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Review

Amphetamine, past and present – a pharmacological and clinical perspective

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Abstract

Amphetamine was discovered over 100 years ago. Since then, it has transformed from a drug that was freely available without prescription as a panacea for a broad range of disorders into a highly restricted Controlled Drug with therapeutic applications restricted to attention deficit hyperactivity disorder (ADHD) and narcolepsy. This review describes the relationship between chemical structure and pharmacology of amphetamine and its congeners. Amphetamine's diverse pharmacological actions translate not only into therapeutic efficacy, but also into the production of adverse events and liability for recreational abuse. Accordingly, the balance of benefit/risk is the key challenge for its clinical use. The review charts advances in pharmaceutical development from the introduction of once-daily formulations of amphetamine through to lisdexamfetamine, which is the first *d*-amphetamine prodrug approved for the management of ADHD in children, adolescents and adults. The unusual metabolic route for lisdexamfetamine to deliver *d*-amphetamine makes an important contribution to its pharmacology. How lisdexamfetamine's distinctive pharmacokinetic/pharmacodynamic profile translates into sustained efficacy as a treatment for ADHD and its reduced potential for recreational abuse is also discussed.

Keywords

Abuse liability, amphetamine, attention deficit hyperactivity disorder (ADHD), drug formulations, lisdexamfetamine, microdialysis

A short history of amphetamine

Although racemic α-methylphenethylamine (amphetamine) was discovered by Barger and Dale in 1910, it was not until 1927 that this molecule was first synthesised by the chemist, G. A. Alles, whilst he was searching for a less costly and more easily synthesised substitute for ephedrine. Experiments performed in animals and human subjects by Alles and others unequivocally revealed α-methylphenethylamine's ability to reverse drug-induced anaesthesia and produce arousal and insomnia (see reviews by Bett, 1946; Guttmann and Sargent, 1937). The trade name 'Benzedrine®' for racemic α-methylphenethylamine was registered by the pharmaceutical company, Smith, Kline and French. 'Amphetamine', which is the generic name for Benzedrine devised by the Council on Pharmacy and Chemistry of the American Medical Association, was not adopted until many years later. It is the reason why the name Benzedrine, not amphetamine, appears in all of the early publications (see Bett, 1946). Smith, Kline and French introduced Benzedrine onto the market in 1935 as a treatment for narcolepsy (for which it is still used today), mild depression, post-encephalitic Parkinsonism and a raft of other disorders (see Bett, 1946; Guttmann and Sargent, 1937; Tidy, 1938).

As a molecule with a single chiral centre, amphetamine exists in two optically active forms, i.e. the dextro- (or *d*-) and levo- (or *l*-) isomers or enantiomers (Figure 1). Smith, Kline and French synthesised both isomers, and in 1937 commenced marketing of *d*-amphetamine, which was the more potent of the two isomers, under the trade name of Dexedrine®. Sales of Benzedrine and Dexedrine in chemist stores were unrestricted until 1939, when these drugs could only be obtained either on prescription from a registered medical practitioner or by signing the Poison Register (Bett, 1946). The cognitive-enhancing properties of amphetamine reduce stress and improve concentration and intellectual performance by academics, students and medical professionals (see Guttmann and Sargent, 1937; Tidy, 1938). In his 1946 review, Bett commented on the widespread use of 'energy pills' by the allied forces in World War II, estimating that 150 million Benzedrine tablets were supplied to British and American service personnel during the course of the global conflict. In spite of considerable coverage in the medical literature and the popular press describing the powerful central effects of these new drugs, the addictive potential of amphetamine was largely dismissed (see Bett, 1946; Guttmann and Sargent, 1937; Tidy, 1938).

It was Bradley (1937) who first reported the beneficial effects of Benzedrine in treating children with severe behavioural problems, who would now be diagnosed as suffering from attention deficit/hyperactivity disorder (ADHD) (American Psychiatric Association, 1994). Bradley treated 30 subjects for a week, and in approximately half of them he observed remarkable improvements in their school performance, behaviour and demeanour. These therapeutic benefits unequivocally derived from the drug because they were apparent from the first day of Benzedrine treatment and disappeared as soon as it was discontinued. Although

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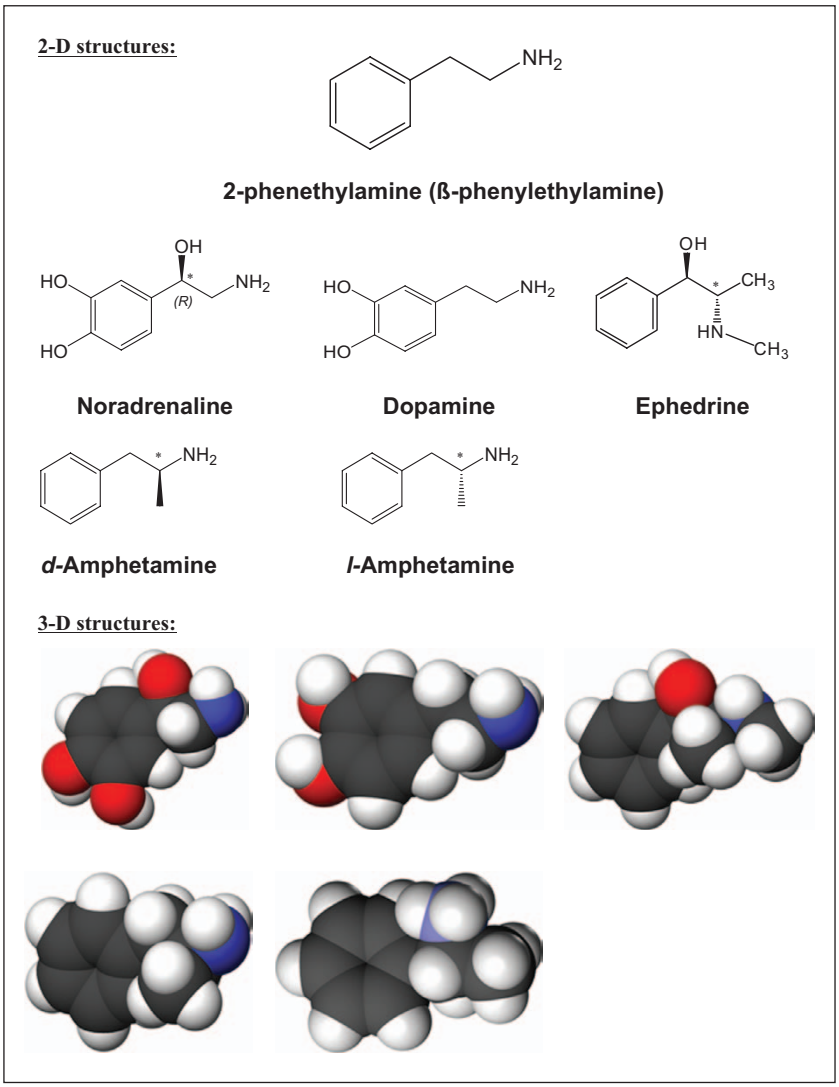

Figure 1. Chemical structures of various biologically active β-phenylethylamines.
* Chiral centre. Red: Oxygen atom; White: Hydrogen atom; Black: Carbon atom; Blue: Nitrogen atom.

l-amphetamine (Cydril®) achieved far less attention than either the racemate or *d*-isomer, clinical trials conducted in the 1970s demonstrated that both isomers of amphetamine were clinically effective in treating ADHD (Arnold et al., 1972, 1973, 1976). The use of Benzedrine to treat ADHD declined dramatically after Gross (1976) reported that the racemate was significantly less clinically effective than Dexedrine. Currently, the only use of *l*-amphetamine in ADHD medications is in mixed salts/mixed enantiomers amphetamine (MES-amphetamine), which consists of a 3:1 enantiomeric mixture *d*-amphetamine:*l*-amphetamine salts that is available in both immediate-release (Adderall®, generic) and extended-release (Adderall XR®, generic) formulations. A recent development in the amphetamine field is the introduction of an amphetamine prodrug, lisdexamfetamine dimesylate (Vyvanse®). Lisdexamfetamine comprises the naturally occurring amino acid, L-lysine, covalently bound to *d*-amphetamine via an amide linking group. It has been approved for the management of ADHD in children (age 6–12), adolescents and adults in the USA and Canada. It is currently being developed for clinical use in

route of lisdexamfetamine is unusual because after absorption into the bloodstream it is metabolised by red blood cells to yield *d*-amphetamine and the natural amino acid, L-lysine, by rate-limited, enzymatic hydrolysis (Pennick, 2010). An overview of amphetamine-based medications is provided in Table 1.

A clinical perspective on the use of amphetamine in the treatment of ADHD

ADHD is arguably the most under-diagnosed and treated of all psychiatric disorders, especially in adults (Kooij et al., 2010). The most recent European data suggest that about 5% of the population suffer from ADHD in any one year, with a total of about 3 million patients in Europe (Wittchen et al., 2011). Further estimates put the cost of each patient at about £5000 per year in the UK (Gustavsson et al., 2011). Of the total just over half are direct treatment costs and the rest indirect costs, for example lost productivity, social harm, negative impact on family life, increased incidence of acci-

Table 1. Amphetamines – past and present.

Product	Salt	Formulation	Trade names	Currently available
Racemic amphetamine	Base	IR	Benzedrine, Actedron, Allodene, Adipan, Sympatedrine, Psychedrine, Isomyn, Isoamyne, Mecodrine, Norephedrane, Novydrine, Elastonon, Ortédrine, Phenedrine, Profamina, Propisamine, Sympamine, Sympatedrin	No
	Sulphate	IR	Benzedrine sulphate, Alentol, Psychoton, Simpamina	No
	Phosphate	IR	Acetemin, Aktedron, Monophos, Profetamine phosphate, Racephen, Raphetamine phosphate	No
d-Amphetamine	Sulphate	IR	Dexedrine sulphate, Afatin, *d*-Amfetasul, Domafate Obesedrin, Dexten, Maxiton, Sympamin, Simpamina-D, Albemap, Dadex, Ardex, Dexalone, Amsustain, Betafedrina, *d*-Betaphedrine, Diocurb, Dextrostat, generic	Some Yes
	Sulphate	Liquid	Procentra	Yes
	Sulphate	XR	Generic	Yes
	Tannate	IR	Synatan, Tanphetamine	No
l-Amphetamine	Succinate	IR	Cydril	No
Mixed enantiomers/ mixed salts amphetamine (3:1 d:l isomers)	Saccharate/ aspartate/ sulphate	IR	Adderall, generic	Yes
	Saccharate/ aspartate/ sulphate	XR	Adderall XR, generic	Yes
Lisdexamfetamine	Dimesylate	Prodrug	Vyvanse	Yes

IR: immediate release; XR: extended release.
Data taken from various sources including the Merck Index, Daily Med, electronic Medicines Compendium.

The impact in terms of lost quality of life (days lived with disability) puts ADHD in the top 10 disorders of the brain in Europe. Treatment of ADHD is generally inadequate, with estimates suggesting that, at best, less than one-third of patients with the diagnosis get appropriate treatment (Gustavsson et al., 2011).

Although amphetamine has been established as an effective treatment for ADHD, as well as other central nervous system (CNS) disorders such as narcolepsy for decades, its use in the UK (and in the wider European context) has been rather limited in comparison with its widespread use in the USA. The reasons for this are complex and relate to social and medical attitudes to the condition of ADHD, pharmaceutical industry marketing policies, as well as to concerns regarding the use of drugs in paediatric indications which are perceived to have a high potential for recreational abuse and to cause addiction.

ADHD has long suffered from being considered an 'American' diagnosis, and for many decades there was a concerted attempt by some experts in child psychiatry to deny, or at least minimise, its existence in the UK. On top of this, on the rare occasions when the disorder was identified, the preferred treatment option was psychotherapy because it fitted with the background of the child psychiatrists and psychologists who were responsible for managing these patients. It was left to certain paediatricians to develop the requisite expertise in the use of stimulants for treating children with ADHD, which many did quite successfully. In recent years, child psychiatrists have begun to assume a prescribing role as well, largely using

Amphetamines, i.e. racemic amphetamine, d-amphetamine and methamphetamine, were widely used to promote wakefulness in World War II, which in turn led to a large increase in production that resulted in large surpluses of these drugs after the war. Much of these stocks got into the 'black market', and in the 1950s *d*-amphetamine abuse became recognised. In a classic study of that period, Connell from the Institute of Psychiatry reported a group of heavy *d*-amphetamine users who had become paranoid (Connell, 1966). This flagged up the potential psychiatric dangers of this drug and may have encouraged prescribers away from *d*-amphetamine and on to methylphenidate. Another factor was the use of *d*-amphetamine as an antidepressant in the 1950s before the discovery of the tricyclic monoamine reuptake inhibitors. There were cases of misuse by patients, and also a significant degree of diversion of the prescribed drug into youth misuse and/or abuse that may also have contributed to wariness by prescribers regarding its clinical use. In later years, local outbreaks of *d*-amphetamine abuse have occurred in various parts of the UK, often using locally synthesised *d*-amphetamine; again, this will have made doctors shy away from prescribing *d*-amphetamine lest it contributes to its misuse. In the USA, *d*-amphetamine-containing medications, especially MES-amphetamine, have been very widely used as treatments for ADHD. Familiarity with prescribed amphetamines together with the increased availability of more and more tamper-deterrent drug formulations to reduce the potential for abuse, for example Adderall XR®, have created a situation where in the USA the abuse risk of *d*-amphetamine is perceived as

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