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Bipolar I disorder

Psychopathology, medical management and dental implications

ARTHUR H. FRIEDLANDER, D.D.S.; IDA K. FRIEDLANDER, R.N., M.S.; STEPHEN R. MARDER, M.D.

Bipolar I disorder, or BD, is a psychiatric illness (formerly known as manic-depressive disorder) that causes a person to experience recurrent episodes of elated and depressed moods separated by well-spaced intervals of euthymia—normal mood. During manic episodes, people appear euphoric and unusually cheerful and display heightened self-esteem and grandiosity that leads them to indiscriminately undertake multiple sexual, occupational, political or religious activities with a sense of conviction and purpose but without regard for the apparent risks or need to complete them.¹ This often is accompanied by restlessness, a decreased need for sleep, “pressured speech” that is loud, rapid and difficult to interpret, and increased sociability that is intrusive, demanding and domineering. When rebuffed or frustrated, however, irritability, anger and rage are likely to ensue.

People with bipolar I disorder who have a depressive episode are at high risk of developing rampant dental caries.

During a manic episode, more than 75 percent of patients who have BD experience psychotic symptoms such as auditory hallucinations, delusions and severely disturbed thought processes.² Delusions are erroneous but firmly held ideas. An example of a common delusion that occurs during a manic episode is patients’ claims of infallibility because of their special relationships to God. The disturbed thought process is inferred from these patients’ speech, which manifests rapid shifts between topics called “flight of ideas” that are loosely associated logically or are completely unrelated.

Patients’ euphoric moods may shift rapidly to the

Background. The authors review the clinical features, epidemiology, pathophysiology, medical management, dental findings and dental management of patients who have bipolar I disorder, or BD, previously known as manic-depressive disorder.

Types of Studies Reviewed. The authors conducted a MEDLINE search for the period 1995 through 2001 using the key terms “bipolar disorder,” “epidemiology,” “pathophysiology,” “treatment” and “dentistry.” The articles they selected for further review included those published in English in peer-reviewed journals; they gave preference to articles reporting randomized, controlled trials.

Results. BD is a psychiatric illness characterized by extreme mood swings. Mania is accompanied by euphoria, grandiosity, racing thoughts and lack of insight. Depression is characterized by marked sadness or loss of interest or pleasure in daily activities. The unpredictable mood swings can distress the person, can impair social function and quality of life and are associated with a significant increase in the risk for substance abuse and suicide. BD is common in the United States, with a lifetime prevalence rate of 1.6 percent and recurrence rate of more than 50 percent.

Clinical Implications. The prevalence of dental disease usually is extensive because of poor oral hygiene and medication-induced xerostomia. Preventive dental education, saliva substitutes and anticaries agents are indicated. To avoid adverse drug interactions with the usually prescribed psychiatric medications, special precautions should be taken when administering certain antibiotics, analgesics and sedatives.

depressive phase, during which patients experience dysphoria (feeling sad, helpless, pessimistic, agitated, anxious or any combination of the preceding), anhedonia (a loss of interest or pleasure in previously enjoyed activities such as hobbies and social or sexual interactions) or both. A sense of worthlessness or guilt accompanied by preoccupation

over minor failings and thoughts of suicide are common. Psychotic components of a depressive episode may include patients believing they deserve to be punished, refusing to eat and making multiple suicide attempts.

During a depressive episode, patients who have BD or their family members may note alterations in appetite that result in a weight loss or gain of more than 5 percent, insomnia characterized by early awakening or by difficulty falling or staying asleep, an inability to sit still (agitation), slowed speech and body movements (psychomotor retardation), extreme fatigue, and an impaired ability to think, concentrate or make decisions. Somatic complaints without physiological basis, such as bodily aches and pains, also are common.

These clusters of symptoms can be emotionally painful and interfere with patients' educations, occupations and social lives. During a manic episode, violent acting out and difficulties with the law or financial institutions often result from the patients' impulsivity, lack of insight and poor judgment. During both manic and depressive episodes, marital instability, alienation from family and an inability to hold a job are common. Approximately 50 percent of people who have BD also abuse illicit substances (for example, amphetamines, cocaine, hallucinogens such as lysergic acid diethylamide and opiates such as heroin and phencyclidine hydrochloride), alcohol or both.³⁻⁵ In addition, these people are at high risk of experiencing attention-deficit hyperactivity disorder, obsessive-compulsive disorder, other anxiety disorders and impulse control disorders such as pathological gambling and kleptomania concurrently.⁶ It is estimated that 25 to 50 percent of patients who have BD attempt to commit suicide and that 10 to 15 percent eventually commit the act.^{7,8}

EPIDEMIOLOGY

BD is common in the United States, with a lifetime prevalence of 1.6 percent; it is the sixth leading cause of disability worldwide.^{9,10} BD, however, may be even more common because an episode of depression may appear before a manic episode, and the disorder initially may be misdiagnosed as a major, unipolar depressive disorder until the manic episode evolves.¹¹ The prevalence of BD is approximately the same in both sexes; however, men are more likely to have a manic episode first, and women are more likely to experience a depressive episode first. In addition, the

frequency of depressive episodes, illicit substance abuse and suicide attempts is higher among women.^{12,13} The peak period of initial onset is between ages 15 and 24 years, and, if it is properly diagnosed and treated, it often is followed by a remission of approximately five years.¹⁴ Recurrence after five years is likely, as remission periods decrease progressively so that over the next five years the average patient has three more major episodes. In later years, the disease tends to stabilize, with the patient having approximately one episode per year.¹⁵

BD can present an emotional and financial burden on people who have BD and their families because of the 95 percent lifetime risk of recurrence, its chronicity and the potential for suicide. In addition, people who have BD have a mortality rate that is twice as high as might be expected in people who do not have BD, because of substance abuse, stress and smoking-related medical illnesses such as cardiovascular and respiratory diseases, and risk-taking behaviors that lead to accidents such as those arising from aggressive car driving.¹⁶ Thus, the illness poses a substantial public health burden with high costs in terms of lifetime medical expenses and lost productivity.¹⁷ In 1998 in the United States, the estimated cost of treating BD and the associated cost of impaired workplace productivity was \$24 billion.¹⁸

PATHOPHYSIOLOGY

The etiology of BD remains ill-defined, though it now is known that it may arise from a complex interaction of genetic predisposition, neurochemical influence, anatomical variation, substance abuse, and stressful perinatal and childhood experiences (for example, verbal, physical and sexual abuse).¹⁹⁻²¹ Although the exact gene or genes and mode of transmission remain illusive, BD's inheritability is demonstrated by the fact that if one parent has BD, there is a 25 percent chance that any of his or her children will have BD or major depressive disorder, and if both parents have BD there is a 50 to 75 percent that their children will have a mood disorder. Concordance rates for BD are 70 percent in monozygotic twins and 15 percent in dizygotic twins.²²

Neurochemical abnormalities have been implicated as contributing to the development of BD. Specifically, a paucity of the "inhibitory" neurotransmitter γ -aminobutyric acid, or GABA, and elevated levels of the neurotransmitters norepinephrine and dopamine at the synapses

between neurons in the brain's limbic system—which regulates mood and emotions—have been implicated as facilitating the excessive transmission of neuronal impulses resulting in a manic episode.²³ Meanwhile, inadequate levels of the neurotransmitters serotonin, norepinephrine and dopamine have been identified as hindering neuronal transmission resulting in a depressive episode.²⁴ Neuroimaging studies support this model by demonstrating abnormalities in blood flow and glucose metabolism in limbic system structures and in the amygdala—the area of the brain known to be involved in processing emotions.²⁵⁻²⁹

MEDICAL MANAGEMENT

An acute manic episode often constitutes a medical emergency and usually is treated in a hospital. Initially, high doses of a mood stabilizer such as lithium, valproate sodium or carbamazepine are prescribed; the latter two also are anticonvulsant medications. In addition to a mood stabilizer, an antipsychotic medication (risperidone, olanzapine or quetiapine) and a high-potency benzodiazepine (lorazepam or clonazepam) often are prescribed to attain a degree of control of acute agitation.^{30,31} People who cannot tolerate the medication may be given electroconvulsive therapy, or ECT.³²

Once the agitation is controlled, the antipsychotic medication and the benzodiazepine usually are discontinued. The dosage of lithium, valproate sodium, carbamazepine or a combination of these medications then is adjusted to obtain long-term mood stabilization and to prevent recurrence of both mania and depression. During this maintenance phase of treatment because of a less-than-optimal response, approximately 50 percent of patients also take an antidepressant (most commonly a selective serotonin reuptake inhibitor, or SSRI, or bupropion), 40 percent take a benzodiazepine, and 30 percent take an antipsychotic agent.^{33,34} Psychosocial interventions such as behavioral, cognitive and interpersonal therapy also are offered at this time and appear to augment the effects of the medications and forestall recurrence.³⁵

Risperidone, olanzapine and quetiapine are classified as second-generation antipsychotic medications. These medications are used to decrease agitation, control psychotic symptoms and promote mood stabilization. They derive their antimanic effect by blocking dopamine neural

transmission and their antidepressive effects by enhancing serotonin and norepinephrine neural transmission.³⁶⁻³⁹ The occurrence of extrapyramidal movement disorders is considerably less frequent than with first-generation antipsychotic medications such as chlorpromazine. However, when extrapyramidal movement disorders do arise, they often have an orofacial component such as acute dystonia creating mastication muscle spasms, pseudoparkinsonism resulting in a masklike face and drooling, and tardive dyskinesia manifesting as lip smacking and tongue protrusion. Occasionally, the use of these medications also is associated with the development of hypotension, orthostatic hypotension, weight gain, tachycardia, anticholinergic effects and sexual dysfunction.

Lorazepam and clonazepam may help control acute agitation, hyperactivity and insomnia by enhancing the activity of GABA—a major inhibitor of the norepinephrine and serotonin neurotransmitter systems in the central nervous system, or CNS. Occasionally, the use of these medications is associated with respiratory depression and hypotension.

The mood-stabilizing agent lithium may derive its antimanic effect from its ability to inhibit the release of the CNS neurotransmitters norepinephrine and dopamine from nerve terminals and synapses, and its antidepressant effect may be derived from its ability to increase CNS serotonin levels.⁴⁰ In some people, lithium may cause nausea, tremor, cognitive impairment and hypothyroidism, which may lead to a goiter—a diffuse, nontender, enlarged thyroid gland—and weight gain. Approximately 30 percent of patients who take lithium develop electrocardiogram changes, the most common of which are bradycardia and a benign, reversible reduction in the amplitude of T waves.⁴¹ Nephrotoxicity also may develop as evidenced by polyuria and polydipsia.

Valproate sodium and its enteric-coated divalproex formulation also is a mood-stabilizing agent. Its actions on inhibitory and excitatory amino acid systems and membrane-associated ion channels in the brain may be responsible for its stabilizing effect.⁴² Long-term use is associated with approximately 9 percent of patients developing leukopenia, 7 percent developing thrombocytopenia and a lesser percentage having a decrease in fibrinogen concentration.^{43,44}

Carbamazepine's mood-stabilizing effect also is believed to be derived from its ability to stabilize

TABLE 1

ADVERSE OROFACIAL REACTIONS TO SECOND-GENERATION ANTIPSYCHOTIC MEDICATIONS.*			
ADVERSE REACTION	MEDICATION		
	Risperidone	Olanzapine	Quetiapine
Xerostomia	+ [†]	+	+
Sialorrhea	+	+	+
Dysphagia	+	+	+
Sialadenitis	0 [‡]	0	0
Dysgeusia	+	0	+
Stomatitis	+	+	+
Gingivitis	+	+	+
Glossitis	0	+	+
Tongue Edema	+	+	+
Discolored Tongue	+	0	0
Bruxism	0	0	+
Miscellaneous	Toothache, tongue paralysis	Neck rigidity, facial edema, oral moniliasis, periodontal abscess	Buccoglossal syndrome, caries, oral ulcers, gingival hemorrhage

* Sources: Physicians' Desk Reference⁵⁴ and McEvoy.⁵⁵
[†] +: Yes.
[‡] 0: No.

episodes with severe agitation or severe depressive episodes that do not respond to medication.⁴⁹ The electrical currents used in ECT create massive neuronal electrical discharges in the CNS that result in a seizure. It is postulated that after a number of treatments, appropriate neuronal activity is restored.⁵⁰ ECT usually is given two to three times a week for several weeks until the patient improves. Approximately 90 percent of patients enter a remission within one to two weeks, which usually is quicker than for patients who take medications. Some psychiatrists recommend a dental examination for

sodium and potassium channels and the upregulation of GABA_B receptors.⁴⁵ Like valproate sodium, long-term use of carbamazepine is associated with decreased white blood cell and platelet counts.

SSRIs such as fluoxetine exert their antidepressant effect by preventing presynaptic neurons from reabsorbing serotonin from the synaptic cleft (the space between two neurons) for recycling. Thus, the concentration of serotonin in the cleft is heightened, and neuronal activity is enhanced.

Use of the majority of SSRIs frequently is associated with diarrhea, nausea, dizziness, insomnia, tremor, headache, sexual dysfunction (for example, decreased libido, ejaculatory dysfunction, erectile dysfunction and anorgasmia) and occasionally an increase in bleeding time.^{46,47} Bupropion, an atypical antidepressant, exerts its effects by preventing the reuptake of norepinephrine and dopamine from the synaptic cleft, thereby facilitating neural transmission.⁴⁸ SSRIs and bupropion are used much more frequently than the tricyclic antidepressant medications, as they are less likely to cause a switch to mania.⁴⁹

ECT is indicated for patients who have manic

their patients before ECT to determine if the anesthesiologist needs to adjust the procedure because of dentures or problem teeth.⁵¹ Positioning the electrodes farther away from the masseter muscles is associated with decreased dental injuries.⁵²

Psychosocial treatment provided as an adjunct to medication appears to decrease the likelihood and severity of recurrent episodes and improve the patient's quality of life. Initiated during or shortly after an acute manic or depressive episode, the therapeutic protocol encourages adhering to the drug regimen, educating the patient and family about the illness (for example, being able to recognize early signs of relapse) and offering practical techniques for coping with stressors such as loss of an important relationship or changes in work, school or home life.⁵³

DENTAL FINDINGS

In a review of the U.S. Food and Drug Administration's medication package inserts that accompany each medication used to treat BD and an analysis of the current medical literature, the

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authors identified adverse orofacial reactions that may occur.^{54,55} The antipsychotic agents have been shown to cause xerostomia, dysgeusia and stomatitis (Table 1). The benzodiazepines are associated with both xerostomia and sialorrhea (Table 2). The mood-stabilizing agent lithium has been shown to cause xerostomia and dysgeusia, while valproate sodium and carbamazepine have been associated with xerostomia and glossitis (Table 3).^{56,57} A majority of the antidepressant medications have been shown to cause xerostomia (which affects approximately 18 percent of patients), stomatitis and glossitis, and a smaller percentage of these medications have been identified as causing sialadenitis, gingivitis, and edema and discoloration of the tongue (Table 4). Bupropion recently has been linked with causing hyperesthesia of the ophthalmic and maxillary divisions of the trigeminal nerve, although the mechanism remains ill defined.⁵⁸

Two studies have catalogued the extent of dental disease among patients who have BD (box, page 1215).^{59,60} Patients admitted to the hospital for the acute management of a manic episode frequently had oral mucosa and gingiva that were severely abraded and on occasion lacerated, secondary to overvigorous use of oral health devices such as toothbrushes, dental floss and water dental stimulators. Patients who had a history of three or more admissions for a manic episode often had advanced cervical toothbrush abrasion and occlusal attrition consistent with severe bruxism. Patients admitted during a depressive episode had an almost total disregard for proper oral hygiene. And those who had a history of three or more hospital admissions for a depressive episode had the highest decayed, missing and filled teeth, or DMFT, count, as well as the most severe periodontal disease.

People whose BD was in remission and who

TABLE 2

ADVERSE OROFACIAL REACTIONS TO BENZODIAZEPINES.*		
ADVERSE REACTION	MEDICATION	
	Lorazepam	Clonazepam
Xerostomia	0 [†]	+ [‡]
Sialorrhea	+	+
Dysphagia	0	0
Sialadenitis	0	0
Dysgeusia	0	+
Stomatitis	0	0
Gingivitis	0	+
Glossitis	0	0
Tongue Edema	0	0
Discolored Tongue	0	0
Bruxism	0	0
Miscellaneous	None	Coated tongue, feelings of a thick tongue, periorbital edema, toothache, pyrosis, jaw pain

* Sources: Physicians' Desk Reference⁵⁴ and McEvoy.⁵⁵
[†] 0: No.
[‡] +: Yes.

went to an outpatient dental clinic also were noted to have extensive dental disease. The most common chief complaint of these patients was xerostomia and a loss in taste acuity. Patients with the highest DMFT count and most advanced cases of periodontal disease had the longest history of lithium ingestion and the greatest number of hospital admissions for BD.

People who have a depressive episode are at high risk of developing rampant dental caries because of a mood-induced disinterest in performing oral hygiene procedures, decreased whole-mouth and parotid gland salivary output, a preference for carbohydrates and high *Lactobacillus* count.⁶¹⁻⁶⁴ In addition to and magnifying the severity of these problems are some of the adverse affects of the medications used to treat BD. Antipsychotic medications, mood-stabilizing agents and antidepressant medications cause xerostomia by interfering with salivary gland function, and lithium and valproate sodium cause an intense craving for carbohydrates.^{65,66} Patients often respond to their xerostomia and carbohydrate cravings by drinking large quantities of cariogenic sugared beverages.⁶⁷

TABLE 3

ADVERSE OROFACIAL REACTIONS TO MOOD-STABILIZING MEDICATIONS.*

ADVERSE REACTION	MEDICATION		
	Lithium	Valproate Sodium	Carbamazepine
Xerostomia	+†	+	+
Sialorrhea	0‡	0	0
Dysphagia	0	0	0
Sialadenitis	+	0	0
Dysgeusia	+	+	0
Stomatitis	+	0	+
Gingivitis	0	0	0
Glossitis	0	+	+
Tongue Edema	0	0	0
Discolored Tongue	0	0	0
Bruxism	0	0	0
Miscellaneous	Carbohydrate craving	Periodontal abscess, sinusitis, neck pain, carbohydrate craving	Erythema multiforme, carbohydrate craving

* Sources: Physicians' Desk Reference⁵⁴ and McEvoy.⁵⁵
† +: Yes.
‡ 0: No.

People who have a depressive episode also are at high risk of developing periodontitis.⁶⁸⁻⁷¹ It is hypothesized that neglect of oral hygiene, increase in smoking and altered immune response facilitate increased colonization of pathological bacteria. This leads to the breakdown of the periodontal attachment.⁷²⁻⁷⁷ Periodontitis may be exacerbated in some patients who receive SSRIs, as these medications have been implicated in causing a movement disorder that includes bruxism.^{78,79} Bruxism may arise because these medications increase extrapyramidal levels of serotonin, thereby inhibiting dopaminergic pathways that control movements.⁸⁰

DENTAL MANAGEMENT

Some patients who receive psychiatric treatment for BD may be reluctant to admit it because of perceived stigma associated with mental illness. To overcome such barriers and obtain necessary information, dentists should exhibit a supportive, nonjudgmental attitude and advise patients that such information will be held confidential and is indispensable to the provision of safe dental care.

Patients who are experiencing an episode of mania or depression may be uncooperative and irritable during dental treatment, appear unappreciative and have numerous complaints that are inconsistent with objective findings. Before a patient begins dental treatment, the dentist should consult with the patient's psychiatrist after informing the patient. Dentists should ask the psychiatrist for the patient's current psychological status and psychiatric medication regimen. The dentist also should ask the psychiatrist about the patient's history of alcohol or substance abuse. Patients who have a history of alcohol abuse should undergo liver function tests that include blood serum levels of albumin and total proteins, a complete blood cell count and a

coagulation profile that includes prothrombin time and partial thromboplastin time.

Preventive dental education is paramount for these patients and their families. They should receive instruction in proper toothbrushing and flossing methods that maximize removal of dental plaque. Artificial salivary products should be prescribed for patients who have signs of xerostomia. Dental treatment should consist of subgingival scaling, root planing and curettage, caries control and restorative treatment. Profound local anesthesia should be achieved in these often-anxious patients before the procedures are performed.

Dentists should perform clinical examinations and oral prophylaxis at three-month follow-up visits and apply a fluoride gel with a fluorine concentration of at least 1.0 percent in patients who have BD. They also should correct any defects in the natural dentition or prostheses during recall visits, as patients may experience enhanced self-esteem as a result of dental treatment, which may contribute to the psychotherapeutic aspect of management.

Adverse drug interactions may occur between

TABLE 4

ADVERSE OROFACIAL REACTIONS TO ANTIDEPRESSANT MEDICATIONS.*						
ADVERSE REACTION	MEDICATION					
	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Bupropion
Xerostomia	+ [†]	+	+	+	+	+
Sialorrhea	0 [‡]	0	0	0	0	0
Dysphagia	0	0	0	0	0	0
Sialadenitis	0	+	0	+	0	0
Dysgeusia	+	+	+	+	+	+
Stomatitis	+	+	+	+	+	+
Gingivitis	+	+	+	+	0	+
Glossitis	+	+	+	+	+	+
Tongue Edema	0	0	0	+	+	0
Discolored Tongue	0	+	0	+	0	0
Bruxism	+	+	0	+	+	+
Miscellaneous	None	Jaw pain, buccoglossal syndrome	Toothache	Caries, dysphagia	Dysphagia, gingival hyperplasia	Toothache, oral edema, dysphagia

* Sources: Physicians' Desk Reference⁵⁴ and McEvoy.⁵⁵
[†] +: Yes.
[‡] 0: No.

BOX

COMMON ORAL MANIFESTATIONS OF BIPOLAR I DISORDER.*

CAUSE	ORAL MANIFESTATION
Manic Phase	Toothbrush/dental floss abrasion of mucosa and gingiva Toothbrush abrasion of cervical aspects of teeth
Depressive Phase	Disregard of oral hygiene High decayed, missing and filled teeth count Severe periodontal disease
Medication Effects	Xerostomia/Sialorrhea Dysgeusia Stomatitis/Glossitis Bruxism

* Sources: Friedlander⁵⁸ and Friedlander and colleagues.⁵⁹

the medications used in dentistry and those used to treat BD.^{81,82} The antifungal agent ketoconazole has been shown to decrease the metabolism of quetiapine. Antihistamines, muscle relaxants, ketoconazole and opioid analgesics enhance the sedative effects of lorazepam and clonazepam. Erythromycin and aspirin inhibit the metabolism

of valproate sodium. Erythromycin, clarithromycin and propoxyphene may inhibit the metabolism of carbamazepine and permit the emergence of its side effects. Doxycycline is rendered less effective because carbamazepine has been shown to accelerate its metabolism. Nonsteroidal anti-inflammatory drugs and metronidazole decrease the renal clearance of lithium and can allow the build-up of toxic levels of the drug.^{83,84} Benzodiazepines such as diazepam and midazolam also must be used with caution because of the potential for excessive CNS depression when they are taken concurrently with lithium. Narcotic analgesics may be less effective than expected because lithium decreases the analgesic effect of opiates in some patients. Codeine, benzodiazepines and ery-



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thromycin should be used cautiously and in reduced dosages in patients receiving SSRIs because the antidepressant medications inhibit the metabolism of these medications.

CONCLUSION

We emphasize that dentists' working in concert with physicians and mental health professionals has much to offer patients who have BD. In this article, we provided dentists with an overview of BD's manifestations and complex pharmacological management so they can feel confident in offering patients who have BD a full range of dental treatment options. ■

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