Methamphetamine addiction: potential substitute treatment

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Stimulant medications have been used to treat the symptoms of attention deficit hyperactivity disorder (ADHD), since a 'paradoxical' response to benzedrine was described by Bradley [Bradley, 1937].

Busardo and colleagues have reviewed the pharmacology, adverse side effects, and abuse/misuse of methylphenidate [Busardo *et al.* 2016]. They concluded that the prefrontal cortex is the main site for therapeutic action. There are now a variety of newer long-acting formulations described by the authors, who found that adverse effects were generally dose related. Misuse as a cognitive enhancer was most common among college students, but the claim that methylphenidate acts as a 'gateway' drug was discredited by multiple sources and was rarely found to lead to addiction or abuse.

Heal and colleagues reviewed the pharmacology of the amphetamines, including the comparative potency of racemic dextro, d-amphetamine *versus* levo or l-amphetamine isomers [Heal *et al.* 2015]. According to the authors, d-amphetamine has larger effects on dopamine, whereas l-amphetamine increases both dopamine and noradrenergic neurotransmission. Abuse liability has been shown to be associated with the number of dopamine D2 receptors (DRD2s), where higher numbers give rise to aversive effects. According to Volkow and Swanson, individual differences in the level of the DRD2 indicated that subjects with low striatal DRD2 levels tended to describe methylphenidate as pleasant, whereas subjects with high DRD2 levels tended to describe it as unpleasant [Volkow and Swanson, 2003]. While both d-amphetamine and methylphenidate misuse in susceptible subjects can give rise to addiction, appropriate oral administration rarely gives rise to abuse [Volkow and Swanson, 2003].

Volkow and Swanson reviewed variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD, including dose level, pharmacokinetics, individual differences, and context in determining the reinforcing effects of methylphenidate [Volkow and Swanson, 2003]. While abuse by oral administration of methylphenidate was found to be rare, intranasal or intravenous injection was more common. Importantly oral methylphenidate at doses used therapeutically required a greater than 50% threshold of dopamine transporter blockade to produce reinforcing effects. In the case of methylphenidate, its slow clearance from the brain was found to be protective, because of the persistence of nonreinforcing side effects. Koob and Volkow [2010] reported hypofunction in DRD2 expression and subsequent decreases in dopamine release, with cycles of abstinence and relapse [Volkow *et al.* 2013]. In methamphetamine addiction a decrease in DRD2s was found, as well as activation of brain stress systems and a decrease in the dopamine transporter in the striatum.

The most recently available amphetamine, lisdexamfetamine, is the first prodrug to have been approved for treatment of ADHD [Heal *et al.* 2015]. According to the authors, "the large molecular size and polar characteristics of lisdexamfetamine predict that the parent molecule is unlikely to cross the blood-brain barrier. *In vitro* experiments revealed that the metabolism of lisdexamfetamine to d-amphetamine occurs in red blood cells by rate-limited enzymatic hydrolysis". Animal studies have shown that compared with d-amphetamine, the *C*max was 50% lower after d-amphetamine and the time to *C*max doubled [Heal *et al.* 2015]. Importantly, intravenous administration at equivalent doses with d-amphetamine did not significantly increase drug-positive effects compared with placebo.

Heal and colleagues pointed out that while rapid release and concentration of dopamine in rats is associated with increased locomotor activity, the relation between ascending and descending

concentration curves for lisdexamfetamine is anticlockwise rather than clockwise for the former [Heal *et al.* 2015]. This 'hysteresis' effect means that the functional effect of lisdexamfetamine occurs as the plasma concentration of metabolized d-amphetamine is falling. In this respect lisdexamfetamine has promise both in prevention of recreational abuse and in a possible treatment of methamphetamine addiction.

According to the National Institute on Drug Abuse, MD, USA, methamphetamine is an extremely addictive stimulant drug that is chemically similar to amphetamine. Owing to its rapid and intense euphoria and fast metabolism, it is often taken repeatedly, resulting in a 'binge and crash' pattern, accompanied by anxiety, insomnia, mood disturbance, and violent paranoia. The pharmacokinetic profile described by Heal and colleagues may represent a potential substitute treatment approach for a severe public health problem [Heal *et al.* 2015].

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Conflict of interest statement

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