July 31, 2018

ProDUR Update: Additive Toxicity Alert Now Focused Only On CNS Depressants

Learning Objectives:

- Describe the drug safety communications by the U.S. Food and Drug Administration (FDA) regarding the combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS).
- Review the changes to the additive toxicity (AT) prospective drug utilization review (DUR) alert.
- Summarize best practices for responsible prescribing of opioid medicines with benzodiazepines or other CNS depressants.

Key Points:

- On August 31, 2016, the FDA announced that it will require *Boxed Warnings* added to the drug labeling of prescription opioid pain and cough medications and benzodiazepines due to serious side effects, including slowed or difficult breathing and deaths.
- Effective June 1, 2018, the Medi-Cal fee-for-service prospective DUR system has been updated to generate an AT alert when a patient reaches a threshold of four active prescriptions within the following therapeutic categories: opioid pain or cough medications, benzodiazepines, skeletal muscle relaxants, other sleep drugs and tranquilizers (non-benzodiazepine), antipsychotic medications, and other selected psychotropic medications with CNS depressant properties. Previously, the AT alert had included all psychotropic and controlled (scheduled) drugs.
- With the AT alert updated to focus exclusively on CNS polypharmacy, a review of the June 2018 AT alert data found a 17% decrease in AT alerts, when compared to June 2017. This indicates the updated AT alert has already been beneficial.
- Among the 1,964 beneficiaries that generated an AT alert in June 2018, the vast majority (n = 1,871; 95%) were enrolled in the Medi-Cal fee-for-service program and were under 65 years of age (n = 1,935; 98%), primarily due to the majority of drugs included in the AT alert being covered through Medicare or Managed Care Plans (MCPs). Many of these beneficiaries had additional risk factors for serious adverse events, including co-morbid mental health conditions (n = 1,248; 64%), suicide attempts and/or ideation (n = 174; 9%), and alcohol and/or substance abuse (n = 158; 8%). A total of 307 beneficiaries (16%) had both a paid claim for an opioid medication and a paid claim for a benzodiazepine.
- If CNS polypharmacy cannot be avoided, health care professionals should work to limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect.
- Health care professionals should take additional actions and precautions when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants, including developing a treatment plan and educating patients about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.

Background
CNS polypharmacy, including the co-prescribing of opioids and benzodiazepines, is associated with increased risks of adverse events, including suicidal ideation, respiratory depression, accidental overdose, and death.[1-5] In 2016, a total of 63,632 drug overdose deaths occurred in the U.S., with opioid overdose deaths increasing by 27.7% from 2015.[6,7] Among the Medicaid population, the rates of prescription opioid overdose have been shown to be significantly higher than among the non-Medicaid population.[8,9]

On August 31, 2016, the FDA announced that it will require class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the use of certain opioid medications in combination with benzodiazepines and other CNS depressants.[10] The new *Boxed Warnings* are the result of an FDA review that found serious side effects, including slowed or difficult breathing and death attributed to co-prescribing of opioids with CNS depressants, including benzodiazepines, non-benzodiazepine receptor agonists, and antipsychotics.[10]

Per recommendations provided by the FDA, effective June 1, 2018, the Medi-Cal fee-for-service prospective DUR system has been updated to generate the AT alert only when a patient reaches a threshold of four active prescriptions from a list of 98 drugs representing the following therapeutic categories: opioid pain or cough medications, benzodiazepines, skeletal muscle relaxants, other sleep drugs and tranquilizers (non-benzodiazepine), antipsychotic medications, and other psychotropic medications with CNS depressant properties (Table 1). The majority of drugs listed in Table 1 appears on the list provided by the FDA.[10] Previously, the AT alert had included all psychotropic and controlled (scheduled) drugs.

Table 1. Drugs with the Additive Toxicity Alert Turned On, Effective June 1, 2018

Category	Drugs (n = 98)		
Opioid Pain or Cough Medications (n = 20)	ALFENTANIL	HYDROMORPHONE*	OXYMORPHONE
	BUPRENORPHINE*+	LEVORPHANOL	PENTAZOCINE
	BUTORPHANOL	MEPERIDINE	REMIFENTANIL
	CODEINE*	METHADONE	SUFENTANIL
	DIHYDROCODEINE	MORPHINE*	TAPENTADOL
	FENTANYL*	OPIUM	TRAMADOL*
	HYDROCODONE*	OXYCODONE*	
Benzodiazepines (n = 14)	ALPRAZOLAM	DIAZEPAM*	OXAZEPAM
	CHLORDIAZEPOXIDE	ESTAZOLAM	QUAZEPAM
	CLOBAZAM	FLURAZEPAM*	TEMAZEPAM*
	CLONAZEPAM*	LORAZEPAM*	TRIAZOLAM*
	CLORAZEPATE	MIDAZOLAM	
Skeletal Muscle Relaxants (n = 9)	BACLOFEN*	CYCLOBENZAPRINE	METHOCARBAMOL
	CARISOPRODOL	DANTROLENE*	ORPHENADRINE
	CHLORZOXAZONE	METAXALONE	TIZANIDINE
Other Sleep Drugs and Tranquilizers (n = 13)	AMOBARBITAL	PHENOBARBITAL*	TASIMELTEON
	BUTABARBITAL	RAMELTEON	ZALEPLON
	BUTALBITAL	SECOBARBITAL	ZOLPIDEM*
	ESZOPICLONE	SODIUM OXYBATE	
	PENTOBARBITAL	SUVOREXANT	
Antipsychotic Medications (n = 26)	ARIPIPRAZOLE*+	LOXAPINE*+	PROCHLORPERAZINE*
	ASENAPINE*+	LURASIDONE*+	QUETIAPINE*+
	BREXPIPRAZOLE+	MESORIDAZINE	RISPERIDONE*+
	CARIPRAZINE+	MOLINDONE*+	THIORIDAZINE*+
	CHLORPROMAZINE*+	OLANZAPINE*+	THIOTHIXENE*+
	CLOZAPINE*+	PALIPERIDONE+	TRIFLUOPERAZINE*+
	FLUPHENAZINE*+	PERPHENAZINE*+	TRIFLUPROMAZINE
	HALOPERIDOL*+	PIMAVANSERIN+	ZIPRASIDONE*+
	ILOPERIDONE*+	PIMOZIDE+	
Other Selected CNS Depressants (n = 16)	AMITRIPTYLINE*	IMIPRAMINE*	PROTRIPTYLINE*
	BUSPIRONE*	LITHIUM*+	TRAZODONE*
	CLOMIPRAMINE*	MIRTAZAPINE*	TRIMIPRAMINE
	DESIPRAMINE*	NEFAZODONE	VILAZODONE
	DOXEPIN*	NORTRIPTYLINE*	
	FLUVOXAMINE*	PAROXETINE*	

* As of the date of publication of this article, these drugs appear on the Medi-Cal fee-for-service *List of Contract Drugs*, although some medications may have additional restrictions, including on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File web page of the Department of Health Care Services (DHCS) website.

\+ As of the date of publication of this article, these drugs are noncapitated and claims are paid through the Medi-Cal fee-for-service program.

According to a subsequent FDA Drug Safety Communication issued on September 20, 2017, buprenorphine or methadone prescribed as medication-assisted treatment (MAT) drugs for opioid use disorder should not be categorically denied to patients taking benzodiazepines or other CNS depressants.[11] The FDA found that although concomitant use of buprenorphine or methadone with benzodiazepines or other CNS depressants increases the risk of adverse reactions, including overdose and death, creating barriers to MAT can pose an even greater risk of morbidity and mortality due to the opioid use disorder.[11]

Additive Toxicity Alerts in the Medi-Cal Population

A review of all 6,676 AT alerts generated by a total of 1,964 Medi-Cal beneficiaries between June 1, 2018, and June 30, 2018, was conducted, in order to assess the potential alert burden and to evaluate whether the AT alert was capturing high-risk polypharmacy, as intended. All drug combinations generating the AT alert were reviewed for the presence of opioids and/or benzodiazepines. In addition, for each beneficiary that generated an AT alert, their date of birth and Medi-Cal status for June 2018 (for fee-for-service or managed care programs) was collected. Finally, pharmacy and medical claims data from July 1, 2017, through June 30, 2018, were reviewed for these beneficiaries, in order to assess the frequency of additional risk factors for adverse events from CNS polypharmacy. Claims data were reviewed for ICD-10-CM codes that indicated adjustment disorders, alcohol-related disorders, anxiety disorders, bipolar disorders, depressive disorders, personality disorders, psychoses, post-traumatic stress disorder, schizophrenia, substance-related disorders, suicidal attempts, and suicidal ideation.

Among the 6,676 AT alerts, ten drugs were responsible for 61% of the alerts in June 2018 (Table 2), including lithium, seven antipsychotic medications and two benzodiazepines.

Table 2. Top 10 Drugs Generating Additive Toxicity Alerts in the Medi-Cal Fee-for-Service Population from June 1, 2018, through June 30, 2018

Drug	Number of Alerts
Quetiapine	720 (11%)
Olanzapine	555 (8%)
Lithium	525 (8%)
Haloperidol	413 (6%)
Aripiprazole	402 (6%)
Clozapine	375 (6%)
Risperidone	333 (5%)
Lorazepam	284 (4%)
Clonazepam	228 (3%)
Lurasidone	220 (3%)

A total of 1,964 beneficiaries generated an AT alert in June 2018. Of these, 256 beneficiaries (13%) had at least one paid claim for an opioid medication contribute to the AT alert, while 359 beneficiaries (18%) had at least one paid claim for a benzodiazepine contribute to the AT alert. A total of 307 beneficiaries (16%) had both a paid claim for an opioid medication and a paid claim for a benzodiazepine medication when the AT alert was generated. The remaining 1,042 beneficiaries (53%) had the AT alert generated from the other CNS depressants listed in Table 1. Among the 563 beneficiaries with a paid claim for an opioid medication, pharmacy claims showed only 25 of these beneficiaries (4%) had a paid claim for naloxone from July 1, 2017, through June 30, 2018.

Medical claims data from this same one-year period revealed additional risk factors for many of these beneficiaries , including co-morbid mental health conditions (n = 1,248; 64%), suicidal attempts and/or ideation (n = 174; 9%), and alcohol and/or substance abuse (n = 158; 8%). Finally, after the updates to the AT alert, the AT alerts generated decreased from this same time period one year ago (June 2017) by 17% (n = 7,998), suggesting a reduced burden from AT alerts by focusing exclusively on CNS polypharmacy instead of including all psychotropic and controlled (scheduled) drugs.

Potential Limitations of the Updated Additive Toxicity Alert

Because the prospective DUR system is designed to look for at least four active prescriptions among the 98 drugs listed, there is a possibility that AT alerts may be generated while following clinical guidelines during initiation of a new or adjunctive medication and/or tapering off an existing medication. In addition, at this time, beneficiaries cannot be excluded from prospective DUR based on specific conditions that may require multiple medications from these categories. In anticipation of these individual, patient-specific issues, the pharmacist can continue to override any AT alert at the point of sale, if all prescriptions are found to be medically necessary.

Conclusion

While the updated AT alert has limitations, it may provide valuable information as a screening tool to pharmacists and prescribers regarding beneficiaries that may be at increased risk for adverse events due to CNS polypharmacy. Further, by focusing the AT alert exclusively on CNS polypharmacy we reduced the number of AT alerts generated each month, decreasing alert burden. Repeated overrides of the AT alert among high-risk beneficiaries that appear to be without medical justification may warrant additional evaluation through retrospective DUR, educational outreach, and/or academic detailing efforts.

General Clinical Recommendations:

- Health care professionals should limit prescribing opioid pain medications with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate. The CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use.
- If CNS polypharmacy cannot be avoided, health care professionals should work to limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect.
- Patients and caregivers should be advised about the risks of respiratory depression and sedation if opioids are used with benzodiazepines and other CNS depressants, including alcohol and illicit or recreational drugs. The use of naloxone should be proactively discussed with patients and caregivers, and prescribed when indicated.
- Pharmacists should review the concomitant prescription data generated by the AT alert with prescribers, especially in cases where beneficiaries have multiple prescribers and/or pharmacies. The AT alert will be able to identify any active prescription processed through the Medi-Cal fee-for-service system.
- Before prescribing any CNS depressant, health care professionals should assess patient-specific risk factors that may put beneficiaries at a higher-risk for adverse events, including the presence of co-morbid mental health conditions, a history of suicidal ideation or attempts, and/or a history of alcohol or substance abuse disorder.

Specific Clinical Recommendations for Buprenorphine and Methadone:

- Health care professionals should take several actions and precautions, and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants, including:
  - Educating patients about the serious risks of combined use, including overdose and death, which can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
  - Developing strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting MAT.
  - Tapering the benzodiazepine or CNS depressant to discontinuation, if possible.
  - Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions.
  - Recognizing that patients may require MAT medications indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
  - Coordinating care to ensure other prescribers are aware of the patient's buprenorphine or methadone treatment.
  - Monitoring for illicit drug use, including urine or blood screening.

References:

1. Gerlach LB, Olfson M, Kales, HC, et al. Opioids and other central nervous system–active polypharmacy in older adults in the United States. *J Am Geriatr Soc*. 2017;65:2052-2056.
2. Park TW, Saitz R, Ganoczy D, et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: Case-cohort study. *BMJ.* 2015;350:h2698. Available at: https://www.bmj.com/content/bmj/350/bmj.h2698.full.pdf. Accessed: July 12, 2018.
3. Eide, RP and Stahlman, S. Polypharmacy involving opioid, psychotropic, and central nervous system depressant medications, period prevalence and association with suicidal ideation, active component, U.S. Armed Forces, 2016. *MSMR*. 2018;25(6):2-9.
4. Collett GA, Song K, Jaramillo CA, et al. Prevalence of central nervous system polypharmacy and associations with overdose and suicide-related behaviors in Iraq and Afghanistan war veterans in VA care 2010–2011. *Drugs - Real World Outcomes*. 2016;3(1):45-52. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4819457/pdf/40801_2015_Article_55.pdf. Accessed: July 12, 2018.
5. Ladapo JA, Larochelle MR, Chen A, et al. Physician prescribing of opioids to patients at increased risk of overdose from benzodiazepine use in the United States. *JAMA Psychiatry*. 2018;75(6):623-630.
6. Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital Signs: Trends in emergency department visits for suspected opioid overdoses — United States, July 2016–September 2017. *MMWR*. 2018;67:279-285. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6709e1-H.pdf. Accessed: July 12, 2018.
7. Hedegaard H, Warner M, Miniño AM. Drug overdose deaths in the United States, 1999–2016. NCHS data brief, no 294. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2017. Available at: https://www.cdc.gov/nchs/data/databriefs/db294.pdf. Accessed: July 12, 2018.
8. Dilokthornsakul P, Moore G, Campbell JD, et al. Risk factors of prescription opioid overdose among Colorado Medicaid beneficiaries. *J Pain*. 2016;17:436-443. Available at: https://www.jpain.org/article/S1526-5900(15)00985-2/pdf. Accessed: July 12, 2018.
9. Coolen P, Best S, Lima A, et al. Overdose deaths involving prescription opioids among Medicaid enrollees—Washington, 2004-2007. *MMWR*. 2009;58:1171-1175. Available at: https://www.cdc.gov/mmwr/pdf/wk/mm5842.pdf. Accessed: July 12, 2018.
10. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain and cough medicines with benzodiazepines; requires its strongest warning. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM518672.pdf. Accessed: July 12, 2018.
11. FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risk. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM576377.pdf. Accessed: July 12, 2018.