

# Depressed, suicidal, and brittle in her bones

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Ms. E, age 20, describes depression, mania, and suicidal ideation. She also has fragile bones that have led to 62 fractures. How would you treat her bipolar disorder, while protecting her bones?



## How would you handle this case?

Answer the **challenge questions** throughout this article

### CASE Broken down

Ms. E, age 20, is a college student who has had major depressive disorder for several years and a genetic bone disease (osteogenesis imperfecta, mixed type III and IV). She presents with depression, anxiety, and suicidal ideation. She reports recent worsening of her depressive symptoms, including anhedonia, excessive sleep, difficulty concentrating, and feeling overwhelmed, hopeless, and worthless. She also describes frequent thoughts of suicide with the plan of putting herself in oncoming traffic, although she has no history of suicide attempts.

Previously, her primary care physician prescribed lorazepam, 0.5 mg, as needed for anxiety, and sertraline, 100 mg/d, for depression and anxiety. She experienced only partial improvement in symptoms, however.

In addition to depressive symptoms, Ms. E describes manic symptoms lasting for as long as 3 to 5 days, including decreased need for sleep, increased energy, pressured speech, racing thoughts, distractibility, spending excessive money on cosmetics, and risking her safety—given her skeletal disorder—by participating in high-impact stage-combat classes. She denies auditory and visual hallucinations, homicidal ideation, and delusions.

The medical history is significant for osteogenesis imperfecta, which has caused

62 fractures and required 16 surgeries. Ms. E is a theater major who, despite her short stature and wheelchair use, reports enjoying her acting career and says she does not feel demoralized by her medical condition. She describes overcoming her physical disabilities with pride and confidence. However, her recent worsening mood symptoms have left her unable to concentrate and feeling overwhelmed with school.

Ms. E is voluntarily admitted to an inpatient psychiatric unit with a diagnosis of bipolar I disorder with rapid cycling, most recent episode mixed. Because of her bone fragility, the treatment team considers what would be an appropriate course of drug treatment to control bipolar symptoms while minimizing risk of bone loss.

### Which medications are associated with decreased bone mineral density?

- citalopram
- haloperidol
- carbamazepine
- paliperidone
- all of the above

continued

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### Disclosures

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

## Table

## The potential risk of fracture presented by class of psychotropic medications

Class of drug	Lowest risk	Moderate risk	Highest risk
Anticonvulsants	Lamotrigine		Carbamazepine Phenytoin Valproic acid
Antidepressants	Maprotiline Mirtazapine Tranlycypromine	Amitriptyline Desipramine Doxepin Nefazodone Nortriptyline Trazodone Venlafaxine	Citalopram Fluoxetine Fluvoxamine Imipramine Paroxetine Sertraline
Antipsychotics	Aripiprazole Asenapine Clozapine Quetiapine Ziprasidone	Iloperidone Lurasidone Olanzapine	Haloperidol Paliperidone Risperidone Typical antipsychotics (all)
Lithium	May be protective but evidence is insufficient		

## Clinical Point

Prolactin-elevating antipsychotics have been associated with decreased bone mineral density and increased risk of fracture

## The authors' observations

Osteogenesis imperfecta is a genetic condition caused by mutations in genes implicated in collagen production. As a result, bones are brittle and prone to fracture. Different classes of psychotropics have been shown to increase risk of bone fractures through a variety of mechanisms. Clinicians often must choose appropriate pharmacotherapy for patients at high risk of fracture, including postmenopausal women, older patients, malnourished persons, and those with hormonal deficiencies leading to osteoporosis.

To assist our clinical decision-making, we reviewed the literature to establish appropriate management of a patient with increased bone fragility and new-onset bipolar disorder. We considered all classes of medications used to treat bipolar disorder, including antipsychotics, antidepressants, lithium, and anticonvulsants.

## Antipsychotics

In population-based studies, prolactin-elevating antipsychotics have been associ-

ated with decreased bone mineral density and increased risk of fracture.<sup>1</sup> Additional studies on geriatric and non-geriatric populations have supported these findings.<sup>2,3</sup>

The mechanism through which fracture risk is increased likely is related to antipsychotics' effect on serum prolactin and cortisol levels. Antipsychotics act as antagonists on D2 receptors in the hypothalamic tuberoinfundibular pathway, therefore preventing inhibition of prolactin. Long-term elevation in serum prolactin can cause loss of bone mineral density through secondary hypogonadism and direct effects on target tissues. Additional modifying factors include smoking and estrogen use.

The degree to which antipsychotics increase fracture risk might be related to the degree of serum prolactin elevation.<sup>4</sup> Antipsychotics previously have been grouped by the degree of prolactin elevation, categorizing them as high, medium, and low or no potential to elevate serum prolactin.<sup>4</sup> Based on this classification, typical antipsychotics, risperidone, and paliperidone have the highest potential to elevate prolactin. Accordingly, antipsychot-



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ics with the lowest fracture risk are those that have the lowest risk of serum prolactin elevation: ziprasidone, asenapine, quetiapine, and clozapine. Aripiprazole may lower prolactin in some patients. This is supported by studies noting reduced bone mineral density<sup>5,6</sup> and increased risk of fracture<sup>1</sup> with high-potential vs low- or no-potential antipsychotics. Because of these findings, it is crucial to consider the potential risk of prolactin elevation when treating patients at increased risk of fracture. Providers should consider low/no potential antipsychotic medications before considering those with medium or high potential (*Table*).

### Antidepressants

In a meta-analysis, antidepressants were shown to increase fracture risk by 70% to 90%.<sup>2</sup> However, the relative risk varies by antidepressant class. Several studies have shown that selective serotonin reuptake inhibitors (SSRIs) are associated with a higher risk of fracture compared with tricyclic antidepressants (TCAs).<sup>7</sup> In addition, antidepressants with a high affinity for the serotonin transporter, including citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and imipramine, have been associated with greater risk of osteoporotic fracture compared with those with low affinity.<sup>8</sup>

The mechanisms by which antidepressants increase fracture risk are complex, although the strongest evidence implicates a direct effect on bone metabolism via the 5-HTT receptor. This receptor, found on osteoblasts and osteoclasts, plays an important role in bone metabolism; it is through this receptor that SSRIs might inhibit osteoblasts and promote osteoclast activity, thereby disrupting bone microarchitecture. Additional studies are needed to further describe the mechanism of the association among antidepressants, bone mineral density, and fracture risk.

Fracture risk is associated with duration of use rather than dosage. Population-

based studies show a higher fracture risk for new users of TCAs compared with continuous users, and the risk of fracture with SSRIs seems to increase slightly over time.<sup>9</sup> No association has been identified between fracture risk and antidepressant dosage. According to the literature, drugs with low affinity for the serotonin transporter, such as maprotiline and mirtazapine, likely are the safest antidepressants for patients at increased risk of fracture. Options also include other TCAs and any antidepressant with low affinity for the serotonin receptor.<sup>7,8</sup>

### Lithium

Studies on lithium and bone mineral density have shown mixed results. Older studies found that lithium had a negative or no effect on bone mineral density or the parathyroid hormone level.<sup>10</sup> More recent investigations, however, suggest that the drug has a protective effect on bone mineral density, although this has not been replicated in all studies.

In a mouse model, lithium has been shown to enhance bone formation and improve bone mass, at least in part by activation of the Wnt signaling pathway through an inhibitory effect on glycogen synthase kinase-3 $\beta$ .<sup>11</sup> In humans, lithium-treated adults had lower serum alkaline phosphate, osteocalcin, and C-telopeptide levels compared with controls, suggesting a state of decreased bone remodeling and increased turnover.<sup>12</sup> There is a paucity of clinical data on the effect of lithium on fracture risk. Additional studies are necessary to elucidate lithium's mechanism on bone mineral density and determine the magnitude of the clinical effect.

### Anticonvulsants

The association among anticonvulsants, decreased bone mineral density, and increased risk of fracture is well-established

### Clinical Point

**Fracture risk is associated with duration of antidepressant use rather than dosage**

## Clinical Point

Long-term treatment with valproate may produce reduction in bone mass and increase the risk of fractures

## Related Resources

- NIH Osteoporosis and Related Bone Diseases National Resource Center. [www.niams.nih.gov/Health\\_Info/Bone](http://www.niams.nih.gov/Health_Info/Bone).
- Takahashi T, Uchida H, John M, et al. The impact of prolactin-raising antipsychotics on bone mineral density in patients with schizophrenia: findings from a longitudinal observational cohort. *Schizophr Res*. 2013;147(2-3):383-386.

## Drug Brand Names

Amitriptyline • Elavil	Maprotiline • Ludiomil
Aripiprazole • Abilify	Mirtazapine • Remeron
Asenapine • Saphris	Nefazodone • Serzone
Carbamazepine • Tegretol	Nortryptiline •
Citalopram • Celexa	Aventyl, Pamelor
Clozapine • Clozaril	Olanzapine • Zyprexa
Desipramine • Norpramin	Paliperidone • Invega
Doxepin • Silenor, Sinequan	Paroxetine • Paxil
Fluoxetine • Prozac	Phenytoin • Dilantin
Fluvoxamine • Luvox	Quetiapine • Seroquel
Haloperidol • Haldol	Risperidone • Risperdal
lloperidone • Fanapt	Sertraline • Zoloft
Imipramine • Tofranil	Tranlycypromine • Parnate
Lamotrigine • Lamictal	Trazodone • Desyrel, Oleptro
Lithium • Eskalith, Lithobid	Valproate • Depakote
Lorazepam • Ativan	Venlafaxine • Effexor
Lurasidone • Latuda	Ziprasidone • Geodon

in the literature.<sup>13</sup> However, causality is difficult to determine, because many studies were of patients with a seizure disorder, who often have additional risk factors for fracture, including seizure-related trauma, drowsiness, and slowed reflexes.

Mechanisms through which anticonvulsants increase fracture risk include increased bone resorption, secondary hypoparathyroidism, and pseudohypoparathyroidism. Markers of bone resorption were elevated in patients receiving an antiepileptic.<sup>14</sup> This effect might be enhanced by co-administration of cytochrome P450 (CYP450) enzyme-inducing anticon-

vulsants and CYP450 enzyme-inhibiting medications, such as valproate. Long-term treatment with valproate may produce reduction of bone mass and increased risk of fractures; however, other studies disagree with this finding.<sup>15</sup>

In addition to CYP450-inducing effects, phenytoin, carbamazepine, and phenobarbital can increase catabolism of vitamin D, which is associated with osteomalacia.<sup>14</sup> This results in decreased intestinal absorption of calcium, hypocalcemia, and secondary hyperparathyroidism, which also increases fracture risk. Anticonvulsants also might increase resistance to pseudohypoparathyroidism and inhibit calcitonin secretion.

Lamotrigine has not been shown to interfere with bone accrual<sup>16</sup> and may be a safer mood stabilizer for patients at high risk of fracture. For patients at increased risk of fracture, it is important to select an anticonvulsant wisely to minimize fracture risk.

## How would you treat Ms. E during her hospitalization for bipolar disorder?

- carbamazepine
- lithium
- risperidone
- mirtazapine

## TREATMENT Minimizing polypharmacy

Because many pharmacotherapeutic options for managing bipolar disorder can increase

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## Bottom Line

Different classes of medications—antipsychotics, anticonvulsants, antidepressants, and lithium—used for treating bipolar disorder have been shown to increase risk of bone fracture through a variety of mechanisms. Anticonvulsants and prolactin-elevating antipsychotics are associated with increased fracture risk; evidence on lithium is mixed. Fracture risk with antidepressants is associated with duration of use, rather than dosage.

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the risk of fracture, clinicians must be aware of the relative risk of each class of medication and each individual drug. We initiated lithium, 300 mg, 3 times a day, to stabilize Ms. E's mood. Although clinical data are inconclusive regarding lithium's effect on fracture risk, we felt that the benefit of acute mood stabilization outweighed the risk of decreased bone mineral index.

We selected aripiprazole, 10 mg/d, as an adjunctive treatment because of its minimal effect on serum prolactin levels.<sup>4</sup> We considered prescribing an antidepressant but decided against it because we were concerned about manic switching.

Polypharmacy is another important consideration for Ms. E. Several studies have identified polypharmacy, particularly with antipsychotics, as an independent risk factor for fracture.<sup>3</sup> Therefore, we sought to minimize the number of medications Ms. E receives. Although lithium monotherapy is an option, we thought that her mood symptoms were severe enough that the risk of inadequately treating her bipolar symptoms outweighed the additional risk of fracture from dual therapy with lithium and aripiprazole. Untreated or inadequately treated depression is associated with a higher fracture risk. Therefore, we avoided prescribing >2 medications to mitigate any excessive risk of fracture from polypharmacy.

### Clinical Point

Lamotrigine has not been shown to interfere with bone accrual and may be a safer mood stabilizer for patients at high risk of fracture

### References

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## Coming next issue in Cases That Test Your Skills

Mr. D, age 17, is brought to the hospital visibly agitated after being seen talking to the walls of the house. He had taken 24 tablets of diphenhydramine in a suicide attempt a week after he broke up with his girlfriend. He has a history of major depressive disorder and substance abuse. How would you treat him?