

Editorial

Circumspectives: The Replacements

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In this issue we present our third *Circumspectives*. The purpose of a *Circumspectives* article is to consider an issue from multiple perspectives, with separate sections in which two thought leaders articulate their individual positions on a topic of great importance to our community of researchers. The distinguishing element, however, is that the piece ends with a ‘reconciliation’ that is co-authored by both and includes ideas or experiments to move the field forward.

The current *Circumspectives* is entitled ‘Agonist medications for the treatment of cocaine use disorders’, co-authored by Steve Negus and Jack Henningfield (Negus and Henningfield, 2015). Previous *Circumspectives* articles have been formulated primarily as debates. Rather than being strictly ‘pro versus con’, this piece is better described as ‘hopes versus challenges’, thereby representing an alternative way in which a topic can be viewed from multiple perspectives.

Agonist treatments are perhaps the most compelling success story of pharmacotherapy for addictive disorders to date. Methadone maintenance for opioid addiction is the paradigmatic example. Although controversies raged for decades after Vincent Dole won the Lasker Award for its discovery, the evidence-based jury has now been in for quite some time, and its verdict (broadly beneficial) is clear (Mattick *et al*, 2009). Other examples include maintenance with the partial agonist buprenorphine (Mattick *et al*, 2008) and smoking cessation treatment with the nicotine patch (Stead *et al*, 2008). Dr Negus uses the success of these approaches as a launching point for a review of research aimed at establishing whether maintenance treatment with long-acting cocaine mimics could be used to treat cocaine addiction. At a molecular level, the effects of psychostimulants on the DA transporter are obviously different from those of direct receptor agonists such as methadone or nicotine. It is, however, a credible proposition that the basic strategy is similar. The hope is that a longer-acting ‘mimic’ may substitute for the sought-after cocaine effects, and thereby eliminate the incentive for cocaine seeking and relapse. Dr Negus reviews literature showing that long-acting

DA-selective releasers, such as amphetamine, phenmetrazine, and methamphetamine—but not serotonin releasers such as fenfluramine—indeed reduce cocaine use, both in laboratory animals and people. Perhaps even more importantly they also shift behavioral choice away from cocaine and toward alternative reinforcers, normalizing a characteristic pathology of addiction (Ahmed *et al*, 2013). Having thus established the efficacy of the ‘mimic’ approach to reduce cocaine use and choice, Dr Negus turns to the obvious next question, that of safety and tolerability. He cites literature indicating that amphetamine treatment may be associated with a surprisingly low degree of cardiovascular toxicity, diversion, or abuse. He points out that it may be possible to improve safety further by using pro-drugs such as lisdexamfetamine, an approved ADHD medication with lower abuse liability compared with amphetamine (Jasinski and Krishnan, 2009).

Dr Henningfield, a veteran of research on the efficacy of agonist maintenance in nicotine addiction, does not dispute Dr Negus’ basic assertion that a cocaine-mimic treatment might be effective in cocaine addiction. Instead, based on decades of experience, he views the topic from a regulatory perspective. He concludes that successful development of maintenance treatments with cocaine-mimics such as amphetamine is very unlikely to meet with success for cocaine addiction. In his analysis, he points out that establishing therapeutic efficacy of a medication is a necessary requirement for a drug to be approved, but far from sufficient. In the end, approval decisions are based on an assessment of the risk–benefit ratio. In assessing this trade-off, consideration is given not only to real risks, but also to those that are perceived by the public and policy makers. Once again, the history of methadone maintenance treatment is instructive. Long after the efficacy of this treatment was well documented, its implementation remained illegal in many jurisdictions because ‘replacing one drug with another drug’ was thought to fly in the face of common sense. In a time when methamphetamine is one of the most recognizable and feared addictive drugs, the proposition of using this molecule or its analogs for addiction treatment may confront insurmountable hurdles along the way to FDA approval. As Dr Henningfield points out, it is exceedingly difficult to imagine who might sponsor large-scale studies required for an approval filing. This may,

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however, be an issue on which we as a society 'evolve': in the case of methadone maintenance, evidence-based approaches carried the day in the end, as scientist and clinicians were able to educate policy makers.

These two perspectives perhaps also invite a third. It is not always obvious what outcomes are clinically relevant measures of efficacy. Statins have been prescribed to extremely large numbers of patients because they lower blood lipids, but it is unclear to what extent this translates into real benefits for patients on outcomes that presumably matter more: morbidity and mortality. Similarly, reductions in drug use or retention in treatment *per se* are only surrogate outcomes, and may or may not translate into meaningful clinical benefits. The ultimate reason methadone maintenance was able to break through the resistance was because in high-quality programs it resulted in improvements in social function, reductions in crime, and decreased mortality. These are, ultimately, the outcomes that matter, and they are tremendously challenging to establish in trials of limited duration and with reasonable sample sizes.

It is important to note that advocating for the use of amphetamines to treat cocaine addiction is provocative and has some potential to be unpopular. The Editors are grateful to Dr Negus and Dr Henningfield for having the courage to put their ideas down on paper so they can be discussed in a collegial and productive manner. Other individuals who played key roles in the conceptualization, development, and implementation of this article include Michael Baumann, and David Baker. We welcome suggestions for future

Circumspectives topics and authors, which can be submitted to journal@acnp.org. Please note that articles of this type submitted without pre-approval will not be considered. Our next one is scheduled to appear early in 2016.

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