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History full circle: 'Novel' sympathomimetics in supplements

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Since the banning of ephedrine in over-the-counter nutritional supplements a decade ago, a plethora of untested and/or unsafe sympathomimetic stimulants have taken its place. This paper argues that these 'novel' stimulants in supplements recapitulate the work of synthetic chemists at commercial pharmaceutical firms during the 1930s and 1940s, all seeking substitutes for recently successful products based on ephedrine and amphetamine. Copyright © 2015 John Wiley & Sons, Ltd.

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In the 1920s ephedrine (compound (**7**) in Table 1 and Figure 1) brought a new era in commercial pharmacology. Extracted from the Chinese herb *Ephedra* spp. and characterized to great acclaim by elite pharmacologists Ko Kuei Chen and Carl Schmidt, the drug exhibited a range of adrenaline-like actions – but in a more useful form than adrenaline, the hormone blockbuster of 1901.[1–3] Adrenaline (as the substance was then known, but now as a mixture of epinephrine and norepinephrine (**18**, **19**)) was found to be clinically useful in slowing bleeding from soft tissue surgery and treating shock. Adrenaline was also widely consumed as a decongestant (applied via atomizer, in place of previously popular cocaine) and bronchodilator (injected for cases of severe asthmatic attack). Ephedrine had an important advantage over adrenaline: it was active when taken orally. Ephedrine pills became popular replacements for adrenaline as cold, allergy, and asthma remedies. Ephedrine was also volatile enough to be active as a decongestant inhalant when dissolved in oil. The central nervous system (CNS) stimulation produced by ephedrine was duly noted and shown to be useful in controlling narcolepsy. The Lilly drug firm developed the main uses with great success and by the late 1920s dominated the North American market for ephedrine,[3,4] leveraging a near monopoly on Chinese supplies of *Ephedra* plants (the most economical source for the chemical then and probably still today).

Lilly's success with ephedrine spurred commercially oriented efforts to find other, synthetic adrenaline analogues or 'sympathomimetics' with which to compete for the same clinical markets. In one such effort, chemist Gordon Alles discovered amphetamine (alpha-methylphenethylamine (**2**)) in 1929, which he patented and licensed to the Smith, Kline, and French (SKF) drug firm.[5] In the mid-1930s, SKF developed and aggressively marketed an over-the-counter decongestant called the Benzedrine Inhaler, which contained large quantities of volatile amphetamine base, capturing much of Lilly's market for ephedrine inhalants. Soon after, SKF pursued the development of oral amphetamine salts (Benzedrine Sulfate tablets) for a range of neuropsychiatric indications, especially minor depression.[5,6]

By the end of the 1930s, both the Benzedrine Inhaler and Benzedrine tablets were achieving great market success, so much so that they attracted competitors with imitative products based on methamphetamine (**6**), which was unpatentable (because of the publication of its 1919 synthesis and pharmacological characterization, in the course of structural studies on ephedrine, by Japanese chemist Akira Ogata).[3,7] These methamphetamine products included Pervitin tablets from the German firm Temmler and Methedrine tablets from Burroughs-Wellcome, and the Drinalfa Inhaler from Squibb. Given the mood-elevating and dependence-producing properties of amphetamine and methamphetamine, there is no surprise that by the end of the Second World War these products were causing significant abuse and dependency.[8–10] In practice, the product most prone to abuse, and the origin of medicine's discovery of amphetamine psychosis, was the Benzedrine Inhaler, which could easily be broken open for oral consumption of the large reservoir of amphetamine base inside.[5,11,12]

Emerging problems notwithstanding, by the mid-1940s amphetamine's success motivated an expanded search for substitutes to use in all main indications, by now including weight loss. But the stimulatory 'side-effects' of the Benzedrine Inhaler, even when used as directed (one or two sniffs of the volatile base every few hours) evidently attracted the earliest commercial efforts at improvement. Already in December 1941 SKF was working with Alles on an intensive testing programme to find an active compound to replace the problematic amphetamine in its popular decongestant. The desired replacement would simulate the appealing 'subjective effects' in the nose of amphetamine base, shrink mucosa adequately, exhibit 'negligible anti-sleep effect' in effective decongestant doses, and show low toxicity even with exaggerated doses. At the time SKF's leading candidates were, apart from close amphetamine congeners, the fully saturated α-methylhexylamine (**12**) and derivatives

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Table 1. Trivial and chemical names of the compounds discussed

Number	Chemical name	Trivial name	Remarks
1	2-phenylethylamine	PEA	
2	α-methylphenylethylamine	Amphetamine	The active substance in the Benzedrine products, first marketed in the mid-1930s
3	3-phenyl-propanol-2-amine	Propadrine	First marketed in the late 1930s as a decongestant substitute for ephedrine, both topically and internally
4	1-cyclohexyl-2-aminopropane	Propylhexedrine	The active substance in Benzedrex Inhaler, marketed from the late 1940s
5	β-methylphenylethylamine	BMPEA	
6	*N*,α-dimethylphenylethylamine	Methamphetamine	
7	*N*-methyl-3-phenyl-propanol-2-amine	Ephedrine	
8	2-methylaminoheptane	Oenethyl	
9	phenylpropylmethylamine	Vonedrine	The active substance in the Vonedrine Inhaler, first marketed in the late 1940s
10	*N*,α-diethyl-phenylethylamine	N,α-DEPEA	
11	4-[1-hydroxy-2-(methylamino)propyl]phenol	Methylsynephrine 4-HMP, oxilofrine	
12	α-methylhexylamine, 2-aminoheptane	Tuamine, tuaminoheptane	The active substance in the Tuamine Inahler, first marketed in the 1940s
13	*N*,*N*- dimethyl-2-phenylpropan-1-amine	NN-DMPPA	
14	4-[1-hydroxy-2-(methylamino)ethyl]phenol 4-[1-hydroxy-2-(isopropylamino)ethyl]phenol	Synephrine Deterenol, isopropyloctopamine	R = CH_3 R = $CH(CH_3$
15	2-amino-6-methylheptane		The active substance in Eskay Oralator inhalants from the 1940s
16	β,3,4-trihydroxy-*N*-methylphenylethylamine	Adrenaline, epinephrine	
17	1,3- dimethylamylamine	DMAA	The active substance in the Forthane Inhaler, first marketed in the 1940s
18	β,3,4-trihydroxy-phenylethylamine	Noradrenaline, norepinephrine	
19	1,3-dimethylbutylamine	DMBA	

thereof. Alles and SKF also explored several large families of other alkylamines, including cyclopentyl-, cyclopentenyl-, furyl-, and thio-alkylamines, in 1941–1942. In mid-1945, α-methylhexylamine, or 2-aminoheptane (**12**), was still their leading drug candidate to replace amphetamine in the Inhaler, and at about this time SKF marketed 2-amino-6-methylheptane (**15**) as the active ingredient in its Eskay Oralator inhalant cold remedy.[13]

However, possibly because competitor Lilly was on the same track and in 1944 was granted a patent on amino alkanes as vasocostrictors, and particularly the amino derivatives derivative of 4-methylhexane,[14] SKF devoted diminishing efforts to alkylamines. Indeed Lilly launched competing decongestant inhalers of this type, Tuamine (2-aminoheptane (**12**)) and Forthane (2-amino-4-methylhexane (**15**)) in the 1940s. Other firms also launched competing inhaler products based on aromatic amphetamine congeners, like Wyeth's Wyamine (mephentermine) and Merrell's Vonedrine (phenylpropylmethylamine, i.e., *N*-methyl-BMPEA – see below (**9**)), but the Benzedrine Inhaler remained the most successful product, and the one most associated with disreputable abuse.[5] Driven by competition and mounting pressure from the Food and Drug Administration (FDA), together with state pharmacy authorities and law enforcement, SKF chose fully saturated methylhexylamine derivatives to replace amphetamine in its decongestant inhaler, and by 1947 settled on propylhexedrine (1-cyclohexyl-2-aminopropane (**4**)).[5,15] It launched its new product as the Benzedrex Inhaler in 1948–1949. Like all the other 'non-amphetamine' inhalers of the 1940s through to the 1970s aliphatic and aromatic, the Benzedrex Inhaler proved liable to abuse in much the same way as the original Benzedrine Inhaler.[5] As ever, the multiple adrenergic effects, central and peripheral, proved inconvenient to separate from one another.

These synthetic sympathomimetic compounds were long ago removed from the over-the-counter pharmaceuticals market, due to safety and abuse issues; few are still available by prescription. Yet the last decade has seen a renaissance of these 1940s adventures in pharmacology, in over-the-counter 'nutritional supplements'. A likely impetus for this renaissance – the same which motivated amphetamine's original discovery and development -- is the urge to replace ephedrine after it was banned in supplements by FDA in 2004.[16,17] Several ephedrine, amphetamine, and methamphetamine analogues have been found as major ingredients in dietary supplements in the past decade. A sports supplement called *Craze* was found to contain significant amounts (21–35 mg) of N,α-DEPEA (*N*,α-diethyl-phenylethylamine (**10**)), a close methamphetamine analogue.[18] The stimulant was not listed as an ingredient, but instead presented as a component of a plant extract. However, N,α-DEPEA has so far never been identified in any plant. The amphetamine isomer BMPEA (β-methyl-phenylethylamine (**5**)) was detected in 11 out of 21 supplements labelled as containing *Acacia rigidula* at levels up to a maximum of 90 mg per daily serving.[19] Both BMPEA and NN-DMPPA (*N*,*N*- dimethyl-2-phenylpropan-1-amine (**13**)) were detected in a work-out supplement called *Noxpump*, a product declared to be based upon extracts of *Acacia rigidula* as well.[20] Neither BMPEA nor DMPPA have been detected in extracts of *Acacia rigidula*.[21] Similarly, multiple stimulants were discovered in a supplement called *Dexaprine*. *Dexaprine* contained the ephedrine analogues methylsynephrine (4-[1-hydroxy-2-(methylamino)propyl]phenol, 4-HMP, oxyephedrine, or

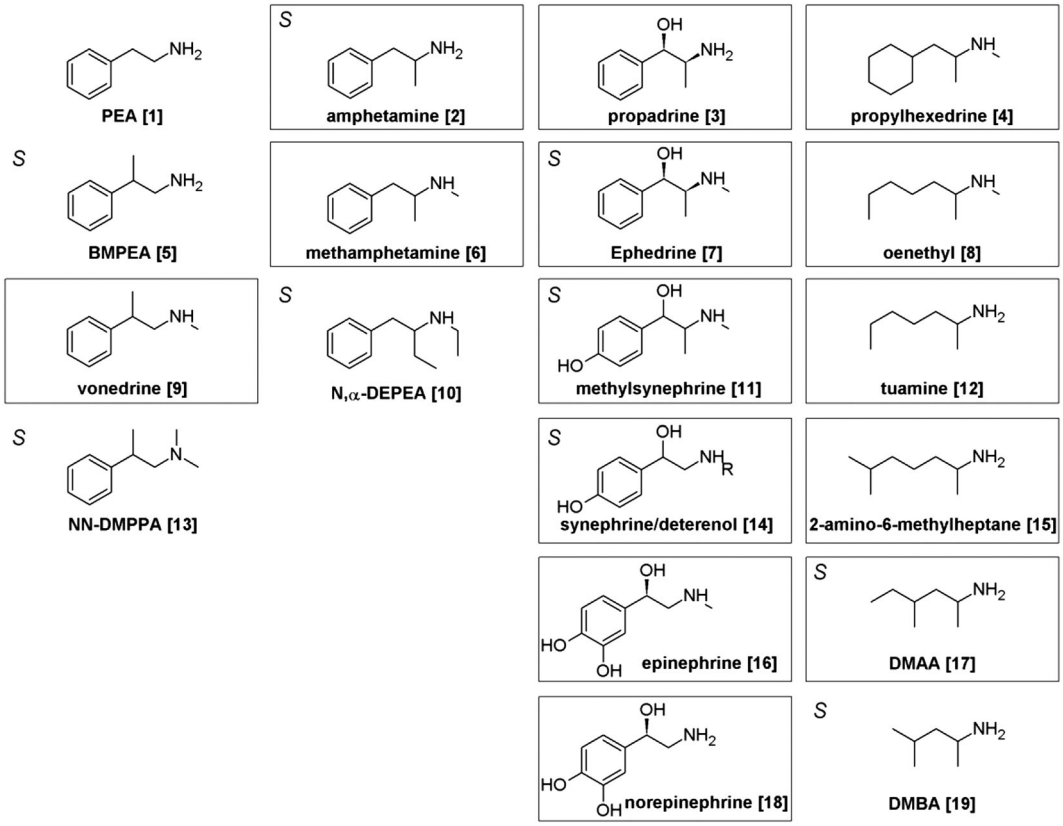

Figure 1. Molecular structures of the compounds discussed. Single modifications are required moving down the columns, as well as moving from **2** to **3** and hopping from **4** to **6**. For convenience, the trivial names of the compounds are added to the structures. Compounds that have previously been marked as pharmaceuticals are put in boxes. *S* indicates identification in a supplement. See Table 1 for other names and remarks.

oxilofrine (**11**)), synephrine (**14**), deterenol (**14**) and other amphetamine analogues.[22]

So it seems that almost a century after ephedrine replacements were aggressively developed by pharmaceutical firms, dietary supplement manufacturers have introduced multiple synthetic stimulants in an effort to replace *Ephedra* in supplements. The majority of the synthetic stimulants in supplements have never before been sold for human consumption, but some have. One of these compounds, formerly sold as Forthane by Lilly, is DMAA (1,3- dimethylamylamine, or geranamine, or 2-amino-4-methylhexane (**17**)) which was present in more than 200 supplements sold in the USA in 2012.[23] DMAA is an aliphatic amine known for its vasopressor activity; as Forthane it was labelled for external use only. On supplement labels it was represented as having a natural source, yet multiple academic studies have been unable to confirm its presence in plants.[24] But whether these sympathomimetics have been rigorously tested for internal use in humans, or not (as is mostly the case,[25,26]), the production of supplements is not under strict manufacturing control, compounding the risks to consumers as the quantity of stimulants may vary from one package to the next.[27]

Chemically, the similarity between amphetamine and DMAA may not look that obvious. In Figure 1 it is a modest molecular evolution from DMAA (**17**) to propylhexedrine (**4**), which is the non-aromatic counterpart of methamphetamine (**6**). Also the close congener compound of DMAA, DMBA (1,3-dimethylbutylamine, or 2-amino-4-methylpentane (**19**)) is found to be frequently added to supplements.[28] With the recent discoveries of N,α-DEPEA, NN-DMPPA, methylsynephrine, BMPEA, DMAA, and DMBA as new dietary supplement ingredients the question arises: which stimulant will be next? There are a number of pressor amines that may be selected, such as the pharmaceuticals oenethyl (**8**) and propylhexedrine (**4**). In addition, many more variants that can be easily synthesized using the basic structure of the compounds illustrated in Figure 1.

Whether the novel sympathomimetic drugs discussed here were initially discovered by botanical analysis or, more likely, synthetic chemistry followed by botanical prospecting to find regulatory cover, there is no reason to suppose that a drug is safe just because it is a component of a plant somewhere in the world.[29] The supplement industry remains less regulated than pharmaceutical industry has been in the USA since 1938, when pre-market toxicity testing was first required. The special exemptions applying to 'natural' supplements,[30] enabling vendors to bypass human testing when ingredients are extracted from natural sources, have become a shield for the sale of untested and unsafe drugs direct to the consumer.

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