

Sibutramine as an adulterant: a prevailing threat

Dr Sammy Chen
HA Toxicology Reference Laboratory

Hospital Authority Toxicology Service
Annual Conference 2011
March 6, 2011

Sibutramine: banned 5 months ago

The End of an Issue?

apple daily
撤銷西布曲明藥品註冊

衛署取消西布曲明藥品註冊

衛生署表示，藥劑業及毒藥管理局轄下註冊委員會在昨日會議上，決定取消所有含西布曲明的藥物產品的註冊；現時本港有二十家公司註冊了四十五款含西布曲明產品。衛生署表示，批發商應立即停止售賣或分發含西布曲明的產品，並應從市面回收產品。衛生署會密切監察批發商回收產品情況。

西布曲明在加拿大、中國、新加坡、新加坡及美國等已被暫停

或禁止使用，美國雅培藥廠已自願取消其四款含西布曲明藥品的香港註冊，並在今年初將貨架回收產品。衛生署呼籲醫生及藥房應立即停止處方及售賣含西布曲明產品，並將剩餘產品交給相關批發商，「正在處理相關產品的人士應與醫生商討其他方法控制體重。」

批發商應立即回收

註冊委員會是考慮「西布曲明藥劑作用，衛生署呼籲批發商應立即停止售賣或分發含西布曲明產品，並將剩餘產品交給相關批發商，正在處理相關產品的人士應與醫生商討其他方法控制體重。」

註冊委員會評估整體情況後，認為西布曲明引致心血管疾病的風險，高於病人體重輕微下降的效益，決定取消所有含西布曲明產品在港的註冊。

45產品即回收

Reductil
10mg

Reductil
15mg

當局取消含西布曲明藥品註冊
當中大部分都是本地藥廠生產

Sibutramine

- Registered since 1997
- Weight reduction through
 - Suppress appetite
 - Increase energy expenditure
- Demonstrated efficacy



It works !





Side effects listed in drug insert

CVS	Tachycardia, palpitation, raised BP/HT, vasodilation
GI	Constipation, hemorrhoid aggregation
Skin	
Sensory	Taste perversion
CNS	Dry mouth, insomnia, light-headedness, paraesthesia

No Psychosis !

Observation

Product stopped;
psychosis resolved



“Ingredients”:
魔芋，決明子，
螺旋藻，左旋肉
鹼，膳食纖維
纖維素

Delusion
Hallucination



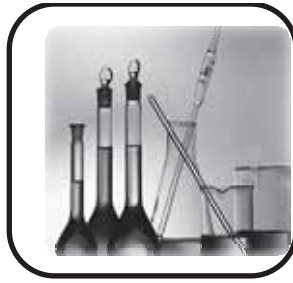
Similar
Case

Referred to
TRL, PMH

Intake for
4 weeks



Sibutramine



Sibutramine Use
since 1997:

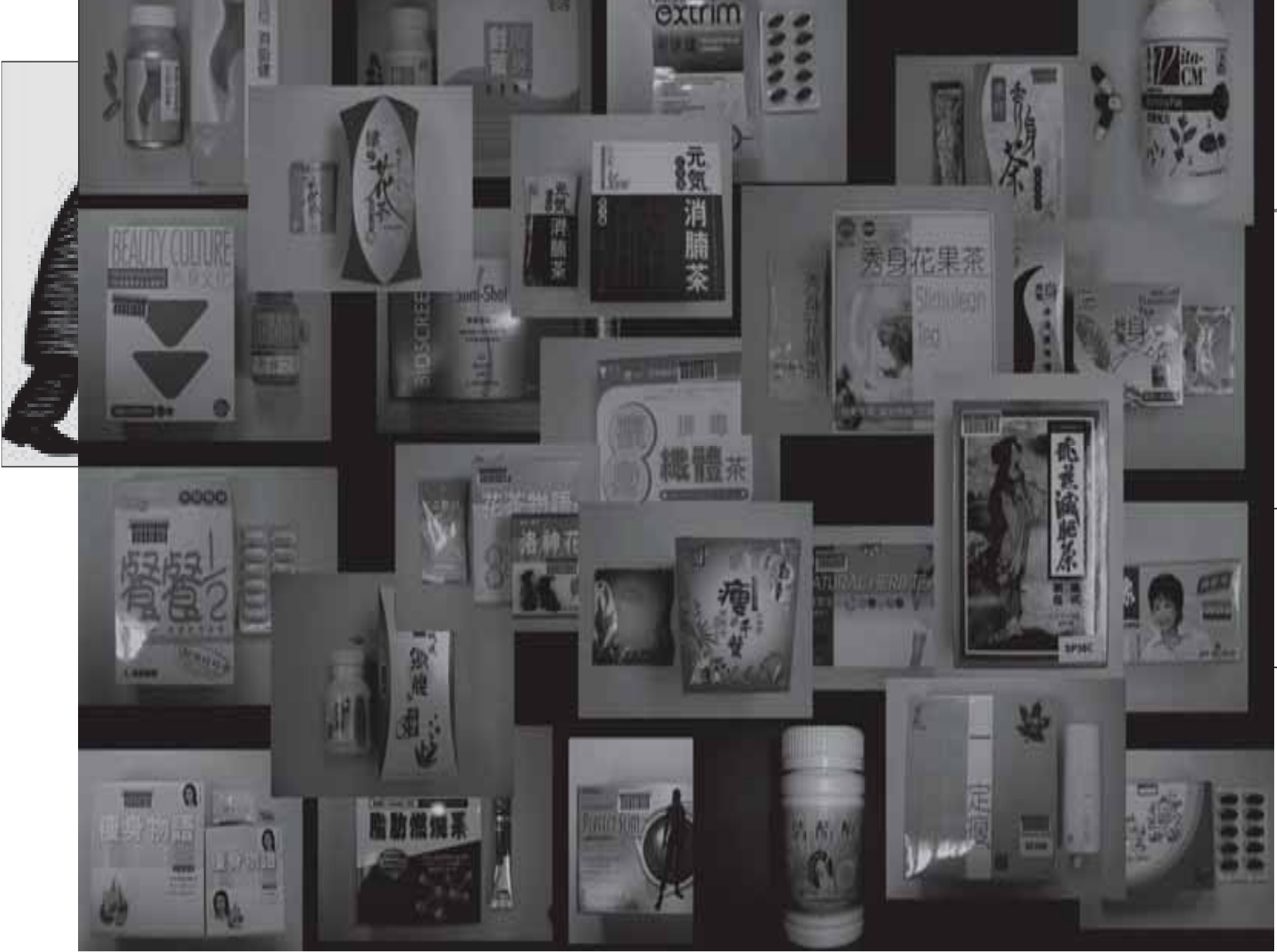
□ □ □ □ □ □

Psychosis documented?



Only 8 case reports (97-09)

Author	Country	Year	Case	Chief Presentation
Taflinski	Poland	2000	F/19	Hallucination
Cordeiro	Brazil	2002	M/20	Delusion
Mei	Holland	2004	F/36	Hallucination
Litvan	Spain	2007	F/40	Delusion
Fernandez	Spain	2007	M/50	Delusion
Lee	US	2008	F/26	Delusion
Dogangun	Turkey	2008	M/15	Hallucination
Gazdag	Hungary	2008	F/39	Delusion





Methods

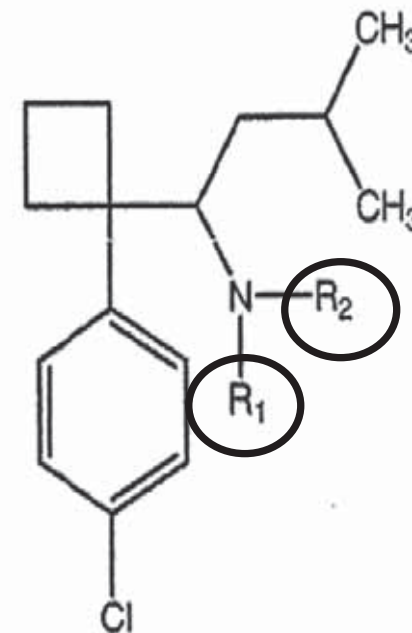
- Retrospective review: 6 years (2004-2009)
- Poisoning cases referred to TRL, who
 - took “herbal” slimming products adulterated with sibutramine or its analogues
 - presented with psychotic features (DSM IV)
- Review:
 - Demographic data, clinical features, drug Hx, toxicology findings
- Ethics approval (KW/EX/09-136)

Sibutramine analogues

■ Drug analogue:

Unlicensed, structurally modified chemical

R1	R2	
CH ₃	CH ₃	Sibutramine
H	CH ₃	N-desmethyl-sibutramine
H	H	N-bisdesmethyl-sibutramine





Methods: product analysis

High performance liquid chromatography (HPLC) - diode array detection (DAD)

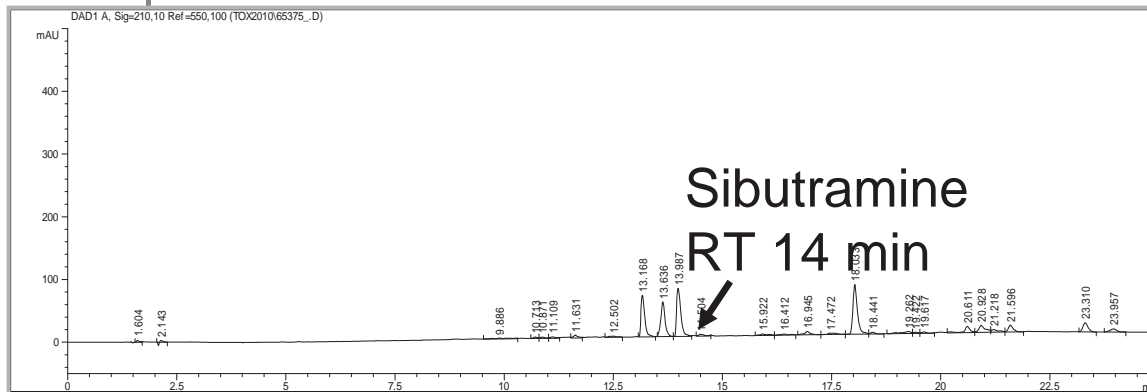
Liquid chromatography-ion trap-time of flight/mass spectrometry (LC-IT-TOF/MS)



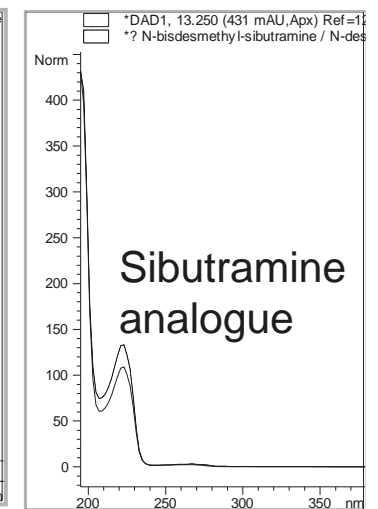
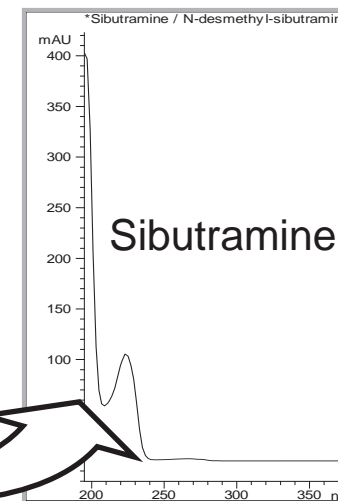


Methods: product analysis

HPLC-DAD: Chromatogram and UV spectrum



Sibutramine vs analogues
→ Similar RT & UV spectrum

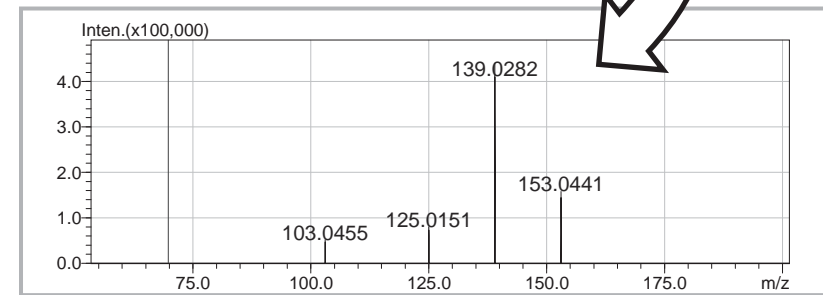
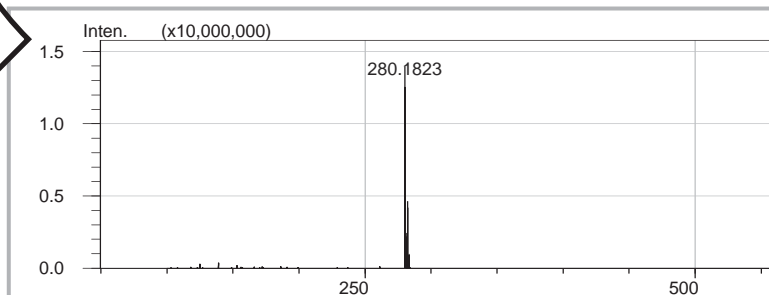


Methods: product analysis

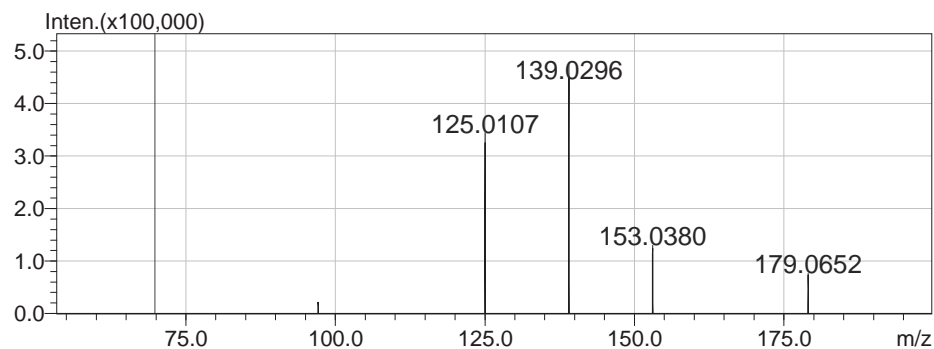
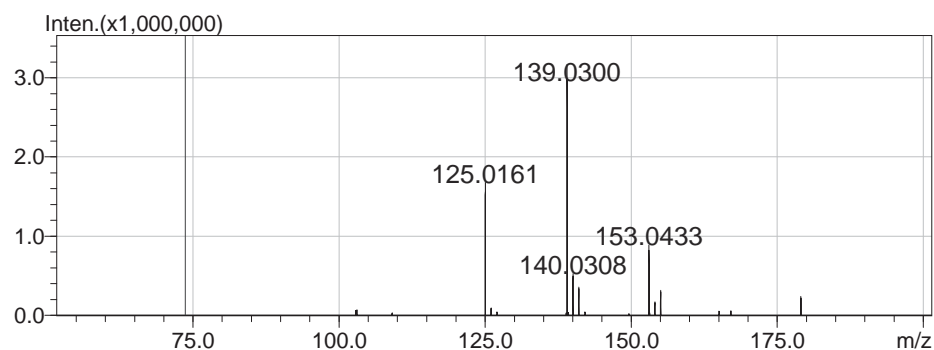
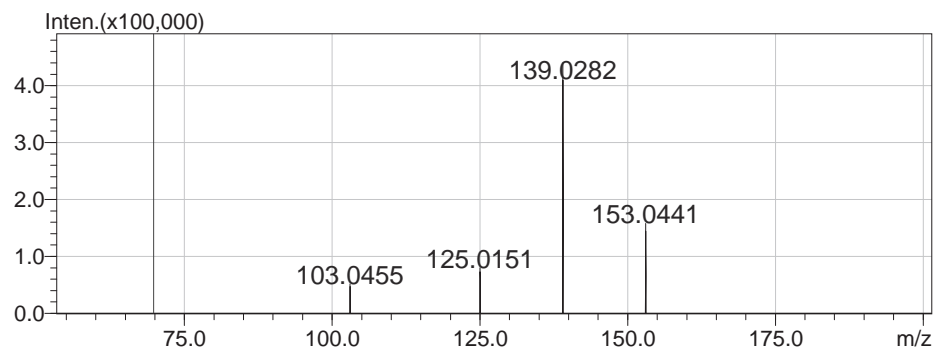


LC-IT-TOF/MS

Precursor ion \rightarrow Product ions

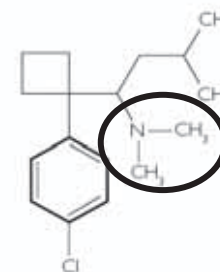


LC-IT-TOF/MS: detecting analogues

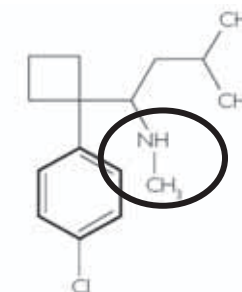


Similar Mass Spectrum

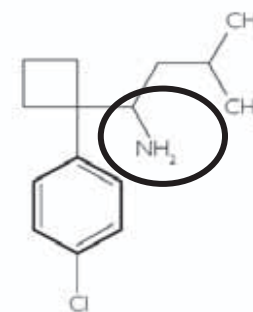
Sibutramine
m/z 280.1827



N-desmethyl
sibutramine
m/z 266.1670



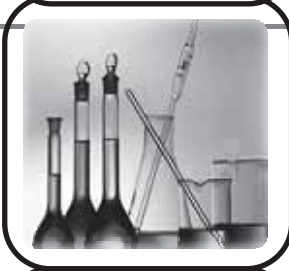
N-bisdesmethyl
sibutramine
m/z 252.1514



Distinguished by
difference in exact mass



Results



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DOI: 10.3109/13503630.2010.517208

ARTICLE

Psychosis associated with s



Results

Total number of “herbal” slimming products analyzed: 92



Confirmed products adulterated with sibutramine / its analogues: 59



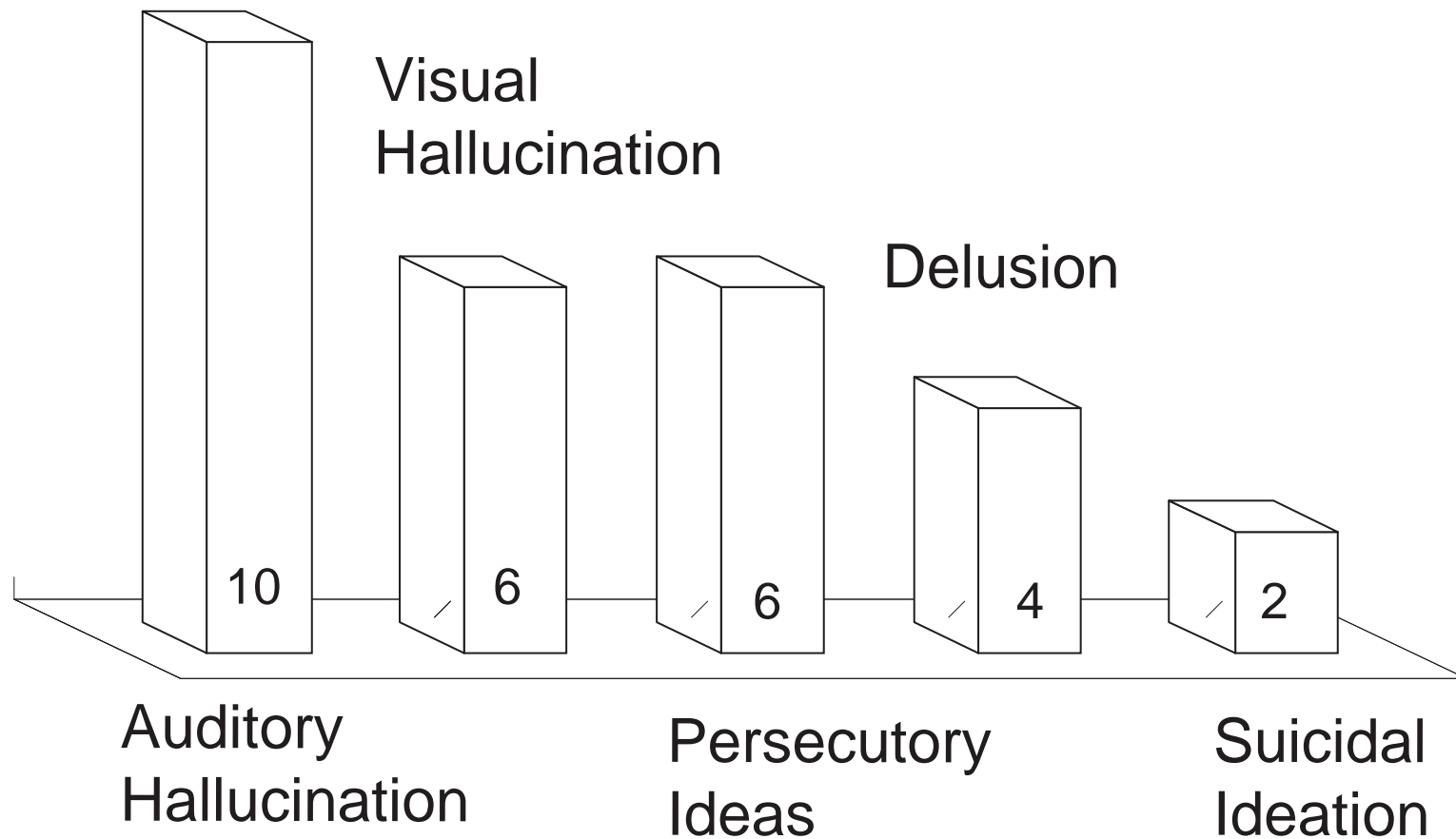
Cases with psychotic presentation: **16**

Female: 15 (94%)

Age: 19 yrs (15–47)

Drug Hx: 4 weeks (1-12)

Results





Results

- Products used by these 16 patients
 - Sibutramine: 16
 - N-desmethyl-sibutramine: 2
 - N-bisdesmethyl-sibutramine: 1
- Other adulterants:
 - Fenfluramine: 1
 - Phenolphthalein: 9
 - Mazindol: 2
 - Hydrochlorothiazide: 1
 - Spironolactone: 1
 - Animal thyroid tissue: 2
- Reported Source: Internet (4), local (1), outside HK (3)



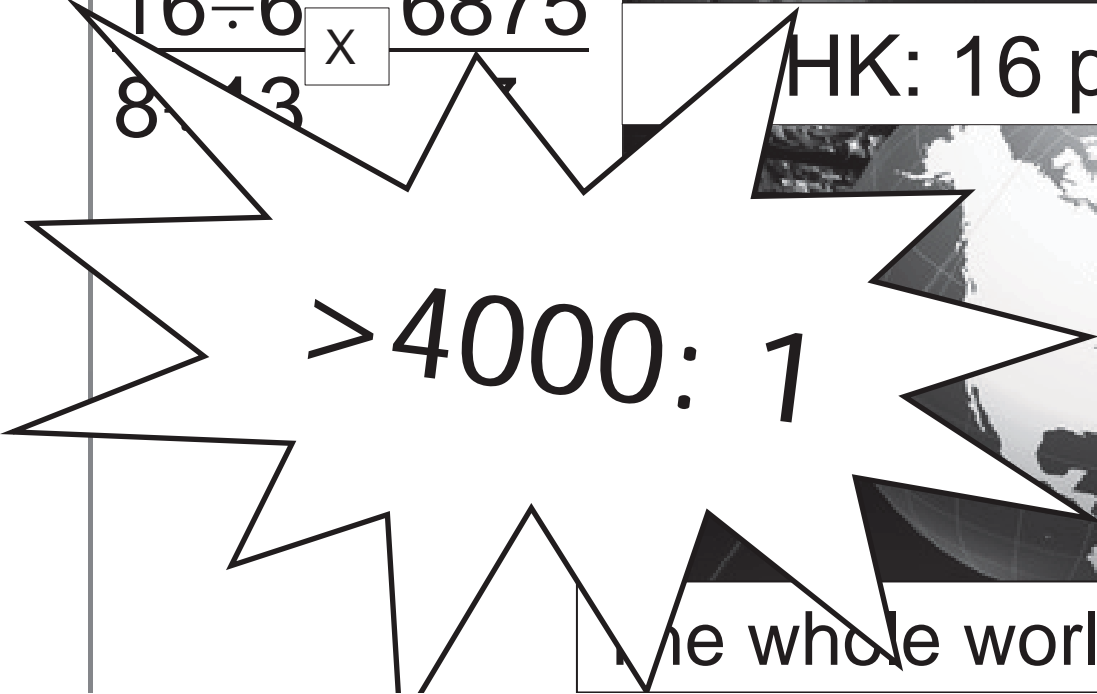
Results



Relative Incidence =

$$\frac{16 \div 6}{8 \div 13} \times 6875$$

HK: 16 per 6 yrs



the whole world: 8 per 13 yrs



Discussion

- Largest & the only case series
 - HK: 16 cases in 6 yrs, *vs*
 - The world: 8 isolated cases in 13 yrs
 - Relative incidence: > 4000:1

 - A very unusual side effect worldwide, but

 - Why so common in HK??



Discussion

■ Why so common in HK?

Sibutramine: adulterated *vs* prescribed

Adulterated sibutramine:

- disguised as “herbal” / “natural” product
- perceived as “safe”
- liberal use: huge single/cumulative dose

➔ Elicited a dose-dependent side effect



Discussion: causally associated?

Criteria for causality:

- | | |
|---------------------------------------|-------------|
| – Plausible time relationship | Yes |
| – Response to withdrawal | Yes |
| – Explained by disease or other drugs | Most not |
| – Rechallenging | Impractical |
| – Biological plausible mechanism | Probable |

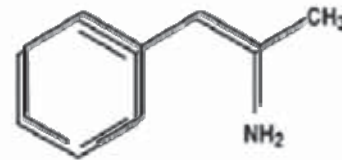
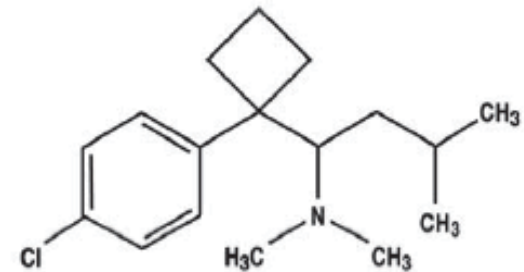
International Society for Pharmacoepidemiology

Discussion:

Postulated biological mechanism

1. Dose-related adverse drug reaction
- +
2. Similar to amphetamine
 - β -phenylethylamine hypothesis

Sibutramine



Amphetamine



Discussion: banned \neq gone!

As a prescribed drug: banned

As an adulterant: stays with us!



End of Oct: Banned

Nov 2: Banned in HK





Discussion: banned ≠ gone!

Baidu 百度

新闻 网页 贴吧 知道 MP3 图片 视频

减肥药

减肥药排行榜

减肥药测评网

减肥药哪种好

减肥药的副作用

减肥药的危害

健康瘦身推荐

不运动
不节食

天然 瘦身更自然

短期轻松减肥

最佳减肥保健产品

植物草本精华

无需节食 轻松快乐减掉脂肪

减肥人士



广东省保健行业协会
副会长单位



广东省保健行业协会
科学减肥示范基地



国食健字 G200501
保健食品 国家食品药品监督管理局



A search on Feb 20, 2011

! sibutramine_雅虎网页搜索

Home Feeds (J)

网页结果

热门搜索：

[春晚最美女观众](#)

[刘翔 出征德国](#)

[家乐福 价格欺诈](#)

[宋丹丹初恋 辞世](#)

[麦当娜再交小男友](#)

[陈慧琳 体外受孕](#)

[联想 NEC 合资](#)

[张韶涵 欠税](#)

[香港富豪 猝死](#)

[天津女排球迷冲突](#)

[buy meridia](#)

forums.slimdevices.com/member.php?u=234... 2010-09-23

[主页](#)

phenoki.easyfreeforum.com 2010-12-11

[Sibutramine 曲美-爱美网品牌库 lady8844.com-时尚美容...](#)

曲美(Sibutramine)是目前全球科技领先的、具有独特双重作用机理的专业减肥药物。...1997年11月获FDA批准,1998年2月正式在美国上市,Sibutramine被欧洲CPMP(专卖药品委员会)确定为减肥首选药物。...

brand.lady8844.com/Sibutramine 2011-01-27

[Sibutramine Rx , Kauf sibutramine Wipperfurth...](#)

Sibutramine 100 Mg Übernachtung Grosshandel Sibutramine Billig...Kaufen

Sibutramine Online-Bestellung Kaufen Sibutramine Fed Ex...

bbs.nhren.com/thread-113036-1-1.html 4 天前

[高血压者服用sibutramine安全有效](#)

摘要:对合并已控制的高血压的超重非洲裔美国人和白种人,sibutramine是安全有效的减肥药。...日出版的Archives of Internal Medicine上报告了sibutramine治疗肥胖的多中心随机双盲试验的结果。...



Case 1

- F/33
- Good past health
- Admitted on 25/11/2010
- Presented with dizziness, palpitation and SOB
- Developed cardiac arrest in AED
 - CPR and intubated
 - ECG after resuscitation: sinus tachycardia and non-sustained polymorphic VT



	26/11/2010	30/11/2010	Ref Range
TSH	0.13 mIU/L	-	0.27 – 4.2
FT4	14.8 pmol/L	-	12 – 22
FT3	-	4.4 pmol/L	3.1 – 6.8

- **Echocardiogram**
 - 26/11/2010: LVEF of 40%
 - 29/11/2010: LVEF of 58%
- **Repeated ECG**
 - Sinus rhythm; normal QTc interval
- **Coronary angiogram**
 - Normal
- **Good recovery and discharged on 7/12/2010**



Took medications prescribed by a GP since 21/11/2010



- Analytical results

- Urine

- Sibutramine and its metabolites

- 3 drug samples:

- Sibutramine

- Tiratricol

- Propanolol



- Deregistration of pharmaceutical products containing sibutramine in HK on 2/11/2010
- Sibutramine prescribed to the patient on 21/11/2010
- Case reported to DH

Case 2

21歲媽媽 減肥猝死

產後婦女胡亂食減肥藥，隨時無命！一名年僅廿一歲的年輕女病人，懷疑因產後「心急」修身，服減肥藥致心臟停頓入院，延至昨日不治，遺下只有兩個月大的新生嬰兒。女病人家屬喪失至親，但希望為死者遺愛人間，昨日無私捐出女病人的肝臟及兩個腎臟，令三名垂危病人受惠。婦產科專科醫生余啟文表示，女性「佻BB」本身已增加心臟負荷，分娩後全身的血液循環需再調節，故更不應亂服減肥藥，以免傷害心血管及心臟健康。他勸喻產後婦女不應怕身材「走樣」而心急減肥。

王者回歸
劉翔三連冠

21歲媽媽
減肥猝死

東方日報
25



F/21

- Found collapsed at home on 19/11/2010
- Developed cardiac arrest and CPR started in ambulance
- On arrival to AED
 - GCS 3/15
 - Intubated and started on mechanical ventilation
 - Ventricular fibrillation
 - defibrillation
 - PEA
 - CPR
 - High dose inotropes
- No neurological recovery; certified brain death on 23/11/2010
- Referred Coroner



- TSH 1.75 mIU/L
- She had taken a herbal slimming product 百邦美曲輕膠囊 for 1 month after her recent delivery





- Analytical results

- Urine:

- Sibutramine and its metabolites

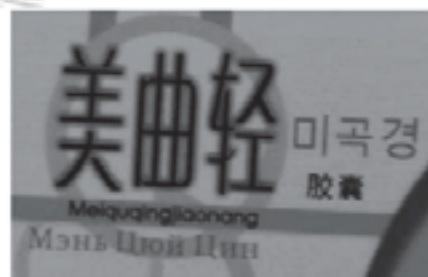
- 百邦美曲輕膠囊:

- Sibutramine

- N-desmethyilsibutramine

- Benign herbal markers

Sudden Cardiac Arrest Associated with Sibutramine Use



Cases **Case 1:** A young woman was found collapsed and brought to an AED. Atrial and ventricular fibrillation were recorded. She developed cardiac arrest and succumbed. She had taken a herbal slimming product – 百邦美曲輕膠囊 – for 1 month after her recent delivery. Sibutramine was detected in the product and in her urine.

Case 2: After taking some prescribed slimming medications, including sibutramine, tiratricol and propanolol, a middle age woman presented with dizziness, palpitation and shortness of breath to an AED and developed cardiac arrest there. She was successfully resuscitated and recovered.



Message

Sibutramine is a slimming agent which has been banned by the European Union in early 2010 due to its cardiovascular side effects: hypertension, tachycardia, arrhythmias, prolonged QT interval, myocardial infarction, cardiac arrest and stroke. Psychosis associated with sibutramine has also been reported by a local team recently.¹

In Hong Kong, pharmaceutical products containing sibutramine have been de-registered since 2 November 2010.² Despite prescribed sibutramine has been de-registered, it was found to be a common adulterant (59 (73%) out of 81 herbal slimming products associated with clinical poisoning) in Hong Kong.³ Healthcare workers are reminded to keep this local, continual poisoning threat in mind.

References



Conclusion

- Despite deregistration, sibutramine-related adverse effects could still be encountered
 - Adulterated proprietary Chinese medicine
 - Adulterated slimming agents
 - Internet
- Largest case series of sibutramine-induced psychosis
- Important, on-going threat posed to the public
 - Continual vigilance





Educate the public

東方日報 29/10/2010

「天然成分」含禁藥 港病發率冠全球

亂食減肥品

唔死都失常

問題產品 亂服食減肥產品如同「玩命」！最近六年最少有七十三人因服食聲稱「天然成分」，但機噏減肥西藥的產品後不進入院個案。醫院管理局毒理參考實驗室追蹤分析○四年至去年的六十六宗服食減肥產品後入院個案，揭出一人死亡，一人因肝衰竭須換肝，十六人更因服食含減肥西藥西布曲明成分的減肥產品出現精神錯亂等驚人結果。「食到傷」的比率更較全球同類個案發病率高出四千多倍。市民服「噏」減肥產品可能付上沉重代價，而毒理參考實驗室每揭發違規個案後即時通報衛生部門追查堵截。

果，接受治療時間最長超過五周。毒理參考實驗室顧問醫生李永權表示，受化驗及藥理追蹤的減肥產品聲稱「成分天然」，但證實機噏西藥，甚至其他成分如動物甲狀腺組織，「呢啲(甲狀腺組織)係天然產品，但亂食就死得人。」至於西布曲明是引致精神錯亂的字眼副作用，更因該類產品大行其道，令市民大量服食這類機噏西藥成分的產品而令精神錯亂個案大幅攀升。

圖沒有標示含西布曲明的「新康康」導致有市民服用後精神異常。

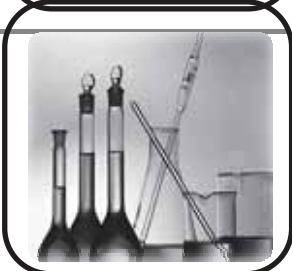
圖「玲瓏曲線清賢減肥膠囊」含西布曲明量比註冊的減肥西藥高。

圖「瘦身派」機噏出沒有標示含西布曲明及成份。

藝人向減肥藥說「不」

楊靜
「減肥藥物有副作用，好耐以前都有發生！其實做帶氣運動係好好噏減肥方法，我就鍾意游水、晨好多餐食菜，總之減肥唔係唔食嘢。」

莊思敏
「我一向都唔主張內服食藥減肥，減肥方法可以去美容院做機噏，針對部位去做，再平時我都會跑步。飲食方面食少啲，少煎。」



Oriental Daily: slimming products cause psychosis

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 04 1556-3630 print / 1556-9519 online
 It 10.310915563630.2010.517208

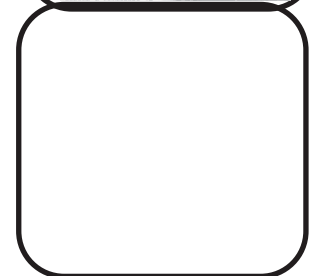
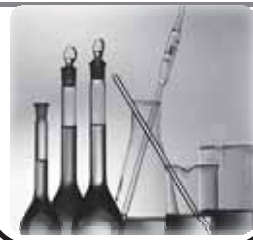
RTICLE
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References

Tang MHY, Chen SPL, Ng SW, Chan AYW, Mak TWL. Case series on a diversity of illicit weight-reducing agents: from the well known to the unexpected. *Br J Clin Pharmacol* 2011 Feb;71(2):250-3

Chen SP, Tang MH, Ng SW, Poon WT, Chan AY, Mak TW. Psychosis associated with usage of herbal slimming products adulterated with sibutramine: a case series. *Clin Toxicol (Phila)*. 2010 Oct;48(8):832-8.

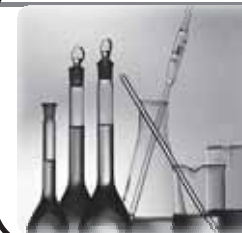
Yuen YP, Lai CK, Poon WT, Ng SW, Chan AY, Mak TW. Adulteration of over-the-counter slimming products with pharmaceutical analogue--an emerging threat. *Hong Kong Med J*. 2007 Jun;13(3):216-20



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CPO, PIC, PTC, DH, etc



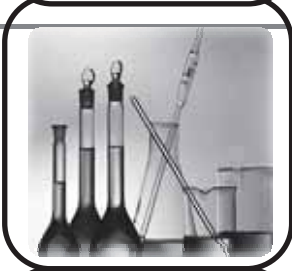
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Psychosis associated with
substance use



Banning: SCOUT Trial

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Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

W. Philip T. James, M.D., D.Sc., Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S.,
Luc F. Van Gaal, M.D., Ph.D., Aldo P. Maggioni, M.D., Christian Torp-Pedersen, M.D., Ph.D.,
Arya M. Sharma, M.D., Ph.D., Gillian M. Shepherd, B.Sc., Richard A. Rode, Ph.D., and Cheryl L. Renz, M.D.,
for the SCOUT Investigators*

To assess the cardiovascular consequences of weight management with and without sibutramine in subjects at high risk of cardiovascular events




- Randomized, double-blind, placebo-controlled, multicenter trial
- Jan 2003 – Mar 2009
- 298 centers in 16 countries
- 10744 overweight or obese subjects
 - 55 yo or older
 - BMI 27 – 45; 25 – 27 with increased waist circumference
 - Pre-existing cardiovascular disease, type 2 DM or both



■ Results

- Mean duration of treatment: 3.4 years
- Mean weight loss
 - Lead-in period: loss of 2.6 kg
 - Sibutramine group: further loss of 1.7 kg
 - Placebo group: gain of 0.7 kg



	Primary outcome event	Non-fatal MI	Non-fatal stroke
Sibutramine group	11.4%	4.1%	2.6%
Placebo group	10.0%	3.2%	1.9%
 Hazard ratio	1.16 (1.03 – 1.31)	1.28 (1.04 – 1.57)	1.36 (1.04 – 1.77)

- Rates of cardiovascular death and death from any cause are increased in sibutramine group