

GUEST EDITORIAL

Herbal simulation of ephedrine and caffeine in treatment of obesity

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Every year millions of individuals diet to lose weight, but the long-term prognosis of such treatment is poor since, to quote Albert Stunkard:

'Most obese persons will not stay in treatment for obesity. Of those who stay in treatment, most will not lose weight, and of those who do lose weight, most will regain it'.¹

The reasons behind such failures are multiple and reside in a highly complex inter-relationship between food intake, metabolic rate and changes in body composition. The bottom line is that in response to food deprivation, the drive to eat increases² and the metabolism slows down,³ thereby counteracting the efficacy of dieting. Pharmacotherapy aimed at dampening these compensatory mechanisms is therefore an appealing adjuvant to assist dietary approaches. The recent advances made in unravelling molecular pathways underlying appetite regulation, thermogenesis and fat oxidation, together with earlier discovery of atypical (β_3) adrenoceptors specific for thermogenesis, have provided a wide array of new targets for therapeutic development. It is therefore not immediately comprehensible why an old drug combination of ephedrine and caffeine—which has been utilized clinically for the treatment of asthma, bronchitis and nasal decongestion for more than 60 y—is still considered by many in the academic research community to be a viable therapy for obesity. The underlying arguments for such considerations were compiled in the proceedings of an international conference held in Geneva in 1992 and was summarized in its editorial as follows:⁴

- (i) ephedrine and caffeine are tried-and-tested drugs that could (in combination) be put into large scale clinical trials immediately;
- (ii) the combination of ephedrine and caffeine has both anorectic and thermogenic actions, thereby assisting weight loss and weight maintenance by affecting both aspects of energy balance;

(iii) the modes of actions of ephedrine and caffeine and their interactions, particularly in relation to their stimulatory effects on thermogenesis, have been described—with ephedrine promoting the release of noradrenaline and caffeine potentiating or prolonging noradrenaline-mediated thermogenesis by reducing negative feedback mechanisms that inhibit noradrenaline release and actions;⁵

(iv) most, if not all of the undesirable side-effects of ephedrine or the combination of ephedrine and caffeine subside during treatment (ie exhibit tachyphylaxis),^{6–9} whereas the thermogenic effects are preserved or even enhanced by chronic treatment.¹⁰ This latter phenomenon suggests that it may not be necessary to develop selective thermogenic drugs (eg β_3 -agonists) if tachyphylaxis and receptor downregulation provides a natural, endogenous mechanism for transforming a non-selective sympathomimetic into a selective thermogenic agonist.

In the longest controlled trial conducted with this drug combination, the administration of 20 mg ephedrine and 200 mg of caffeine, three times daily for 24 weeks, was found to be more effective than ephedrine or caffeine alone in inducing weight and fat losses and to be well-tolerated.⁶ Furthermore, it spared the loss of lean body mass¹⁰ and improved blood lipid profile.¹¹ In Denmark and some other Scandinavian countries, this ephedrine and caffeine mixture is licensed under the trade name of Letigen and is currently available as a prescription drug. In the United States, there has also been controlled clinical studies—lasting 2–6 months—demonstrating safety and efficacy for weight loss with drug cocktails containing either ephedrine and caffeine¹² or ephedrine, caffeine and aspirin,¹³ but these drug combinations have not been approved for obesity treatment by the regulatory agencies.

Paradoxically, the sale of herbal preparations that contain ephedrine and caffeine as supplements for weight loss is now widespread in the US. It is estimated¹⁴ that some 12 million people utilized these herbal supplements in 1999 alone,

often as mixtures of *Ma Huang* (a source of ephedra alkaloids) and *Guarana* or *kola nuts* (sources of caffeine).¹⁴ Not surprisingly, their sales under the category of 'dietary' supplements are promoted with the findings of safety and efficacy derived from controlled study with pharmaceutical grades of these compounds. The herbal industry contends that their botanical products are safe and effective for weight loss when used within the labelled dosage range. However, numerous reports, albeit largely anecdotal, of serious adverse effects attributed to the consumption of these herbal supplements (in particular hypertension, tachycardia and strokes) have raised concerns in the United States regulatory committee.¹⁴ The Food and Drug Administration (FDA) has proposed regulations that would restrict the use of these herbal products and reduce their contents in ephedra alkaloids.¹⁵ Subsequent review of that proposal, however, led the Government Accounting Office to declare that the evidence for the FDA recommendation was inadequate.¹⁶ The FDA is now re-assessing the need to intervene to protect the public.

In the light of these disturbing reports of serious adverse events associated with the use of herbal products, it is important to make a clear distinction between synthetic ephedrine and caffeine mixtures on one hand and herbal or botanical products containing these pharmacologically active ingredients on the other. The results from placebo-controlled studies conducted in different academic research institutes and in several countries,^{6–13} and which have been recently reviewed,¹⁷ are highly consistent that at prescribed doses for anti-obesity therapy, the combination of synthetic ephedrine and caffeine is effective and is well tolerated. There is also evidence that this combination of drug treatments for obesity is more effective for weight loss than single drug treatments.¹⁸ Furthermore, the assumption that the mixture of synthetic ephedrine and caffeine should cause rises in blood pressure, particularly in hypertensive patients, is not supported by a double-blind placebo-controlled study in which ephedrine (20 mg) and caffeine (200 mg), administered three times daily for 6 weeks, showed no rise in blood pressure in either normotensive or hypertensive obese patients.⁸

A key question that arises is how then does one explain the discrepancy between the mild and mostly transient side-effects observed during therapy with synthetic mixtures of ephedrine and caffeine and the reports of serious adverse cardiovascular effects associated with the herbal products, particularly when the latter are promoted at doses much less than that utilized in controlled studies with synthetic ephedrine and caffeine? Does the explanation reside in the fact that patients in clinical trials are prescribed the drugs under medical supervision whereas those suffering from serious adverse events associated with use of botanical products are not, and are hence at higher risks for abuse and overdose? Or does it reside in the fact that the largely unregulated herbal supplements contain not only ephedrine and caffeine, but also a variety of other ingredients which could contribute to the undesirable effects? Several of these supple-

ments include non-negligible amounts of ephedrine isomers, some of which have been implicated in adverse cardiovascular effects,¹⁹ and a plethora of other ingredients ranging from magnesium and zinc chelate to bee pollen and royal jelly.

Whatever the explanations for such discrepancy, however, individual susceptibility to potentially serious adverse effects associated with the consumption of these herbal supplements cannot be ignored. That they may be relatively safe and efficacious as anti-obesity supplements in a clinical setting, but also that their use may pose a health risk to some individuals, are illustrated in two recent detailed reports of controlled clinical trials assessing the safety and efficacy of herbal supplements containing ephedrine and caffeine for weight loss.^{20,21} When administered over periods lasting 2 or 6 months, the herbal supplements were clearly effective in inducing greater weight and fat losses than placebo treatment and at the final evaluation visits, the 'tolerable' undesirable effects in some patients were as anticipated based on studies with synthetic ephedrine and caffeine. However, the authors went to great length in describing the adverse events that led a substantial number of subjects in the herbal group of the first clinical trial²⁰ to withdraw from treatment (7 out of 35), namely because of palpitations ($n=4$), elevated blood pressure ($n=2$), and extreme irritability ($n=1$). Although none of these adverse effects were long-lasting, these findings in a controlled trial on selected subjects after medical screening for being healthy and under medical supervision during the trial²⁰ underscore the need for concern about the safety of such products when they are bought over-the-counter by a public desperate to lose weight, and used without physician counselling or supervision.

Based upon the Danish experience, the FDA might consider that the licensing under prescription of synthetic mixtures of ephedrine and caffeine could offer a viable and cost-effective approach to treat obesity and that large clinical trials with this drug combination are both necessary and ethically justified.

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