Web appendix 3: Profiles of 23 centrally-acting anti-obesity medicinal products withdrawn over the last 50 years because of adverse drug reactions

Amfepramone

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Introduced as an anti-obesity agent in 1957
- Pickwickian syndrome attributed to its use first reported in 1974 [1]
- Withdrawn in several countries in 1974
- Fatal case of primary pulmonary arterial hypertension attributed to its use reported in the UK in 1995 [2]
- Reintroduced in the UK in 2002 with restrictions

Amfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Initially used for narcolepsy
- Observed that patients with narcolepsy lost weight while taking amfetamine
- Approved in 1939 as an obesity treatment when the results of a trial showed that it was effective [3]
- Over dosage with its use as an anorectic first reported in 1957 [4]
- Several studies showed that it had a potential for abuse [5]
- Withdrawn as an anti-obesity agent in 1973
- Still largely consumed illegally as a psychostimulant
- Several cases of deaths from its misuse have been published since its withdrawal [6]

Aminorex

- Mechanism of action: serotonin reuptake inhibitor
- First introduced in 1962
- Became available within three years of introduction as an over-the-counter weight loss pill
- Between 1965 and 1972, there was a large increase in the incidence of primary pulmonary hypertension[7]
- The pulmonary hypertension epidemic ended in 1972 following withdrawal of aminorex from the market

Benfluorex

- Mechanism of action: serotonin reuptake inhibitor
- Approved in 1976 as an add-on treatment in obese patients with diabetes mellitus
- Cases of valvulopathy attributed to its use began to appear from 2003
- Withdrawn in 2009 following an epidemic of valvulopathy attributed to its use

- Several deaths reported
- To date over 3000 hospitalizations and at least 1300 deaths attributed to its use in France alone[8]

Chlorphentermine

- Mechanism of action: serotonin reuptake inhibitor
- Approved for obesity treatment in 1962 based on the results of short-term clinical trials [9,10]
- In 1969, animal studies began to emerge consistently suggesting an association with an increased risk of pulmonary phospholipidosis [11,12]
- Withdrawn in the same year
- No case reports of pulmonary hypertension in humans

Clobenzorex

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Approved in 1966 as an appetite suppressant
- Cases of drug abuse and psychiatric adverse reactions appeared from 1986 [13]
- Withdrawn from the market in 2000

Cloforex

- Mechanism of action: serotonin reuptake inhibitor
- A prodrug of chlorphentermine (see above)
- Introduced for obesity treatment in1965
- Cases of suspected pulmonary hypertension attributed to its use reported in Germany
- Animal studies suggested an association with pulmonary vasculopathy [14]
- Withdrawn in 1967

Dexfenfluramine

- Mechanism of action: serotonin reuptake inhibitor
- Approved in 1995 as an anti-obesity agent
- Several cases of cardiovascular adverse reactions reported shortly after [15]
- Withdrawn within two years of approval
- Cases of pulmonary hypertension attributed to its use were reported before regulatory approval [16,17]

Fenbutrazate

- Mechanism of action: norepinephrine-dopamine releasing agent
- Approved for use in obesity in 1957
- Cases of drug abuse reported in France [18]
- First withdrawn in 1969, and then withdrawn in all of Europe in 1995 [19]

Fenfluramine

- Mechanism of action: serotonin reuptake inhibitor
- First approved in in 1973
- Reports of pulmonary hypertension first appeared in 1981
- Several other case reports subsequently published
- Epidemiological studies showed an association between fenfluramine and pulmonary hypertension [20]
- Withdrawn worldwide in 1997

Fenproporex

- Mechanism of action: norepinephrine releasing agent
- First approved as an anti-obesity drug in 1966
- Cases of drug abuse attributed to its use first reported in 1997 [21]
- Withdrawn in Europe and Brazil within two years of the initial reports
- A recent systematic review evidence concluded that its abuse potential and amphetamine-like adverse effects remain a cause of concern [22]

Levamfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Introduced in 1944 as an anti-obesity agent
- Within 10 years of approval, cases of psychiatric reactions due to misuse were reported [23]
- Several cases of abuse and dependence (with psychoses) were subsequently reported [24]
- Withdrawn from the market in 1970

Mazindol

- Mechanism of action: norepinephrine-dopamine releasing agent
- Approved as an anti-obesity drug in 1970
- Neurotoxicity due to an interaction with lithium reported in 1980 [25]
- Several cases of testicular pain attributed to its use also reported [26]
- Further cases of psychiatric adverse reactions subsequently published [27]
- Withdrawn from the market in 1987

Meferonex

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Approved for treatment of obesity in 1966
- Serious neuropsychiatric adverse reactions due to abuse reported in 1995
- Withdrawn in Europe four years later [28]

Metamfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- First approved for obesity treatment in 1944

- Cases of abuse-related suspected psychiatric adverse reactions first appeared 10 years later [29]
- Several cases of abuse resulting in neurotoxicity or cardiotoxicity subsequently reported
- By 1968 reports of deaths from its use had appeared [30]
- A further case series of harms was reported two years later [31]
- Withdrawn in 1973

Phendimetrazine

- Mechanism of action: Norepinephrine-dopamine releasing agent
- First approved for obesity management in 1961
- Cases of abuse were first reported in 1979 [32]
- Withdrawn in 1982

Phenmetrazine

- Mechanism of action: norepinephrine-dopamine releasing agent
- First approved for management of obesity in 1956
- Cases of drug abuse and addiction appeared within three years of approval [33]
- Withdrawn as an anti-obesity agent in 1982

Phentermine

- Mechanism of action: norepinephrine-dopamine releasing agent
- First approved in 1959
- Several cases of lung phospholipidosis in animals and humans reported thereafter
- Reports of deaths began to appear in 1974 [34]
- Withdrawn from most countries where it was marketed in 1981
- Still available for short-term management of obesity in the USA

Phenylpropanolamine (norpseudoephedrine)

- Mechanism of action: norepinephrine-dopamine releasing agent
- Initially used as a nasal decongestant
- Introduced in 1947 for obesity
- Cases of psychosis attributed to its use began to appear in 1966 [35]
- Cases of intracranial haemorrhage reported in 1985 [36]
- Withdrawn within two years of the reports of haemorrhages

Pipradrol

- Mechanism of action: norepinephrine-dopamine reuptake inhibitor
- Approved as an adjunct to dietary management of obesity in 1953
- Associated with several cases of drug abuse [37]
- Withdrawn as an anti-obesity agent in 1982
- Still available for management of ADHD and narcolepsy

Pyrovalerone

- Mechanism of action: norepinephrine-dopamine releasing agent
- Introduced as a weight loss drug in 1974
- Within a year of introduction, cases of abuse started to appear [38]
- Withdrawn as an anti-obesity 1979 owing to problems associated with abuse and dependence
- A derivative, methylenedioxypyrovalerone (MDPV), is marketed illegally as a designer recreational drug under the name of "Bath Salts" [39]

Rimonabant

- Mechanism of action: cannabis CB_1 receptor antagonist/inverse agonist
- Approved in Europe in 2006 for obesity treatment
- Within 1 year of approval, cases of severe psychiatric adverse reactions were reported [40]
- 5 deaths attributed to its use in the UK
- Withdrawn in 2007

Sibutramine

- Mechanism of action: serotonin-norepinephrine reuptake inhibitor
- Approved in 1997 in the USA and Europe in 2001
- Within a year of its European approval, serious cardiovascular adverse reactions were reported, resulting in temporary withdrawal in Italy [41]
- Several cases of severe cardiovascular adverse reactions, including deaths, subsequently reported [42]
- Withdrawn in Europe and the USA in 2010

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