

## “Bath Salts” and the Return of Serotonin Syndrome

J. J. Rasimas, MD, PhD

Changing trends in drug abuse present diagnostic and therapeutic challenges in psychiatry. Issues surrounding synthetic stimulants highlight a convergence of both new and old clinical problems. Although “bath salts” (or “plant food”), named for their white crystalline-pellet appearance, are the latest class of widely available abusable substances, they have ancient, natural origins.

The majority of psychoactive substances in these products are cathinones—derivatives of phenethylamines found in the khat (also *gat* and *qat*) plant, *Catha edulis*. Natives of East Africa and the Arabian Peninsula have chewed the leaves of this shrub for centuries to experience a combination of stimulation and relaxation in a manner that is at least widely tolerated, if not socially sanctioned. Interestingly, the demographic group that indulges in this practice in Ethiopia, Egypt, Saudi Arabia, and elsewhere is analogous to those who most commonly abuse synthetic derivatives of the same in the West—mostly unmarried men in their early 20s to late 30s.<sup>1</sup>

Synthetic cathinones are available in concentrated form, having been chemically modified to enhance their central nervous system effects and packaged for global marketing and distribution via the Internet. Some legislation has been passed to make these more potent and addictive psychostimulants illegal in similar fashion to the cocaine and methamphetamine they cheaply replace. Regulation, however, may be even more challenging than with those familiar illicit substances, since information, advertising, and materials delivery all move so rapidly in the electronic marketplace.

Despite all of what is new about this class of compounds, the case reported by Joksovic and colleagues<sup>2</sup> highlights how bath salts produce a rather old and sometimes forgotten medical problem. In the definitive volume of psychosomatic medicine, serotonin syndrome is called “an uncommon but potentially life-threatening complication of treatment with serotonergic agents,”<sup>3(p969)</sup> and recent editions of the largest comprehensive textbook<sup>4</sup> of modern psychiatry give it little more than a paragraph of attention. It is true that standard pharmacologic care and therapeutic dosing of antidepressants and other drugs rarely produce serotonin syndrome. It is also true that severe serotonin toxicity is rare in settings where the majority of psychiatrists practice. Psychiatric patients, however, especially those with substance abuse comorbidity, are frequently found in medical hospitals with this syndrome. In emergency departments, general wards, and intensive care units, these patients are cared for by physicians for whom

the diagnostic term *serotonin syndrome* is not commonly employed to describe what they see. What they see, though, is exemplified by the case Joksovic et al<sup>2</sup> describe—a picture of autonomic excess, neuromuscular excitability, and psycho-behavioral unrest all referable to the toxic effects of substances that enhance the activity of monoamine neurotransmitters. If the agents responsible for these states of agitated delirium are known, diagnoses are typically rendered in terms of those compounds (eg, “dextromethorphan intoxication”) or simply labeled as an adverse drug reaction or overdose.

This illustrative case is most important, however, in how it reminds us to care for the acutely altered patient with toxicologic causes in mind even when the causative agent is not obvious. The face of substance abuse is ever-changing, and more rapidly now in the Internet age with free flow of both commerce and recipes for chemical synthesis. However, the human brain, with all its desires and vulnerabilities, is not evolving so rapidly; thus, the substances chosen for such misuse continue to produce recognizable pathophysiologic patterns. This means that since enhanced monoamine activity alters perceptions, energy, and goal-directed activity in desired ways, compounds that may not be well known to clinicians or yield any relevant findings on drug screening assays will be used recreationally and sometimes cause serotonin syndrome. In a patient with acute delirium, autonomic excess, and hyperreflexia (clonus), serotonin toxicity is the most likely cause. And those individuals, who demand prompt diagnostic recognition and aggressive treatment, will more often be psychiatric patients who already take medications we prescribe.

In 2008, a study<sup>5</sup> conducted by acute care toxicologists with serotonin syndrome in their diagnostic lexicon identified cocaine use in a patient concurrently taking a selective serotonin reuptake inhibitor as the most common cause of serotonin toxicity in bedside practice. This finding highlights what we have known for some time about serotonin syndrome: that it is more likely to emerge in patients exposed to agents that simultaneously enhance serotonin activity by multiple mechanisms.<sup>6</sup> That same toxicology service began caring for patients who admitted to using bath salts shortly after the cathinones leapt from the club scene in Europe to the East Coast of the United States at the end of the last decade. Standard urine drug screens in such patients were generally negative for psychostimulants and occasionally showed a positive result for phencyclidine (due perhaps to assay cross-reactivity or to actual comorbid use). Many of the patients presented with features consistent with serotonin excess and were managed as such. After specialized laboratory testing became available to the practice, many cases confirmed by advanced toxicologic testing showed that patients had ingested mephedrone, methylone, or methylenedioxypyrovalerone (MDPV) and no phencyclidine, and the majority of them met the most widely

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Corresponding author: J. J. Rasimas, MD, PhD, NIMH Experimental Therapeutics and Pathophysiology Branch, 10-CRC, Room 7-5541, 10 Center Dr, MSC 1282, Bethesda, MD 20892-1282 (rasimasj@mail.nih.gov).

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accepted criteria<sup>7</sup> for serotonin syndrome. This finding makes pharmacologic sense, as the cathinones listed above enhance serotonin activity via multiple mechanisms in and of themselves; they act like medicinal psychostimulants to enhance monoamine release and block monoamine reuptake to some degree, and they may act as direct agonists of both dopamine and serotonin receptors, as well.<sup>8</sup> Medical toxicologists successfully treat the acute problems of agitation, hypertension, tachycardia, hyperthermia, acidosis, hypertonicity, rhabdomyolysis, and associated renal injury with benzodiazepines, intravenous fluids, and cooling measures. Deaths in bath salts cases typically occur only when patients present or are diagnosed late, or when there is severe comorbid risk to health such as opioid coingestion, accompanying trauma and blood loss, or underlying cardiac disease.<sup>9-12</sup>

A feature of toxicity from synthetic cathinones that is of additional relevance to psychiatric practice is reflected even in cases that do not meet Hunter criteria<sup>7</sup> for serotonin syndrome at the time of presentation. Joksovic et al<sup>2</sup> also noted this problem in their case report. Synthetic cathinones will produce psychosis, and patients will frequently describe the symptoms and associated affective states as being highly unpleasant. Furthermore, both psychosis and nondelusional agitation can persist even after the autonomic storm has passed. So, while the cornerstone of early pharmacologic treatment for bath salts toxicity is benzodiazepines, these lingering psychiatric symptoms can require treatment with antipsychotic medication and even demand mental health hospitalization, depending on severity and safety risk. Psychosis typically resolves between 1 and 4 days after bodily symptoms have abated, but there are reports of thought disorder persisting for weeks.

Anecdotally, after they recover acutely, some patients indicate that despite the low cost and availability of bath salts, they do not intend to return to using these substances because of the intense dysphoria, frightening hallucinosis, and paranoia they have experienced. Without long-term follow-up, however, it is unclear if such patients abstain, switch choice of substances, or are drawn back to bath salts by the addictive power of these mixtures. It is clear that synthetic cathinones have high addiction potential, as more than half of mephedrone users in one survey study<sup>13</sup> reported tolerance with continued use; ongoing cravings to indulge despite adverse consequences were frequent, and withdrawal symptoms (eg, tiredness, difficulty concentrating, depression) were common after abstinence.

So, in addition to the reminder that serotonin syndrome is not as uncommon as we may believe if our psychopharmacologic practice experiences do not extend to the emergency setting, cathinone toxicity cases should emphasize the importance of both collaboration and prevention. We as psychiatrists should be prepared to assist medical colleagues in the complex psychosomatic management of these patients. It is important to recognize the manifestations of serotonin syndrome that cannot be adequately treated in contemporary psychiatric settings, but it is equally important to be willing to take on the care of acute, ongoing psychosis precipitated by bath salts that

is no longer best addressed in the medical hospital. And, if we have the opportunity to consult directly in medical settings, knowledge of this pattern of physical and mental symptoms produced by the synthetic cathinones can aid in differential diagnosis and cooperative treatment planning.

With respect to prevention, the demands are clear. In light of new trends in the availability and use of addictive substances, we must stay current in the language of drug abuse and have open care discussions with our patients about their choices, symptoms, and struggles. The case report by Joksovic et al<sup>2</sup> illustrates an area of medical practice in which professionals (including those in mental health) frequently lag behind the public with respect to their knowledge about and comfort with the topic.

Compounds like bath salts pose increased risk of an old and easily forgotten but serious syndrome, especially considering the inconsistency in doses of substances synthesized and packaged for sale without regulated quality control. Combine these drugs with a prescribed antidepressant or other serotonergic agent, and a well-meaning psychopharmacologist may become an unwitting partner with the patient in a toxic overdose.

**Drug name:** haloperidol (Haldol and others).

**Author affiliations:** Experimental Therapeutics and Pathophysiology Branch, Division of Intramural Research Programs, National Institute of Mental Health, Bethesda, Maryland; and Departments of Psychiatry and Emergency Medicine (Hershey, Pennsylvania) and PinnacleHealth Toxicology Program (Harrisburg, Pennsylvania), Penn State College of Medicine.

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## REFERENCES

- Spiller HA, Ryan ML, Weston RG, et al. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)*. 2011;49(6):499-505.
- Joksovic P, Mellos N, van Watum PJ, et al. "Bath salts"-induced psychosis and serotonin toxicity. *J Clin Psychiatry*. 2012;73(8):1125.
- Levenson JL, ed. *Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill*. Washington, DC: APA Publishing; 2011.
- Tasman A, Kay J, Lieberman JA, et al, eds. *Psychiatry*. West Sussex, England: John Wiley and Sons; 2008.
- Kirschner RI, Cimikoski WJ, Donovan JW. Drug combinations associated with serotonin syndrome in patients admitted to a toxicology treatment center. *Clin Toxicol*. 2008;46:612.
- Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
- Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642.
- Hill SL, Thomas SH. Clinical toxicology of newer recreational drugs. *Clin Toxicol (Phila)*. 2011;49(8):705-719.
- Dickson AJ, Vorce SP, Levine B, et al. Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. *J Anal Toxicol*. 2010;34(3):162-168.
- Lusthof KJ, Oosting R, Maes A, et al. A case of extreme agitation and death after the use of mephedrone in the Netherlands. *Forensic Sci Int*. 2011;206(1-3):e93-e95.
- Maskell PD, De Paoli G, Seneviratne C, et al. Mephedrone (4-methylmethcathinone)-related deaths. *J Anal Toxicol*. 2011;35(3):188-191.
- Murray BL, Murphy CM, Beuhler MC. Death following recreational use of designer drug "bath salts" containing 3,4-methylenedioxypropylvalerone (MDPV). *J Med Toxicol*. 2012;8(1):69-75.
- Winstock A, Mitcheson L, Ramsey J, et al. Mephedrone: use, subjective effects and health risks. *Addiction*. 2011;106(11):1991-1996.