al., 2000; Olfson and Klerman, 1993). It is more likely that this trend of increased utilization will continue in the future and therefore the antidepressant related adverse effects including hypomanic reactions might need more attention. Fourth, the controversy whether antidepressant treatment-emergent hypomania in unipolar depression is pharmacologically induced adverse effect (secondary hypomania) or a manifestation of underlying bipolar diathesis remains unresolved. In this context, more research is focused on elucidating risk factors and studying phenomenological and nosological aspects of antidepressant-associated hypomania.

A few studies examined whether antidepressants-associated hypomania or manic states phenomenologically differ from spontaneous hypomania and mania. Antidepressant associated mania was found to be milder in psychopathology with less severe levels of psychotic symptoms, psychomotor agitation and bizarre behaviour than spontaneous mania (Stoll et al., 1994). In contrast, another study suggests that antidepressant-induced mania could be severe requiring hospitalization (Howland, 1996). However, there were no differences in phenomenological and nosological status between antidepressant-induced hypomania and spontaneous hypomania in bipolar II (Akiskal et al., 2003). Although the recent concept of bipolar disorder recognizes the existence of subthreshold forms of hypomania (hypomanic symptoms only, brief hypomania lasting for 1–3 days) (Angst, 1998; Angst et al., 2003; Benazzi and Akiskal, 2003a), and the clinical importance of hypomanic behaviour in the diagnosis of spontaneous-hypomania (Benazzi and Akiskal, 2003b), little is known about milder behavioural expressions of hypomania during antidepressant treatment.

This report describes a case series presenting with dysfunctional behavioural activation during antidepressant treatment in the absence of observable mood elation or persistent irritability. The implications of antidepressant-associated behavioural expression of hypomania have been discussed.

2. Case reports

2.1. Case 1

The patient was a 37-year-old, single, Caucasian woman with a 2-year history of chronic depression and comorbid obsessive compulsive disorder (OCD). She was treated initially with incremental doses of paroxetine in an outpatient mood disorder clinic. She was prescribed paroxetine initially at the dose of 20 mg/day, which was gradually increased to 80 mg/day. Her clinical response was positive and linear to the increasing doses of paroxetine. She had shown complete remission in depression and partial recovery from OCD in 3–4 months time. She then resumed her job as a secretary in a firm. On subsequent monthly follow-ups, she was found to be normothymic for 9 months. However, her sister reported over the phone a significant qualitative change in patient's personality from being quiet and passive to socially and sexually overactive, which were considered to be totally uncharacteristic of her premorbid personality functioning. The retrospective chart review did not reveal any documentation of hypomania during the period of observable behavioural changes.

On further clinical inquiry, the patient admitted having increased libido and being sexually overactive and partying excessively in the previous three months. She was having indiscrete, unsafe sex with multiple male partners during that period. Her sexual relationship with a retired general practitioner alienated her from her family and friends. She was reported to be sleeping less than 3–5 h a night because of excessive partying and increased sexual activity. Her alcohol consumption increased marginally from 3–4 units to 10–14 units a week during the period of sexual overactivity. The recent mental status examination did not reveal elated or irritable mood, pressure of speech, flight of ideas, grandiosity or distractibility. Interestingly she felt good about herself and reported a sense of excitement in social and heterosexual encounters. She justified her actions as compensatory for what she missed during her depression. She lacked judgement and had only partial insight about her behaviour. There was no previous or family history of bipolar disorder and past history of borderline or antisocial personality disorder, substance abuse or impulse-control disorder involving sexual behaviour. Medical investigations, including thyroid functions, were normal. Two weeks after the reduction of paroxetine, 80–40 mg/day, patient noticed a decrease in her sexual libido. After a month, she stopped seeing the retired family doctor and regained insights about her previous hypersexual behaviour.

2.2. Case 2

A 55-year-old, married, Caucasian man was referred to the mood clinic with an 8-month history of treatment resistant major depression. He was an executive in a federal office and became disabled due to depression. Since this patient showed partial response to previous treatment with paroxetine, a Selective Serotonin Reuptake Inhibitor (SSRI), a second trial with another SSRI was considered. Sertraline treatment was initiated at the dose of 50 mg/day and gradually titrated to 300 mg/day over a period of 12 weeks. Patient responded positively to high doses of sertraline. He

appeared normothymic on subsequent monthly follow-ups for 3 months. However, his family doctor called over the phone and conveyed his wife's concerns regarding his recent personality change. His wife found that he had been gambling a lot, and spent time thinking and planning expensive vacations. He was trying to make more money by gambling to spend for expensive vacations. He seldom stayed at home during the recent weeks. He displayed irritable moods when his behaviour and whereabouts were questioned. She also found that he had lost 10,000 dollars in a poker game in a casino and despite his losses, he booked an expensive cruise vacation for 5000 dollars with his credit cards. He bought a new car although his old car was in sound condition and crashed his new car into another stationary car. This behaviour of gambling and excessive spending was considered to be totally out of his character. There was no previous or family history of bipolar, personality, substance abuse, and other impulse-control disorders. Medical history revealed bilateral carpel tunnel syndrome but no hypothyroidism. On subsequent clinical interview, he admitted feeling good with increased energy, interest and decreased need to sleep. However, the psychiatric evaluation performed during the period of problem behaviour did not show any evidence suggestive of persistent hypomanic moods (irritability, elation lasting for at least 1 week). Further, cross-sectional mental status examination did not reveal pressure of speech, flight of ideas or grandiosity. Subsequently, sertraline was decreased from 300 to 200 mg in a week. The energized risk-taking, gambling and excessive spending behaviours disappeared in 2–3 weeks after the reduction of sertraline.

2.3. Case 3

A 56-year-old, married, Caucasian male was referred with a history of major depression following a right medullary stroke resulting in left hemiparesis, numbness and mild ataxia. Magnetic resonance imaging (MRI) showed small vessel disease. Major depressive episode began within 2 weeks after stroke and continued for several months even after complete recovery from stroke without any residual deficits. This medical condition, including hyperlipidemia, hypertension was stable with treatments (atorvastatin 10 mg/day; ramipril 5 mg/day). He was also taking preventive aspirin treatment. Citalopram was prescribed for post-stroke depression. He showed partial response to citalopram at the dose of 20 mg/day, there was a marginal improvement in mood, energy interest and vegetative symptoms. Further attempts to increase the dose of citalopram to 60 mg/day were unsuccessful because of nausea and dizzy spells. Hence, it was decided to augment citalopram with lamotrigine a novel antiepileptic drug with antidepressant and mood stabilizing potentials. Patient showed remarkable improvement in 3–4 weeks after the addition of lamotrigine 100 mg/day on citalopram 40 mg/day. A month later, he became asymptomatic and fully functional. Then he resumed his business of running a trucking company. He appeared normothymic on monthly follow-ups. During the following 2 months he missed the appointments but got his prescription renewed over the phone.

One morning he attended with his wife as an emergency for urgent psychiatric evaluation. His wife expressed grave concern regarding his behavioural changes in recent months. Apparently, he was missing his work and found in casinos gambling and socializing with prostitutes. He had spent 50,000 dollars within 2–3 months. He concealed the gambling and extramarital sexual activities from his wife. His wife could not find any major change in mood or behaviour at home when he was involved in gambling. According to the patient and his wife, he never mismanaged his finances and business and never had sexual relationship outside his marriage prior to this episode. His wife expressed shock and disbelief of his behavioural changes. There was a family history of bipolar disorder but he never had any past history of spontaneous hypomania. Further, there was no evidence suggestive of personality and substance-abuse disorders. Considering that these behavioural changes were hypomanic in nature, divalproex sodium 750 mg/day was substituted for lamotrigine (Divalproex appears to demonstrate a more robust antimanic prophylactic effect as compared to lamotrigine). Citalopram was decreased to 20 mg/day and divalproex sodium was increased to 1250 mg/day (plasma concentration 400 mmol/l). After a couple of weeks, he regained good insight about his previous risk taking impulsive behaviours. He sold his business to a new ownership and he got a job in a different firm. He maintained euthymia with the combination of citalopram 20 mg/day and divalproex sodium 1250 mg/day.

2.4. Case 4

A 56-year-old, separated, Caucasian woman with a 6-month history of depression following ischemic stroke involving right carotid territory was referred to post stroke mood clinic for evaluation and treatment of her depression. MRI showed right internal carotid artery dissection causing watershed infarcts within periventricular region. She underwent a stent surgery within a week after stroke. Major depression began 3–4 weeks after the stroke, which gradually worsened despite full neurological recovery. Prior to the stroke she had a long history of anxiety disorder and characterological depression. Citalopram was initiated at the dose of 20 mg/day and was increased gradually to 60 mg/day. After 8 weeks of citalopram monotherapy, methylphenidate 20 mg/day was added to mitigate the residual anergia and amotivation. Although she evidenced a complete recovery from depression with the combination treatment, she relapsed within 3 months after she returned to work. Venlafaxine (serotonin norepinephrine reuptake inhibitor) was prescribed after discontinuation of citalopram and methylphenidate. When she was taking venlafaxine at the

dose of 300 mg/day with risperidone 0.5 mg/day (for severe guilt feelings) she became more energetic, socially active. Her daughter and close friends raised concerns regarding her rapid voluminous speech in social gatherings and increased socialization.

On further enquiry, patient disclosed that she had been buying antiques through the Internet (E-Bay) using her credit cards and accumulated a debt of 3000 dollars within 2 weeks. She openly criticized a television talk show host on a live show. She was also writing critical letters to a local newspaper about government policies. Her sleep apparently was diminished with initial insomnia during this period. Her over assertiveness, and impulsive buying were considered to be out of her normal character and she never had a history of impulse-control disorders or borderline-personality disorder. Further, there was no family or past history of bipolar disorder. Repeat neurological examination, electroencephalogram (EEG) and computerized tomography (CT) scans did not reveal any progression of cerebrovascular disease or evidence of seizure disorder. Her blood pressure was normal with antihypertensive medication (ramipril 5 mg/day) and her thyroid stimulating hormone level was normal. On cross-sectional examination she did not have any evidence suggestive of hypomanic moods or increased psychomotor activity, pressure of speech, grandiosity, flight of ideas. Addition of divalproex 1000 mg/day at bedtime (plasma concentration 420 mmol/l) resolved behavioural changes and sleep disturbance within 2–3 weeks. There were no reports of hypomanic behaviour in the subsequent 6 months of follow up.

2.5. Case 5

A 54-year-old, married, Caucasian man was referred to the post-stroke mood clinic with a history of probable major depression associated with one minor stroke and one transient ischemic attack involving left carotid territory. MRI did not show any infarct. His blood pressure and hyperlipidemia were under control with entalapril 10 mg/day and atrovastatin 10 mg/day. After the diagnosis of major depressive disorder was established, citalopram was prescribed at the dose of 20 mg/day and increased to 40 mg/day over a period of 4 weeks. He responded well to the citalopram treatment and remained asymptomatic for several months. Then he resumed his job as a truck driver in a local municipality office and was also attending mood clinic for monthly follow-ups. Although he was observed to be normothymic on cross-sectional mental status examination, several complaints about his recent behavioural changes were made by his employer, co-workers, stroke neurologist and family doctor. He was reported to be increasingly verbally abusive, aggressive and excitable in social situations. He seemed to get involved in arguments frequently with others. Patient also admitted feeling more angry and irritable in social situations for trivial reasons. However, he justified his angry outbursts saying that he could not tolerate insults, exploitations, disrespect from others. Sleep was disturbed with early insomnia. His wife did not notice any major changes in his mood or behaviour at home. Mental status examination performed after the disclosure of behavioural change did not reveal any hypomanic moods, pressure of speech, flight of ideas or grandiosity.

He had a history of childhood sexual abuse and post-traumatic disorder, which was reported to be resolved with long-term psychotherapy. Initial psychiatric evaluation did not reveal personality, impulse control, substance abuse or bipolar disorders. A repeat neurological, EEG and CT scans did not show any fresh neurological deficits or brain infarcts. Reducing the dose of citalopram to 20 mg/day resolved verbal aggression, but his depression got worse. Then citalopram was increased to 40 mg/day and epival 1000 mg/day (plasma concentration 386 mmol/l) was added gradually. He maintained the normothymic state without any behavioural activation following the changes in medication.

3. Results: clinical evaluation of the problem behaviours

At the phenomenological level, these problem behaviours reported in these case series could be characterized as impulsive or disinhibited behaviours since these behaviours concur with the characteristics of impulsiveness (failure to resist impulse, drive, or temptation, deficient tolerance of delay of gratification, inability to inhibit or delay voluntary behaviours). They were considered as dysfunctional and maladaptive because of negative social and financial consequences.

At the syndromal level, they were judged to be the expression of minor form of hypomania because these dysfunctional, risky behaviours were associated with sleep disturbances, poor judgement and insight, and were uncharacteristic of the patients, and changes in behaviours and functioning were observed by others. Further they could not be accounted for by previous history of primary impulse control personality or psychotic disorders. Hypomanic behaviours are diagnostically and clinically more important than hypomanic moods in spontaneous hypomanic states (Benazzi and Akiskal, 2003b; Angst et al., 2003). However, these patients did not meet the DSM IV criteria for hypomania or mania due to the absence of historical or clinical evidence of persistent hypomanic moods (elevated, irritable). This aspect has been further discussed in the discussion section.

At the etiological level, these behaviors were judged to be related to antidepressant treatment because the emergence of these behaviours was temporarily related to antidepressant treatment. Further, in two patients, these behaviours were correlated with high doses of SSRIs (cases 1 and 2) and reduction of SSRI antidepressants resolved the behaviours rapidly in three patients (cases 1, 2 and 5) suggesting a dose-dependent relationship between hypomanic behaviours and SSRI treatment (Ramasubbu, 2001).

The addition of anti-manic agent (divalproex) resolved problem behaviours in two patients (cases 3 and 4).

Three patients (cases 3, 4 and 5) had a history of brain vascular lesions which might have contributed to impulsive behaviours and impaired judgement. This raises the diagnostic possibility of personality change due to stroke. However, the temporal relationship between antidepressant treatment and the emergent impulsive behaviours and rapid resolution of these symptoms with pharmacological intervention suggest that they were antidepressant-treatment related. The higher representation of depression associated with stroke in this case series reflect the author's involvement in providing psychiatric services for patients with post-stroke depression and hence this clinical observation of behavioural activation during antidepressant treatment cannot be generalized to other patients with post-stroke depression. At the same time it is possible that stroke patients might be more vulnerable to develop dysfunctional behavioural activation secondary to antidepressant treatment.

4. Discussion

This clinical report is the first to document that antidepressant-associated manic states may include behavioural expression of milder forms of hypomania in addition to Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM IV) (American Psychiatric Association [APA], 1994) defined hypomania, mania and rapid cycling. Furthermore, this case series demonstrate that dysfunctional behavioural activation could be a predominant clinical manifestation of antidepressant-associated hypomania.

There are several reasons for the failure to recognize or report hypomanic behaviours during the antidepressant treatment as the milder expression of antidepressant treatment emergent hypomania. First, most studies investigating antidepressant-associated manic states used descriptive approach based on DSM IV (APA, 1994) and International Classification of Diseases-Tenth Edition (ICD-10) (World Health Organization [WHO], 1992) diagnostic criteria which do not recognize the concept of subthreshold or minor forms of hypomania. Furthermore, both diagnostic systems considered the hypomanic moods as more fundamental than hypomanic behaviour in diagnosis of hypomania (DSM IV, APA, 1994; ICD-10, WHO, 1992). Since these internationally recognized diagnostic systems are widely used in psychiatric practice, clinicians will be reluctant to consider the diagnosis of hypomania in the absence of observable hypomanic moods. However, given the wide range in the reported incidence rates of antidepressant-associated hypomania (Akiskal et al., 1995; Coryell et al., 1995; Kupfer et al., 1998; Nasarallah et al., 1982; Peet, 1994; Rouillon et al., 1992), it is possible that there might be differences in the identification of hypomania between studies and hypomanic symptoms or behaviour might have been reported as hypomania by some but had not been explicitly stated. Second, the prominence of behavioural activations coupled with less observable and fluctuating hypomanic moods could be regarded as manifestations of personality disorder or impulse control disorder. Third, the lack of subjective suffering and insight regarding these behaviours may prevent reporting to clinicians or seeking treatment. Fourth, these behaviours can be concealed from significant others and often can be missed by clinicians due to the absence of overt hypomanic moods during the follow up care.

The reported dysfunctional behaviours in this case series may occur in conditions other than hypomanic state, which needs further discussion. Since dysfunctional impulse behaviour is the stem criteria for impulse-control disorders or associated feature of other mental disorders such as substance abuse and personality disorders, they should be ruled out prior to considering that these impulse behaviours were signs of hypomania. Most of the primary impulse control disorders typically begin in early adolescence and remain chronic (DSM IV, APA, 1994). However, in this case series, these behaviours were non-existent prior to antidepressant treatment and lasted for a limited period of time and resolved quickly with reduction of antidepressants or addition of mood stabilizers. Unlike patients with impulse-control disorders, the patients reported in this case series did not have a past history of primary impulse-control disorders, substance abuse disorders or associated antisocial and borderline personality disorders.

It could be argued that the treatment emergent impulsive behaviours might represent impulse-control disorders secondary to antidepressant treatment. However, there is more evidence to support the anti-impulsive effect of SSRIs than its impulsogenic potentials (Kim and Grant, 2001). Compared to vast literature concerning antidepressant-associated hypomania (Akiskal et al., 1995; Coryell et al., 1995; Kupfer et al., 1998; Nasarallah et al., 1982; Peet, 1994) there were only a few case reports documenting the association of antidepressant treatment with the emergence of impulsive behaviours such as hypersexual behaviour and kleptomania (Adamou and Hale, 2003 ; Elmore and Quattlebaum, 1997; Kindler et al., 1997). Furthermore, in one report (Elmore and Quattlebaum, 1997) the three women who manifested with SSRIs induced hypersexuality had had clinical indicators of bipolarity (depression with psychosis) and other common, co-morbid conditions of bipolar illness including alcohol abuse, attention deficit disorder and personality disorders. Hence it is possible that the hypersexual behaviours emerged during SSRIs treatment in these patients could be the soft signs of hypomania.

The rare occurrence of SSRIs-induced impulse-control disorders coupled with documented efficacy of SSRIs in the treatment of impulse-control disorders support the serotonin deficient hypothesis of impulse-control disorders. The observed paradoxical impulsive behaviours associated with

antidepressant treatment have been speculated to be due to dose dependent activation of dopamine and or noradrenergic neurotransmission during treatment with sertraline, paroxetine and venlafaxine (Elmore and Quattlebaum, 1997; Kindler et al., 1997). Similar mechanisms involving dopamine and noradrenergic systems have also been implicated in hypomanic and manic states that could explain the interrelationship between bipolarity and impulsivity (McElroy et al., 1996).

The fundamental question is how these impulsive dysfunctional behaviours could be qualified as hypomanic behaviour in the absence of observable elated or irritable mood. Emerging evidence suggest that impulsivity and bipolarity are interrelated (McElroy et al., 1996; LeJoyeux et al., 2002). Impulsive behaviours are common in bipolar disorder and vice-versa. Impulse-control disorder and bipolar disorder share common psychophysiologic abnormalities (McElroy et al., 1996). The evidence from two major studies supports the importance of hypomanic behaviours in the expressions of spontaneous hypomania or Bipolar II disorder. Based on the results from a large epidemiologic cohort (Angst et al., 2003) advocated the inclusion of hypomanic behaviour (symptoms of overactivity) as essential criterion of hypomania just as euphoria or irritability. Similarly, in a recent study, energized activity emerged as a prominent clinical factor with greater diagnostic importance than elated mood in self-rated hypomania in a large outpatient population with combined sample of unipolar and bipolar disorders (Benazzi and Akiskal, 2003b). Consistent with above reports, this clinical observation suggests that antidepressant-associated hypomania may also be predominately manifested with hypomanic behaviours rather than with hypomanic moods. This awaits further investigation.

Prior to discussing the implications, the limitations of this clinical observation need to be addressed. First, this is a small case series of five depressed patients with three patients having secondary depression due to stroke. This limits generalization. Second, the diagnostic or clinical importance of hypomanic behaviours reported in spontaneous hypomania may not be applicable to antidepressant induced hypomania with out empirical evidence from large data. Third, this clinical observation should not mislead clinicians because not all behavioral activation during antidepressant treatment can be considered as expression of hypomania unless there are other associated disturbances such as poor sleep, impaired judgement, insight and functioning. Compensatory behavioral activation related to euthymia should be considered as differentials.

If proven in a large data, hypomanic behaviour as a predominant expression of antidepressant-associated hypomania may have clinical and research implications. In accordance with the recent findings of large epidemiologic studies (Angst, 1998; Angst et al., 2003; Benazzi and Akiskal, 2003b) the inclusion of hypomanic behaviour as stem criterion in the diagnostic criteria for hypomania may facilitate the recognition or identification of milder expressions of hypomania manifesting in the form of hypomanic behaviour both in spontaneous and antidepressant-associated hypomania. As observed in this case series, hypomanic behavioural symptoms could be more reliably elicited and corroborated with collateral information than hypomanic moods. In minor forms of hypomania, the symptoms of hypomanic moods may be more subjective, less observable and less pervasive than in full-blown or DSM IV (APA, 1994) defined hypomania. Hence, subjective and behavioural specific mood elation or irritability could be easily missed in cross-sectional clinical evaluation as in this case series.

Careful clinical enquiry about the behavioural indicators of hypomania during treatment with antidepressants may facilitate earlier identification and appropriate management of antidepressant-associated hypomania. Failure to identify or recognize antidepressant-associated hypomanic behaviour may lead to misdiagnosis and mismanagement of these behaviours as symptoms of impulse-control disorders or associated feature of depression with the resulting increase in the doses of SSRIs or antidepressants. Since antidepressant-associated hypomania could be a manifestation of bipolar spectrum disorder missing this phenomenon may result in financial, vocational and medico-legal consequences.

The major concerns in recognizing the existence of minor forms of antidepressant-associated hypomania will be over-diagnosis of hypomania secondary to antidepressant treatment or bipolar disorder with the resulting increased utilization of mood stabilizers. The over-diagnosis of antidepressant induced secondary hypomania on the basis of hypomanic behaviour can be minimized by a careful clinical assessment as discussed in the previous section. However, the recognition of the nosological status of antidepressant-associated hypomania as bipolar type III (Akiskal et al., 2003) may contribute to over-diagnosis of bipolar disorder.

The recent introduction of operational diagnostic criteria for bipolar spectrum disorder (BSD) (Ghaemi et al., 2002) will help to distinguish BSD from pharmacologically induced secondary hypomania in patients with antidepressant treatment-associated hypomania. Following these criteria, BSD can be diagnosed even in the absence of spontaneous hypomania or mania. Antidepressant-associated hypomania in patients with anxiety or other non-mood disorders would not qualify for the diagnosis of BSD. Furthermore, the presence of antidepressant-associated hypomania in major depression is not sufficient for the diagnosis of BSD unless the criterion of clinical indicators of bipolarity is met. However there is a limitation in this criteria. Although family history of bipolar disorder is a recognized risk for antidepressant-associated manic switch (Howland 1996), the importance of it can be overlooked if the existing criteria for BSD are applied. Hence, it might be appropriate to consider family history of bipolar disorder as

an equivalent criterion to clinical indicators of bipolarity for the diagnosis of BSD in antidepressant-associated hypomania. This needs further validation. On the basis of this modified BSD criteria, case 3 can be considered as BSD.

The potential advantages of improved awareness of the magnitude of this problem will facilitate more research with respect to the utilization of non-pharmacological approaches (cognitive behavioural and interpersonal therapy) in the long-term maintenance treatment of unipolar depression. In addition, this would facilitate research into the discovery of novel agents with both antidepressant and mood-stabilizing properties such as lamotrigine (Calabrese et al., 1999). More research on minor forms of antidepressant-associated hypomania may improve our understanding of its prevalence, nature and relationship with bipolar disorder.

5. Conclusions

This report suggests that emergent dysfunctional behavioural activation during antidepressant treatment may represent milder expression of hypomania. More studies are warranted to determine the clinical and diagnostic importance of hypomanic behaviour both in spontaneous and antidepressant-associated hypomania.

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