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Drugs with Withdrawal Effects

Nausea. Dizziness. Paresthesia. Insomnia. Anxiety. These are the leading symptoms reported by patients who discontinue taking a variety of psychoactive drugs, including antidepressants, sedative/hypnotics, and opioids. While issues involving opioid withdrawal are well known, the safety issue extends to drugs with even larger patient populations, most notably antidepressants and a large group of pain and anti-anxiety drugs. For many of these drug classes, the severity, duration, and likelihood of withdrawal effects is underestimated in prescribing information for physicians and medications guides for patients. In other cases, withdrawal effects are too poorly studied to support adequate estimates of injury rates.

The Institute for Safe Medication Practices (ISMP) recently analyzed adverse event reports from 2016 and identified 42 drugs with indications of withdrawal effects. Suspected drugs had to meet the following criteria:

- those with at least 10 reported cases of withdrawal effects,
- those with twice as many cases as expected given the number of total adverse events for the drug, and
- those with at least 95% probability that the number of withdrawal symptoms was not due to chance.

ISMP noted that a variety of adverse effects can occur when drugs are withdrawn, especially for drugs that alter the functioning of neurotransmitter or receptor circuits. They wrote, “Basic neuroscience reveals that the chemical intrusion of psychoactive drugs into complex, interacting signaling circuits changes how they function. When the drugs are withdrawn, especially abruptly, a wide array of symptoms occurs as these circuits seek to readjust.”

Five categories were identified: drugs with effects on serotonin (e.g. antidepressants), drugs that affect gamma-aminobutyric acid (GABA) (e.g. anticonvulsants, benzodiazepines, sedatives), drugs that affect opioid receptors (e.g. analgesics, addiction treatment medications), drugs that affect dopamine (e.g. antipsychotics, ADHD medications), and drugs with other unique mechanisms of action (e.g. antihistamines, proton pump inhibitors, muscle relaxants). The top five drugs with the highest number of cases from each of the five categories above are summarized in Table 2. A complete list can be found in the full report.

Table 1. Top 10 Most Common Withdrawal Symptoms (≥ 1% of cases)

1. Nausea
2. Dizziness
3. Paresthesia
4. Insomnia
5. Anxiety
6. Suicidal Ideation
7. Headache
8. Agitation
9. Fatigue
10. Irritability

Additional withdrawal symptoms that occurred can be found in the full report.

ISMP found that antidepressants with signs of withdrawal symptoms are more frequent and severe for drugs with a half-life of 12 hours or less, while symptoms were less frequent for drugs that remain in circulation for days. In addition, initial withdrawal symptoms can mimic the original condition, misleading patients to believe their problems are recurring after discontinuation of the drug.

Table 1. Top 5 Drugs with Signals for Withdrawal Symptoms

Has Effect On	Drug	Number of Cases
Serotonin	Duloxetine	888
	Paroxetine	275
	Venlafaxine	119
	Desvenlafaxine	59
	Sertraline	55
GABA	Pregabalin	198
	Vigabatrin	59
	Gabapentin	45
	Clonazepam	36
	Alprazolam	34
Opioid Receptors	Buprenorphine; Naloxone	195
	Oxycodone	159
	Fentanyl	154
	Buprenorphine	130
	Naltrexone	84
Dopamine*	Quetiapine	26
	Olanzapine	19
	Methylphenidate	17
Other Mechanisms	Baclofen	315
	Cetirizine	41
	Ziconotide	22
	Omeprazole	17
	Pramipexole	13

*Only three drugs reported

The report also notes that controls, warnings, and other measures are in effect to manage the risks of long-term use and of the physiological problems that may occur when a drug is discontinued for some medications while others lack this valuable information. Opioid narcotics, benzodiazepine tranquilizers for anxiety, and other sedatives have better documented warnings and controls surrounding withdrawal, whereas warnings and patient information for antidepressants with the highest likelihood of withdrawal symptoms are inadequate. Additionally, information regarding discontinuation was not found in the package inserts for olanzapine or quetiapine and there is only a brief mention of an increased risk of seizures if pregabalin or gabapentin are abruptly discontinued.

According to the report "Widespread adult exposure to these drugs with these withdrawal symptoms is compounded by two other problems: Clinical testing for withdrawal effects ranges from limited to non-existent, and standard information for physicians and patients is inadequate for many drugs, and, in some cases, frankly misleading.

Reference

1. http://www.ismp.org/QuarterWatch/pdfs/2016Q4.pdf

Medicaid Statistics for Prescription Claims
July/August 2017

	FFS	Amerigroup	AmeriHealth	United Healthcare
# Paid Claims	25,679	409,393	484,026	350,748
Total Dollars Paid	$1,586,733	$32,255,678	$34,150,964	$24,246,473
# Unique Users	6,660	72,591	87,170	64,868
Average Cost/Rx	$59.54	$78.79	$70.56	$69.13
Top 5 Drugs by Prescription Count	Hydrocodone/APAP 5-325mg	Hydrocodone/APAP 5-325mg	Omeprazole	Omeprazole
	Tramadol 50mg	Escitalopram 20mg	Hydrocodone/APAP	Hydrocodone/APAP
	Fluoxetine 20mg	Omeprazole 40mg	Lisinopril	Lisinopril
	Trazodone 50mg	Omeprazole 20mg	Levothyroxine	Levothyroxine
	Omeprazole 20mg	Gabapentin 300mg	Sertraline	Atorvastatin
Top 5 Drugs by Paid Amount (pre-rebate)	Epclusa	Vyvanse	Vyvanse	Vyvanse
	Vyvanse	Humira Pen	Latuda	Humira Pen
	Latuda	Methylphenidate ER	Humalog	Harvoni
	Humalog	Humalog	Methylphenidate ER	Humalog
	Methylphenidate ER	Latuda	Humira Pen	Latuda
Top 5 Therapeutic Class by Paid Amount (pre-rebate) Therapeutic class taxonomy differs among each plan	Hepatitis C Agents	ADHD/Anti-Narcolepsy	Insulins	Insulin
	Anticonvulsants	Antidiabetics	Antipsychotics – Atypical, Dopamine, Serotonin Antagonist	Anti-Inflammatory TNF Inhibitors
	Antipsychotics - Atypicals	Antiasthmatic & Bronchodilator Agents	Anticonvulsants	Antipsychotics – Atypical, Dopamine, Serotonin Antagonist
	Diabetic - Insulin	Antipsychotic/AntiManic Agents	Adrenergics, Aromatic, Non-Catecholamine	Adrenergics, Aromatic, Non-Catecholamine
	Anti-Inflammatories, Non-NSAID	Analgesics – Anti-Inflammatory	Anti-Inflammatory TNF Inhibitors	Hep C Virus-NS5B Polymerase & NSA Inhib. Combo
Top 5 Therapeutic Class by Prescription Count Therapeutic class taxonomy differs among each plan	Antidepressants – Selected SSRIs	Antidepressants	Anticonvulsants	SSRIs
	Anticonvulsants	Antiasthmatic & Bronchodilator Agents	SSRIs	Anticonvulsants
	Narcotics – Misc.	Anticonvulsants	PPIs	Narcotics
	Antipsychotics - Atypical	Antihypertensives	Antipsychotic, Atypical, Dopamine, Serotonin Antagonist	PPIs
	Antihypertensives - Central	Ulcer Drugs	Antihistamines – Second Generation	NSAID, Cox Inhibitor