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Journal of Affective Disorders 84 (2005) 267–272

JOURNAL OF AFFECTIVE DISORDERS

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Preliminary communication

Antidepressant-associated chronic irritable dysphoria (acid) in bipolar disorder: a case series

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Received 28 July 2003; accepted 18 August 2004

Abstract

Background: Antidepressants administered to bipolar subjects may induce manias, mixed states, or rapid cycling. More recently, we have noted that long-term use of antidepressants may induce a chronic dysphoric, irritable state.
Method: A case series is presented in which six type I bipolar subjects receiving antidepressants continuously for several years developed chronic irritable dysphoria.
Results: A triad of dysphoric mood, irritability, and middle insomnia that is frequently associated with occupational and social dysfunction can occur in some bipolar patients receiving antidepressants for at least 3 years. Typically, initial treatments with antidepressants for the index episode were effective. Over time, depressive symptoms returned and would transiently improve with dose increase or change of agents. Ultimately, the dysphoria and associated symptoms became chronic and resulted in dysfunction. Concomitant mood stabilizer did not appear to alter this pattern. Discontinuation of antidepressants was associated with a slow and gradual improvement in these symptoms over the ensuing year.
Conclusion: Additional studies are required to investigate safety of long-term use of antidepressants in bipolar illness.

1. Introduction

Depression in bipolar disorder may be particularly problematic. Judd et al. (2002, 2003) found the duration of depression accounts for three to four times the duration of mania or hypomania. Antidepressants appear to be beneficial in the short-term management of bipolar depression (Himmelhoch et al., 1982, 1991; Cohn et al., 1989; Simpson and DePaulo, 1991; Thase et al., 1992; Amsterdam, 1998; Amsterdam et al., 1998; Biederman et al., 2000). Unfortunately, over the last three decades, evidence has accumulated that antidepressants may induce mania or rapid cycling in some bipolar subjects (Kukopulos et al., 1980; Ghaemi et al., 2000, Wehr and Goodwin, 1987; Stoll et al., 1994; Altshuler et al., 1995).

While the absolute rate of induction of mania secondary to antidepressant treatment is quite variable, it is consistently two to three times the back-

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0165-0327/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2004.08.004

ground rate (Angst, 1985; El-Mallakh and Karippot, 2002). Additionally, subjects with cyclothymia may convert to a type II illness when given antidepressants (Akiskal et al., 1977). Antidepressant-induced manias have a significant irritable component (Stoll et al., 1994). They resolve relatively quickly once the antidepressant is discontinued (Stoll et al., 1994). However, not all studies have found an increase in manic induction, and this remains a debated topic in psychiatry. In an influential study performed by Lewis and Winokur (1982), antidepressants did not appear to increase manic relapse risk.

In the pre-antidepressant era (pre-1950s), rapid cycling among bipolar subjects was quite rare (Kukopulos et al., 1983). Since then, several studies have now confirmed that antidepressants are associated with rapid cycling (Kukopulos et al., 1983; Wehr et al., 1988; Altshuler et al., 1995; Ghaemi et al., 2000). Kukopulos et al. (1983) found that in 80 subjects, onset of rapid cycling was associated with antidepressant treatment that continued through euthymic periods (n=17), or persisted at least 1 year (n=33), 2 years (n=14.), or longer (n=5). Rapid cycling faded quickly in 29% of 51 subjects studied by Wehr et al. (1988), and in 8 of 9 subjects studied by Altshuler et al. (1995). Altshuler et al. (1995) also noted that individuals who had previously experienced antidepressant-induced manic induction were the ones most likely to have antidepressant-associated rapid cycling.

We have noted a phenomenon that is probably related to rapid cycling. Several bipolar individuals who received long-term antidepressant treatment developed a chronic, dysphoric, irritable state [Antidepressant-associated Chronic Irritable Dysphoria (ACID)]. Improvement following antidepressant discontinuation was slow, gradual, and usually required months. A similar phenomenon was noted by Akiskal and Mallya (1987). They described 25 patients with bipolar spectrum illness who were referred for treatment-resistant depression, and in whom chronic use of tricyclic antidepressants was associated with a chronic irritable, dysphoric state (Akiskal and Mallya, 1987).

2. Case series

We are reporting on six individuals with a remarkably consistent pattern of antidepressant-associated worsening. Most had type I illness with an average duration of illness of 9.7 years. All received continuous antidepressant treatment for a protracted period of time (mean 6.6 years, range 3–7 years). They were followed for 13.7 months after discontinuation of antidepressant. All subjects had experienced significant dysphoria, irritability, and middle insomnia and exhibited severe social and occupational dysfunction. Prior to antidepressant discontinuation, five had stopped working, two lost their homes, and one had declared bankruptcy. Two had terminated long-term relationships, and two had significant relationship problems. The following case histories provide a better understanding of the course of these events.

2.1. Case 1

Mr. A is a 29-year-old married man with a 6-year history of bipolar illness. For the preceding 5 years, he had received lithium and a variety of serotonin reuptake inhibiting (SRI) antidepressants (paroxetine, sertraline, fluoxetine). Despite ongoing antidepressants and several attempts at optimization of treatment, he noted slowly increasing depressed mood, frustration and irritability, amotivation, middle insomnia, and difficulty at work. At the time of antidepressant discontinuation, the patient had been unable to work for 6 months and was experiencing significant marital discord. Discontinuation of antidepressant was not associated with an immediate change in symptoms and low-dose quetiapine (25–100 mg/day) was used to provide mild tranquilization. Approximately 4 months after discontinuation of antidepressants, the patient began working (in temporary and part-time jobs). He noted a significant improvement in mood, irritability, and his ability to concentrate. At 1 year after discontinuation of antidepressants, he was working (in a permanent job) with no marital problems. The only residual symptom was ongoing early insomnia (the middle insomnia had resolved).

2.2. Case 2

Mr. B is a 45-year-old divorced man with a certificate in public accountancy. He had a type II bipolar illness which was diagnosed 7 years pre-

viously. He was initially treated with sertraline. Lithium was added when his hypomanic episodes were recognized after 4 years of antidepressant treatment. Prior to sertraline discontinuation, he was experiencing persistent dysphoria, irritability and decreased frustration tolerance, labile mood, and a sleep disturbance with both early and middle insomnia. These symptoms had previously improved transiently with sertraline dosage increases, but had become continuous for at least 1 year. He became unable to maintain continuous employment and declared bankruptcy. His mother supplemented his income so that he was able to keep his house. He separated from his girlfriend and his infant son. Sertraline was tapered and lamotragine was added to lithium and advanced to 200 mg/day. There was minimal initial change in his symptoms. After 1 year off sertraline, the patient was able to work full time. He improved his financial situation and reconciled with his girlfriend. Despite the notable improvement in his quality of life, he continued to complain of dissatisfaction with life and to experience mild variations in mood and energy.

2.3. Case 3

Ms C is a 48-year-old lesbian attorney with type I bipolar illness for 5 years. Following onset of her illness, she was treated with divalproex, paroxetine, and amitriptyline. She experienced initial improvement. Her symptoms appeared to recur with worsening depressed mood, irritability, middle insomnia, lethargy, and poor motivation. Changes in antidepressant treatment resulted in progressively briefer transient improvements. She became unable to work, lost her home, and broke up with her lover. Ultimately, after 4 years of continuous antidepressant exposure, her most recent regiment was discontinued (paroxetine, nefazodone, and trazadone). Divalproex was continued and quetiapine (25–75 mg/day) was added transiently. She became asymptomatic 4 months later, restarted a private practice as an attorney, and reestablished her lesbian relationship.

2.4. Case 4

Mr. D is a 61-year-old married man with a type I bipolar illness for over 13 years. He had initially done quite well with lithium alone for 8 years. When he experienced a depressive episode, antidepressants were started. Initial nonresponse to SRIs was followed by a good response to doxepin. However, 2 years after continuous treatment with lithium and doxepin, he noted a crescendo of depressive episodes to a rapid cycling pace of 4 per year for two consecutive years. This was followed by a great increase in the number (1–2/month), but briefer duration of depressive episodes for the last 2 years. In addition, the interepisode period was characterized by a continuous dysphoric, irritable, low-energy state. He took a leave of absence from his work, and was making plans to discontinue his job as a minister. Doxepin was discontinued and zolpidem or lorazepam used intermittently for insomnia. The brief depressive episodes continued for 5 months and then became less frequent. Interepisode mood improved markedly but residual mild irritability and dysphoria persisted. Insomnia was episodic. Over the 16 months off doxepin, he experienced two significant depressive episodes that responded well to transient, brief (2 months) use of bupropion. He returned to work full time and felt he was more effective.

2.5. Case 5

Ms E is a 34-year-old woman with a type I bipolar disorder since age 19. She was treated over the previous 6 years with a mood stabilizer (lithium or divalproex) and an antidepressant (most recently sertraline). She complained of persistent depression, irritability, middle insomnia, and loss of motivation. She slowly withdrew from all her friends, became unable to work, and failed at attempts to return to school. Her financial state declined and she had to sell her house and move in with her parents. Sertraline was discontinued and she was maintained on lithium with occasional alprazolam for anxiety. There was no immediate change in her symptoms, but 7 months later, she felt more energetic and returned to work. At 1-year follow-up, she had obtained and maintained a full-time job, moved out of her parents' home and married. She continued to have ongoing unhappiness and anxiety, but the irritability and middle insomnia resolved. One episode of mild mania was treated as an outpatient with transient use of olanzapine.

2.6. Case 6

Ms F is a 52-year-old married woman with type I bipolar illness for 12 years. Most recently, she was treated with bupropion for depression, clonazepam for anxiety, and maintained on divalproex for her bipolar illness. After initial resolution of the depression, she noted a gradual onset of persistent depressed mood, significant irritability, middle insomnia, and anxiety. Antidepressant was discontinued. At 4 months, there was a noted mild improvement; at 6 months, she had total resolution of the dysphoria, insomnia, and irritability. Ongoing anxiety prevented taper of clonazepam.

3. Discussion

These patients share several characteristics. All received antidepressants for protracted periods of time. All had a good antidepressant response for their index depressive episodes which persisted for at least several months. All had recurrent depressive symptoms while still taking the antidepressant, which would transiently improve with optimization of antidepressant treatment. And all experienced severe work or social dysfunction. A triad of irritability, dysphoria, and middle insomnia was noted in all six subjects. There was minimal change in clinical status immediately after antidepressants were discontinued. Beginning at 2 months, and slowly increasing thereafter, the subjects noted an improvement in dysphoria, irritability, middle insomnia, and other symptoms. Return of occupational function occurred relatively late in the course of recovery and was frequently associated with difficulties.

A similar phenomenon was described by Akiskal and Mallya a quarter of a century ago (1987). They presented 25 subjects with bipolar spectrum disorder who had been treated with tricyclic antidepressants for an extended period of time. After an initial good response, these subjects entered into a chronically symptomatic state. Similar to our sample they developed the following: "(1) unrelenting dysphoria, (2) severe agitation, (3) refractory anxiety, (4) unendurable sexual excitement, (5) intractable insomnia, (6) suicidal obsessions and impulses, and (7) 'histrionic' demeanor" (Akiskal and Mallya, 1987). Similar to our subjects, these patients also improved after discontinuation of antidepressants and initiation of lithium or carbamazepine.

The process leading to these symptoms is probably related to the one leading to rapid cycling. Previous workers have noted that cycling may accelerate to the point that the illness becomes continuous (Crane, 1956; Arnold and Kryspin-Exner, 1965; Kukopulos et al., 1980; Wehr et al., 1988, pp. 23–26). In other words, as cycling accelerates, the course of bipolar illness is altered from episodic to chronically continuous (Arnold and Kryspin-Exner, 1965; Kukopulos et al., 1980). It is possible that ACID is a milder manifestation of this same phenomenon. Alternatively, this may represent a process that is parallel to the observation of loss of antidepressant efficacy in unipolar depression (reviewed in Byrne and Rothschild, 1998).

The slow time course of both onset and resolution suggests that the process may involve antidepressant-induced neuroplastic changes (El-Mallakh et al., 1999, 2000). Studies with the simple nervous systems of snails show that alteration of synaptic serotonin levels alters axonal branching. Specifically, increasing synaptic serotonin (Baker and Croll, 1996) (as probably occurs with antidepressants; Bel and Artigas, 1992). For example, one can hypothesize that a relative serotonin deficit (depression) might transiently improve with a serotonin reuptake inhibitor. However, the excess synaptic serotonin may reduce serotonergic neuron branching thereby aggravating the original problem, or inducing a chronically similar state (dysphoria).

These observations are clearly tentative. A small sample and numerous uncontrolled factors raise the possibility that alternative explanations may exist. The course of bipolar illness can be quite varied and spontaneous remissions of symptomatic states cannot be ruled out. ACID superficially resembles the depressive mixed states in type I bipolar patients of Perugi et al. (2001) and some unipolar depressive patients (Benazzi, 2001); it is important to note that such states are episodic while ACID is continuous. In type II bipolar patients, depressive mixed states occur in the absence of antidepressant treatment and may be either episodic or fluctuating-chronic (Benazzi and Akiskal, 2001; Akiskal and Benazzi, 2003). Furthermore, the unfailing presence of the symptomatic triad

of dysphoria, irritability, and middle insomnia is notable. Larger, randomized, prospective studies of patients treated continuously (as is currently recommended for recurrent major depression) or intermittently (as is currently the practice for patients who experience antidepressant worsening but still require antidepressant treatment) with antidepressant may answer the question. Our data run contrary to the recommendations of Altshuler et al. (2003), who suggested that bipolar patients who respond to antidepressants should continue receiving them, if they are on mood stabilizers. Our patients did initially respond to antidepressants, and despite coverage with mood stabilizers, developed the ACID syndrome. Large naturalistic data bases [such as is currently being amassed in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study] may yield useful information on this unresolved issue.

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