CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

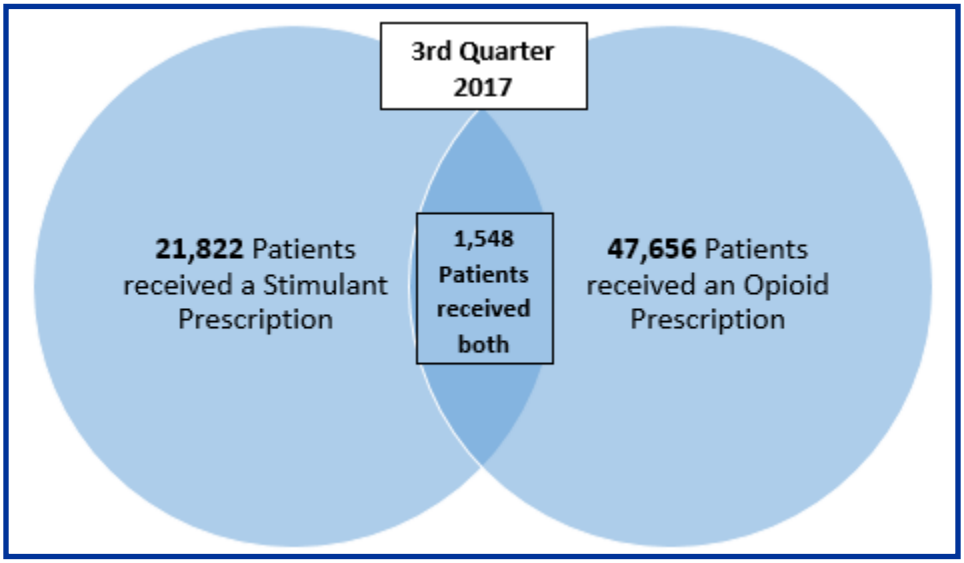
A recent evaluation of the Connecticut Medical Assistance population showed that during 3rd quarter 2017, 3,479 patients received a stimulant prescription medication without a supporting medical diagnosis for use. The cost associated with the prescriptions stimulants received by these patients was approximately $1.5 million during 3rd quarter.

The World Health Organization (WHO) defines psychoactive substance misuse and abuse as the use of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications[1]. Poly-psychoactive substance misuse or abuse can then be defined as the use of more than one substance for a purpose not consistent with legal or medical guidelines.

Concurrent use of prescription opiates with other prescription medications is a pressing public health concern. Misuse of opiates with prescription medications such as benzodiazepines or sedative hypnotics often overshadow misuse of opiates with stimulants medications because the former can increase the risk of adverse events such as respiratory depression and death. Concurrent use of these medications is often a "red flag" for medical health professionals because of the severity of the adverse events that can occur. Misuse of opiates with stimulants is a less recognized issue but can be problematic for patients who misuse these classes of medications concurrently. For the purpose of this article, we will focus on the concurrent use of opioid and stimulant prescription medications within the Connecticut Medical Assistance Program population to determine the number of patients who may be abusing these classes of medications.

It is estimated that 54 million people have used prescription medications for non-medical reasons at least once in their lifetime.[2] Non-medical use of prescriptions is shown to be highest among adults aged 26 years of age or older.[3] The SAMHSA 2016 National Survey on Drug Use and Health estimated that 18.6 million Americans misused prescription medications in the past year.[3] Of those estimated to be misusing prescription medications, 11.5 million misused pain relievers (including opiates), and 5.6 million misused stimulants.[3] Furthermore, The Monitoring the Future National Survey Results on Drug Use, reported that 1 in 13 high school seniors reported past-year nonmedical use of the prescription stimulant Adderall® in 2015 and 1 in 23 seniors misused the opioid Vicodin® that same year.[4]

Stimulant and opioid prescription medications are subject to abuse and misuse both nationally and at the state level. Overlapping prescriptions by different prescribers for both classes of medications is an ongoing issue that needs to be evaluated, monitored, and intervened on. During 3rd QTR 2017, 47,656 CT Medical Assistance program patients received at least one opioid prescription and 21,822 patients received at least one stimulant prescription. 1,548 patients received both an opioid and stimulant during 3rd quarter 2017. While this does not confirm that all patients were using the medications for non-medical reasons, additional evaluation of the individual patients and outreach to their prescribers was performed by the state's Retrospective Drug Utilization Review Program. During December, Medicaid recipients who were found to be receiving an opiate prescription and a stimulant prescription from two different prescribers had intervention letters sent to



December 2017
Published Quarterly by Health Information Designs, LLC
Heather L. Kissinger, PharmD

their prescribers alerting them of the risk of polysubstance abuse. If you are a prescriber who received such correspondence, your feedback is important to the program. Please take the time to fill out the prescriber response form included in the letter packet.

Patients who abuse a specific drug or class of drugs have a higher risk of abusing other drugs or classes of drugs with abuse potential.[5-8] Opiates and stimulants increase dopamine activity in the reward system. While both classes increase dopamine, they have different pharmacodynamic profiles: stimulants block dopamine reuptake and invert dopamine transport; while opiates exert their action mainly through μ-opioid receptors, indirectly increasing dopamine levels.[9,10-13]

In addition to differences in mechanisms of action, the chronic effects of prolonged substance abuse may differ between users of amphetamines and opiates.[14-20] Another important distinction between opiates and stimulants was reported by Badiani, et al. who found that the rewarding effects of heroin and cocaine seem to be encoded by distinct neuronal subpopulations.[21]

While misuse of multiple drugs is common with users of any drug, besides mechanism of action or reward pathways, few studies have analyzed the motivation of poly-psychoactive substance misuse. A study published in the Journal of Pharmacology, Biochemistry and Behavior examined the relationship between the use of methamphetamine and morphine. The authors documented three likely reasons why patients would self-administer opiate-stimulant combinations[22]:

- Administration of the combination produces effects greater than either drug alone (such as a greater high or greater rush);
- Administration of one decreases the side-effects of another (such as the opiate decreasing stimulant-induced agitation or anxiety, or conversely, stimulant tempering opiate-induced sedation)
- The combination produces unique subjective effects desired by the user

Some of the above patterns of use associated with concurrent methamphetamine and prescription drug use can be applied to the concurrent use of prescription stimulants and opioids. Patients may use one prescription to counteract the side effects of the other. For example, a patient may use a prescription stimulant to counteract the sedating effects of an opioid. Other patients may use an opioid to decrease the negative side effects associated with stimulants, such as insomnia or paranoia. Or patients may use both classes of medication for greater euphoria or desired effect.

When considering a patient's motivation for misuse, knowing that differences occur between stimulants and opiates at the neurobiological and pharmacodynamic level, as well as the behavioral and psychological level, is important to keep in mind. Because of these differences, addiction treatment should be specific for each individual class of medications. Cognitive Behavioral Therapy (CBT) and Medication Assisted Treatment (MAT) exists for opioid addicted patients. Available MAT treatments include; long acting naltrexone (Vivitrol®), methadone, and buprenorphine products. CBT is also used to help patients with addiction to stimulant medications, however, there are no FDA approved medications currently available for treating stimulant addiction.[23] Some studies indicate buprenorphine treatment can help with methamphetamine cravings but, this medication is not FDA approved to treat stimulant addiction.[24] Development of clinical policies, steps toward prevention, and educational strategies for reducing prescription opioid and stimulant abuse requires knowledge of which agents are being abused and insight into motives for drug use.[10]

3rd Quarter 2017 Utilization

Medication Class	Number of Prescriptions	Cost	Number of Unique Patients
Stimulants	55,563	$11,353,074	21,822
Opioids	100,987	$4,135,536	47,656

1. World Health Organization (WHO) management of substance abuse. http://www.who.int/substance_abuse/terminology/abuse/en/
2. Substance Abuse and Mental Health Services Administration. Results from the 2014 National Survey on Drug Use and Health: Detailed Tables. 2015. http://www.samhsa.gov/data/sites/default/files/NSDUHDetTabs2014/NSDUH-DetTabs2014.pdf Accessed November 8, 2017.
3. Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD.
4. The University of Michigan Institute for Social Research. Monitoring the future national survey results on drug use, 1975-2015. Overview, key findings on adolescent drug use. February 2016. http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2015.pdf
5. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev* 2011;31(3):328–341.
6. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain* 2008;24(6):497–508
7. Michna E, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manag* 2004;28(3):250–258
8. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain* 2007;8(7):573–582
9. De Vries TJ, Shippenberg TS. Neural systems underlying opiate addiction. *J Neurosci* 2002;22:3321–3325
10. Teter CJ, McCabe SE, LaGrange K, et al. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy 2006; 26(10): 1501-1510
11. Di Chiara G. Drug addiction as dopamine-dependent associative learning disorder. *Eur J Pharmacol* 1999;375:13–30
12. Wise RA. Dopamine, learning and motivation. *Nature Rev Neurosci* 2004;5:483–494
13. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* 2002;22:3306–3311
14. Ersche KD, Clark L, London M, et al. Profile of executive and memory function associated with amphetamine and opiate dependence. Neuropsychopharmacology 2006; 31: 1036-47
15. Kish SJ, Kalasinsky KS, Derkach P, Schmunk GA, Guttman M, Ang L, et al. Striatal dopaminergic and serotonergic markers in human heroin users. Neuropsychopharmacology 2001;24:561–567
16. Danos P, Van Roos D, Kasper S, Bromel T, Broich K, Krappel C, et al. Enlarged cerebrospinal fluid spaces in opiate-dependent male patients: a stereological CT study. Neuropsychobiology 1998; 38:80–83
17. Manes F, Sahakian BJ, Clark L, Rogers RD, Antoun N, Aitken M, et al. Decision-making processes following damage to the prefrontal cortex. Brain 2002;125:624–639
18. Fein G, Di Sclafani V, Meyerhoff DJ. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug Alcohol Depend* 2002;68:87–93
19. Goldstein RZ, Leskovjan AC, Hoff AL, Hitzemann R, Bashan F, Khalsa SS, et al. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 2004;42:1447–1458
20. Rogers RD, Everitt BJ, Baldacchino A, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 1999b;20: 322–339
21. Badiani A, Belin D, Epstein D, et al. Opiate versus psychostimulant addiction: the differences do matter. *Nat Rev Neurosci* 2013;12(11): 685-700
22. Trujillo KA, Smith ML, Guaderrama MM. Powerful behavioral interactions between methamphetamine and morphine. *Pharmacol Biochem Behav* 2011; 99(3): 451-458
23. National Institute on Drug Abuse (NIDA) Misuse of Prescription Drugs. August 2016. https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/summary
24. Salehi M, Emadossadat A, Kheirabadi GR, et al. The effect of buprenorphine on methamphetamine cravings. *J Clin Psychopharmacol* 2015; 35(6): 724-727
25. Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. Annu Rev Pharmacol Toxicol. 1993; 33: 639–676.
26. Lamonica AK, Boeri M. An exploration of the relationship between the use of methamphetamine and prescription drugs. J Ethnogr Qual Res. 2012;6(3): 160-177
27. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron 2011;69:680–694
28. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005;162:1403–1413
29. Carelli RM, King VC, Hampson RE, Deadwyler SA. Firing patterns of nucleus accumbens neurons during cocaine self-administration in rats. *Brain Res* 1993;626:14–22
30. Chang JY, Zhang L, Janak PH, Woodward DJ. Neuronal responses in prefrontal cortex and nucleus accumbens during heroin self-administration in freely moving rats. *Brain Res* 1997;754:12–20
31. Chang JY, Janak PH, Woodward DJ. Comparison of mesocorticolimbic neuronal responses during cocaine and heroin self-administration in freely moving rats. *J Neurosci* 1998;18:3098–3115
32. Ettenberg A, Pettit HO, Bloom FE, Koob GF. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacology 1982;78:204–209
33. Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 1996;14:375–424
34. Huang CC, Lin HJ, Hsu KS. Repeated cocaine administration promotes long-term potentiation induction in rat medial prefrontal cortex. *Cereb Cortex* 2007;17:1877–1888
35. Lu H, Cheng PL, Lim BK, Khoshnevisrad N, Poo MM. Elevated BDNF after cocaine withdrawal facilitates LTP in medial prefrontal cortex by suppressing GABA inhibition. Neuron 2010;67:821–833
36. Van den Oever MC, et al. Prefrontal cortex AMPA receptor plasticity is crucial for cue-induced relapse to heroin-seeking. *Nature Neurosci* 2008;11:1053–1058
37. Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse Neuropharmacology 2004 ; 47: 33–46
38. Russo SJ, et al. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. *Trends Neurosci* 2010;33:267–276
39. Badiani A, et al. Environmental modulation of amphetamine-induced cfos expression in D1 versus D2 striatal neurons. *Behav Brain Res* 1999;103:203–209
40. Ferguson SM, Robinson TE. Amphetamine-evoked gene expression in striatopallidal neurons: regulation by corticostriatal afferents and the ERK/ MAPK signaling cascade. *J Neurochem* 2004;91:337–348
41. Uslaner J, et al. Amphetamine and cocaine induce different patterns of cfos mRNA expression in the striatum and subthalamic nucleus depending on environmental context. *Eur J Neurosci* 2001;13:1977–1983
42. Fuchs RA, et al. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 2005; 30:296–309
43. Bossert JM, et al. Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. *Nature Neurosci* 2011;14:420–422
44. Tsuang MT, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry* 1998;55:967–972
45. Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. *Ann NY Acad Sci* 2010;1187:184–207
46. Nielsen DA, et al. Genome-wide association study identifies genes that may contribute to risk for developing heroin addiction. *Psychiatr Genet*. 2010;20:207–214.
47. Albertson DN, Schmidt CJ, Kapatos G, Bannon MJ. Distinctive profiles of gene expression in the human nucleus accumbens associated with cocaine and heroin abuse. Neuropsychopharmacology 2006 ; 31: 2304–2312
48. Ettenberg A, et al. Opponent process properties of self-administered cocaine. *Neurosci Biobehav Rev* 2004;27:721–728
49. Bozarth MA, Wise RA. Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. *J Am Med Assoc* 1985;254:81–83
50. Caprioli D, et al. Opposite environmental regulation of heroin and amphetamine self-administration in the rat. Psychopharmacology 2008;198:395–404
51. Caprioli D, et al. Environmental modulation of cocaine self-administration in the rat. Psychopharmacology 2007;192:397–406
52. Caprioli D, et al. Ambience and drug choice: cocaine-and heroin-taking as a function of environmental context in humans and rats. *Biol Psychiatry* 2009;65:893–899
53. McNamara R, Dalley JW, Robbins TW, Everitt BJ, Belin D. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. Psychopharmacology 2010;212:453–464
54. Dalley JW, et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science. 2007;315:1267–1270
55. Ersche KD, et al. Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. Psychopharmacology. 2005;180:612–623
56. Ersche KD, Roiser JP, Robbins TW, Sahakian BJ. Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. Psychopharmacology. 2008;197:421–431
57. London ED, et al. Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. *Biol Psychiatry* 2005;58:770–778
58. Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav* 2005; 81:319–330
59. Ahn WY, Vassileva J. Machine-learning identified substance-specific behavioral markers for opiate and stimulant dependence. *Drug Alcohol Depend* 2016; 161: 247-257
60. Wilens TE, Adler LA, Adams J, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J *Am Ac Child Adolesc Psychiatry* 2008; 47(1): 21-31
61. Cepeda MS, Fife D, Berwaerts J, et al. Shopping behavior for ADHD Drugs: results of a cohort study in a pharmacy database. Drugs RD 2014; 14: 205-211
62. Ahn WY, Vasilev G, Lee SH, et al. Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. Frontiers in Psychology 2014; 5(849)