



## Interactions Between Pain Medications And Illicit Street Drugs

To prevent fatal drug-drug interactions, a clinician who suspects illicit drug use should rule out their presence before prescribing pain medications, as well as other commonly known CYP 450 inhibitors or inducers.

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**F**atal drug interactions between opioids and benzodiazepines, alcohol, and other sedative-hypnotic drugs have been well publicized and studied. Less publicized, however, are serious and potentially fatal drug interaction between pain medications and illicit drugs, including the ever-growing number of novel street drugs. In fact, the specific pharmacologic interactions between prescription medications commonly prescribed for pain and habitually abused illicit drugs have not been studied extensively.

When a person dies from a drug overdose, medical examiners frequently look at results from a standard detectable prescription drug(s) panel and a standard illicit substance of abuse panel. This latter panel includes commonly abused

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chemicals that are predetermined by specific manufacturers' test kits. Closer scrutiny, however, could help clarify a patient's opioid tolerance level by reviewing prescription drug history—a simple task that, in the authors' experience, generally is not considered. But, additive or synergistic effects from untested synthetic compounds, such as cathinones (bath-salts) or JWH-type cannabinoids, increasingly are the unsung culprits causing or contributing to death.<sup>1</sup> Medical examiners, unfortunately, don't routinely test for these; if they do, commercially available assays have not reliably kept up with frequent chemical alterations by savvy street chemists that make it more difficult to determine causation.<sup>2,3</sup> In the end, cardiorespiratory collapse and other findings often are attributed to opioids without considering other factors,

especially undetected synthetics.<sup>4,5</sup>

Numerous peer-reviewed journals have published case reports describing adverse effects and deaths associated with illicit substances, including novel and ever-changing synthetic derivative agents of abuse.<sup>6-28</sup> Many of these reports recommend that synthetics be included in the differential diagnosis, although they acknowledge that non-definitive immune assay (IA) urine drug tests (UDTs) frequently will be negative for prescription drugs, cannabinoids, and synthetics. The reason for these pervasive false negatives is that the current forensic use of in-office IA UDTs, which detect only classes of drugs but not individual drugs, is not definitive and not chromatography based. It would seem prudent and logical, therefore, that physicians and other clinicians validate the presence of illicit substances or the lack thereof by integrating policy standards requiring confirmatory, definitive testing by gas or liquid chromatography mass spectrometry (GC-MS or LC-MS), even when in-office testing yields a negative result.

This review highlights the potentially serious drug interactions between commonly used illicit drugs and the newer synthetic drugs of abuse when they are combined with prescription medications. Available evidence regarding such interactions, as well as the primary mechanisms of action for various illicit agents, will be reviewed.

### Drug Overdoses

We used keyword and medical subject headings (MeSH) terms in PubMed, Google Scholar, DrugCite, and MedWatch databases to identify case reports of drug overdoses and interactions of prescription medications with each illegal, synthetic, or traditional drug of abuse. Keywords included drug interactions, drug overdose, as well as the prescription medication

names combined with the names for each substance of abuse. All results were reviewed for relevance and included if the case report attributed the adverse reaction to the specific drug of abuse as the “primary” cause with a high degree of probability.

Available evidence, summarized in Table 1 (starts on page 56), includes street names, mechanisms of action, acute effects, health risks, and specific drugs that may potentiate the risk for serious toxicity if combined with the illicit drugs. The toxic mechanism is listed, if known, as are potential outcomes. Lastly, the table addresses limitations of standard IA UDT compared to definitive testing with GC-MS or LC-MS. The reliance on case reports, even from trustworthy sources such as poison control centers and FDA’s MedWatch, reflects the disturbing lack of data on these potentially fatal drug interactions, which are alarming considering that many of medications discussed are among the most widely prescribed.<sup>29</sup>



### Marijuana

The active ingredient of marijuana is delta-9-tetrahydrocannabinol (THC), a partial agonist binding to cannabinoid (Cb) type 1 receptors in the brain. THC causes various acute effects including anxiolytic and sedative effects, analgesia, and appetite stimulation.<sup>30-32</sup> Common adverse effects include blurred vision, dizziness, xerostomia and xerophthalmia

(dry mouth and eyes), hallucinations, tachycardia, hypotension, hypertension, memory loss, somnolence, and urinary retention.<sup>30</sup>

THC is metabolized via the cytochrome P (CYP) 450 system as substrates of 3A4, 2C9, and, when smoked, can induce 1A2. THC is detectable in the urine for at least 3 days after a single use and up to 27 days with chronic use.<sup>30</sup>

There are many documented interactions between marijuana and prescription, non-prescription, and illicit substances. Some drug concentrations are increased by THC (ie, lithium) and some are decreased (ie, protease inhibitors, various xanthines including theophylline). This may result in additive central nervous system (CNS) depression or sedation, especially when marijuana is used with barbiturates, anticholinergic agents, and alcohol or other CNS depressants. More serious interactions have resulted in tachycardia and delirium when cannabis is combined with tricyclic antidepressants and cyclobenzaprine, and myocardial infarction (MI) when cannabis is combined with sildenafil (Viagra).<sup>30</sup> Combining warfarin and THC displaces protein binding and has resulted in very serious bleeding requiring hospitalization.

### Synthetic Cannabinoids

Synthetic cannabinoids (Spice, K2) are full agonists at endogenous Cb type 1 and type 2 receptors.<sup>32</sup> Numerous reports in recent years of serious adverse effects highlight the need for increased scrutiny with both marijuana and synthetic cannabinoids. Some of the cases have involved pulmonary infiltrates, acute kidney injury, MI, seizures, coma, and severe psychiatric effects, including suicidal ideation and self harm. Some evidence suggests that frequent use can precipitate psychotic symptoms in susceptible individuals perhaps unmasking an underlying psychiatric disorder.<sup>16-20,33-36</sup>



Please note that a number of synthetic cannabinoids are being studied for approval by the Food and Drug Administration. Probably the best known is Sativex, a cannabinoid that is approved in Canada for the treatment of spasticity due to multiple sclerosis. Sativex is also being studied for the treatment of cancer pain and neuropathic pain. These agents will be studied for efficacy, pharmacokinetic and pharmacodynamics effects, as well as potential drug-drug interactions prior to approval.



### Methamphetamine

Methamphetamine is the active metabolite of amphetamine.<sup>30</sup> Amphetamines inhibit the presynaptic reuptake of dopamine, serotonin, and norepinephrine, resulting in euphoria, increased alertness, decreased appetite, and heightened libido.<sup>3,37</sup> Amphetamines are metabolized via CYP 2D6 demethylation and are eliminated primarily by the kidneys within 24 hours (62%).<sup>30</sup> Common adverse effects

of amphetamines include hypertension, hyperthermia, tremor, arrhythmia, and stroke.<sup>30</sup> Even without considering interactions of amphetamine with other agents, amphetamine use is associated with significant cardiovascular effects (it is associated with quadruple the risk for stroke and double the risk for intracranial hemorrhage as cocaine).<sup>38</sup>

Problematic interactions between amphetamines and numerous prescription medications, particularly those that potentiate the mechanism of action of the stimulant (ie, tricyclic antidepressants, monoamine oxidase inhibitors [MAOIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs]) have been noted. When amphetamines are combined with these agents, interactions can result in hypertension, CNS stimulation, hypertensive crisis, and possibly stroke, MI, and/or aneurysm. When combined with opiates, amphetamines potentiate the sense of euphoria. Amphetamines can decrease the respiratory depression seen with opioid overdose. Amphetamines also counter the sedative effects of triazolam and other benzodiazepines, but do not reverse the cognitive impairment.

The efficacy of antiretrovirals (ART) used to treat HIV, such as ritonavir, is decreased when these agents are combined with amphetamines, potentially compromising ART therapy for HIV patients. Quetiapine (Seroquel), and other serotonergic drugs, can interact with amphetamines, resulting in priapism.<sup>39</sup> The efficacy of the smoking cessation drug varenicline (Chantix) also is reduced with concomitant administration of amphetamines.

### MDMA

MDMA (3,4 methylene-dioxy-N-methyl-amphetamine), or Ecstasy, is a CNS stimulant that is structurally similar to methamphetamine and mescaline.<sup>30</sup>



MDMA use can induce hallucinations. The major toxicities of MDMA, which result from excessive production of serotonin, are hypertension, hyperthermia, tremor, and memory loss. More serious adverse effects include rhabdomyolysis (breakdown of muscle fiber and release into the blood) and acute renal failure.<sup>30</sup> MDMA is metabolized via CYP 2D6, and acts as a 2D6 inhibitor.<sup>30</sup> Despite the clinical relevance of CYP 2D6 metabolism of MDMA, 75% of the dose is excreted through the kidneys unchanged.<sup>30</sup>

Serious drug-drug interactions have been reported when MDMA and the MAOI meclizemide were combined, including serotonin syndrome that resulted in several deaths. This finding suggests that MDMA increases serotonin or inhibits 2D6; this could also present serious risks when MDMA is combined with SSRIs.<sup>30</sup> An AIDS patient died when he took MDMA with ritonavir, a CYP 2D6 inhibitor.<sup>30</sup>

### Cocaine

Cocaine is used topically as a local anesthetic, but it causes systemic increases of dopamine, serotonin, norepinephrine, and acetylcholine at pre-synaptic nerve terminals. The euphoria experienced with cocaine use is associated with dopamine accumulation in the mesocortical and mesolimbic pathways.<sup>40,41</sup> Catecholamine release results in vasoconstriction and CNS stimulation. These effects result in numerous adverse events,



including surges in blood pressure, stroke, vasospasm, thromboemboli, and aneurysms.<sup>37,40,42-44</sup>

Cocaine is metabolized primarily in the liver via CYP 3A4, but it strongly inhibits CYP 2D6. Cocaine's half-life is 1 hour, but its vasoconstrictive metabolites can last for days.<sup>42</sup> In addition, cocaine is eliminated by the kidneys, but only 10% is excreted unchanged.<sup>30</sup>

According to the American Heart Association,  $\beta$ -blockers should be avoided when treating cocaine-associated MI because they can increase blood pressure and decrease coronary perfusion.<sup>7,45</sup> Dangerous elevations in blood pressure have been seen when cocaine is combined with amphetamines, MDMA, lidocaine, and MAOIs.<sup>30</sup> Class I antiarrhythmic agents and methadone when combined with cocaine have resulted in rhythm abnormalities (QTc prolongation) and arrhythmias.<sup>8</sup> Interestingly, zolpidem (Ambien) combined with cocaine has resulted in increased frequency of cocaine use.<sup>30</sup> Combining the antidepressant escitalopram (Lexapro) and cocaine has resulted in serotonin syndrome.<sup>22</sup> We expect that any such interactions seen with cocaine will have commensurate risks when using illicit cathinones (another type of stimulant), considering the pharmacologic mechanism of action on neuroamines.

### Synthetic Cathinones

Synthetic cathinones, often marketed as “plant food” or “bath salts,” are CNS



stimulants available as mephedrone, methylenedioxypropylvalerone (MDPV), and methylone. Cathinones, derived from the Khat plant that grows in Southeast Asia, have been used for their stimulant properties for hundreds of years. Cathinones have adverse effects that are similar to those of cocaine, amphetamines, and Ecstasy—tachycardia, agitation, dilated pupils, arrhythmias, hyperthermia, profuse sweating, rhabdomyolysis, and seizures.<sup>11</sup> Higher doses of cathinones can result in severe behavioral changes including panic attacks, paranoia, hallucinations, suicidal ideation, and extreme agitation and psychosis, resulting in aggressive, violent, and self-destructive behavior.<sup>11</sup> These compounds have been implicated in recent deaths, leading the Drug Enforcement Agency to reschedule them as Schedule I substances.

Like cocaine, MDPV produces outward currents at the voltage-gated hDAT (human dopamine transporter), which inhibit dopamine reuptake, whereas mephedrone induces inward currents at hDAT, increasing intracellular dopamine concentrations. The two are often mixed together to potentiate their effects.<sup>10</sup> Chemically, Khat is a  $\beta$ -keto analogue of the phenylalkylamine amphetamine. Similarly, mephedrone is the  $\beta$ -keto analogue of methamphetamine. Methylone is the  $\beta$ -keto analogue of MDMA (Ecstasy).<sup>10</sup> MDPV's mechanism of action is similar to that of cocaine. In terms of affinity for the hDAT receptor, MDPV

displays 10-times higher affinity than the amphetamine analog (achieved by removing a carbonyl group).<sup>10</sup> Bupropion, a cathinone derivative, carries similar risks when combined with illicit chemical cathinones in the same class.<sup>12</sup> The  $\beta$ -ketone group increases polarity and decreases penetration across the blood-brain barrier, resulting in decreased potency compared to MDMA.<sup>12</sup> Methylone's receptor profile shows equal dopamine and norepinephrine potency compared to MDMA and similar or less serotonin activity.<sup>13,46,47</sup> In laboratory studies, mephedrone was found to increase dopamine concentrations in the rat brain to a greater extent than MDMA, but it was less potent at increasing serotonin concentrations.<sup>48</sup> MDPV inhibits norepinephrine and dopamine but may have little effect on serotonin concentrations.<sup>49</sup> Reports of toxicity surrounding “bath salts” from numerous case reports support the mechanisms outlined and are consistent with toxicity of excessive catecholamines.<sup>14,15,50</sup>



### Heroin

Diacetylmorphine (heroin) is an opioid agonist at the  $\mu$  receptor. It has an extremely short half-life (5-7 min) and is rapidly converted to morphine in the body. Heroin's rapid onset and potency result in euphoria. Common adverse effects include sedation, dizziness, nausea, vomiting, respiratory depression, and constipation.<sup>30</sup> More serious adverse effects include somnolence, hypogonadism (as seen

with other opioids), rhabdomyolysis, acute myelopathy, and serious infections.<sup>21,22,30</sup> Heroin is 16 times less likely to cause hemorrhagic stroke and 5 times less likely to cause thromboembolic stroke than amphetamines.<sup>42</sup> Most strokes attributed to heroin use are caused by infective endocarditis or heroin additives that get lodged in the lungs.<sup>42</sup> Heroin is hydroxylated in the liver to morphine, and then 42% to 70% is excreted through the kidneys.<sup>30</sup>

The most common drug-drug interaction with heroin is with benzodiazepines, which potentiate the sedative and respiratory depressant effects of heroin. This combination is associated with more accidental overdoses than any other combination of drugs.<sup>30,51</sup> Other serious interactions can occur with alcohol, MAOIs, and prescription opioids, all of which increase sedation, hypotension, and respiratory depression.<sup>30</sup> Heroin often is missed on IA UDT because of its rapid metabolism to morphine. Even recent use shows positive for opiates, so when patients are already taking opioids, detection of concurrent heroin use requires a more specific test for 6-monoacetylmorphine (MAM).

### Krokodil

Krokodil is a drug of abuse emerging from Russia and Europe. However, an increasing number of cases now are being reported in the United States.<sup>52</sup> Chemically, krokodil is desomorphine (dihydrodesoxymorphine), which was first synthesized in 1932 in an effort to reduce the side effects and addiction potential of morphine. However, the opposite proved to be true: desomorphine is 8- to 10-times more potent than morphine, with a much shorter half-life and more rapid onset of action.<sup>52,53</sup> Desomorphine can be synthesized in any home kitchen, requiring only prescription codeine, iodine, and red phosphorus (obtained from

matches).<sup>52,54</sup> The crude method of preparation can lead to a myriad of serious adverse effects, including thrombophlebitis, gangrene, and large-scale necrosis (hence the nickname, crocodile skin, or krokodil).<sup>52,54</sup> Note: Krokodil was not included in the Table.



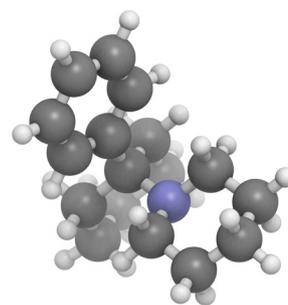
### Kratom

*Mitragyna speciosa*, a tree indigenous to Southeast Asia, is grown mostly for the traditional medicinal properties of its leaves. The leaf extract contains more than 40 alkaloids, and is used for the treatment of musculoskeletal pain, hypertension, coughing, and diarrhea, and as a replacement for morphine in addicts.<sup>55</sup> Kratom is one of the only known natural non-poppy or synthetically-derived opiates.

Kratom's effects appear to be dose-dependent, with lower doses increasing alertness, physical energy, and talkativeness and higher doses resulting in sedation and analgesic effects.<sup>29</sup> Mitragynine is the most widely used kratom alkaloid. It possesses analgesic properties similar to opioids by activating  $\mu$  and  $\kappa$  opioid receptors. Compared to morphine, kratom has less affinity for the  $\mu$  opioid receptor and is roughly 2 orders of magnitude less potent.<sup>55</sup> Kratom is an  $\alpha$ -2-adrenergic agonist with sympathomimetic

activity.<sup>27,55</sup> In addition, kratom also binds to serotonin (5-HT<sub>2A</sub>), and dopamine 1 and 2 receptors, and is considered clinically a D2 antagonist.<sup>29,55</sup> Common side effects include tachycardia, hypertension, agitation, nausea, vomiting, respiratory depression, confusion, tremor, and diaphoresis.<sup>29</sup> Serious adverse effects include seizures and coma.<sup>1</sup>

Kratom toxicity reports to poison control centers have increased significantly since 2008 and include a few fatalities.<sup>24,29</sup> In one fatality attributed to kratom toxicity, the only other drug found in the patient's blood was a benzodiazepine, which is consistent with the known risk with benzodiazepines and opiates. Serious withdrawal symptoms upon cessation of kratom and intrahepatic cholestasis requiring hospitalization also was reported.<sup>25</sup> Nine cases of fatal toxicity of mitragynine and O-desmethyltramadol (Tramadol) have been reported, which demonstrates the risk of combining kratom even with less-potent opioid analgesics.<sup>26</sup> At least one death has been reported from combining kratom with the nasal decongestant propylhexedrine, suggesting that sympathomimetic medications combined with kratom may lead to serious toxicity.<sup>27</sup>



### Phencyclidine

Phencyclidine (PCP) was originally used as anesthesia that did not paralyze the diaphragm. PCP has several mechanisms of action including

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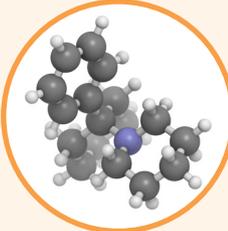
**Table. Illicit Drugs Relevant to UDT**

Illicit Drug	Street Names	Mechanism of Action	Acute Effects	Health Risks	Prescription Drugs With DI Risk
<b>Marijuana</b> <sup>30-32</sup> 	Pot, THC, Dope, Joint, Reefer, Weed	CB <sub>1</sub> partial agonist	Antianxiety effects, sedation, hallucinations, appetite stimulation	Blurred vision, dizziness, tachycardia, memory loss, hallucinations, somnolence, anticholinergic effects	Lithium PIs Theophylline Barbiturates Anticholinergics Alcohol TCAs/cyclobenzaprine Sildenafil Warfarin
<b>Synthetic Cannabinoids</b> <sup>16-20,31-36</sup> 	Spice, K2	CB <sub>1</sub> full agonist, CB <sub>2</sub> full agonist	Same as marijuana but increased effects likely due to greater potency of synthetic drug	Same as marijuana but increased effects likely due to greater potency of synthetic drug	Same as marijuana
<b>Amphetamine/Methamphetamine</b> <sup>3,30,37-39,42-44, 70</sup> 	Speed, Juice, Bennie, Uppers, Meth, Ice, Crank, Crystal, Glass	Inhibit presynaptic reuptake of DOP, NE, 5-HT	↑Alertness Euphoria ↓Appetite ↑Libido	HTN, hyperthermia, tremor, arrhythmia, stroke	ART TCA MAOI SARI NRI SSRI SNRI Quetiapine Varenicline
<b>MDMA</b> <sup>3,30,42</sup> 	Ecstasy, Adam, Eve, Peace,	Stimulant and hallucinogenic structurally similar to methamphetamine and mescaline	↑Alertness, euphoria ↓Appetite ↑Libido	HTN, hyperthermia, tremor, memory loss, hallucinations	Same as amphetamines + meclobemide
<b>Cocaine</b> 3,6-9,22,30,37,38,40-45,71 	Crack, Coke, Blow, Candy, Snow, Rock	Presynaptic release of NTs (DOP, 5-HT, NE, Ach)	Local anesthetic, CNS stimulation	HTN, stroke, vasospasm, thromboembolism, systemic vasoconstriction, aneurysm	β blockers MAOIs Class I antiarrhythmics Methadone Zolpidem Escitalopram TCAs, SSRIs, SNRIs, etc.

**Table. Illicit Drugs Relevant to UDT**

	<b>Mechanism of ↑ Risk</b>	<b>Potential Outcome</b>	<b>Standard UDS Immunoassay</b>	<b>Confirmatory GC-MS or LC/MS</b>
	↑ Lithium	Lithium toxicity	Yes; high percentage of false positive results	Yes; no false positive results
	↓ PI blood levels	↓ PIs efficacy		
	↓Theophylline	↓ Theophylline efficacy		
	↑CNS depression	Respiratory depression, death		
	↑Sedation	↓ADLs, ↑Fall risk		
	↑CNS depression	Respiratory depression, death		
	↑HR, delirium	Arrhythmias, TdP		
	MI	Death		
	↓Protein Binding	Serious bleeding		
	Same as marijuana	Same as marijuana + pulmonary infiltrates AKI, MI, seizure, coma, psychosis, suicidal ideation	No	Yes
	↓ART efficacy	↑ Risk AIDS	Yes; high percentage of false positive results	Yes; no false positive results
	↑5-HT, ↑NE	↑Risk stroke, arrhythmia, serotonin syndrome		
	↑5-HT, ↑NE, ↑DOP	↑Risk HTN, stroke, serotonin syndrome		
	↑5-HT	↑ Risk serotonin syndrome		
	↑NE	↑HTN, stroke		
	↑5-HT	↑Risk serotonin syndrome		
	↑5-HT, ↑NE	↑Risk HTN, stroke, serotonin syndrome		
	↑5-HT	Priapism		
	Unknown	↓ Varenicline efficacy		
	↑5-HT	↑ Risk serotonin syndrome	No	Yes
	↓Cardiac perfusion	↑Risk MI	Yes	Yes
	↑5-HT, ↑NE, ↑D	↑Risk HTN, stroke, serotonin syndrome		
	↑QTc	↑Risk arrhythmia, TdP		
	↑QTc	↑Risk arrhythmia, TdP		
	Unknown	↑Cocaine abuse		
	↑5-HT	↑ Risk serotonin syndrome		
	↑Catecholamines	↑Risk stroke, PE, aneurysm, serotonin syndrome		

**Table. Illicit Drugs Relevant to UDT (continued)**

Illicit Drug	Street Names	Mechanism of Action	Acute Effects	Health Risks	Prescription Drugs With DI Risk		
<b>Synthetic Cathinones</b> <sup>10-15,46-50</sup> 	Bath Salts, Plant food	CNS stimulants with effects similar to:	↑Alertness Euphoria ↓Appetite ↑Libido	Tachycardia, agitation, arrhythmias, hyperthermia, diaphoresis, dilated pupils, rhabdomyolysis, seizures, panic attacks, paranoia, hallucinations, psychosis	SSRIs, SNRIs, TCAs, MAOIs, NRIs, SARIs		
			<b>Methylone</b>			Ecstasy	β-keto analogue of MDMA
			<b>Methylenedioxypropylone</b>			Cocaine	Cathinone analogue
			<b>Mephedrone</b>			Methamphetamine	β-keto analogue, methamphetamine
<b>Heroin</b> <sup>30,42,21-23, 51</sup> 	Smack, Dope, Brown Sugar, China White, Junk	μ-opioid pure agonist	Euphoria	Sedation, dizziness, nausea, vomiting, respiratory depression, constipation, hypogonadism, somnolence, rhabdomyolysis	Benzodiazepines		
					Alcohol		
					MAOIs		
					Prescription opioids		
<b>Kratom</b> <sup>24-29,55</sup> (Mitragynine) 	Thang, Kakuam, Thom, Ketum, Biak	μ- and κ-opioid agonist, α-2-adrenergic agonist, 5-HT <sub>2A</sub> agonist, DOP-receptor agonist, DOP-2 antagonist	Lower doses: ↑Alertness, physical energy  Higher doses: Sedation, analgesia	Tachycardia, HTN, agitation, nausea, vomiting, respiratory depression, confusion, tremor, diaphoresis	Modafinil		
					Tramadol		
					Benzodiazepines		
					Decongestants		
					Prescription opioids		
					SSRIs, SNRIs, MAOIs		
<b>Phencyclidine</b> <sup>42,56,57-66,73</sup> 	Angel Dust, Love Boat, Hog, Peace Pill	NMDA antagonist, nicotinic Ach antagonist, DOP agonist	Dissociative hallucinogenic	HTN, asphyxia, seizures, hemorrhagic stroke, acute renal failure, rhabdomyolysis, prolonged psychosis	Ketamine		
					Methadone		
					Dextromethorphan		
					DRI		

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Table based on references 3, 6-51, 55-75.

**ACh**, acetylcholine; **ADLs**, activities of daily living; **AKI**, acute kidney injury; **ART**, antiretroviral therapy; **CNS**, central nervous system; **DI**, drug interaction; **DOP**, dopamine; **DRI**, dopamine reuptake inhibitor; **GC-MS**, gas chromatography mass spectrometry; **HR**, heart rate; **5-HT**, serotonin; **HTN**, hypertension; **LC-MS**, liquid chromatography mass spectrometry; **MAOI**, monoamine oxidase inhibitor; **MDMA**, 3,4-methylenedioxy-N-methylamphetamine; **MI**, myocardial infarction; **NE**, norepinephrine; **NRI**, norepinephrine reuptake inhibitor; **PI**, protease inhibitor; **SARI**, serotonin antagonist and reuptake inhibitor; **SNRI**, serotonin-norepinephrine reuptake inhibitor; **SSRI**, selective serotonin reuptake inhibitor; **TCA**, tricyclic antidepressant; **TdP**, Torsades de pointes; **UDS**, urine drug screening

**Table. Illicit Drugs Relevant to UDT (continued)**

	<b>Mechanism of ↑ Risk</b>	<b>Potential Outcome</b>	<b>Standard UDS Immunoassay</b>	<b>Confirmatory GC-MS or LC/MS</b>
			No	Yes, for most common
	↑Catecholamines	↑Risk stroke, PE, aneurysm, MI, serotonin syndrome, arrhythmia, suicide	No	Yes
	↑Catecholamines		No	Yes
	↑Catecholamines		No	Yes
	↑Respiratory depression		↑Risk overdose	No; result positive for opiates so not specific
	↑CNS depression	↑Risk overdose		
	↑5-HT, ↑NE, ↑DOP	↑Hypotension, ↑sedation		
	↑Respiratory depression	↑Risk overdose, ↑sedation		
	↑HTN ↑HR	↑Risk stroke, seizure	No	
	↑Respiratory depression	↑ Risk overdose, ↑sedation		
	↑Respiratory depression	↑ Risk overdose, ↑sedation		
	↑HTN, ↑HR	↑Risk stroke, seizure		
	↑Respiratory depression	↑Risk overdose, ↑sedation		
	↑HTN, ↑HR, ↑5-HT	↑Risk stroke, seizure, serotonin syndrome		
	↑NMDA antagonism	↑Risk respiratory depression, neurological damage	Yes; high percentage of false positive results	Yes; no false positive results
	↑NMDA antagonism	↑Risk respiratory depression, neurological damage		
	↑NMDA antagonism	↑Risk respiratory depression, neurological damage		
	↑DOP	↑Risk hallucinations, acute renal failure		

N-methyl-D-aspartate (NMDA) receptor antagonism (similar to ketamine), nicotinic acetylcholine antagonism, and dopamine agonism.<sup>42,56</sup> Antagonizing NMDA and activating dopamine receptors both result in dissociative and hallucinogenic properties. PCP is extremely lipophilic so that redistribution from tissue stores results in recurrent symptoms for days.<sup>56</sup> PCP is hepatically metabolized; 10% of PCP is excreted unchanged and can be detected in a UDT.<sup>42,57</sup> Sinusoidal theta rhythm interrupted every few seconds by slow-wave complexes is fairly diagnostic for PCP intoxication.<sup>58</sup>

PCP can cause a variety of adverse effects, including hypertension, asphyxia, seizures, hemorrhagic stroke, acute renal failure, or rhabdomyolysis.<sup>42,59-62</sup> Perhaps the most disturbing side effect is prolonged psychosis resistant to antipsychotics and potentially requiring electroconvulsive therapy (ECT) to induce remission. Due to difficulty in treating prolonged psychosis, accurate diagnosis is critical; IA UDT provides numerous false positives, with commonly prescribed medications complicating the differential diagnosis.<sup>59,63-66</sup> Availability of a rapid

and specific confirmatory testing would be a valuable tool.

### Summary

Considering the morbidity and mortality associated with illicit drugs, it is incumbent upon healthcare providers, policy makers, regulators, and third-party payers to recognize the serious risks associated with prescribed drugs combined with synthetic illicit substances. These risks may be preventable by early identification at the point of initial office contact that is confirmed with UDT definitive testing with chromatography mass spectrometry, even after an initially negative report by in-office IA testing. ■

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