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Editorial Open Access

Can we Learn from Past Iatrogenic Effects When Managing Obesity?

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Editorial

Obesity is one of the main causes of preventable death in modern society and associated with multiple comorbidities. The management of obesity by individual or combinations of pharmacological agents has resulted in adverse rather than positive effects of adipose tissue weight loss.

In the USA, the Food and Drug Administration (FDA) and in the UK, the National Institute for Health and Care Excellence (NICE) will only approve weight loss drugs to be used as part of a comprehensive weight loss program. This should include dietary therapy and physical activity, for patients with a body mass index (BMI) of ≥30 kg/m^2, with no concomitant obesity-related risk factors or diseases, and for patients with a BMI of ≥28 kg/m^2, with concomitant obesity-related risk factors or diseases" [1].The risk factors and diseases considered important enough to warrant pharmacotherapy at a BMI of ≥28 kg/m^2, are hypertension, dyslipidaemia, coronary heart disease (CHD), type 2 diabetes mellitus (DM), and sleep apnoea [2].

As recent as the last decade, medicines that were believed to be safe have been shown to have been inadequately tested in the prescribed doses and durations of treatment.

In the 1990s fenfluramine (Fen) and phentermine (Phen) were individually approved appetite suppressants (anorectics), but despite the US FDA never approving the use of the combination (Fen-Phen) more than 18 million prescriptions for "Fen-Phen" were issued in the United States in 1996 with catastrophic cardiovascular side effects, resulting in withdrawal from the market [3].

Fenfluramine is a sympathomimetic amine that has an anorectic action mediated through the activation of serotonergic pathways in the brain [4]. Phentermine is an amphetamine derivative and a noradrenergic agent and acts mainly on the hypothalamus by causing the adrenal gland to produce noradrenaline on adrenergic postsynaptic α- and β-receptors and releases noradrenaline, dopamine and serotonin, producing anorexia [5]. Commonly used doses of these medications were 20-120 mg of fenfluramine per day and 15-30 mg of phentermine hydrochloride per day [3].

In 2010, Sibutramine a centrally-acting serotonin and noradrenaline reuptake inhibitor (SNRI) anorectic, was also withdrawn from the market as a consequence of cardiovascular and cerebrovascular events [6].

In 2012, the first approval since 1999, the FDA approved the combination pill phentermine (Phen) plus topiramate. Topiramate (TPM) is a drug used as an anti-epileptic and antimigraine drug having effects on the central nervous system (CNS). It is thought to act as a γ-aminobutyric acid agonist that increases satiety.

In trials, the combination of the drug in low dose (3 mg Phen plus 23 mg TPM) intermediate dose (Phen 7•5 mg plus TPM 46 mg) and high dose (15 mg Phen plus 92 mg TPM) have improved systolic blood pressure (SBP) and diastolic blood pressure (DBP), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels, and fasting serum glucose relative to placebo. At a two year follow-up, phentermine plus topiramate reduced glycosylated haemoglobin (HbA1C) in patients with DM [7]. HbA1C serves as a marker for the average blood glucose levels, over the previous 8 weeks prior to the measurement, as this is the half-life of red blood cells. An average weight loss of 8.1 kg and 10.2 kg, respectively was attained at the end of 56 weeks with Phen 7•5 mg plus TPM 46 mg, and Phen 15 mg plus TPM 92 mg [8].

Is it possible that the lower dose of this combination, compared to the previously withdrawn medication dosages, will not lead to any long-term cardiovascular events, in such an "at risk population"?

Continued research is necessary because of the effects of sympathetic nervous system stimulation, and current risk-factor analysis is surely insufficient to assess the long-term safety of such pharmacotherapy combinations.

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