Chapter 5. Conclusions

Efficacy

The efficacy of herbal ephedra–containing dietary supplements has not been extensively studied in randomized clinical trials. We identified no clinical trials of herbal ephedra–containing dietary supplements that assessed their effect on athletic performance and only five clinical trials that assessed their effect on weight loss. Many more studies assessed the effects of ephedrine on weight loss; however, studies of the effects of ephedrine on athletic performance are still relatively sparse. The majority of studies—of both ephedra and ephedrine—are plagued by methodological problems known to be associated with bias, particularly high attrition rates. All of the conclusions on efficacy need to be considered with these methodological limitations in mind.

Given the above considerations, the evidence we identified and assessed supports the following conclusions:

Weight Loss

- The short-term use of ephedrine, ephedrine plus caffeine, or the assessed dietary supplements containing ephedra and herbs with caffeine is associated with a statistically significant increase in short-term weight loss (compared to placebo).

- There are no studies assessing the long-term effects of the use of ephedra-containing dietary supplements or ephedrine on weight loss or maintenance. In order to improve health outcomes and reduce the risk of morbidities associated with being overweight, long-term weight maintenance is necessary.

- There are no data to indicate that the effects of ephedrine plus caffeine are different from the effects of ephedra-containing dietary supplements with caffeine-containing herbs.

- The effect of either ephedra-containing dietary supplements with caffeine-containing herbs or ephedrine plus caffeine is a weight loss that is approximately two pounds per month greater than that of placebo, for up to four to six months in duration.

- As a percentage of pretreatment weight, the weight losses in these studies average between 5 percent and 11 percent in the treatment groups.

- The only two studies that compared ephedrine plus caffeine to prescription weight loss pharmaceutical products reported no differences in effectiveness between products, but these studies were statistically underpowered to detect differences of moderate size.

- The addition of caffeine to ephedrine is associated with a statistically significant increase in short-term weight loss.

- One study of ephedra without caffeine-containing herbs reported a statistically significant increase in short-term weight loss that was comparable to the effects reported by four studies of ephedra with caffeine-containing herbs.

- The data suggest a dose-response relationship with respect to ephedrine and weight loss.

- All published studies on herbal ephedra and weight loss have used a medium dose of ephedra per day; consequently, no dose-response analysis is possible.

Athletic Performance

- There are no studies assessing the effect of herbal ephedra–containing dietary supplements on athletic performance.

- The few studies that assessed the effect of ephedrine on athletic performance did so only in small samples of mostly fit individuals (young male military recruits) and only on very short-term immediate performance. This model does not reflect the use patterns in the general population. These data support a modest effect of ephedrine plus caffeine on very short-term athletic performance.

- No studies assessed the effect of the sustained use of ephedrine on performance over time.

- It is probable that ephedrine alone, without the addition of caffeine, has little or no effect on athletic performance.

- In the data we reviewed, the smallest dose of ephedrine that produced a measurable effect on athletic performance was 0.8 mg per kg of body weight. However, the effect of smaller doses has not been assessed. Higher doses produced unacceptable gastrointestinal side effects.

Adverse Consequences

The data we reviewed on adverse consequences came from both clinical trials and case reports submitted to the FDA. The strongest evidence of causality should come from clinical trials; however, in most circumstances, such trials do not enroll sufficient numbers of patients to adequately assess the possibility of rare outcomes. Such was the case with our review of ephedrine and ephedra-containing dietary supplements. For rare outcomes, we reviewed case reports. However, we could not determine definite causality from case reports.

With these considerations in mind, the evidence we identified supports the following conclusions:

- There is sufficient evidence from short-term controlled trials to conclude that the use of ephedrine and/or the use of ephedra or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and

change in mood, autonomic hyperactivity, and palpitations. It is not possible to separate out the contribution of caffeine to these events.

- There were no reports of serious adverse events in the controlled trials of ephedrine or ephedra, but these studies are insufficient to assess adverse events that occurred at a rate of less than 1.0 per 1000.

- A large number of adverse event reports regarding herbal ephedra–containing dietary supplements have been filed with FDA. The majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra-containing dietary supplements and the adverse event in question.

- A very large number of adverse events were reported to one manufacturer of ephedra-containing dietary supplements. Nearly all of the case reports were too poorly documented to permit us to make any judgments about the potential relationship between ephedra use and the event.

- We identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events with prior ephedra consumption; and three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events with prior ephedrine consumption. Classification as a sentinel event does not imply a proven cause and effect relationship.

- We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events with prior ephedrine consumption.

- About half of the sentinel events occurred in persons aged 30 years or younger.

- Scientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events. Given the rarity of such events, a properly designed case control study would be the appropriate next step. Such a study would need to control for caffeine consumption.