

The return of amphetamine-like anorectics: a backward step in the practice of evidence- based medicine in Brazil

A volta dos anorexígenos anfetamínicos:
um retrocesso na prática da medicina
baseada em evidências no Brasil

La vuelta de los anorexígenos de tipo anfetamínico:
un paso atrás en la práctica de la medicina
basada en la evidencia en Brasil

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That clinical practice should always stand on the best available scientific evidence may seem obvious. Practitioners, however, often use their own clinical judgement or reasoning rather than the best available evidence to choose the therapy prescribed to their patients. Clinical judgement, the cognitive process by which physicians analyze data, derive diagnosis, decide on therapies, and evaluate the outcomes, is influenced by individual beliefs, prior experience, and education and values and, therefore, is amenable to error and biases that may lead to equivocal decisions regarding the most effective and safest treatment for the patient.

In his landmark book *Clinical Judgement* (1967), Alvan Feinstein ¹ critically appraised this process of thinking by which physicians reach a decision in clinical practice. Archibald Cochrane ² in *Effectiveness and Efficiency: Random Reflections on Health Services* (1972) also described that many clinical practices and therapeutic interventions that physicians believed to be effective were in fact unsupported by randomized controlled trials (RCTs). Subsequent contributions by Sackett et al. ³ laid down the foundations of an evidence-based approach to guide decision-making in clinical practice, known as Evidence-Based Medicine (EBM), a term coined by Eddy in 1987. EBM was defined by Sackett et al. ³ (p. 71) as "...the conscientious, explicit and judicious use of current best evidence in making decisions about care of individual patients", i.e., "...integrating the individual clinical expertise with the best available external clinical evidence from systematic research".

Some physicians reacted with skepticism to EBM, arguing that it is no more than a "cooking book", a tyranny of the evidence that constrains freedom of choice in medical practice, and that EBM neglected the fact that even high quality external evidence (from RCTs) might not be applicable (or might be inappropriate) to an individual patient ¹. Notwithstanding such criticism (responded by Sackett et al. ³), EBM has been widely accepted and adopted. In Brazil, EBM-inspired clinical guidelines and protocols were developed by medical associations and health authorities, which were adopted to guide health care in the Brazilian Unified Health System (SUS).

In the past 15 months or so, the Brazilian Congress passed two controversial laws that put EBM and benefit-risk balance in drug regulation to the center stage. The first law (*Law 13,269/2016*) authorized the production, prescription, dispensing, and use of the so-called synthetic phosphoethanolamine anticancer pill, whose efficacy and safety has not yet been demonstrated by clinical trials. The second law (*Law 13,454/2017*) authorized the production, sales, and consumption of sibutramine and

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three amphetamine-like anorectics (amfepramone or diethylpropion, fenproporex and mazindol) that, due to a clearly unfavorable benefit-risk balance, had been banned by the Brazilian National Agency for Sanitary Surveillance (Anvisa) in 2011.

The Federal Medicine Council (CFM), the Brazilian Medical Association (AMB), and Anvisa strongly opposed *Law 13,269/2016* arguing that there was no RCT demonstrating the efficacy and safety of the anticancer pill. The reaction of CFM to the second law, however, was in the opposite direction. CFM not only supported, but also enthusiastically celebrated the return of the amphetamine-like anorectics to Brazil's pharmaceutical market, a point of view shared by the Brazilian Society of Endocrinology and Metabolism (SBEM) ⁴. A note posted on the CFM website on June 23rd, 2017 stated that the new law was "...an important advancement for the treatment of diseases that depend on the use of anorectic drugs, as it is the case of patients with obesity", and informed that CFM had lobbied the Congress for its approval ⁴.

It is of note that CFM point of view on this topic does not represent the opinion of all physicians, and many psychiatrists, cardiologists, and public health scientists, as well as the Brazilian Association of Collective Health (ABRASCO) roundly condemned the return of the "amphetamines" and the interference of politicians in purely technical-scientific questions, such as whether amphetamine-like anorectics are safe and effective options for the treatment of obesity ⁵. The arguments used by CFM and SBEM to support their view that amphetamine-like anorectics are needed to treat obesity are not compatible with the basic tenets of EBM.

A recent systematic review found only four controlled trials of fenproporex, which had in common a flawed study design with a high risk of selection, performance, and detection biases as well as incomplete outcome data ⁶. Another systematic review of clinical trials of amfepramone, fenproporex, and mazindol revealed that 19 out of 25 studies included in the review showed a high risk of bias and authors' conclusion was that these drugs "...showed poor evidence of efficacy in the treatment of overweight and obese patients" ⁷ (p. 317).

Due to their poor efficacy, weight-loss drugs are indicated as adjunct therapy to life-style change approaches such as diet and exercise. Nonetheless, clinical studies have consistently demonstrated that weight reductions – in comparison to those achieved with life-style changes – are modest. Moreover, the weight is partially regained when anorectics are used for long periods and totally regained when they are discontinued. In other words, the available evidence suggests that anorectics do not help patients change their eating habits.

Another common problem of these drugs is that the primary efficacy endpoint measured in clinical trials is weight-loss, a surrogate endpoint for clinically relevant outcomes, i.e., the prevention and or attenuation of overweight-related co-morbidities. Due to the limited duration of most clinical trials, the long-term beneficial effects of weight-loss drugs on obesity-related deaths and co-morbidities remain unproven. Although it is plausible to think that even a modest weight reduction achieved with life-style modifications is potentially beneficial to prevent obesity-related diseases, this is not necessarily true for weight-loss achieved with drugs. A long-term study revealed that, although causing modest weight reduction, sibutramine (a 5-HT and norepinephrine reuptake inhibitor) also increased heart rate and caused a small (1-2mmHg) but sustained rise in blood pressure (due to its adrenergic effects), which resulted in a higher risk of heart attacks and strokes ⁸. Amphetamine-like anorectics have adrenergic effects and their long-term use may also cause consistent elevations in heart rate and blood pressure. Besides being a risk factor for cardiovascular morbidity, amphetamines are psychostimulant drugs and may induce sleeplessness, mood changes, and psychiatric disorders. Several cases of abuse and dependence to fenproporex (converted into amphetamine in the body) were reported ⁶.

In summary, systematic reviews found that clinical trials on the efficacy and safety of amfepramone, fenproporex, and mazindol presented flawed study design and a high risk of biases, thus being unacceptable to support marketing approval. Furthermore, health risks associated with short- and long-term use of amphetamine-like anorectics far outweigh the meagre benefit of causing a clinically relevant body weight reduction.

The argument that amphetamine-like anorectics are needed to treat a subgroup of obese patients unresponsive to other weight-loss drugs is unfounded, since this hypothetical subpopulation of patients has never been characterized by clinical studies. At any rate, even if this subgroup existed, the benefit-risk balance of amphetamine-like anorectics would continue to be unfavorable due to

their dangerous side effects and increased risk of heart attacks and strokes. Due to substantial risks and poor efficacy, sibutramine and amphetamine-like anorectics were removed from the market (or never approved for sale) in the United States, Canada, European Union, Japan, Australia, and most other countries with a few exceptions and only for a short-term use, no longer than a few weeks (e.g. phentermine in the United States).

The return of amphetamine-like anorectics has two other worrisome consequences. First, it weakens the authority of the national drug regulation agency. A respected, technically competent, and independent agency is necessary to successfully face regulated sector powerful lobbying and take the best decisions to protect consumers' health. Moreover, CFM lobbying to approve drugs and therapies unsupported by the best available scientific evidence is a backward step in the practice of EBM in Brazil. CFM is a respected public agency that regulates the practice of medicine and supervises the observance of medical ethics. Therefore, CFM fierce lobby for a therapeutic intervention unsupported by the best available evidence may encourage physicians to adopt clinical practices that are at odds with EBM principles.

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