Weigh gain is a common side effect of drugs used for headache prevention. Weight gain can adversely affect patient health, exacerbate comorbid metabolic disorders, and encourage noncompliance. Additionally, obesity may promote the chronification of episodic migraine. Few studies have looked specifically at the effect that headache medications have on weight. The practicing physician needs accurate information about important side effects, including weight gain, when selecting appropriate pharmacologic regimens. This article discusses the potential effects the more common headache medications have on weight.

Introduction
Sixty-four percent of Americans are overweight or obese [1••]. Treatment-related weight gain is an important side effect of headache therapy that often adversely affects general health, self-esteem, and quality of life. The problem of medication-related weight gain is confounded by the possibility that successful treatment of the underlying disorder may have an effect on weight. For example, having fewer migraine days could increase overall caloric consumption. Treatment-related weight gain can exacerbate common physical and psychologic comorbidities and aggravate noncompliance. Because headache-preventive medications are often administered chronically, their widespread use may also contribute to the prevalence of obesity.

Headache affects a large proportion of the population in industrialized countries. Migraine headaches affect about 6.5% of men and 18.2% of women in the United States [2]. Chronic daily headache affects between 4% and 5% of the US population [3]; approximately 50% of these individuals have chronic migraine (also called transformed migraine). Several categories of migraine-preventive drugs exist. These include antidepressants, antiepileptic drugs (AEDs), β-blockers, calcium channel antagonists, and other agents, such as serotonin receptor blockers (Table 1); tension-type headache treatment generally involves antidepressants and muscle relaxants.

In recent years, researchers have investigated obesity’s relationship to migraine. In a population-based study, migraine prevalence was not associated with increasing body mass index (BMI), but attack frequency and severity, as well as clinical features of migraine, increase with BMI. The odds ratio of having frequent migraine, defined as 10 to 14 headache days per month, increased from 1.3 for overweight individuals to 2.9 for obese and 5.7 for morbidly obese individuals [1••]. A longitudinal study has shown that obesity is a risk factor for the evolution of episodic migraine to daily headache [4]. In a cross-sectional study, obesity was associated with chronic migraine but not chronic tension-type headache [1••]. These studies contrast with a smaller Swedish study, in which neither migraine diagnosis nor headache frequency correlated with obesity [5]. In a clinic-based study, Tierjen et al. [6•] found a correlation between obesity, anxiety, and depression. They did not investigate the use of antidepressants as a covariate. To our knowledge, the possible etiologic role of antidepressants in the obesity epidemic has not been studied. Bigal et al. [7] speculated on the physiology underlying the relationship between migraine and obesity. They did not consider if preventive medication or medications used to treat comorbid conditions could explain some of the observed relationship.

In a clinic-based study, increased weight did not correlate with poor outcome from headache treatment. Although there were no differences in the number of severe headache days per month, treatment effects were greater in the obese (reduction in 2.7 days with treatment) and overweight (3.9) patients, in contrast with those of normal weight (1.5). Contrary to the authors’ hypothesis, obesity at baseline did not seem to be related to follow-up refractoriness to preventive treatment. Although this study included small numbers of patients and was subject to referral bias, it suggests, at a minimum, that obese patients with chronic or transformed migraine can be successfully treated [8].
Antidepressants

Tricyclic antidepressants (TCAs) are commonly used to treat migraine. The acute and chronic effects of TCAs on weight in the treatment of psychiatric disorders are well documented [9], but the magnitude of this effect is controversial. Amitriptyline and imipramine, for example, may cause more weight gain than other TCAs, such as desipramine and nortriptyline [10]. In 217 patients treated for depression for up to 2 years, both amitriptyline and mirtazapine were associated with reports of weight gain; the percentage of patients exhibiting an increase in body weight of 7% or more was higher for amitriptyline (22%) than mirtazapine (13%) [11]. Another study found that patients treated with either amitriptyline or nortriptyline gained an average of 3.5 kg over 6 weeks [12].

However, a 6-month study of agoraphobic patients treated with imipramine found no evidence of long-term weight gain [13]. A large study of elderly patients who used antidepressants for at least 6 months found that TCAs were not generally associated with weight gain, nor were selective serotonin reuptake inhibitors (SSRIs) generally associated with weight loss [14]. Protriptyline, a TCA with little serotonin reuptake inhibition, can induce weight loss and has shown efficacy in chronic tension-type headache. These studies suggest that different TCAs have different effects on weight, and that age and underlying reason for treatment possibly influence a drug’s effect on weight.

SSRIs

SSRIs and selective serotonin and norepinephrine reuptake inhibitors have been used with some success for migraine prophylaxis. Furthermore, they are frequently used to treat migraine comorbid conditions. The conventional thought that SSRIs are generally associated with weight loss has been disproven [9]. The weight changes associated with SSRIs appear to differ between individual drugs over time.

Some SSRIs may be associated with a greater incidence of weight gain than others. At 26 to 32 weeks, paroxetine treatment was associated with a significantly greater percent net weight change (3.6%) than either sertraline (1.0%) or fluoxetine (-0.1%) [15], and greater than 7% weight gain (26% vs 4.2% vs 6.8%, respectively). In contrast with studies in psychiatric settings, migraine patients treated with fluoxetine gained more weight at 36 weeks than patients treated with nortriptyline or divalproex [16]. Perhaps migraine predisposes to fluoxetine-induced weight gain. Additional reports state that as many as 25% to 30% of patients taking SSRIs chronically may gain weight [17]. However, a study in elderly patients concluded that neither TCAs nor SSRIs were disproportionately associated with weight gain or loss during chronic treatment [14].

In some studies, sertraline was associated with weight loss. In two short-term studies, sertraline was associated with weight loss of less than 1 kg [18]. In an 8-week study examining the antidepressant efficacy and effects on sexual functioning of sertraline and bupropion, treatment with sertraline was associated with a mean weight loss of 0.8 kg [19].

Short-term venlafaxine treatment was associated with weight loss in 41 of 42 migraine sufferers [20], whereas another case series reported weight gain associated with mammoplastia in women suffering from depression [21]. Duloxetine is associated with initial weight loss followed by modest weight gain during longer-term treatment, with a 2-kg weight gain 1 year from treatment initiation among patients receiving daily doses of 80 to 120 mg [22]. Mirtazapine, an atypical antidepressant effective for chronic tension-type headache, has a significant association with weight gain [9].

AEDs

AEDs can cause weight gain or loss. Physicians need to take into account the full range of potential pharmacologic side effects when prescribing these medications to migraine sufferers.

Valproic acid

Weight gain is one of the most common side effects associated with valproic acid and divalproex sodium.