ABSTRACT

Weight gain with medication use is often considered to be a mild to moderate side effect, only considered after efficacy and other serious adverse events are reviewed in choosing a therapy. However, weight gain is not benign in terms of health risk, and many of the drugs neurologists typically prescribe cause significant weight gain. Weight gain also exacts a large toll on patients' self-esteem and therefore has significant impact on adherence. Antiepileptic drugs, antidepressants, and antipsychotics are commonly associated with significant weight gain. While some drugs within each class may at best be associated with weight loss or at least have no effect on weight, many of the drugs in these classes cause changes in weight. Weight gain with these agents may be independent of pretreatment weight and resistant to normally effective dietary regimens for weight loss. The degree of weight gain and other metabolic changes for these 3 classes of drugs are reviewed here. Given that these medications are often prescribed as long-term or even lifelong treatment, understanding their effects on weight can help the neurologist and patient make the best choice for therapy and can prepare them for the adverse events they will face.

overweight and obesity in the US population. Valproate is used in the treatment of both generalized and partial seizures and is also now widely used for the treatment of other disorders including migraine prophylaxis and bipolar disorders.

Studies have suggested that approximately 50% of epileptic patients experience excessive (>4 kg) weight gain, with mean gains of 7 to 20 kg when treated with valproate. Also of note, the weight gain typically appears within the first 3 to 6 months of treatment and is frequently resistant to dietary interventions, and may be independent of pretreatment body weight.2-4

The mechanisms of valproate-associated weight gain are not clearly defined but appear to be multifactorial. Valproate inhibits mitochondrial beta-oxidation, which leads to an impaired energy utilization and, therefore, impaired utilization of free fatty acids. Free fatty acids are then stored as fat.6 In rats, inhibition of beta-oxidation results in increased appetite and increased consumption.7 Valproate also causes a decrease in the protein-binding of palmitate, thus increasing the availability of long-chain free fatty acids, which increase insulin production and therefore increase appetite and lipogenesis.8 Valproate may also increase γ-aminobutyric acid (GABA) levels, which increase appetite.9 Serum leptin levels are elevated in female patients who have gained weight with valproate treatment (1 year): 33.1 ± 3.1 ng/mL vs 9.8 ± 2.5 ng/mL in those who have not gained weight with treatment and 9.2 ± 1.9 in lean controls.10 The role of leptin, as described by Aronne in this issue, appears to be appetite control, and leptin levels are unusually high in overweight individuals, perhaps due to decreased sensitivity to leptin with excess weight. Valproate may trigger an avenue for leptin resistance but the mechanism is unknown.

The effect of valproate on energy expenditure is important because it may explain why patients taking valproate are so resistant to weight loss with typically effective dietary regimens. A study of 38 patients with epilepsy showed that the resting energy expenditure (ie, basal metabolic rate) is significantly reduced with valproate therapy. Interestingly, energy intake, as measured by patient-completed food diaries, did not differ significantly among the groups.11

Among the newer-generation AEDs, effects on body weight may differ markedly. Gabapentin is associated with weight gain in perhaps as many as 15% to 20% of patients.12 Felbamate, topiramate, and zonisamide are all associated with weight loss; for felbamate and topiramate, weight loss can be noted in 10% to 75% of patients and may be dose dependent.13,14 The data regarding weight loss with zonisamide are limited.15 Recent data in obese adults suggest that zonisamide treatment can result in modest weight loss as compared with placebo (57% of patients taking zonisamide vs 10% taking placebo lost at least 5% body weight).16 Lamotrigine and levetiracetam are considered to be weight neutral.17 A retrospective review of data from 32 clinical trials of epilepsy patients taking lamotrigine (N = 463; mean daily dose: 259 [±-155] mg; duration of therapy: 318 [±-87] days) suggests that weight remains stable overall with lamotrigine therapy (Table).18 A head-to-head study comparing valproate and lamotrigine demonstrates a significant difference in associated weight changes during 30 weeks of treatment with valproate vs lamotrigine (Figure 1).19 In this study, treatment with valproate was associated with significant change in body weight over a 32 week period (12.8 ± 9.3 lbs), whereas patients randomized to lamotrigine had no significant change in body weight (1.3 ± 11.9 lbs). Valproate associated weight gain occurred in both adult and adolescent patients, and did not appear to be correlated with valproate dose or plasma concentration.20

Weight loss associated with topiramate has been reported in both epileptic and nonepileptic patients. A study of 36 patients with bipolar I/II depression in an outpatient treatment environment showed that topira-

### Table. Weight Changes Associated With Lamotrigine

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine Dose (mg/day)</th>
<th>Duration of Treatment (days)</th>
<th>Change in Weight (kg)</th>
<th>Range of Weight Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>All patients</td>
<td>463</td>
<td>299 ± 155</td>
<td>318 ± 87</td>
<td>0.5 ± 5</td>
</tr>
<tr>
<td>Female</td>
<td>193</td>
<td>251 ± 143</td>
<td>313 ± 57</td>
<td>0.4 ± 5</td>
</tr>
<tr>
<td>Male</td>
<td>270</td>
<td>264 ± 162</td>
<td>321 ± 104</td>
<td>0.6 ± 5</td>
</tr>
</tbody>
</table>

mate causes significant decreases in both weight and leptin levels (5.8-kg weight loss, 3.5% leptin decrease, mean dose 250 mg/day) compared with bupropion sustained-release (1.8-kg weight loss, 0.1% leptin decrease, mean dose 176 mg/day). However, the full significance of the change in leptin levels is not yet fully appreciated. Van Ameringen et al reported weight loss following the addition of topiramate to patients with anxiety disorders who were concomitantly receiving an SSRI and had experienced weight gain. In this small patient series, patients lost a mean of 4.2 kg over a 10-week period. Average topiramate doses were 135 mg/day.

The mechanisms behind weight loss with topiramate are also not fully delineated; however, animal data suggest several avenues including altered energy expenditures, reduced appetite, inhibition of fat deposition with concomitant reduced activity of lipoprotein lipase, and changes in leptin and blood glucose levels. Importantly, topiramate can induce substantial loss of body weight in a number of patients. The degree of weight loss can have substantial benefits as reviewed by Bloomgarden in this issue. Overweight or obese individuals, which now constitute the majority of US adults. In a recent report, Rosenfeld and Slater reported that adjunctive treatment with topiramate resulted in weight loss in a group of adults with epilepsy. In this analysis of a clinical trial database (n=1319), 85% of patients reported weight loss. Weight loss was most pronounced in patients with a baseline body weight of >100 kg (8.4% relative weight loss) vs those individuals <100 kg (4.2% relative weight loss). Although these effects on body weight also appear to be dose dependent, modest weight loss was noted at topiramate doses <200 mg/day. Importantly, weight loss was not transient, and appeared to be maintained over time. Given the high rate of weight loss with placebo, further studies with weight change as a defined endpoint are needed to substantiate not only the degree of weight loss in this population, but also to confirm that these effects are maintained.

**Antidepressants**

The older antidepressants are frequently associated with weight gain, although these observations are not consistent. They include amitriptyline, imipramine, nortriptyline, and doxepin (TCAs), and phenelzine (monoamine oxidase inhibitor). In one long-term evaluation of imipramine in patients with unipolar depression, no significant differences were noted in weight gain between those patients being treated with active drug, versus those not receiving drug treatment. Clearly, some patients may experience weight gain with these various agents however, and this may relate, at least in part to other clinical factors such as resolution or recurrence of depressive symptoms. Whether one TCA vs another is more or less prone to causing weight gain is quite unclear.

Three antidepressants have been associated with weight loss: bupropion, nefazadone, and venlafaxine. Bupropion is a norepinephrine and dopamine reuptake inhibitor, venlafaxine is a serotonin and norepinephrine reuptake inhibitor, and nefazadone is a selective serotonin reuptake inhibitor (SSRI). The data for bupropion and venlafaxine regarding weight loss are not conclusive but they appear to be encouraging.

Selective serotonin reuptake inhibitors are widely prescribed antidepressants because of their very tolerable side-effect profile. Initially, short-term clinical trials suggested that SSRIs caused weight loss. However, subsequent open-label, postmarketing studies have indicated that the weight loss was not sustainable. Up to one third of patients lose weight during the first 12 weeks of treatment. By 6 months, patients' weights gradually return to baseline. A recent study compared nefazodone with imipramine and showed weight loss with short-term nefazodone use but weight gain with long-term use. Interestingly, one SSRI, paroxetine, has been suggested to cause weight gain in some patients.

**Figure 1. Weight Change Associated With Lamotrigine and Valproate Monotherapy**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Weight Change (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
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<tr>
<td>10</td>
<td>1</td>
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<td>35</td>
<td>6</td>
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LTG = lamotrigine; VPA = valproate.
With treatment of depression, the overall return of appetite and weight may be multifactorial. Patients whose depression has remitted may find that their appetite has returned or increased due to clinical improvement of depressive symptoms. On a molecular level, an increase in appetite has been associated with blockade of the histamine H₁ receptor with TCA use; H₂-receptor agonism can produce the reverse. SSRIs and TCAs can produce an increased craving for carbohydrates, and there is also rising interest in a subset of serotonin receptors. Serotonin is a satiety inducer and SSRIs are associated with 5-HT₂C hyposensitivity or antagonism at this receptor. Conclusive evidence, though, is lacking both in an animal model and in humans.31-35

ANTIPSYCHOTICS

Atypical antipsychotics are particularly prone to causing significant weight gain. Allison et al, in a meta-analysis, compared international studies of 10 different antipsychotics (classic and atypical) as well as nonpharmacologic therapy and their effect on weight. As shown in Figure 2, the antipsychotics most strongly causing weight gain were sertindole, thioridazine, olanzapine, and clozapine. Mean changes in body weight reached up to 4 kg.36 More specifically, in a population of patients with bipolar disorder (n = 42), olanzapine produced significantly more weight gain than risperidone over the entire study period, with differences in weight increase reaching significance by 8 weeks. By 12 weeks, the weight gain was >20 pounds for the olanzapine group.37

As with antidepressants, the mechanisms causing weight gain are not fully understood but the histamine H₁ receptor and serotonin 5-HT₂C receptor appear to be involved. Affinity for the H₁ receptor may produce sedation, resulting in decreased physical activity, decreased energy expenditure, and weight gain. Figure 3 shows the relationship between H₁-receptor affinity and weight gain.38 Of note, olanzapine and clozapine are associated with the greatest amount of weight gain and the highest receptor affinity of those compared.

CONCLUSION

Antiepileptic drugs, antidepressants, and antipsychotics are commonly prescribed by neurologists and are, as classes of drugs, associated with significant changes in body weight. While some drugs within each class may be associated with weight loss or at least have no effect on weight, a number of drugs in these classes appear to be associated with weight increase. Understanding the effects of these drugs on weight, especially with the often long-term treatment, can help the neurologist and patient make the best choice for therapy and can prepare them for the adverse events they will face.
REFERENCES


