SUICIDAL RISK EMERGING DURING ANTIDEPRESSANT TREATMENT: RECOGNITION AND INTERVENTION

Maurizio Pompili, Leonardo Tondo, and Ross J. Baldessarini

Summary

Object: To review current understanding of risks of adverse behavioral responses to antidepressant treatment that include newly emerging agitation, anger, and suicidality.

Method: We report a series of illustrative cases after briefly reviewing the relevant research literature.

Results: We describe 10 cases involving suicidality arising with increasing anxiety, insomnia, restlessness, agitation, irritability, anger, psychosis, or mixed manic-depressive features. In each case, rapid improvement followed recognition of the problem, stopping or curtailing antidepressant treatment and adding or substituting an antimanic, antipsychotic or anxiolytic agent.

Conclusions: Suicidality can emerge with virtually any mood-elevating agent, particularly if given without a mood-stabilizing or other protective agent in vulnerable persons, notably those with known or previously unrecognized bipolar disorders. We suggest risk- or early-warning factors to aid in the timely recognition of such reactions, as well as means of limiting their danger. We also propose that they be considered manifestations of a recognizable cluster of symptoms, in which suicidality is not an isolated phenomenon.

Key Words: Aggression – Agitation – Antidepressants – Suicidal risk

Declaration of interest: Dr. Baldessarini serves as a consultant or has engaged in research studies with several pharmaceutical corporations that produce antidepressant, antipsychotic, or mood-stabilizing drugs

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Major affective disorders, particularly major depression and the depressive or mixed-dysphoric phases of bipolar disorder, are strongly associated with suicidal behavior. Risks for suicide average approximately 20-times greater in such illnesses (Harris and Barraclough 1997, WHO 2004, Tondo and Baldessarini 2005), and the ratio of attempts to fatalities is several-times lower than in the general population, indicating higher average lethality of attempts or greater lethal intent (Tondo et al. 2003, Tondo and Baldessarini 2005). The general symptomatic clinical effectiveness of modern antidepressant, antimanic, and mood-stabilizing treatments is well established (Baldessarini 2005, Baldessarini and Tarazi 2005). However, only recently have the effects of such treatments on suicidal behavior and the increased overall mortality associated with major psychiatric disorders become a focus of research interest (Angst et al. 1998, Baldessarini and Jamison 1999, Meltzer and Baldessarini 2003).

Among modern psychotropic drug treatments, only long-term use of lithium salts has shown substantial and consistent evidence of reduced risk of completed suicides as well as life-threatening attempts among persons with a range of manic-depressive disorders (Baldessarini et al. 2001, 2003; Tondo et al. 2001; Tondo and Baldessarini 2005). This evident beneficial effect of lithium treatment appears to be greater than that associated with other antimanic agents including carbamazepine (Thies-Flechtner et al. 1996), divalproex (Goodwin et al. 2003), and perhaps lamotrigine (Bowden et al. 2003; Calabrese et al. 2003). Uniquely among antipsychotic drugs, there is also evidence of reduction of at least nonfatal suicidal risks by long-term clozapine treatment of chronically psychotic patients (Meltzer et al. 2003, Hennen and Baldessarini 2005).

Surprisingly, the available evidence indicates no overall average difference in risk of suicides or attempts among depressed patients treated with either older or

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modern antidepressants (Baldessarini 2005; Baldessarini et al. 2005a, b), although there may be beneficial effects on suicidal thinking as other depressive symptoms improve (Montgomery 1992, Möller and Steinmeyer 1994). Explanations for the evident lack of overall beneficial effect on risk of suicides and attempts during treatment with antidepressant drugs are currently lacking, but various possibilities are considered elsewhere in this issue, including limitations in the clinical effectiveness of antidepressants, particularly in younger age-groups, and for some features of depressive illnesses that may be particularly pertinent to suicidal risk, as well as technical limitations of available studies of antidepressant treatment and suicide (Baldessarini et al. 2005b). An additional possibility is that antidepressants may have both beneficial and adverse effects, with a net null average impact on suicidal risk.

Support for this counter-intuitive possibility has been suggested by a long tradition of clinical observations. These include the proposal that temporal separation of relatively earlier energizing effects of mood-elevating drugs from later benefits on anhedonic features of depression might increase risk of suicidal behaviors during recovery from acute major depressive episodes (Schweitzer et al. 1988, Matthews and Fava 2000). Additional support can be found in a series of clinical observations of newly emerging aggressive and suicidal preoccupations or behaviors among patients being treated with antidepressants. Such reactions may or may not be more likely with modern selective serotonin-reuptake inhibitors (SRIs) than with older antidepressants such as tricyclics (TCAs). They have been associated with over-stimulation, restlessness resembling akathisia, agitation, insomnia, severe anxiety, mixed-dysphoric bipolar states, or psychosis in some antidepressant-treated patients (Baldessarini and Willmuth 1968; Teicher et al. 1990, 1993; Damluji and Ferguson 1988; Healy and Whitaker 2003). Such seemingly paradoxical effects of antidepressant treatment have received renewed attention in recent international discussions of risk/benefit considerations arising from studies of SRIs in juvenile depressive disorders. These discussions consider the seemingly limited benefits of antidepressant treatment of all types in juvenile depression against concern about potential increases in broadly defined suicidality that includes still-uncertain risks of life-threatening suicide attempts and very low rates of completed suicides (US FDA 2004, Whittington et al. 2004).

The scientific and clinical significance of effects of antidepressant treatment on risks of suicidal or other aggressive and otherwise dangerous behaviors requires further critical study. Nevertheless, our clinical impression is that antidepressant treatment can present certain behavioral risks that require close clinical monitoring, ongoing differential clinical assessment, and appropriate interventions to optimize the effectiveness and safety of antidepressant treatment. As a contribution to improved clinical practice, in this report, we summarize representative experiences that illustrate these clinical challenges and suggest effective means of managing them.

Case reports

Case 1. A 45 year-old part-time laborer had a 10-year history of "double-depression," with dysthymia and at least three episodes of major depression, all without suicide attempts. He had many treatment trials, most recently including paroxetine, fluoxetine, and *R,S*-citalopram. He presented in an acute episode of major depression, and was started on nortriptyline. As the daily dose was gradually increased over four weeks to 150 mg, he became newly and increasingly agitated, irritable and anxious. He reported new angry and aggressive feelings towards neighbors, with whom he had always been friendly, as well as suspiciousness about their intentions toward him. He also acknowledged new preoccupations with thoughts of suicide, and imagined jumping from a high window. In view of these emerging angry, aggressive, and agitated changes, paranoid flavor, and newly emerging suicidality, nortriptyline was gradually discontinued over a week, and replaced with quetiapine (gradually increased to 800 mg/day) and lamotrigine (slowly increased to 200 mg/day). Within another week, he showed striking improvement, as he became less dysphoric, irritable, suspicious, and potentially aggressive, much less restless and agitated, and his suicidal thoughts virtually disappeared.

Case 2. A 63 year-old housewife had experienced recurrences of major depressive episodes every year or two after an initial episode during mid-adolescence; one serious suicide attempt led to psychiatric hospitalization for five months. She tended to be unusually energetic, sociable and generous in periods between depressive episodes. At presentation, she complained that her family were unsupportive, and reported increasing depression, with moderate initial insomnia and anxiety, but denied recent or current suicidal thinking or plans. A trial of paroxetine, gradually increased to 40 mg/day over four weeks, led to some improvement in her depressed mood, but was associated with intolerable nausea. A change to *R.S*-citalopram (to 30 mg/day) was better tolerated initially, but over another four weeks, she became increasingly sleepless, dysphoric, irritable, and newly agitated, with repeated rubbing and scratching of her hands, face and hair. She also reported newly emerging suicidal thoughts that culminated in an impulsive overdose with approximately 300 mg of citalopram that required brief evaluation at a hospital emergency service. The antidepressant was removed over a period of 5 days, and replaced with a moderate dose of divalproex (250 mg twice daily), supplemented with a low dose of chlorpromazine (50 mg) at bedtime. In less than another week, she was no longer restless or irritable, slept better, and denied further suicidal thoughts.

Case 3. A 38 year-old unemployed laborer had been diagnosed in his early 20s with schizoaffective disorder, mainly with retarded-depressive features, but with periods of excitement and agitation as well, variable unreasonable suspiciousness and occasional auditory hallucinations. He had also abused alcohol and cannabis chronically, but had never been suicidal. He was variably cooperative with treatment that nominally included olanzapine (5 mg/day) and lithium carbonate (900 mg/day), and had discontinued all medication for at least three months. At presentation, he was severely depressed, and was treated initially with fluoxetine (20 mg/day). Over the following three weeks, he became

increasingly pessimistic, anxious, angry, and reported feeling purposeless and artificial energy, a tendency to awaken earlier before daylight, and previously unfamiliar preoccupation with suicidal thoughts. His relationships with family members and neighbors deteriorated, due to his increasing hostility and suspiciousness, despite some improvement in his depressed mood. The antidepressant was continued, but supplemented with olanzapine, starting at 10 mg daily, and later 20 mg. Within 10 days, his acute irritability and suspiciousness improved markedly, and he reported no longer feeling artificially energized or suicidal. He continued to maintain this improvement on the combination of the antidepressant and atypical antipsychotic for the following six months, when he again refused to return for follow-up care.

Case 4. A 56 year-old professional woman who had been widowed a year earlier sought psychiatric consultation following the unexpected suicide of her only child, a 25-year old daughter. She denied any psychiatric history but reported new depressive symptoms and poorly sustained sleep, and experienced panic attacks for the first time. She cried inconsolably during initial assessments. Paroxetine was started, and increased to 20 mg/day. Within four weeks, she complained of new rapid heart-rate and palpitations, with worsening insomnia and increasing agitation, as well as newly arising suicidal preoccupation that was alien and unfamiliar to her. Paroxetine was discontinued in 5-mg steps every other day, as alprazolam was introduced at 0.5 mg twice daily and at bedtime. Within another week, her palpitations and severe anxiety had virtually disappeared, sleep improved, suicidal thoughts were no longer acknowledged, and she agreed to begin grief counseling with an experienced social worker while continuing to take only a total of 1.0 mg of alprazolam daily for the following three months, with further gradual improvement and ability to return to work.

Case 5. A 58 year-old, recently divorced woman had a history of at least ten years of moderate dysthymia and one episode of major depression following the birth of her only child, but no previous suicidal behavior or ideation. She again became depressed, was being treated by her primary-care physician with venlafaxine (gradually increased to 300 mg/day), and was referred for psychiatric assessment for increasing agitation, anxiety, initial and sustained insomnia, with exaggerated fears about her financial security and unprecedented concern about possible malevolent intentions of her former husband's family. She was also newly and increasingly intensely preoccupied with suicidal thoughts. The antidepressant was discontinued gradually over two weeks to limit risk of a withdrawal reaction, and replaced with divalproex (up to 500 mg/day) and a low dose of olanzapine (2.5 mg/day). During this initial two-week period, she gradually became much more calm and her suicidal preoccupations and agitation virtually disappeared. After another month of follow-up with sustained improvement, she returned to the care of her referring physician.

Case 6. A 42 year old, single woman became increasingly discouraged over three months in the setting of a stressful relationship with a much younger, married woman supervisor at a new clerical job. She reported a series of unstable romantic relationships and failed employment experiences since her early 20s, but denied personal or family history of major psychiatric illness, or any previous psychiatric treatment. Her initial evaluation suggested moderate depression with mild generalized anxiety, and a trial of sertraline was initiated at 50 mg daily, and gradually increased to 150 mg/day. Within four weeks, she was sleeping only three or four hours a night, became increasingly energized, uncommonly optimistic, changed the color of her hair, began drinking heavily after work, and started an intense sexual relationship with a married man she met at work. Following this initial period of evident hypomania, she became dysphoric, irritable and severely anxious. At work, she became openly accusatory and litigious toward her supervisor. She also doubted the competence of her psychiatrist and reported becoming nearly overwhelmed with anger and unprecedented thoughts about suicide as her new lover avoided her. Her diagnosis was changed to bipolar mixed-state. The antidepressant was terminated over three days, and she was started on lithium carbonate, which was increased over one week to 600 mg twice daily, with a stable trough serum lithium concentration of 0.75 mEq/L. Over the next four weeks, her agitation, anger, and insomnia improved markedly, despite being asked to leave her job. By three months of treatment only with the mood stabilizer, she had broken off the relationship with the married colleague, found a new job, and remained stable for the following several months.

Case 7. A 36-year-old, shy, socially inhibited, unmarried man with mild obsessive-compulsive traits had two previous episodes of major depressive illness successfully treated with moderate doses of imipramine for several months. He presented with feelings of hopelessness, guilt, worthlessness, and anhedonia, with worsening obsessive-compulsive tendencies. Newly emerging compulsions included counting, and repeated showering and hand-washing, with growing distress about new, obsessively entertained aggressive inclinations toward his older sister, with whom he lived. He was again treated with imipramine, gradually increased to 150 mg/day over two weeks. Within six weeks from presentation he was substantially less depressed but his obsessive-compulsive symptoms did not improve. He was also newly obsessed with thoughts of death and suicide, and in the seventh week of treatment, he took a moderate overdose of imipramine (approximately 500 mg) that required an emergency service visit for gastric lavage, without loss of consciousness or medical complications. The dose of imipramine was then reduced to 75 mg/day, and divalproex was added (at 500 mg/day), with a low dose of risperidone (2 mg/day). Over the following four weeks, he showed marked improvement, was substantially less preoccupied with obsessive concerns, and expressed surprise and puzzlement by his suicide attempt.

Case 8. A 51-year-old, divorced professional man had approximately six recurrent episodes of major depression since age 23, and had been maintained on a series of SRIs in recent years, most recently paroxetine

and sertraline, with erratic psychiatric follow-up. A woman had recently ended an unstable romantic relationship with him that had continued for three years. A week later, he overdosed with an unknown quantity of antidepressant and other psychotropic medicines acquired over several years. This attempt required emergency gastric lavage and brief hospitalization on a psychiatric unit of a general hospital, with the re-starting paroxetine (20 mg/day) and referral to a psychiatrist. A week later, he presented with ongoing depression of moderate severity, with initial and terminal insomnia and normal appetite, but evidence of agitation (hand-wringing) and bitterness, with angry thoughts of harming his ex-girlfriend alternating with recurring thoughts of suicide. He was started on olanzapine (5 mg) as the SRI was discontinued over one week, and was enrolled in supportive interpersonal psychotherapy with an experienced psychologist. He gradually became much less agitated, angry and suicidal over one month, continued taking only olanzapine for another three months, remaining stable over the following year, during which he developed a new romantic relationship.

Case 9. A 62-year-old woman who worked in a business office had a diagnosis of bipolar-II disorder, with depression and alcohol abuse among several paternal relatives. Her father had committed suicide by jumping from a building shortly after the death of her mother of cancer. Her 25 year-old son had been treated with lithium since adolescence for an illness similar to the patient's, and a 22 year old son had been treatment for more than a year with *R,S*-citalopram for recurrent depression. She had remained quite stable for 15 years while maintained at moderate trough serum concentrations of lithium (0.60–0.75 mEq/L) alone. Shortly after divorcing her unfaithful husband, she presented to her primary-care physician with mild depressive symptoms, initial insomnia and moderate anxiety, with fears about financial security and living alone for the first time since her early 20s. She was treated for two weeks with clonazepam (1–2 mg/day) as her depression worsened. She was asked to take a leave of absence from work and was started on sertraline (increased to 100 mg/day over two weeks) as lithium and clonazepam were continued. Over the following two weeks, she became increasingly tense, sleepless, and irritable, with growing preoccupation with death and a plan to repeat her father's suicide. She was then hospitalized in a private psychiatric sanatorium and continued at an increased dose of lithium (to yield serum levels of 0.85–0.95 mEq/L), with addition of quetiapine (to a maximum daily dose of 300 mg), as sertraline was discontinued over three days. Her irritability, pessimism and suicidal thoughts improved gradually over two weeks. She was able to return to work within a month and remained well over the following six months while taking only the increased dose of lithium.

Case 10. A 45-year-old, childless, salesman married to an alcoholic woman had had recurrent episodes of agitated depression persisting for several months each year over the preceding decade, with prominent anxiety symptoms and moderate obsessive-compulsive tendencies with indecisiveness and some excessive checking and washing behaviors. His mother had been depressed following his birth, as had her mother before her. During three years of treatment with clomipramine at daily doses of 100–150 mg, and monthly supportive visits to his internist, he was typically only moderately depressed and somewhat irritable about one week a month, considerably less obsessive, and had remained employed steadily, with two or three periods of extraordinary business success, each sustained for about one month each year. During a particularly stormy period in his marriage, he presented with severe agitated depression, and his physician increased the dose of clomipramine, stepwise, to 250 mg/day. After worsening over nearly a month, with newly emerging suicidal thoughts and profound anger toward his wife, he was referred to a psychiatrist, who considered a diagnosis of bipolar II disorder, discontinued the TCA over a week, and added lithium carbonate to produce daily trough serum concentrations averaging 0.75 mEq/L. He showed initial improvement in his agitation, anger, and suicidal hopelessness within two weeks, with gradual lifting of his mood over another three or four weeks. However, over the following three months, without an antidepressant, he returned to being depressed, irritable, and indecisive, one week out of four. Lamotrigine was then added and gradually increased to 200 mg/day. He again showed gradual improvement and more stable mood over the next three months. With the two mood-stabilizing agents and no antidepressant, for two years, he remained more emotionally stable than in the preceding decade, and decided to consult an attorney to initiate divorce proceedings.

Discussion

These cases illustrate common presentations of newly emerging suicidality in the setting of agitated, irritable, angry, dysphoric, anxious, sleepless, hopeless states arising during treatment with antidepressant drugs. *Case 1* was a man with depression started on a TCA, with emerging dysphoric agitation with near-psychosis, and intense new suicidal preoccupations. He improved rapidly when the antidepressant was discontinued, and the mood-stabilizing anticonvulsant lamotrigine and atypical antipsychotic quetiapine were given. *Case 2* involved a woman with a history of dysthymia with major depressive episodes with a suggestive history of bipolar II disorder or cyclothymia who became agitated and newly suicidal after starting the SRI citalopram, and overdosed with it. She then did much better without the antidepressant and only divalproex and small doses of a sedating neuroleptic to enhance sleep. *Case 3* involved a man with a possibly bipolar type of schizoaffective illness presenting depressed, with increasing anger, irritability, insomnia and emerging paranoid psychosis and suicidality when treated with fluoxetine only. He did much better with olanzapine added to the antidepressant at antipsychotic doses. *Case 4* involved a grieving widow whose daughter committed suicide. During treatment with paroxetine, she developed severe anxiety and palpitations initially, and later agitation and unprecedented suicidal preoccupations. She did much better after the antidepressant was discontinued and a benzodiazepine substituted. *Case 5* involved a divorced woman with a history of postpar-

tum depressive illness and chronic dysthymia, who was started on venlafaxine by her primary-care physician, but became anxious, agitated, sleepless, possibly psychotic, and suicidal. She was much better soon after the antidepressant was stopped and she was given divalproex with a low-dose of olanzapine. *Case 6* represents a woman with previously undiagnosed bipolar disorder who developed hypomania followed by a probable mixed state with suicidal thinking during treatment with an SRI antidepressant. She improved when the antidepressant was stopped and lithium was added. *Case 7* involved a young man with obsessive-compulsive features who was treated with the TCA imipramine and became increasingly agitated and probably psychotic, with suicidal preoccupations that led to an overdose of imipramine. He improved after reducing the dose of imipramine by half and adding divalproex and risperidone. *Case 8* involved a man with recurrent agitated depression and a suicide attempt with an overdose of accumulated drugs, who became increasingly angry and again suicidal after restarting an SRI. He was successfully treated with olanzapine and psychotherapy. *Case 9* was a woman with bipolar II disorder and strong family loading for mood disorders and suicide who became depressed during long-term treatment with lithium. When a benzodiazepine proved to be ineffective and sertraline was added, she became more agitated, newly suicidal, and required hospitalization. She improved markedly when the SRI was stopped and quetiapine was added to an increased dose of lithium. *Case 10* was a man with either rapid cycling unipolar depression or possible bipolar II disorder and obsessive-compulsive features who became depressed and then more agitated and newly suicidal during treatment with an increased dose of clomipramine. He improved after stopping the TCA and adding lithium, and improved further after adding lamotrigine.

Several of these cases involve patients with possible, but usually unrecognized, bipolar disorder (*Cases 2, 6*, and possibly *2* and *10*) or psychotic-affective illness (*Case 3*) who became agitated and dysphoric during treatment with an antidepressant alone, and did much better with the antidepressant replaced or supplemented with anticonvulsant, antipsychotic, or anxiolytic agents. At least five cases (*1, 4, 5, 7* and *8*), however, involved no previous indications of bipolarity or psychotic illness. In all 10 of the cases reported, there was new suicidal ideation shortly after the start of treatment with various types of antidepressants (TCAs or SRIs), and two cases involved suicide attempts by overdose (*Cases 2* and *7*). It is also important to emphasize that removing the antidepressant or adding a centrally active agent with sedative, anxiolytic, antimanic, antipsychotic, or anti-aggressive activity led to a favorable outcome in all cases.

It is not known how often such cases of psychiatrically adverse reactions to antidepressant treatment occur, but they do not seem to be rare in routine clinical practice. This circumstance calls for a high level of vigilance for such reactions, particularly in patients who are unknown and newly engaging in treatment with an unfamiliar clinician, as well as in young patients whose psychiatric diagnosis may not yet be well established (Faedda et al. 2004). Additional warning signs include presenting initially with prominent anxiety and irritability, anger, or agitation, or developing such emotions early in the use of an antidepressant, particularly in antidepressant monotherapy. Those with likely or suspected bipolar features or psychotic illnesses call for particular concern for potential behavioral risks of antidepressant monotherapy, without the presumably protective effects of mood-stabilizing or antipsychotic agents. These and other suggested warning signs or risk factors are summarized in Table 1.

Although recent interest has focused on an hypothesized specific risk of newly emerging suicidality with SRI antidepressants (US FDA 2004, Whittington et al. 2004), we suspect that all types of mood-elevating agents carry some risk for such reactions (Baldessarini 2005). Whether there is a differential risk by type of antidepressant requires specific clarification. Alternative treatments that may prove to be helpful in managing reactions appear to include a wide range of drugs with antimanic, anxiolytic, or antipsychotic properties, whose

Table 1. *Proposed risk factors and warning signs for emerging suicidality during antidepressant treatment*

- Previous suicide attempts or violent acts
- Known or suspected bipolarity
- Severe, recurring depression
- Known or suspected psychotic illness
- Juvenile depression
- Agitation, akathisia, anxiety
- Insomnia
- Anger, aggression or threats of aggression
- Irritable dysphoria
- Switching into mixed bipolar or psychotic states
- Worsening of depression, hopelessness, anguish
- Helplessness or social isolation
- Current stressors (loss, separation, scandal, financial crisis)
- New somatic symptoms
- Abuse of alcohol or other disinhibiting central depressants, including anxiolytics such as benzodiazepines
- Ready access to firearms, hoarded drugs or other toxins
- Inadequate clinical supervision and follow-up

Table 2. *Proposed interventions for emerging suicidal risk during antidepressant treatment*

• Decrease dose, or suspend antidepressant therapy if new agitation, insomnia, or anger emerges
• Introduce an atypical antipsychotic, anticonvulsant, or sedative
• Consider lithium for cooperative patients, especially following *inadequate* antidepressant responses
• Make explicit the collaborative and flexible nature of treatment; emphasize the clinician's availability for extra routine visits or calls, as well as in emergencies
• Express explicit concern for growing discomfort and despair
• Address suicidality directly and repeatedly, and monitor for access to lethal means of self-injury, including hoarded drugs, other toxins, or firearms
• Enlist the help of a family member to monitor the patient and perhaps to dispense medicines

specific application can best be guided by the clinical history and presenting symptoms. Suggested pharmacological interventions and other clinical steps aimed at safe management of patients at risk for the types of adverse behavioral responses to antidepressants described here are summarized in Table 2.

In conclusion, we report a series of 10 clinical anecdotes in which there is a common theme of newly emerging suicidality during treatment with an antidepressant drug. However, we would emphasize that suicidality, in particular, is almost incidental, and often predictable, given the types of reactions involved. They had in common newly emerging anxiety, insomnia, agitation, restlessness, anger, mixed-states, or psychosis prior to, or along with, newly emerging suicidality. Such reactions can be considered a group of adverse responses to antidepressant treatment that seem not to be uncommon. Usually they can be anticipated and managed by close monitoring of depressed patients, particularly early in the treatment of new and unknown patients, by discontinuing the antidepressant in favor of antipsychotic, antimanic, mood-stabilizing, anti-aggressive, or sedative agents, the selection of which can be guided by the specific clinical circumstances (Baldessarini and Tarazi 2005).

Acknowledgments

Supported, in part, by funds from the University of Rome "La Sapienza" (MP), by an award from NARSAD (LT), by a grant from the Bruce J. Anderson Foundation, and by the McLean Hospital Private Donors Psychopharmacology Research Fund (RJB). Dr. Baldessarini has consulting or research relationships with pharmaceutical corporations, whose products are discussed in this paper, including Eli Lilly, IFI, Janssen, JDS, and Novartis. The clinical vignettes reported are disguised to protect the identity of patients, and some involve presentations or treatments derived from more than one similar case to further maintain anonymity.

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