The Journal of Emergency Medicine, Vol. 46, No. 5, pp. 632–642, 2014

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2013.11.104

Selected Topics: Toxicology

SYNTHETIC CATHINONES ("BATH SALTS")

Matthew L. Banks, PHARMD, PHD,* Travis J. Worst, PHD,† Daniel E. Rusyniak, MD,‡ and Jon E. Sprague, PHD§

*Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, †Ohio Attorney General's Bureau of Criminal Investigation, London, Ohio, ‡Departments of Emergency Medicine and Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana, and §Department of Pharmaceutical Sciences, College of Pharmacy, Ferris State University, Big Rapids, Michigan

Reprint Address: Jon E. Sprague, PHD, Department of Pharmaceutical Sciences, College of Pharmacy, Ferris State University, 220 Ferris Drive, Big Rapids, MI 49307

☐ **Abstract—Background: Synthetic cathinones are popularly referred to in the media as "bath salts." Through the direct and indirect activation of the sympathetic nervous system, smoking, snorting, or injecting synthetic cathinones can result in tachycardia, hypertension, hyperthermia, myocardial infarction, and death. Objective: The chemical structures and names of bath salts identified by the Ohio Attorney General's Bureau of Criminal Investigation are presented. Based on their common pharmacophores, we review the history, pharmacology, toxicology, detection methods, and clinical implications of synthetic cathinones. Through the integration of this information, the pharmacological basis for the management of patients using synthetic cathinones is presented. Discussion: Synthetic cathinones activate central serotonergic and dopaminergic systems contributing to acute psychosis and the peripheral activation of the sympathetic nervous system. The overstimulation of the sympathetic nervous system contributes to the many toxicities reported with bath salt use. The pharmacological basis for managing these patients is targeted at attenuating the activation of these systems. Conclusions: Treatment of patients presenting after using bath salts should be focused on reducing agitation and psychosis and supporting renal perfusion. The majority of successfully treated synthetic cathinones cases have used benzodiazepines and antipsychotics along with general supportive care.**

☐ **Keywords—sympathomimetic; synthetic cathinones; amphetamine; phenethylamine; bath salts**

INTRODUCTION

Phenylisopropylamine and α-methylphenethylamine are chemical names for the clinically used but also commonly abused medication amphetamine. Amphetamine was initially synthesized in 1887 by the German chemist Edeleano as part of a series of compounds to improve upon ephedrine (1). Amphetamine is a synthetic compound that is not based on a natural product like ephedrine. Physicians noted the potential for amphetamine abuse and addiction, even in the context of medical use, as early as the 1940s (2). Amphetamine and its N-methyl analogue methamphetamine were used extensively by both Japanese and German armies to stimulate soldier efforts during World War II (3). After the war, Japan made amphetamines readily available without a prescription. Subsequently, the rates of amphetamine abuse and addiction escalated (4). In the United States, the initial epidemic of amphetamine abuse emerged in the 1960s, and regulatory efforts that included classifying amphetamine as a Schedule II controlled substance under the Controlled Substance Act and increasing regulatory control over the manufacturing and distribution of amphetamine were marginally effective (5). However, as regulatory and law enforcement officials focused efforts to reduce amphetamine abuse, an amphetamine analogue 3,4-methylenedioxymethamphetamine (MDMA) began to emerge in the illicit drug scene (6).

RECEIVED: 23 July 2013; FINAL SUBMISSION RECEIVED: 11 October 2013;
ACCEPTED: 17 November 2013

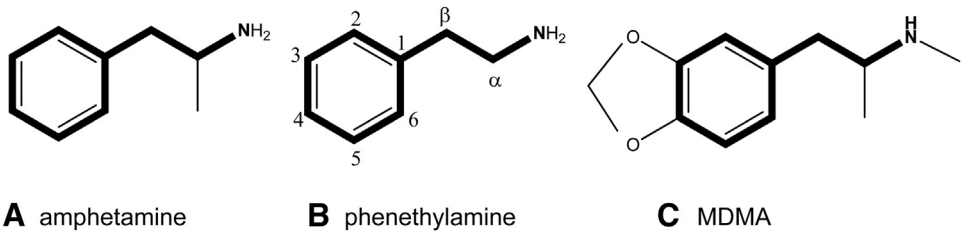

Figure 1. General chemistry of phenethylamine, amphetamine and 3,4-methylenedioxy-methamphetamine (MDMA). The phenethylamine pharmacophore is bolded in each of the structures. The α and β-carbons are the sites of many substitutions to the "bath salts."

MDMA was first synthesized in 1912 by Merck Pharmaceutical, but the compound remained largely ignored by both the scientific community and illicit drug users until the late 1970s, probably because of the availability of amphetamine and methamphetamine (7). In one of the first scientific reports, Shulgin et al. noted that MDMA induced an "easily controlled altered state of consciousness with emotional and sensual overtones" (8). These pharmacological effects of MDMA were in stark contrast to the hyperarousal, compulsive and sometimes paranoid behaviors from amphetamine use (9). Reasons for these differential pharmacological effects between MDMA and methamphetamine are ostensibly linked to the chemical structure differences (discussed in the next section). MDMA was placed on the Drug Enforcement Agency's Schedule I list of controlled substances in 1985 (10).

Presently, the latest versions of sympathomimetic compounds to emerge as abused drugs are the synthetic cathinone derivatives. Cathinone is a naturally occurring β-ketone analogue of amphetamine found in the leaves of the *Catha edulis* plant indigenous to northeast Africa and the Arabian Peninsula. Methcathinone, the N-methyl analogue of cathinone, was first synthesized in 1928 (11). These compounds are commonly classified in the popular media as "bath salts" because of the packaging and distribution techniques used by the illicit manufacturers to circumvent the Federal Analog Act. These synthetic cathinone compounds are not chemically or pharmacologically similar to epsom bath salts, but are central nervous system active drugs that are chemically and pharmacologically similar to amphetamine and MDMA.

CHEMISTRY AND HOW IT PREDICTS PHARMACOLOGY

The chemical structure of amphetamine and MDMA are shown in Figure 1 and are presented in order to identify the region of the substance known as the pharmacophore. The pharmacophore of a chemical structure is the portion of the structure that confers the substance's activity. In the case of amphetamine and MDMA, these drugs have the exact same pharmacophore (phenethylamine; see Figure 1). Because of this, MDMA would be considered a chemical analogue of amphetamine. Comparing the three structures further, the phenethylamine pharmacophore can be identified in all agents. Amphetamine has the addition of a methyl group off the α-carbon; hence the chemical name for amphetamine is α-methylphenethylamine. MDMA has the addition of the methyl group off the terminal amine generating the methamphetamine portion of the molecule. Increasing carbon substitutions has the ability to increase lipophilicity and, in some cases, protect against enzyme degradation. MDMA further has the methylenedioxy substitution off the three and four carbons. All these substitutions are responsible for MDMA's chemical name, 3,4-methylenedioxy-methamphetamine. Therefore, amphetamine and MDMA would have a predictably similar pharmacological activity (12,13).

The synthetic cathinones are chemical analogues of methcathinone and are classified chemically as β-ketone due to the carbonyl group (=O) at the β-carbon (see Figure 2). The synthetic cathinones also differ between each other in the length of carbon substitutions off the α-carbon and nitrogen (N) terminus. Through the addition of electron withdrawing groups such as fluorine (F) or increasing carbon length, the lipophilic nature of the synthetic analogue can be increased. The addition of carbons to the N-terminus is referred to as N-alkylation. N-alkylation maintains the stimulant activity of phenethylamine analogues (14–16).

Based on the structure–activity relationships of these phenethylamine analogues, synthetic cathinones and MDMA analogues would be predicted to have very similar pharmacological effects. Table 1 presents the chemical structures and names of novel bath salts identified by the Ohio Attorney General's Bureau of Criminal Investigation. Not all the agents listed in Table 1 have been pharmacologically tested in controlled human or animal studies. Most of the agents presented have also not been scheduled by the Drug Enforcement Administration. However, these synthetic cathinones, in general, have been shown to increase monoamine concentrations in the synaptic