Associations Between Bipolar Disorder and Metabolic Syndrome: A Review

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Objectives: To examine the pathophysiologic mechanisms that may link bipolar disorder and metabolic syndrome and to discuss whether the consequences of metabolic syndrome underlie a substantive portion of the premature morbidity and mortality observed in persons with bipolar disorder.

Data Sources: A MEDLINE search, citing articles from 1966 onward, supplemented by a review of bibliographies, was conducted to identify relevant studies. *Bipolar disorder*, *mood disorder*, *metabolic syndrome*, *diabetes*, *cardiovascular illness*, and *obesity* were used as keywords. Criteria used to select studies included (1) English language, (2) published studies with original data in peer-reviewed journals, and (3) studies that confirmed the nature of the mood disorder examined.

Results: Ninety-seven studies met criteria and were reviewed for evidence of dysregulation in various physiologic systems. Bipolar disorder and metabolic syndrome share features of hormonal, immunologic, and autonomic nervous system dysregulation.

Conclusion: Lifestyle features may account, in part, for the premature mortality observed in bipolar disorder, but the somatic correlates of the illness may also predispose patients to metabolic syndrome and the consequent increased risk of diseases such as diabetes and vascular disease.

(J Clin Psychiatry 2006;67:1034–1041)

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Persons with bipolar disorder are at higher risk of premature mortality than the general population and those with major depressive disorder,[1] but there is a striking paucity of data examining factors that increase this risk in bipolar disorder. Most research examining the excess mortality associated with mood disorders has focused on the increased mortality in major depressive disorder and it is not known whether people with bipolar disorder are simply at risk by virtue of also spending a significant portion of time in the depressed state or whether there are independent factors conferred by the diagnosis of bipolar disorder that further increase the risk of developing another chronic illness.

Epidemiologic evidence indicates that an array of somatic illnesses are associated with bipolar disorder. Patients with bipolar disorder die earlier than those without mood disorders from cardiovascular, gastrointestinal, respiratory, urogenital, infectious, metabolic, and specific malignant conditions. Mortality data obtained from inpatients with mood disorders as early as 1916 reflected this increase in premature mortality.[2,3] A study spanning a 4-decade period[4] found excess mortality for manic and depressed patients of both genders, with the increase in mortality most prominent in the first 10 years after admission for a mood episode. Women with mania were at risk for premature mortality throughout the follow-up period. A population-based study[5] of the standardized mortality ratios for people with unipolar depression or bipolar disorder from 1973 to 1995 found that standardized mortality ratios for all natural causes of death were 1.9 for males and 2.1 for females with bipolar disorder and 1.5 and 1.6, respectively, for unipolar depression. For persons with bipolar disorder, most excess deaths were from natural causes, whereas for unipolar depression, most premature deaths were from unnatural causes—suicide, violence, and accidents. These rates are consistent with results from other studies comparing the 2 illnesses.[6,7] There are no meta-analytic data examining excess mortality in bipolar disorder, probably because there are few studies comparing mortality rates in people with bipolar disorder to those with no mood disorder. A meta-analysis[8] that examined excess mortality in unipolar depression, however, reported that depressed subjects' overall relative risk of dying was 1.81 (95% CI = 1.58 to 2.07) compared with non-

depressed subjects. A portion of this increased premature mortality may be secondary to the prevalence of metabolic syndrome in people with mood disorders, which is higher than in the general population.[9]

We conducted a review to examine the pathophysiologic mechanisms that may link bipolar disorder and metabolic syndrome and to discuss whether the consequences of metabolic syndrome underlie a substantive portion of the premature morbidity and mortality observed in persons with bipolar disorder.

METHOD

A MEDLINE search, citing articles from 1966 onward, supplemented by a review of bibliographies, was conducted to identify relevant studies. *Bipolar disorder*, *mood disorder*, *metabolic syndrome*, *diabetes*, *cardiovascular illness*, and *obesity* were used as key words. Criteria used to select studies included (1) English language, (2) published studies with original data in peer-reviewed journals, and (3) studies that confirmed the nature of the mood disorder examined.

RESULTS

Ninety-seven studies met criteria and were reviewed for evidence of dysregulation in various physiologic systems.

Metabolic Syndrome and Bipolar Disorder

The features that are now classified as metabolic syndrome were first presented in the literature in the early 1950s with reports on the sexual differentiation of obesity and its consequences. Subsequent work identified intra-abdominal fat or visceral fat as a risk factor for cardiovascular disease and diabetes.[10] Later, the term *Syndrome X* was used to describe the relationship between hypertension, impaired lipid metabolism, impaired glucose tolerance, insulin resistance, obesity, and coronary heart disease and metabolic syndrome.[11] The World Health Organization definition of metabolic syndrome requires 3 of the following 5 symptoms: an elevated waist:hip ratio, decreased high-density lipoprotein (HDL) level, elevated triglyceride levels, high fasting glucose level, and hypertension (Table 1). The etiology of this syndrome remains controversial[12] as does consensus regarding its usefulness as a diagnostic category. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement[13] suggesting that this group of risk factors is not greater than the sum of its parts. This was challenged by the American Heart Association and the National Heart Lung and Blood Institute in a position statement[14] highlighting metabolic syndrome as a clinically significant entity, the consequences of which are manifest in a variety of diseases.[15] Many illnesses linked to metabolic syndrome are also found with increased prevalence in people with bipolar disorder.

Table 1. Diagnostic Criteria for Metabolic Syndrome According to the Adult Treatment Panel III

Risk Factor	Defining Level
Central/abdominal obesity	Waist circumference
Men	> 40 in (102 cm)
Women	> 35 in (88 cm)
Fasting triglycerides level	≥ 150 mg/dL (1.69 mmol/L)
High-density lipoprotein cholesterol level	
Men	< 40 mg/dL (1.04 mmol/L)
Women	< 50 mg/dL (1.29 mmol/L)
Fasting glucose level	≥ 110 mg/dL (6.1 mmol/L)
Blood pressure	≥ 130/85 mm Hg

Contribution of Lifestyle to Metabolic Syndrome in Bipolar Disorder

Unhealthy lifestyles may contribute to risk of somatic disease in bipolar disorder. Bipolar disorder is observed across socioeconomic classes[16] and is less associated with the downward drift linked to schizophrenia. Nonetheless, up to 25% of patients hospitalized with mania fail to return to work in the year after hospitalization,[17] and nearly 50% experience marital difficulties.[18] Changes in psychosocial variables and support affect access to care and duration of illness.[19]

Other lifestyle factors that exert an unhealthy effect are cigarettes and alcohol,[20] poor diet,[21] and lack of exercise,[21] as these variables increase mortality in the general population.[22,23] Approximately 70% of outpatients with bipolar disorder are nicotine dependent, a significantly greater proportion than the general population. Bipolar disorder is also associated with increased rates of abuse of alcohol and other substances. In fact, the lifetime prevalence of substance abuse in people with bipolar disorder exceeds 60%.[20]

Weight gain as a result of dietary changes is also an issue in people with bipolar disorder, especially during the depressive phase of the illness.[21] Fatigue and increased sleep is also common during depression, and people with depression are less likely than healthy individuals to exercise.[21] These problems are compounded by the pharmacologic treatment for bipolar disorder, which can lead to sedation and increased appetite.[24,25]

Obesity and Metabolic Syndrome in Bipolar Disorder

Individuals with bipolar disorder are at risk for obesity. In 50 people who were treated for at least 12 months after remission,[26] the prevalence of obesity exceeded that of the general population (32.0% vs. 19.8%, respectively). In another study,[27] obese people with bipolar disorder had a greater number of lifetime depressive and manic episodes, a more severe and difficult-to-treat index affective episode, and they were more likely to have a recurrence of

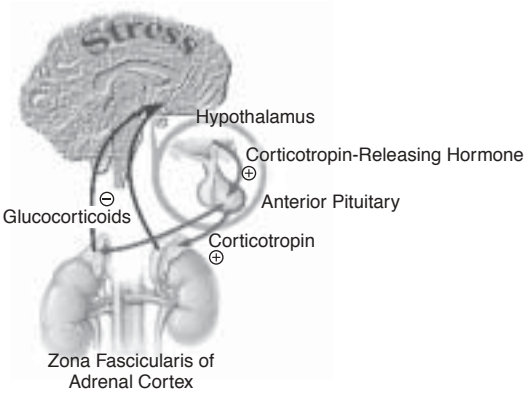
depression. Because of the confounding effects of lifestyle factors and medications that affect weight, much of the available data examining the mechanisms by which obesity is linked to bipolar disorder have been inconsistent. A Danish study[28] reported that weight gain was associated with female sex, weight at diagnosis, and antidepressant use but not with thyroid concentration or lithium or antipsychotic use. Another study[29] found that weight gain was associated with antipsychotic use but not lithium use. A large study[30] recently confirmed that overweight, obesity, and extreme obesity were common states in people with bipolar disorder and were associated with patient and treatment variables in a complex manner.

Weight gain is most likely not the only factor linked to an increase in morbidity from obesity-related diseases; another factor may be the increased amount of centrally deposited adipose tissue. Body fat distribution predicts coronary heart disease better than the total body fat.[31,32] A measure of this distribution is waist:hip ratio, and high waist:hip ratio is positively associated with increased incidence of myocardial infarction, stroke, and death from all causes in both men and women, after adjusting for body mass index (BMI). While BMI gives an overall quantity of body fat, waist:hip ratio is a better reflection of visceral levels of fat.[33] Waist:hip ratio is associated with increased blood pressure,[34,35] increased triglycerides level,[27,31] and decreased HDL cholesterol level.[36] Body fat distribution is related to fasting, stimulated levels of glucose and insulin,[37] and increased rates of diabetes.[38] Increased visceral fat is a risk factor for illnesses such as diabetes mellitus, hypertension, and certain female carcinomas.[39] People with bipolar disorder had a high waist:hip ratio and were classified as more centrally obese than a control population matched for age in one study.[29] In addition, those treated with antipsychotic medications were more obese than patients not receiving these drugs.[29] Visceral fat may therefore be a key pathologic factor accounting for increased prevalence of some types of cardiovascular illness, type 2 diabetes mellitus, and dyslipidemia in people with bipolar disorder.

Stress and Metabolic Syndrome in Bipolar Disorder

Chronic stress is associated with elevated cortisol, as are both the depressed and manic phases of bipolar disorder.[40] Retrospective and prospective studies suggest that major psychological stressors often precede the first episode of a mood disorder[41,42] and that stress is also related to relapse.[43] The hypothalamic-pituitary-adrenal (HPA) axis is central to the stress response (Figure 1), and hyperactivity of the HPA axis is the most prominent neuroendocrine abnormality in major depression.[44] Abnormalities in HPA function are apparent in persons with bipolar disorder; tests of the HPA axis show increased levels of basal cortisol, lack of suppression of cortisol levels by dexamethasone, and abnormal responses of the HPA to various physical and psychological stressors.[45] Furthermore, the normal diurnal variation of cortisol is perturbed, the cortisol troughs normally present at night are not blunted,[46] and the daytime peaks are higher.[47] Basal cortisol levels appear higher even in euthymic patients[48] and in healthy probands with a family history of mood disorders[49] than in comparison subjects, suggesting that HPA axis dysfunction may be a trait abnormality in bipolar disorder.

Figure 1. Hypothalamic-Pituitary-Adrenal (HPA) Axis Involvement in Stress Response



Symbols: ⊕ = increase, ⊖ = decrease.

Abnormalities in cortisol are not confined to the depressive phase, with abnormal dexamethasone/corticotropin-releasing hormone (DEX/CRH) test results in people with mania as well,[50] and medications used in either phase may have an impact on the cortisol response. Successful resolution of depressive symptoms normalizes the HPA axis,[51,52] but a recent study showed that in the absence of a treatment response, antidepressants did not alter the cortisol output on the DEX/CRH test.[53] Lithium augmentation in treatment-resistant unipolar depression may increase the cortisol response to the DEX/CRH test,[54] although a recent study of people with bipolar disorder did not show this increase.[48] A treatment study of people with schizophrenia found that typical neuroleptic drugs suppress blood cortisol levels and decrease the number of patients who are dexamethasone nonsuppressors.[55]

Chronically elevated glucocorticoids impede the ability of insulin to promote glucose uptake, which in turn promotes the deposition of body fat as well as the formation of atherosclerotic plaques in the coronary arteries.[56] HPA axis hyperactivity is directly associated with obesity and with elevated levels of leptin, a satiety hormone,[57] suggesting that dysregulation of the HPA axis may be associated with obesity through inefficient leptin signaling. Indeed, studies in rats have shown that glucocorticoids diminish leptin signals.[58]

Another consequence of elevated cortisol secretion is increased visceral fat. The mechanism underlying this as-

sociation appears to be activity of lipoprotein lipase, the main regulator of fat influx into adipocytes, through binding of the cortisol-glucocorticoid receptor complex of the lipase gene.[59] Because the density of glucocorticoid receptors is higher in visceral than other fat deposits, more cortisol is bound here and more triglycerides are assimilated into adipose tissue.[60] Elevated cortisol secretion also causes insulin resistance localized to muscle[58] and affects the action of glycogen synthase, a well-established cause of insulin resistance.[61]

Analysis of anthropometric, metabolic, and hemodynamic factors associated with metabolic syndrome have thus revealed significant relationships between factors associated with metabolic syndrome and a dysfunctional HPA axis.[62] The dysregulation of cortisol that is apparent in persons with bipolar disorder may contribute to frequent aspects of metabolic syndrome including insulin resistance, abdominal obesity, and dyslipidemia.

Immune Function and Metabolic Syndrome in Bipolar Disorder

Recent studies have found that bipolar disorder is associated with increased expression of inflammatory markers,[63,64] but this relationship remains poorly articulated. Some studies suggest that depression promotes an inflammatory process; the most compelling evidence of this process derives from studies that have shown amelioration of depressive symptoms through psychotherapy and found corresponding declines in the magnitude of inflammation.[65] Conversely, inflammatory processes contribute to depression. Exposure to inflammatory mediators produces a constellation of sickness behaviors (e.g., hyposomnia, anhedonia, and anorexia) that resemble depressive symptoms.[66,67] Because experiments involving illness generation are difficult to perform in humans, the clinical evidence is restricted to situations in which people are exposed to high doses of inflammatory cytokines as a result of medical treatment (e.g., radiation and cytokine therapies for cancer). Patients frequently develop symptoms of depression in these circumstances,[68] which can be prevented through prophylactic administration of antidepressant medication.[69]

Several molecules that are elevated in individuals with depression and mania, including interleukin-6 and C-reactive protein, predict cardiac morbidity and mortality[64,70] The association between adiposity and elevated interleukin-6 and C-reactive protein levels in clinically depressed individuals is proposed to explain the increased morbidity and mortality.[71] Physiologic pathways include expanded adipocyte tissue release of interleukin-6, which induces hepatic release of C-reactive protein,[72,73] and leptin-induced up-regulation of interleukin-6 by white blood cells.[74,75] Interleukin-6 is a potent stimulator of corticotropin-releasing hormone production, a mechanism that leads to heightened HPA activity, including elevated levels of plasma corticotropin and subsequently an increase in cortisol levels.[76] Elevations in adrenocorticotropic hormone and cortisol can provoke multiple adverse immunologic responses.[77] In addition to increasing levels of proinflammatory cytokines, depression and distress can adversely affect other immunologic mechanisms, including the down-regulation of cellular and humoral responses.[77]

The proinflammatory cytokine interferon-γ has been recently studied as a possible contributor to depression. Interferon-γ causes induction of the enzyme indolamine 2,3 dioxygenase, which converts tryptophan into kynurenine. Indolamine 2,3 dioxygenase activation leads to reduced levels of tryptophan, the precursor of serotonin (5-HT), and thus to reduced central 5-HT synthesis.[78] As well, kynurenine metabolites such as 3-hydroxykynurenine and quinolinic acid have toxic effects on the brain.[78,79] The changes in cytokines are clinically relevant, as inflammation has been linked to a spectrum of conditions. For example, interleukin-6 promotes the production of C-reactive protein, a marker of risk for myocardial infarction.[80] Elevated levels of C-reactive protein and interleukin-6 predicted development of diabetes in a 4-year follow-up period in healthy women after adjustments for BMI, family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy.[81] Among women in the highest vs. lowest quartile, the relative risk for developing diabetes was 7.5 for interleukin-6 and 15.7 for C-reactive protein. Inflammation has been linked to a spectrum of other conditions including osteoporosis, arthritis, Alzheimer's disease, and cancer.[82]

Diabetes Mellitus and Bipolar Disorder

A number of studies have indicated that depression constitutes a risk factor in the development of type 2 diabetes and may accelerate the onset of diabetes complications.[83] These findings have also been observed in people with bipolar disorder.[84–87] Impaired glucose tolerance and insulin resistance are more common in people with bipolar disorder than in the general population and are just as common as in schizophrenia, an illness that is now identified by diabetes associations as an independent risk factor for diabetes.[88] Some data suggest that rates of diabetes mellitus in people with bipolar disorder are actually higher than for schizophrenia and that BMI, but not medication use, is positively correlated with new-onset type 2 diabetes mellitus.[89] High rates of insulin resistance and impaired glucose tolerance in individuals with psychiatric illness were recognized before the introduction of neuroleptics.[90,91] Theories link a tyrosine hydroxylase/insulin/insulin-like growth factor II (TH/INS/IGF-II) gene cluster on the short arm of chromosome 11 as a susceptibility locus for diabetes mellitus[92,93] and link tyrosine hydroxylase markers to an association with bipolar disorder.[94,95]

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Cardiovascular Disease and Bipolar Disorder

There is substantial evidence that depression is a risk factor for cardiac morbidity and mortality. This risk relates both to major depressive disorder and bipolar disorder. People with depression have a 2- to 4-fold increased risk of developing cardiovascular disease[96–98] and a 2- to 4-fold risk of mortality after experiencing a cardiac event.[99–100] Symptoms of depression predict future coronary events for initially healthy individuals, as well as a poor prognosis for those who suffer from established cardiovascular disease.[101,102] One explanation for this association involves the components of hemostasis (blood coagulation, anticoagulation, fibrinolysis, and platelet activity) that are crucial in the development and prognosis of cardiovascular disease. A study investigating procoagulant factors in depression found evidence of hypercoagulability in depressed individuals.[103] As well, untreated depressed people have abnormalities of platelet function that lead to platelet activation.[104] Platelet activity up to 40% more than that of controls has been demonstrated in depressed people,[105] with a degree of activation similar to that observed in people with large-vessel atherosclerotic disease.[106] Depression is also associated with abnormalities in platelet 5-HT_{2A} receptors, including receptor up-regulation.[107] This up-regulation is apparent in medication-free people with bipolar disorder, and the increase in 5-HT_{2A} receptor density was further increased in suicidal patients and in those treated with lithium.[108]

The models linking cardiovascular disease to autonomic nervous system abnormalities in depression may be extrapolated to bipolar disorder as there is evidence suggesting autonomic nervous system involvement in this illness.[109–111] People with bipolar disorder have higher sympathetic tone than controls[110,112,113] and higher systolic blood pressure when experiencing manic events.[114] Interestingly, a recent study did not show a difference in the resting heart rate of normal controls and euthymic people with bipolar disorder. However, people with bipolar disorder did have significantly lower heart rate variability.[115] Excessive regularity in heart rate may reflect a level of cortical control that has been reset to withstand stressful changes to mood stability. This tightened control may dampen changes associated with fluctuating mood but may also manifest with tight control of normal cardiac fluctuations.

Abnormalities of the autonomic nervous system are of particular interest in understanding the link between bipolar disorder and metabolic syndrome, as dysregulation of the sympathetic nervous system is one of the pathophysiologic mechanisms proposed to underlie the metabolic syndrome. Insulin-mediated glucose uptake in the central nervous system regulates sympathetic nervous system activity in response to dietary intake. Mounting evidence links this insulin-mediated sympathetic stimulation to the pathogenesis of hypertension.[116] The sympathetic nervous system also displays increased activity in obesity.[117] Indicators of elevated activity of the sympathetic nervous system are more closely associated with elevated activity of the HPA than with insulin,[118] suggesting that the HPA axis and sympathetic nervous system may be activated in parallel. The hypothalamic centers controlling the HPA axis and sympathetic response are linked in such a way that it is difficult to stimulate one center without affecting the other.[119] People with bipolar disorder have increased activity of the sympathetic nervous system, as outlined, and increased activity along the adrenocortical axis. This link may partially account for the common cluster of symptoms found in bipolar disorder and metabolic syndrome.

Role of Medication in Increasing Risk for Metabolic Syndrome in Bipolar Disorder

Lithium is a mainstay of treatment for bipolar disorder. Weight gain associated with lithium occurs in up to 60% of patients, and estimates of typical gain range from 4.5 to 15.6 kg (10.0–34.6 lb) over 2 years.[120] This gain is quite likely related to factors including increased appetite, fluid retention, altered carbohydrate and fat metabolism, or hypothyroidism.[24] Valproate is also associated with weight gain, insulin resistance, hyperlipidemia, impaired glucose tolerance, and hyperinsulinemia.[25,121] These risks are lower with carbamazepine, sometimes recommended for patients who are particularly concerned about weight gain.[122] The risks of weight gain and symptoms of metabolic syndrome appear to be much lower with lamotrigine than with the other anticonvulsants, and in studies of anticonvulsant use in epilepsy, substitution of lamotrigine for valproate appears to reduce metabolic syndrome risk.[123]

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors may be more likely to cause weight gain than selective serotonin reuptake inhibitors (SSRIs) or newer antidepressants,[124] with the exception of mirtazapine, which may be placed between TCAs and SSRIs in terms of relative risk for weight gain.[125] Paroxetine may be more likely to cause weight gain than the other SSRIs,[126] and bupropion may be less likely to cause weight gain than SSRIs.[127]

Much has been written of the association between antipsychotic medications and weight gain, glucose intolerance, and dyslipidemia. All atypical antipsychotics appear to cause some amount of weight gain, but the effects range from minimal to significant. In general, clozapine and olanzapine cause the most weight gain, ziprasidone and aripiprazole cause the least, and risperidone and quetiapine are between the others.[128] Associated with increased weight is an increased risk for type 2 diabetes, and some studies suggest that use of any antipsychotic medication confers risk,[129] although this finding remains controversial. Lipid profiles may also be negatively affected by atypical antipsychotics.[130]

Medication effects may compound the inherent risk for metabolic syndrome, and although their effects cannot account for all the metabolic abnormalities observed in patients, their role in this process may be substantial, as is their benefit in treatment of the underlying psychiatric illness. In notable contrast to the data suggesting that medications worsen or cause an underlying propensity toward metabolic syndrome in persons with bipolar disorder, however, a study comparing standardized mortality ratios in people with bipolar disorder found overall mortality in the treated group to be considerably lower than in the untreated group for both natural and nonnatural causes of death.[131]

SUMMARY

People with bipolar disorder develop a host of medical illnesses that contribute to the premature mortality associated with this illness. Many of the physical symptoms observed in bipolar disorder are components of metabolic syndrome, and the illnesses share pathophysiologic and lifestyle risk factors. This review describes various ways in which key systems—the HPA axis, the immune and autonomic nervous systems, glucose and insulin regulation, and regulation of hemostasis—can be dysregulated in both bipolar disorder and metabolic syndrome. Future studies are required to determine whether optimal control of mood symptoms reduces the occurrence of metabolic syndrome and its sequelae in people with bipolar disorder. Conversely, studies are also needed to confirm whether intervention aimed at reducing components of the metabolic syndrome in bipolar disorder, such as reducing visceral fat deposition with weight loss, can improve symptom control and outcome related to bipolar disorder. While we await such studies, it is important for clinicians to understand the risks of comorbid physical diseases in people with bipolar disorder; to work collaboratively with primary care physicians to test for, monitor, and reduce risk factors for metabolic syndrome; and to be aware of the potential influences—both positive and negative—of pharmacologic and nonpharmacologic treatments for bipolar disorder on metabolic parameters.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Equetro and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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