

# Adulteration of over-the-counter slimming products with pharmaceutical analogues—an emerging threat

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**Objectives** To review pharmaceutical analogue adulteration of non-prescription slimming products.

**Design** Retrospective study.

**Setting** Tertiary referral centre for toxicology analysis, Hong Kong.

**Patients** All patients known to have been hospitalised after taking slimming products adulterated with pharmaceutical analogues from September 2004 to December 2006.

**Main outcome measures** Age, reasons for hospital admission, major biochemical findings, and toxicology analysis results of the offending slimming products.

**Results** N-nitrosofenfluramine, an analogue of fenfluramine with hepatotoxic effect, was found in two slimming products. Three patients were hospitalised after taking these slimming products, one of whom developed liver failure treated by liver transplantation. Another slimming product was found to contain N-desmethyl-sibutramine, an analogue of sibutramine. A patient with an unremarkable medical history developed acute psychosis after taking the latter product for 1 week.

**Conclusions** Analogues, created by modifying the chemical structures of pharmaceuticals, are used as adulterants in non-prescription slimming products, in an attempt to evade regulatory inspection. The imperceptible use of these analogues is very dangerous because they have not been tested formally for efficacy and safety. In view of the potential harm to the public, more effective and proactive measures are required to guard against the illicit use of pharmaceutical analogues. There is also a need for increased awareness among the public and the medical professionals about this emerging threat.

## Introduction

Analogues are created by replacing or adding functional groups to the original chemical. For pharmaceutical companies, analogue generation is a common strategy used in creating investigational drugs. On average it takes 9.5 years and costs US\$802 million for an investigational drug to be approved as a marketed pharmaceutical.<sup>1</sup> However, many of the investigational drugs are abandoned at different stages of development either for lack of pharmacological effects or association with significant toxicities to animals or humans. On the other hand, analogues are also created for illicit use. Examples include designer drugs like 3,4-methylenedioxymethamphetamine and methamphetamine, which are analogues of amphetamine. Intuitively, the danger of consuming drug analogues, which have not been tested thoroughly, is very great and unpredictable. In this report, we describe the identification of fenfluramine and sibutramine analogues in three non-prescription slimming products. Four patients were hospitalised after taking these products.

## Methods

All patients who were referred to the Hospital Authority Toxicology Reference Laboratory for investigation of slimming product-related adverse effects between September 2004 and December 2006 were reviewed. Those found to have consumed adulterated slimming products were reviewed in detail. All specimens for toxicology studies were analysed by various

### Key words

Anti-obesity agents; Fenfluramine; Liver failure, acute; Weight loss

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techniques in stages. The initial screen entailed an in-house high performance-liquid chromatography (HPLC) assay.<sup>2</sup> If necessary HPLC findings were then confirmed by either gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry.<sup>3,4</sup>

## Results

From September 2004 to December 2006 inclusive, a total of 979 patients were referred to the Hospital Authority Toxicology Reference Laboratory for investigation. Among these 979 patients, 42 patients were suspected to have clinical problems related to the use of slimming products. Either the alleged slimming products, corresponding urine samples from these patients, or both were analysed. Positive results were defined as the detection by analytic methods of: fenfluramine, non-prescribed sibutramine, non-prescribed thyroid hormones, any undeclared western slimming drugs and their analogues in the product or in relevant urine samples. Regarding the 28 patients testing positive, seven yielded positive results in urine samples only, as the offending slimming product was not available for analysis. A total of 26 slimming products were received from the remaining 21 patients; 18 patients used only one slimming product, one used two slimming products, and two used three. Fifteen of the products were adulterated with a single compound: sibutramine in seven, tiratricol in four, fenfluramine in two, thyroxine in one, and phentermine in one. More than one adulterant was found in the other 11 products, which consisted of variable combinations of sibutramine and its analogue, fenfluramine and its analogue, phenolphthalein, thyroid tissues, propranolol, hydrochlorothiazide, mazindol and caffeine, and possibly other substances. Among these, pharmaceutical analogues were detected in slimming products from four patients.

In September 2004, an over-the-counter (OTC) slimming product called "Supreme Quick Slim" was received for analysis. Clinical details of the relevant patient were reported elsewhere.<sup>5</sup> Briefly, a 33-year-old woman (patient 1) developed fulminant hepatic failure after taking this product for 6 weeks. The patient received a liver transplant and recovered satisfactorily. This OTC slimming product was stated to be composed of 12 herbal ingredients. Chemical analysis yielded the presence of N-nitrosfenfluramine, fenfluramine, caffeine, nicotinamide, emodin, and aloe-emodin.

Another slimming product called "Ever Youth" was received for analysis from two different hospitals in June and July 2005. The two patients were hospitalised with the history of taking this product for unknown durations. The first was a 53-year-old woman (patient 2) with a history of hyperthyroidism, who was admitted via the Accident and Emergency Department with sudden cardiac arrest. She had pulmonary hypertension, moderate aortic regurgitation, and right heart failure. Thyroid function

## 非處方瘦身產品被摻入藥品衍生物： 一個日見嚴重的問題

**目的** 檢討非處方瘦身產品被摻入藥品衍生物的情況。

**設計** 回顧研究。

**安排** 香港一個毒理學分析專科轉介中心。

**患者** 在2004年9月至2006年12月間，服用含藥品衍生物的非處方瘦身產品後送院治療的所有病人。

**主要結果測量** 年齡、入院原因、主要生化測檢發現、肇事瘦身產品的毒理學分析結果。

**結果** 在兩種瘦身產品驗出含N-亞硝基二乙基苯胺(N-nitrosfenfluramine)，這是一種氟苯丙胺的衍生物，會令肝臟受損。三人服用這些產品後送院治療，其中一人出現肝衰竭，需接受肝臟移植手術。另一種瘦身產品則含有一種西布曲明衍生物—西布曲明N-去甲基活性代謝物(N-desmethyl-sibutramine)，一名健康一向無大礙的病人服用此產品一星期後，患上精神病。

**結論** 有商人改變藥品的化學結構而製成衍生物，摻入非處方瘦身產品，試圖避過藥檢。由於這些衍生物的功效和安全性均未經正式測試，即使使用微量，仍然十分危險。基於對公眾可能造成傷害的考慮，政府必須採取更有效的防範措施，打擊違禁使用藥品衍生物，而且也要提高公眾以及醫護人員對這個日見嚴重的問題的警覺性。

tests showed a suppressed thyroid-stimulating hormone (TSH) level and an elevated free thyroxine (fT4) level of 30.4 pmol/L (reference range, 12.0-22.0 pmol/L). Urine toxicology analysis detected fenfluramine, propranolol, and dobutamine. The patient was not known to be taking propranolol, whereas dobutamine was prescribed after admission. Despite active treatment, this patient succumbed 4 days after admission.

The second patient (patient 3) who took "Ever Youth" was a 41-year-old man that presented with generalised weakness. Laboratory investigations revealed a plasma potassium level of 2.1 mmol/L (reference range, 3.5-4.5 mmol/L). His TSH level was suppressed whereas the fT4 and free triiodothyronine levels were within respective reference ranges. Urine toxicology analysis detected fenfluramine, propranolol metabolites, phenolphthalein, diclofenac, paracetamol, codeine, promethazine, and chlorpheniramine. His medical history and family history were both unremarkable. His symptoms subsided after correction of his plasma potassium level, and he was discharged 3 days after admission. No further investigation was performed as the patient defaulted.

The "Ever Youth" capsules obtained from both patients contained: N-nitrosfenfluramine, fenfluramine, sibutramine, phenolphthalein, propranolol, caffeine, thyroid tissues, a number of herbal anthraquinones, and various vitamins. Due to the presence of N-

TABLE. Important clinical and laboratory findings of the four patients hospitalised after taking slimming products adulterated with pharmaceutical analogues.

Patient	Sex/age (years)	Major clinical features and investigation results*	Outcome	Slimming product	Duration of use	Results from analysis of the slimming product
1	F/38	Fulminant hepatic failure	Liver transplantation	Supreme Quick Slim	6 months	N-nitrosufenfluramine, fenfluramine, caffeine, nicotinamide, emodin and aloe-emodin
2	F/53	Sudden cardiac arrest, pulmonary hypertension, moderate aortic regurgitation, and right heart failure. Abnormal LFT and TFT results	Died	Ever Youth	Unknown	N-nitrosufenfluramine, fenfluramine, sibutramine, phenolphthalein, propranolol, caffeine, thyroid tissues, a number of herbal anthraquinones and various vitamins
3	M/41	Generalised weakness, hypokalaemia, and suppressed TSH	Complete recovery with symptomatic treatment	Ever Youth	Unknown	Same as above
4	F/47	Acute psychosis	Symptoms improved after admission	Unknown	1 week	N-desmethyl-sibutramine

\* LFT denotes liver function tests, TFT thyroid function tests, and TSH thyroid-stimulating hormone

nitrosufenfluramine, the liver function tests of patients 2 and 3 were reviewed. For patient 2, the tests performed on admission showed a low albumin level (28 g/L; reference range, 36-48 g/L) and mildly elevated alanine aminotransferase (59 U/L; reference level, <35 U/L) and alkaline phosphatase (278 U/L; reference range, 35-115 U/L) activities. In patient 3, liver function test results were normal.

In August 2006, an unnamed slimming product obtained from a 47-year-old woman (patient 4) admitted to a hospital for acute psychosis was received for analysis. The patient had taken the product for 1 week before the onset of symptoms, for which reason she was suspected to have a drug-induced acute psychosis. Chemical analysis revealed the presence of N-desmethyl-sibutramine (an analogue of sibutramine). This patient was observed for 4 days and then discharged, without any definitive psychiatric diagnosis.

The key clinical features and laboratory findings of the four patients are summarised in the Table.

### Discussion

Fenfluramine with phentermine was popular in North America as long-term (off-label) treatment of obesity, though the former drug was already implicated as a cause of pulmonary hypertension.<sup>6</sup> After the report of unusual valvular disease in patients taking fenfluramine-phentermine, the sole supplier of fenfluramine in the United States voluntarily withdrew the drug from the market.<sup>7</sup> The use of fenfluramine was banned by the US Food and Drug Administration (FDA) since September 1997, and subsequently also in Hong Kong. Another centrally acting anorectic, sibutramine, was approved by the FDA in November 1997. Sibutramine is a combined serotonin and noradrenaline re-uptake inhibitor. After absorption, it is rapidly metabolised to N-desmethyl-sibutramine and N-bisdesmethyl-sibutramine (Fig 1). In vivo, the anti-obesity effects of sibutramine are

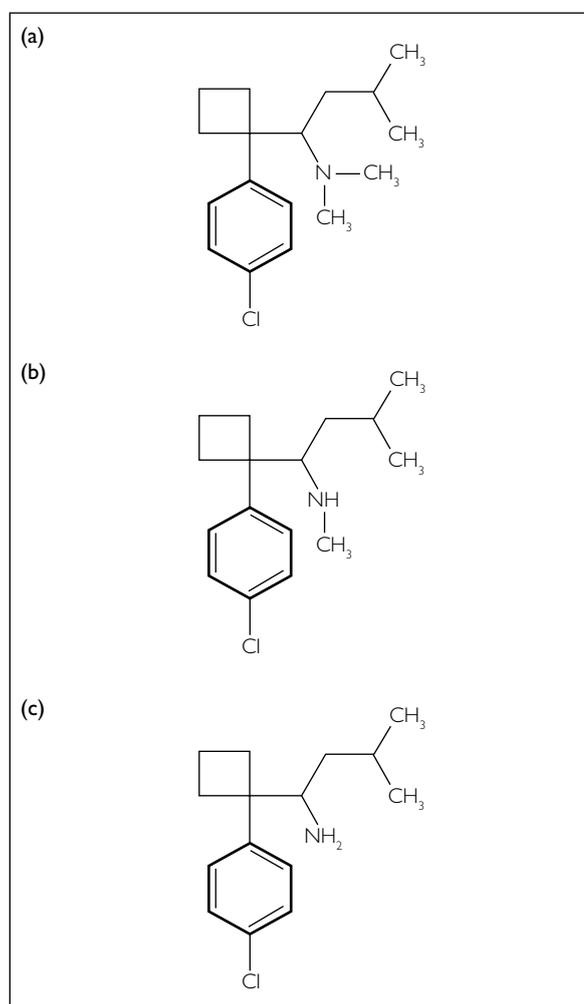


FIG 1. Chemical structures of (a) sibutramine, (b) N-desmethyl-sibutramine, and (c) N-bisdesmethyl-sibutramine

believed to be predominantly mediated by these two pharmacologically active metabolites.<sup>8</sup> Sibutramine is generally well-tolerated; its most commonly reported side-effects are headache, constipation, nausea,

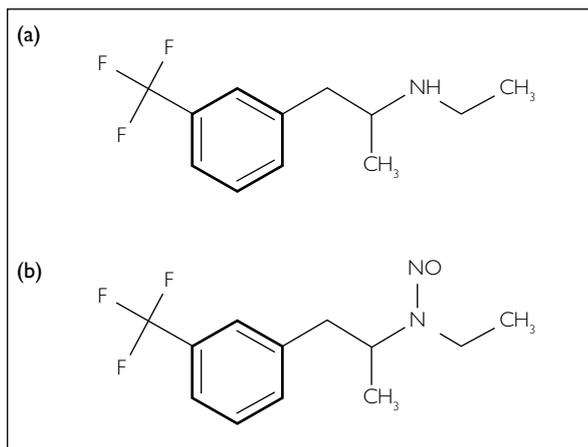


FIG 2. Chemical structures of (a) fenfluramine and (b) N-nitrosfenfluramine

dizziness, dry mouth, and insomnia.<sup>8</sup> Because of its pressor effect, sibutramine use is associated with a slight increase in heart rate and blood pressure, but in recent years, more severe adverse effects including psychotic and manic episodes, panic attacks, and mood changes have also been reported.<sup>9-13</sup> In Hong Kong, sibutramine is registered as a prescription-only medicine. Although the use of fenfluramine is banned and the use of sibutramine controlled, illicit use of these two drugs takes place locally; very likely via OTC slimming products. Since 2002, at least 17 slimming products were found to be adulterated with sibutramine, and eight with fenfluramine (<http://www.psdh.gov.hk>).

We believe that some manufacturers adulterate their slimming products with anti-obesity drug analogues, instead of the original molecules in an attempt to evade interception by regulatory authorities. Since analogues are structurally modified, they might not be detected by ordinary laboratory methods. These analogues are presumed to exhibit pharmacological properties similar to the original parent compound. However, by and large there have been no formal animal or human studies to support these presumptions. Moreover, the adverse effects of such analogues may be significantly different from those of the original drug. Therefore, the unperceived use of such analogues could be very dangerous and associated with unpredictable risks.

N-nitrosfenfluramine is an analogue of fenfluramine (Fig 2). This chemical, used as an adulterant in slimming products, was associated with more than 800 cases of liver damage in Japan.<sup>3</sup> Similar cases have also been reported in Singapore and the United Kingdom.<sup>14,15</sup> The majority of affected patients showed complete recovery after discontinuation of the offending agents. However, a few died or developed fulminant hepatic failure.<sup>14-16</sup> An animal study performed by a Japanese group demonstrated the hepatotoxic and potential nephrotoxic effects of N-nitrosfenfluramine.<sup>17</sup> This study also concluded that the slimming effect of

N-nitrosfenfluramine was only speculative. Had the latter compound been formally evaluated as an agent for human use, it would have been abandoned during the early stages of drug development.

For the three patients exposed to N-nitrosfenfluramine described above, only one (patient 1) developed significant liver disease. This is consistent with a Japanese report that only a fraction of those who are exposed to N-nitrosfenfluramine developed liver derangement.<sup>18</sup> Moreover, according to that report, there was no obvious dose-response relationship between N-nitrosfenfluramine exposure and the resultant liver damage, for which reason the authors postulated that the cytochrome P450 (CYP) enzyme phenotypes of the exposed individuals might be critical. The clinical problems of patients 2 and 3 were likely attributable to other active adulterants in the offending slimming drug. Fenfluramine could be the cause of valvular abnormality and pulmonary hypertension in patient 2, as no alternative aetiology could be identified.<sup>6,7</sup> The underlying thyroid problem and the intake of exogenous thyroid tissues and N-nitrosfenfluramine might have played a contributory role, which aggravated her cardiac and pulmonary problems. The hypokalaemic paralysis and abnormal thyroid function test results of patient 3 might have been related to the intake of exogenous thyroid tissue present in the slimming product.

For registered medications, uncommon, idiosyncratic toxicity may only manifest after a drug is marketed, for which post-marketing surveillance and adverse drug reaction reporting and monitoring systems have been specifically developed. Thalidomide-induced congenital malformations and more recently rofecoxib-associated cardiovascular toxicity provide spectacular examples of such toxicity.<sup>19,20</sup> Accordingly, even if N-nitrosfenfluramine were to have become a registered pharmaceutical, it would no doubt have been withdrawn soon after marketing. Being a concealed adulterant without any known pharmaceutical company association, the usual monitoring and regulatory mechanisms cannot effectively control the use of such illicit pharmaceutical analogues.

Herbal slimming products adulterated with sibutramine, N-desmethyl-sibutramine, N-bisdesmethyl-sibutramine, and an analogue of sibutramine named homosibutramine were first reported by Zou et al in 2007.<sup>21</sup> N-desmethyl-sibutramine was detected in the slimming product consumed by patient 4, before the onset of acute psychosis. In contrast to the fact that N-nitrosfenfluramine is a synthetic analogue of fenfluramine, N-desmethyl-sibutramine is a natural metabolite of sibutramine (the parent compound). N-desmethyl-sibutramine possesses the same pharmacological properties as sibutramine, and is at least partially responsible for the observed adverse effects of sibutramine.<sup>8</sup> Patient 4 described in this report developed a reversible acute psychotic episode after taking N-desmethyl-sibutramine for 1 week. Without

any other obvious alternative cause, this patient's clinical problem was very likely an adverse effect of N-desmethyl-sibutramine. Adulteration of sibutramine analogues in slimming products is not unique to Hong Kong, as the problem was also reported in Japan<sup>22</sup> and Taiwan.<sup>23</sup> Although N-desmethyl-sibutramine is a natural metabolite of sibutramine, using it in a pure form as a pharmaceutical has not been approved. The unperceived use of N-desmethyl-sibutramine in slimming products should be regarded as dangerous, especially for those in whom sibutramine may be contra-indicated.<sup>8</sup>

Anti-obesity drug analogues are not limited to N-nitrosfenfluramine and N-desmethyl-sibutramine. Because of high commercial demand, one can foresee that new analogues will keep emerging in the market.

Apart from local OTC availability, people can easily purchase such adulterated products outside Hong Kong or through the Internet. Furthermore, anti-obesity drug analogue is just one component of the whole analogue problem, since related compounds can be developed for any pharmaceutical with diverse proven effects. In view of this potential danger, more effective and proactive measures are urgently required to guard against illicit use of such pharmaceutical substitutes. Psychoactive designer drugs are tightly controlled by the Hong Kong legislation; chemicals with a structure similar to any of these dangerous drugs have to be considered as such. However, there is no similar provision in current Hong Kong legislation to govern analogues of other drug classes. This loophole requires prompt remedial action.

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