1521-0103/385/3/159–161$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

dx.doi.org/10.1124/jpet.123.001650
J Pharmacol Exp Ther 385:159–161, June 2023



# Viewpoint

# Bath Salts to Therapies: Can Separation of Adverse and Therapeutic Effects of Substituted Cathinones Lead to a Medication for Psychostimulant Use Disorder?

Cathinone is the main psychoactive compound derived from the leaves of the shrub Khat (*Catha edulis*). The Khat plant is native to East Africa and the Arabian Peninsula, and residents of those regions have, for centuries, chewed or brewed Khat leaves for their stimulant properties (Capriola, 2013). Cathinone shares the phenethylamine structure of amphetamine and, along with that, its psychostimulant effects (Baumann et al., 2018; Simmons et al., 2018; Riley et al., 2020). Although chewing Khat leaves is seen as commonplace and relatively nonproblematic in some regions of the world, more recently, synthetic derivatives of cathinone entered the recreational drug market and have proven to be problematic. Around 2009, clandestine laboratories began altering the structure of cathinone to produce derivatives with pharmacodynamic, pharmacokinetic, and potency profiles that aligned with high abuse potential as well as high toxicity. These synthetic cathinones, including 4-methylmethcathinone (mephedrone), 3,4-methylenedioxypyrovalerone (MDPV), and 3,4-methylenedioxymethcathinone (methylone), were aggressively marketed internationally, had a legal status, and were readily available and affordable to consumers. As a result, their popularity as recreational stimulants rose accordingly. Synthetic cathinones were sold on the internet and at "smart shops," "head shops," and other retail establishments as fictitious products labeled as "bath salts," "plant food," or "fertilizer" and marked "not for human consumption" to bypass Food and Drug Administration regulations (Riley et al., 2020; Soares et al., 2021). Within a few years, their use in the United States, Europe, and other parts of the world had grown, along with an alarming increase in calls to poison control centers and reports of their harmful effects, including death (LaMaida et al., 2021). Because of "an imminent threat to public safety," mephedrone, MDPV, methylone, and their isomers were placed in Schedule I of the Controlled Substance Act in 2011 by the Drug Enforcement Administration through emergency scheduling (Bonson et al., 2019). As specific chemical entities became scheduled, new synthetic cathinone derivatives were found on the market as reported by the National Forensic Laboratory. This trend has continued, with the synthesis and release of a variety of novel compounds based on the cathinone structure occurring at an alarming rate world wide (Riley et al., 2020; Soares et al., 2021).

The pharmacological profile of cathinones, like amphetamines, involves enhancement of monoamine neurotransmission, including dopamine, norepinephrine, and serotonin. This is achieved through augmentations of monoamine release and/or attenuation of presynaptic reuptake mechanisms (Baumann et al., 2018). In addition to producing euphoria and hallucinations, adverse sympathomimetic effects are common and can include excess cardiovascular stimulation, hyperthermia, and seizures, which can lead to death (Bonson et al., 2019). Manipulation of the chemical structure of the synthetic cathinones can result in changes in their pharmacological and toxicological profile, making the analysis of structure activity relationship on this class of compounds of great value.

In this issue of *the Journal of Pharmacology and Experimental Therapeutics*, Chojnacki et al. (2023), at the National Institutes on Drug Abuse and Alcohol Abuse and Alcoholism, report on the pharmacology of 4-chloro ring–substituted cathinones. One of these, 4-chloromethcathinone (4-CMC), is associated with significant toxicities and deaths in human users (Tomczak et al., 2018; La Maida et al., 2021). As variations in structure profoundly affect the ability of compounds to interact with cellular targets, the investigation by Chojnacki et al. (2023) on the structure activity relationship and physiologic effects of the 4-chloro ring–substituted cathinones is of high importance.

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No author has an actual or perceived conflict of interest with the contents of this article.
dx.doi.org/10.1124/jpet.123.001650.

The synthetic cathinones are $\beta$-keto analogs of amphetamine and, as such, produce their effects by interacting with transport proteins on the plasma membrane of neurons that synthesize and release dopamine, norepinephrine, and serotonin. Facilitation of monoamine neurotransmission, especially dopamine transmission, is a critical driver in their abuse liability. Although these compounds all facilitate monoamine transmission, their molecular mechanisms vary depending on the specific structure. Some cathinones act as substrates at monoamine transporters and promote release (similar to amphetamine), whereas others act as blockers of the monoamine transporters (similar to cocaine). In their current study, Chojnacki et al. (2023) investigated the pharmacological mechanisms of three 4-chloro ring–substituted cathinones in comparison with mephedrone. Because of the known cardiotoxic effects of the synthetic cathinones, they also investigated these compounds on blood pressure, heart rate, and body temperature in male rats. Results demonstrate that 4-CMC has similar neurochemical and pharmacological actions as mephedrone, which are likely related to heightened dopamine efflux and their structural similarities. In contrast, 4-chloro-$\alpha$-pyrrolidinopropiophenone (4-C$\alpha$PPP) has little effect on the serotonin transporter (SERT) and is devoid of releasing activity all together. 4-C$\alpha$PPP has the least potent effects on blood pressure and heart rate, although other studies have shown that 4-C$\alpha$PPP has abuse liability as it is self-administered by rats (Xu et al., 2021). 4-Chloroethcathinone (4-CEC) is a low-potency reuptake inhibitor of dopamine and norepinephrine but facilitates serotonin and, to a lesser extent, norepinephrine release. This is reflected by reduced effects on blood pressure and heart rate. A potential caveat to the results of this study is related to the lack of testing for differences in brain penetrance of the four compounds, which could influence the findings if blood-brain barrier permeability were significantly different between compounds. Taken together, the results from this analysis indicate that additional steric bulk at the amine position reduces substrate activity, especially for the dopamine (DAT) and norepinephrine (NET) transporters. On the other hand, SERT perhaps contains a binding pocket capable of handling the larger amine substitution.

The increased understanding of synthetic cathinone pharmacology could also lead to the development of therapeutic molecules for psychostimulant use disorder, which still lacks Food and Drug Administration–approved medications. Because synthetic cathinones target the same monoamine transporters that are impacted by cocaine and methamphetamine, a cathinone-based therapeutic for psychostimulant addiction is plausible. This strategy is analogous to the medications used for treatment of opioid use disorder which target opioid receptors. In fact, it has been suggested that hybrid transporter compounds may serve as important leads for medication development (Blough et al., 2014). If so, as done in the present study, it will be important to characterize structurally diverse synthetic cathinones to separate adverse and therapeutic effects.

There is, indeed, no a priori reason why a cathinone structure cannot be a drug candidate for psychostimulant use disorders. The norepinephrine/dopamine reuptake inhibitor bupropion is the only cathinone derivative currently approved for therapeutic use in the United States, but the positive impacts of bupropion in managing depression and nicotine addiction are undeniable as evident from being consistently ranked in the top 20 in number of prescriptions in the United States. Bupropion does lack efficacy against cocaine use disorders in clinical trials (Margolin et al., 1995; Kampman, 2008). However, compared with 4-CMC and the 4-chlorocathinones characterized by Chojnacki et al. (2023), bupropion has a mechanistic profile that is quite different, most notably the negligible effects on SERT and serotonin transmission (DeBattista, 2022). In the present article, Chojnacki et al. (2023) showed that 4-chloro ring–substituted cathinones are active and produce effects that are pharmacologically similar to mephedrone. In the context of drug discovery, one approach is to focus on characterization of 4-position ring substitutions to discriminate therapeutic and addictive effects. Indeed, Negus and Banks (2017) have shown that increasing the size of 4-position ring substitutions on synthetic cathinones increases the potency at SERT versus DAT and reduces abuse liability. A next step could be to determine how alterations in the size of these 4-positon ring substitutions impact NET and norepinephrine transmission. Relative to dopamine, a role for norepinephrine in psychostimulant use disorders remains understudied. Many amphetamine-like stimulants, including methamphetamine, are 5–10-fold more potent at NET versus DAT (Rothman et al., 2001; Ferrucci et al., 2019), underscoring the importance of identifying and characterizing synthetic cathinones with enhanced NET potency.

In the context of adverse effects, broadening our understanding of how 4-chloro ring–substituted cathinones interact with specific serotonin 5-HT receptors will also be important. Mephedrone itself displays hallucinogenic effects that are probably related to 5-$HT_{2A}$ receptor activation (Lopez-Arnau et al., 2012; Simmler et al., 2013) and cardiovascular effects resulting from 5-$HT_{2B}$ receptor activation (Rothman et al., 2000). Another dual serotonin/dopamine-releasing agent with preferential serotonin-releasing effects that has shown promising actions against addictive-like effects of cocaine in preclinical models is PAL287 (Rothman et al., 2006); however, PAL287 also displays agonist activity at both 5-$HT_{2A}$ ($EC_{50}$ = 466 nM) and 5-$HT_{2B}$ ($EC_{50}$ = 40 nM) receptors that may increase the risk of $5HT_{2A}$ receptor-mediated hallucinations and $5HT_{2B}$ receptor-mediated cardiovascular effects. Thus, synthetic cathinones that are devoid of agonist activity at 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors would be expected to display reduced risks of adverse effects and toxicities.

In summary, the findings of Chojnacki et al. (2023) shed important new light on the pharmacology of 4-chloro ring–substituted cathinones and emphasize the translational importance of identifying cathinones with enhanced SERT and NET potency relative to DAT. This scientific research raises hope that through a combination of different strategies, such as increasing the size of 4-position ring substitutions or enantiomeric separation of addictive and therapeutic properties (Philogene-Khalid et al., 2017), an effective and safe, cathinone-based therapeutic for psychostimulant use disorder could be identified.

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