Review

Mephedrone: Public health risk, mechanisms of action, and behavioral effects

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A B S T R A C T

The recent shortage of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) has led to an increased demand for alternative amphetamine-like drugs such as the synthetic cathinone 4-methylmethcathinone (mephedrone). Despite the re-classification of mephedrone as a Class B restricted substance by the United Kingdom and restrictive legislation by the United States, international policy regarding mephedrone control is still developing and interest in synthetic amphetamine-like drugs could drive the development of future mephedrone analogues. Currently, there is little literature investigating the mechanism of action and long-term effects of mephedrone. As such, we reviewed the current understanding of amphetamines, cathinones, and cocaine emphasizing the potentially translational aspects to mephedrone, as well as contrasting with the work that has been done specifically on mephedrone in order to present the current state of understanding of mephedrone in terms of its risks, mechanisms, and behavioral effects. Emerging research suggests that while there are structural and behavioral similarities of mephedrone with amphetamine-like compounds, it appears that serotonergic signaling may mediate more of mephedrone's effects unlike the more dopaminergic dependent effects observed in traditional amphetamine-like compounds. As new designer drugs are produced, current and continuing research on mephedrone and other synthetic cathinones should help inform policymakers' decisions regarding the regulation of novel 'legal highs.'

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1. Introduction

During the mid-2000s, a law enforcement crackdown on 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') led to a drug shortage in many major countries (Brunt et al., 2011). As law enforcement agencies placed stronger restrictions on MDMA precursors, drug makers turned to novel products to satisfy the demand for MDMA (Brunt et al., 2011). The change in MDMA precursors led to a marked decrease in drug purity, with the number of pills sold as MDMA actually containing the compound dropping from 90 to 50% (Brunt et al., 2011). The most common MDMA replacement was the synthetic cathinone mephedrone (4-methylmethcathinone) (Brunt et al., 2011). At the time of their initial use, mephedrone and related compounds were legal designer drugs; however, legislation in April 2010 reclassified mephedrone as a Class B restricted substance in the United Kingdom (UK) and American President Barrack Obama signed a law banning mephedrone in July 2012 (Haggin, 2012). Many other countries are adopting similar legislation, often citing a
small but growing mephedrone literature base and comparing the designer drug to well researched drugs of abuse; however, these bans have been unable to stop the spread of designer drugs.

The natural analogue to mephedrone, cathinone, is the active compound in the leaves of the khat plant (Catha edulis), which have been chewed for centuries in Africa due to their amphetamine-like effects (Carroll et al., 2012). Molecularly, cathinone is extremely similar to amphetamine, with the only difference being the presence of a beta-ketone on the cathinone molecule (Fig. 1; Carroll et al., 2012). The synthetic cathinone mephedrone is produced by replacement of the 4-position aromatic hydrogen of cathinone with a methyl group, and carries a similar molecular structure to many common street drugs including amphetamine and MDMA (Carroll et al., 2012). From 2008–2009, online searches for mephedrone rose exponentially, particularly in the UK and Scandinavia (Psychonaut WebMapping Research Group, 2009). Along with street dealing, the market for mephedrone has extended to the Internet. Multiple websites sell drugs labeled ‘mephedrone’ as well as other synthetic cathinones under the premise that they are a ‘legal-high.’ Street names and pseudonyms for mephedrone range from ‘bath salts’ to ‘plant food’ to ‘bubbles’ (Psychonaut WebMapping Research Group, 2009). The absence of research on the synthetic drugs made initial legislation difficult, and gave short-term truth to the ‘legal-high’ status of mephedrone (Winstock et al., 2011).

While the drug was legal, mephedrone users reported taking between 0.5 and 1 g of drug in a typical session, most commonly by snorting or ingestion (James et al., 2011; Winstock et al., 2011). Typically, the drug takes effect between 15 and 45 min after administration and shows clinical effects for approximately 2 to 5 h (Karila and Reynaud, 2011). Compared to other recreational drugs with similar effects including cocaine and MDMA, users felt that mephedrone had a longer lasting, better high with a reduced risk of addiction (Winstock et al., 2010). These subjective measures are validated by empirical evidence that suggests that the effects of cocaine last between 5 and 30 min, and the effects of MDMA last between 1 and 2 h (National Highway Traffic Safety Administration, 2004). Mephedrone users stated that the effects of the drug are most similar to MDMA, though MDMA was still preferred (Carhart-Harris et al., 2011). After the ban on mephedrone in the UK, multiple web-based surveys investigated the effects of new legislation on continuing use of the drug (Carhart-Harris et al., 2011; Winstock et al., 2011). These studies showed similar results to the initial Winstock et al. (2010) survey, suggesting that the legal status of mephedrone had little impact on user’s habits (Carhart-Harris et al., 2011; McElrath and O’Neill, 2011 Winstock et al., 2011).

Without regulations on sales of designer drugs, the drug’s label does not always reflect its composition. After the initial ban on mephedrone, a new market for second generation ‘legal-highs’ quickly emerged, with new synthetic drugs supposedly taking the place of clearly identified mephedrone packets. Multiple studies have shown that these packets often do not contain the drug that is advertised and frequently include illegal products, including mephedrone (Baron et al., 2011; Brandt et al., 2010). The presence of banned substances in second generation ‘legal highs’ and the continued use of banned drugs reinforces the need to continue to characterize the mechanisms and effects of synthetic cathinones.

Prevalence rates for mephedrone use are extremely difficult to measure due to inaccurate labeling of products, increasing popularity, primarily underground usage, and ineffective objective screening methods. A report by the American National Institute of Drug Abuse in 2011 showed a sharp increase in mephedrone related calls to the Center for Disease Control (National Institute on Drug Abuse, 2011). In Ohio, the number of calls jumped from 2 to 77 between 2010 and May of 2011. Similarly, calls in Texas jumped from 20 to 118 between 2010 and the beginning of 2011. By the time of publication, these estimates are likely inaccurate, and not all of the regions that contributed to the report tracked mephedrone usage. Among the most recent prevalence reports, a study from Australia showed that 5% of regular ecstasy users also used mephedrone in 2012 (Sindicich

![Fig. 1. Molecular structure of mephedrone and related compounds.](image-url)
and Burns, 2012). While this rate is down from 13% usage in 2011, mephedrone remained one of the most used “emerging psychoactive substances” (Sindicich and Burns, 2012).

Research is quickly supplying information about the mechanism of action for mephedrone, how the drug is metabolized, mephedrone-induced behavioral effects, and what long-term effects result from its use. In this review, we aim to describe the current state of mephedrone literature with a focus on the translational aspects of mephedrone use and a particular emphasis on comparing and contrasting mechanisms of action and behavioral effects to structurally and functionally similar drugs.

2. Mephedrone’s mechanism of action

Mephedrone and many other drugs of abuse are sympathomimetic drugs, meaning that they mimic neurotransmitters of the sympathetic central nervous system. Historically, there have been few studies investigating the molecular mechanisms of mephedrone specifically; however, several studies have been published within the last four years likely due to the growing popularity of the drug (Meyer et al., 2010; Schifano et al., 2011). Due to the structural similarities and user substitution of mephedrone for amphetamines and methcathinones, researchers initially hypothesized that mephedrone may act through similar molecular processes as other psychostimulants (Fig. 1). This hypothesis has been supported by several studies (Baumann et al., 2011, 2013b; Meyer et al., 2010; Schifano et al., 2011). For this reason it is beneficial to develop a structure-activity relationship for designer drugs as a whole by means of comparison. Such an understanding can expedite research into novel designer drugs, neuropharmacology, and importantly will likely improve response rates of legislation and expedite research into novel designer drugs, neuropharmacology, and drugs as a whole by means of comparison. Such an understanding can.

One of the best-studied areas of overlap between synthetic cathinones and amphetamines is their similar effects on monoamine reuptake, including serotonin, dopamine, and norepinephrine (Fleckenstein et al., 2007; Johnson et al., 1991; Steele et al., 1987). Several of the synthetic cathinones, including mephedrone, seem to act as monoamine transporter substrates and therefore act more similarly to methamphetamine and MDMA than cocaine (Baumann et al., 2013b). Nagai et al. (2007) demonstrated the ability of two synthetic cathinones, methylone and methylenedioxymethylamphetamine (MBDB), to inhibit monoamine reuptake in a rat brain synaptosome model system (Nagai et al., 2007). Specifically they found that methylone and MBDB elicited an inhibitory effect against dopamine, serotonin, and norepinephrine. In addition, they observed that methylone increased the release of all three neurotransmitters; however, MBDB only increased the release of serotonin and norepinephrine (Nagai et al., 2007). Another study examined transporter potency and selectivity and found that the potency of mephedrone for plasma membrane monoamine transporters was double that of methylone (Baumann et al., 2011). Interestingly, Cozzi et al. (1999) demonstrated that while methcathinone and methylone exhibit similar potency to methamphetamine and MDMA against plasma membrane transport of monoamines, they exhibit a 10-fold less potent vesicular inhibition against VMAT2 (Cozzi et al., 1999). These and other studies strongly suggest that while synthetic cathinones deviate in some aspects of mechanism and effects from amphetamines, they exhibit similar inhibition of monoamine reuptake, which is likely their main mode of action (Cozzi and Foley, 2003; Cozzi et al., 1999; Nagai et al., 2007).

Several studies have been published in the last three years investigating the specific mechanisms of mephedrone. Baumann et al. (2013a) demonstrated that mephedrone, similar to methylone, is a nonselective substrate for plasma membrane monoamine transporters with a similar potency and selectivity to MDMA in a rat brain synaptosome model. Additionally, Martínez-Clementine et al. (2012) supported these findings and demonstrated that mephedrone has a lower IC_{50} against serotonin reuptake than

### Table 1

<table>
<thead>
<tr>
<th>Mechanistic comparison of mephedrone with other drugs of abuse.</th>
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<tbody>
<tr>
<td><strong>Monoamine reuptake inhibitor</strong></td>
</tr>
<tr>
<td>Mephedrone</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Methamphetamine</td>
</tr>
<tr>
<td>MDMA</td>
</tr>
<tr>
<td>Methcathinone</td>
</tr>
<tr>
<td>Methylene</td>
</tr>
</tbody>
</table>

* Norepinephrine was not considered due to its currently underappreciated role for mephedrone.

* References to sources outlining metabolism and metabolites in detail.
dopamine. These authors also showed that in vivo microdialysis of mephedrone or methylene to the rat nucleus accumbens causes dose-related increases in extracellular dopamine and serotonin. Furthermore, they showed that while short-term repeated doses of MDMA cause a persistent depletion of cortical and striatal amines, mephedrone and methylene do not (Martínez-Clementine et al., 2012). This finding may be an important point for future research aimed at elucidating the long-term effects of mephedrone and how they differ from conventional drugs of abuse.

As Saunders et al. (2000) and others have established, many amphetamines impair monoamine signaling in part by inducing internalization of monoamine transporters, specifically the dopamine transporter (DAT) (Fleckenstein et al., 2007; Kokoshka et al., 1998). This mechanism of impairment persists even after the amphetamines have been removed from the medium in cell culture, suggesting that this may be one of the mechanisms that contribute to long-term dopaminergic abnormalities in amphetamine abusers (Fleckenstein et al., 2007; Saunders et al., 2000).

Researchers originally believed that these same dopaminergic toxicities would be observed from mephedrone abuse; however, recent data suggests dopaminergic toxicities may differ. It has been shown that in rat synaptosomes from the cortex or striatum that normal signaling was observed following the removal of administered mephedrone (Martínez-Clementine et al., 2012). This finding suggests that mephedrone does not induce internalization of the transporters under the tested conditions. More evidence in support of a different mechanism of action comes from work by Angoa-Peréz et al. (2012), demonstrating that high doses of mephedrone, consistent with those taken by human binge-users, failed to produce the classical signs of methamphetamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) striatal dopaminergic neurotoxicity at two and seven days post-treatment. Additionally, mephedrone also failed to elicit astrocyte or microglial activation in the striatum as seen in methamphetamine or MPTP toxicity (Angoa-Peréz et al., 2012). These results, along with the molecular data demonstrating that mephedrone inhibits serotonin reuptake more effectively than dopamine reuptake, support the growing hypothesis that mephedrone does not have the same long-term effects on dopamine signaling observed with other amphetamines (Angoa-Peréz et al., 2012; Baumann et al., 2011; Martínez-Clementine et al., 2012; Saunders et al., 2000).

Complicating evidence from McCann et al. (1998) demonstrated similar decreases in striatal DAT density as detectable by positron emission spectroscopy in both 3 years abstinent methamphetamine and 3 years abstinent methcathinone users, as compared to control individuals (3 years was the average period of abstinence across the individuals in the study). This study also compared the abstinent users to patients with Parkinson's disease and noted that while the patients displayed less dense striatal DAT than the abstinent users, the trend of decreasing striatal DAT density was suggestive that long-term methamphetamine and methcathinone users were at a higher risk of reaching a Parkinson's-like level of degeneration (McCann et al., 1998). In addition, methylene has been shown to cause pervasive depletion of serotonin, and mephedrone has been linked to long-term damage to working memory in mice (den Hollander et al., 2012). The structural similarities of methcathinone and methylene with mephedrone suggest that we may still not appreciate the long-term risks of mephedrone use. Despite this, it is known that acute toxicity by high doses of mephedrone, a commonality in its user base, seems to cause common clinical signs of amphetamine toxicity including hyperthermia and serotonin syndrome (Angoa-Peréz et al., 2012; Garrett and Sweeney, 2010; Wood and Dargan, 2012). Future research is required to determine the exact long-term effects of mephedrone and other synthetic cathinones.

3. Methcathinone pharmacology

Traditional views of metabolites focus on their use in identifying substances present in the body after the substances have been partially or fully processed. While these processes are vital in the case of amphetamines due to their frequent polydrug use (e.g., marijuana and alcohol), metabolites hold a greater potential role in the exploration of new designer drugs (Winstock et al., 2010). Modern research highlights the importance of identifying the metabolites of drugs in order to gain a greater understanding of the drug's path through the body and the molecular derivative directly responsible for the drug's effects. Metabolites thus become an important clue when seeking to understand the unidentified pharmokinetic or pharmacodynamic effects of designer drugs. Identification of metabolites allows for comparisons to existing substances, including MDMA, giving potential insights into the mechanisms of new designer cathinones, such as methylene and mephedrone (Hadlock et al., 2011; Kehr et al., 2011).

Gas chromatography-mass spectrometry techniques have been used to identify the metabolites and potential metabolic pathways of both methylene and mephedrone (Winstock et al., 2010). This technology was first used on methylene for which three identified phase 1 metabolites were identified: 3,4-methylenedioxyamphetamine (MDC), 4-hydroxy-3-MeO-methcathinone (HMCC), and 3-OH-4-MeO-methcathinone (3-OH-MeO-MC). The same study also proposed the metabolism of mephedrine, suggesting that the majority of product produced from methylene may be HMCC (Fig. 2; Kamata et al., 2007; Meyer and Maurer, 2010).

In humans, mephedrone is believed to have five phase 1 metabolites. These include normephedrone, nor-dihydro mephedrone, nor-hydroxy mephedrone, hydroxyethyl mephedrone, and 4-carboxy-dihydro mephedrone (Meyer et al., 2010). However, 4-carboxy-dihydro mephedrone is not identifiable in rats after mephedrone exposure and occurs in humans due to further oxidation of nor-hydroxyethyl mephedrone. As seen in Fig. 3, the metabolic pathway of mephedrone is suggested to include N-demethylation to the primary amine, reduction of the keto moiety to an alcohol, and oxidation of the tolyl moiety to the respective alcohol (Meyer et al., 2010).

At present, the roles of the specific metabolites of mephedrone and methylene in the brain are unknown. The initial N-demethylation present in both mechanisms, however, does closely resemble the N-demethylation that occurs in the breakdown of MDMA and methamphetamine to their active, toxic, metabolites 3,4-methylenedioxymethamphetamine (MDA) and amphetamine (Baumann and Rothmann, 2009; Schep et al., 2010; Shima et al., 2009). The prolonged half-lives of these active metabolites, if similar to products of designer beta-ketoamphetamine metabolites, may also help explain the reported occurrences of toxic mephedrone binges (Kehr et al., 2011). A better understanding of the molecular effects of these metabolites may clarify the observed mechanistic similarities between these drugs of abuse in the future.

4. Behavioral implications of synthetic methcathinone analogs

Mephedrone has a wide range of behavioral effects that both imitate and greatly vary from the effects of similar drugs, such as MDMA and methamphetamine (Table 2). Desired, or ‘pleasant,’ effects include stimulated mood and sex drive, while generally unwanted or dangerous effects may include altered levels of consciousness, increased body temperature, elevated heart rates, drug addiction, and full body convulsions (Miyaawa et al., 2011; Winstock et al., 2011). The most commonly reported undesired symptom of synthetic cathinones in behavioral research is a decrease in locomotor behavior. Numerous cases of toxicity
in drug users due to synthetic cathinone ‘binging’ have also been reported (Dargan et al., 2011). Multiple other effects of these drugs, both desired and unwanted, have been reported in humans. Researchers have only recently begun to quantify these effects in rodents and invertebrates in order to more fully understand mephedrone’s behavioral implications, and draw casual relationships between observed phenomena and previously identified mechanisms of synthetic cathinones.

Few studies have focused on the desired effects of synthetic cathinones; however, these effects are particularly important for continuing research due to their role in promoting drug abuse. Case studies frequently report that mephedrone users take the drug for both its mood enhancing properties and its role as a psychomotor stimulant in social situations (Winstock et al., 2010). In rodents, increased prosocial behaviors were also observed by Motbey et al. (2011), who related increased prosocial behaviors in rats and mephedrone treatments via a decrease in social preference for familiar animals. These results were further supported by increased activation of mesolimbic sites, as quantified by c-Fos expression, typically observed with other stimulant drugs, including amphetamine, methamphetamine, cocaine, and MDMA (Motbey et al., 2011). Future research attempting to measure other desired outcomes of these designer drugs, such as testing for elevated mood through a forced swim test, would be beneficial to more fully understand the wide range of effects reported by drug users.

Mephedrone’s propensity for inducing short increases in locomotor behavior in humans has led to it becoming one of the most popular “club drugs” in Europe. Cameron et al. (2012) report that this may be
Table 2
Behavioral effects of mephedrone in comparison with other drugs of abuse, in both humans and rodents.

<table>
<thead>
<tr>
<th>Human</th>
<th>Mephedrone</th>
<th>Drug comparison</th>
<th>Rodent</th>
<th>Mephedrone</th>
<th>Drug comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locomotor</strong></td>
<td>Increased motor activity, reports of seizures (Jerry et al., 2012; Mas-Morey et al., 2012; Winstock et al., 2011)</td>
<td>Acts similarly on hDAT as Meth, increases locomotor activity (Cameron et al., 2012; Cameron et al., 2013)</td>
<td>Short-term hyperlomotion due to increased dopamine and endogenous 5-HT (Angoa-Peréz et al., 2012; Kehr et al., 2011; Lisek et al., 2012; López-Arana et al., 2012)</td>
<td>Shorter than amphetamine, similar to MDMA (Baumann et al., 2011; Kehr et al., 2011; Marusch et al., 2011)</td>
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<tr>
<td><strong>Temperature</strong></td>
<td>Uncomfortable decrease in body temp; cold fingers/toes; Can cause increase (“mephedrone sweat”) (Vardakou et al., 2011; Winstock et al., 2011; Wood and Dargan, 2012)</td>
<td>Similar effects seen in MDMA and other stimulants (Falkowski, 2011; Green et al., 2004a, 2004b)</td>
<td>Transient decrease in temperature (Angoa-Peréz et al., 2012; Hadlock et al., 2011; Shortall et al., 2013)</td>
<td>Shorter than long-term decrease with MDMA dependant on external temperature (Shortall et al., 2012; Shortall et al., 2013; Wright et al., 2012)</td>
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<tr>
<td><strong>Binging</strong></td>
<td>Compulsion to use and addictive behaviors seen in users (Freeman et al., 2012; Schiavo et al., 2011; Winstock et al., 2011)</td>
<td>Users reported that they believe that it is less addictive than cocaine, unless snorting (Winstock et al., 2011) More addictive than MDMA (Brunt et al., 2011)</td>
<td>Rats will self-administer (Hadlock et al., 2011; Kehr et al., 2011; Robinson et al., 2012)</td>
<td>Similar binging and self-administration habits to cocaine and meth (Cornish et al., 2012; Robinson et al., 2012)</td>
<td></td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td>Increased blood pressure, tachycardia (Baumann et al., 2012; Jerry et al., 2012; Winstock et al., 2011)</td>
<td>MDMa can increase blood pressure; 5-HT agonists typically associated with heart toxicity (Dawson and Moffart, 2012; Vollenweider et al., 1998)</td>
<td>Produces hemodynamic effects (Meng et al., 2012; Varner et al., 2012)</td>
<td>MDMA-related to some cardiovascular effects, but not as strongly as mephedrone (Badon et al., 2002; Varner et al., 2012)</td>
<td></td>
</tr>
<tr>
<td><strong>Changes in social behavior</strong></td>
<td>Elated mood, increased impulsivity, psychosis (Freeman et al., 2012; Loefler et al., 2012; Olives et al., 2012)</td>
<td>Similar to other stimulants, users listed as ‘better high’ than cocaine (Van Hout and Bingham, 2012; Winstock et al., 2011)</td>
<td>Decreases social preference, increases conditioned place preference (Lisek et al., 2012; Motbey et al., 2011)</td>
<td>Similar results to MDMA and methamphetamine hybrid (Motbey et al., 2012; Shortall et al., 2012)</td>
<td></td>
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<tr>
<td><strong>Cognitive function</strong></td>
<td>Chronic use: impaired probe recall and cognitive function (Colzato et al., 2012; Freeman et al., 2012) Short term: increased cognitive function similar to other stimulants (Nyberg, 2012)</td>
<td>Similar effects to other stimulants, specifically ecstasy (Freeman et al., 2012; Nyberg, 2012)</td>
<td>Decreases working memory and long-term memory (den Hollander et al., 2012; Motbey et al., 2012)</td>
<td>Similar to other stimulants (Motbey et al., 2012; North et al., 2013)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual behaviors</strong></td>
<td>Sexual disinhibition (Van Hout and Brennan, 2011; Van Hout and Bingham, 2012)</td>
<td>Aphrodisiac properties similar to both natural and synthetic cathinones, stimulants (Bentur et al., 2008; Karila and Reynaud, 2011)</td>
<td>N/A</td>
<td>N/A</td>
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caused by the action of mephedrone on human’s DAT with a similar mechanism to methamphetamine action. Locomotor changes identified in both invertebrates and rodents treated with mephedrone are often less severe compared to similar effects commonly associated with MDMA and methamphetamine (Baumann et al., 2011). These behaviors include increases in overall ambulation and stereotyped movement, and are closely related to serotonergic and dopaminergic bursts, coupled with decreased neurotransmitter re-uptake, elicited by drug intake. In invertebrates, introduction of mephedrone produced stereotyped movements that were diminished via a dopamine receptor antagonist, and conditioned place preference (Ramoz et al., 2012). Rodents demonstrated similar significant increases in stereotyped movement in response to mephedrone (Baumann et al., 2011; Kehr et al., 2011) that have been inconsistently reported in response to high concentrations of methylene (Miyazawa et al., 2011). However, both synthetic cathinone analogues led to increased general locomotor activity in comparison to control animals in both open-field tests and measurements of rearing behaviors (Baumann et al., 2011; Miyazawa et al., 2011; Motbey et al., 2011).

Acute increases in locomotor activity due to synthetic cathinones closely resemble the effects of MDMA, but fall short of the long-term change in locomotor behavior observed in animals treated with amphetamines or methamphetamine. These differences may be attributed to role of amphetamines in the activation of dopaminergic and noradrenergic systems (Baumann et al., 2011; Kehr et al., 2011). Furthermore, the short increase in locomotor activity may be due to a rapid release of dopamine and serotonin in the nucleus accumbens observed after injections with both mephedrone and MDMA (Kehr et al., 2011).

Another commonly observed effect of synthetic cathinones in both humans and rats is severe hyperthermia, which may be related to the incidences of mephedrone-induced serotonin syndrome in humans. Serotonin syndrome occurs as a result of serotonin toxicity and is associated with autonomic instability, significant changes in mental status, and neuromuscular hyperactivity and has been observed in individuals who have taken mephedrone (Thanascoody, 2012). In studies on MDMA and serotonin syndrome, hyperthermia has been heavily implicated as a contributing factor in serotonin depletion (Green et al., 2004a, 2004b). Although current literature consistently identifies increases in core body temperature in rodents after administration of mephedrone, it is still unclear whether increases in core body temperature cause significant long-term serotonin deficits to lead to serotonin syndrome. Baumann et al. (2011) indicate that, while rats treated with high-dose mephedrone demonstrate the acute locomotor activity increases characteristic of serotonin syndrome, they fail to show the appropriate type of locomotor activity due to increased rearing and do not show sustained serotonin deficits. However, Hadlock et al. (2011) utilized high doses of mephedrone in rats housed socially in warmer temperatures, meant to imitate the warmth of the ‘club’ atmosphere in which humans utilize mephedrone, and identified significant serotonin deficiencies a week after mephedrone injections. Due to a lack of data concerning the average
dose of mephedrone required for serotonin syndrome symptoms in humans, it is also currently impossible to determine if dosages utilized in laboratory studies appropriately mimic dosage effects observed in humans (Winstock et al., 2011).

Clinicians and researchers alike have observed the propensity of users and subjects to mephedrone ‘binges’ and subsequent withdrawal behaviors indicative of drug addiction. Humans do not typically report that they are undergoing withdrawal; however, addiction (quantified by drug cravings) and uncontrolled binging behaviors (due to increased drug tolerance) are commonly noted (Freeman et al., 2012; Schifano et al., 2011; Wood et al., 2010). Withdrawal behaviors have been observed in planarians, as evidenced by reduced motility in the absence of mephedrone (Ramoż et al., 2012). Addiction has also been reported in rats in studies on mephedrone, as evidenced through self-administration of these drugs. Recently, Hadlock et al. (2011) reported that rats increased their mephedrone consumption over a period of eight days at a higher rate than rats allowed to self-administer methamphetamine. While these results may be due to significantly higher levels of dopamine release in response to methamphetamine, they still reveal potential for subjects to gain tolerance to synthetic cathinones. This moderate dopamine release, accompanied by inhibition of dopamine reuptake, may increase the risk of ‘binge’ behaviors (Kehr et al., 2011).

A significant amount of research is still needed in order to fully quantify both the short and long-term effects of synthetic cathinones. While steps towards this goal have been taken with recent research implicating mephedrone in reports of cardiovascular toxicity among drug abusers via increases in heart rate and blood pressure (Meng et al., 2012), symptoms reported on medical reports of mephedrone fatalities need to be further examined in order to determine the most fruitful treatments for individuals experiencing mephedrone addictions. Recent studies have also begun to investigate changes in sexual behavior and memory reported in relation to mephedrone use in both humans and rodents (see Table 2 for references). Increasing sales of impure mixtures of synthetic cathinones, typically labeled ‘bath salts,’ also demand a basic understanding of individual drug mechanisms and behavioral consequences.

5. Discussion

Not surprisingly, the growing body of literature on mephedrone suggests both a number of similarities and distinctions between designer drugs and more traditional drugs of abuse. Research shows that mephedrone effects monoamine reuptake like many other stimulants, but inhibits serotonin more strongly than dopamine. This difference between mephedrone and other amphetamines likely accounts for the differences in dopamine toxicity, but may also cause ‘serotonin syndrome.’ Considering the association between MDMA and serotonin syndrome, the short-term behavioral effects of mephedrone mirror traditional drugs of abuse; however, the long-term behavioral effects are not maintained after mephedrone use in the same way as the effects are maintained after MDMA use. Many questions remain regarding the long-term effects of mephedrone use, but research currently suggests that mephedrone does have an addictive quality. Furthermore, research into another synthetic cathinone, methcathinone, shows long-term deleterious effects. Due to many structural and mechanistic similarities between methcathinone and mephedrone, it should be hypothesized that mephedrone has some degree of long-term deleterious effects as well.

Despite the current growing literature base for mephedrone research, certain areas require more attention. In this review, we have already suggested the need for continued research on the long-term effects of mephedrone use, the metabolic pathway of mephedrone and how each metabolite contributes to the mechanism of action, and finally how the desired effects of the drug may affect mephedrone's addictive qualities. In addition to these research paths, we suggest that more attention be given to potential polydrug interactions. Mephedrone and other synthetic cathinones are considered “club drugs,” meaning that they are often taken as part of the nightlife scene with alcohol, marijuana, and other polydrug combinations. Case reports are surfacing which suggest that mephedrone may have potentially fatal interactions with some of these common polydrug combinations. A two patient case study warns that large quantities of alcohol consumed with mephedrone may lead to serious cardiac arrhythmias (McGaw and Kankam, 2010). Another case report suggests that heroin and mephedrone can have a potentially fatal interaction, though without additional research the actual contribution of each drug to the death of an individual cannot be measured (Dickson et al., 2010). While each of these assertions is the result of individual case studies, it is important to realize that mephedrone and other synthetic cathinones will likely have adverse interactions with many drugs. Considering the likelihood that mephedrone will be taken as part of a polydrug combination, drug interactions will be increasingly important in treatment of mephedrone users.

6. Conclusions

While the rise in mephedrone use may not be permanent, research on mephedrone and other synthetic cathinones remains extremely important. Drug makers and users are shifting toward a designer drug mindset, where it is difficult for law enforcement and regulatory offices to keep up with the chemicals that are created. While all designer drugs will not have the same effects and interactions, working knowledge of the mechanisms and behavioral responses of an individual drug will likely assist and guide research of others. Additionally, first generation designer drugs including mephedrone continue to appear in new ‘legal-highs’. Individuals are unknowingly taking mephedrone that has simply been repackaged and rebranded. Thus far, mephedrone use has not been seriously affected by its legal status and it appears to be a common product for designer drug manufacturers, which suggests that long-term mephedrone use will continue.

Designer drugs, specifically synthetic cathinones, constitute a very real threat to public health for which the scientific community will be asked to provide assistance and knowledge. Moving forward, a key component of informative research lies in the ability to identify relevant similarities to promote quick legislation and observe relevant differences to aid successful treatment of the complications associated with mephedrone usage. We suggest researchers continue to focus on the translational aspects of designer drugs to avoid slowing down the research process and policymaking as each new designer drug is produced.

References


