

Drug Use Evaluation: Combination Therapy with Antipsychotics and Other Psychotropic Drugs

Research Questions:

1. How frequently are Medicaid patients prescribed an antipsychotic in combination with another psychotropic drug? Are there age groups (e.g., children, adolescents, or adults) in which combination prescribing is more frequent?
2. How many patients are prescribed ongoing long-term combination therapy?
3. What providers commonly prescribe combination stimulants and antipsychotics?
4. What are common diagnoses for patients prescribed combination stimulants and antipsychotics?

Conclusions:

1. Frequency of combination therapy
 - Of the 29,460 patients identified with claims for an antipsychotic in 2018, 37% (n=10,989) had combination use of at least one other mental health drug. This included 738 children, 938 adolescents, and 9,313 adults.
 - The most common concurrent drug therapy included antipsychotics in combination with antidepressants (84%), benzodiazepines (17%), and stimulants (13%).
 - About 2% of all patients had claims for 5 or more mental health drugs for more than 90 days (n=237).
2. Proportion of patients with long-term combination therapy
 - More than 75% of patients with at least 90 days of concomitant therapy were likely to continue use of combination therapy beyond 150 days.
3. Prescriber characteristics of stimulant and antipsychotic co-prescribing
 - Antipsychotics were most commonly prescribed from specialists (including mental health nurse practitioners and psychiatrists).
 - In only 55% of patients, antipsychotics and stimulants were prescribed from the same provider.
4. Diagnostic characteristics of stimulant and antipsychotic co-prescribing
 - The most common indications identified via medical claims in patients prescribed antipsychotics in combination with stimulants included depression (35%), bipolar disorder (26%), autism (20%) and conduct disorder (20%). ADHD was diagnosed in 81% of patients.
 - Twenty-one percent of patient did not have an identified FDA-approved indication for antipsychotics, and 16% of patients did not have an identified indication for stimulant based on analysis of their medical claims. Other common diagnoses in this population included severe stress reactions/adjustment disorders, anxiety disorders, disorders of abuse and dependence (including opioid, alcohol, and cannabis), eating disorders (including anorexia), and other developmental or personality disorders.
 - Diagnoses related to box warnings of antipsychotics or stimulants were infrequent and most commonly pertained to suicidal ideation or suicide attempts (n=127; 9%). Diagnoses of stimulant abuse was identified in 59 patients (4%) prescribed combination antipsychotics and stimulants.

Recommendations:

- Review profiles of patients with the following high risk categories to identify opportunities for therapy optimization or de-prescribing:
 - Patients with long-term use (>90 days) of 6 or more mental health drugs (or >4 drugs in children)
 - Patients with possible contraindications to therapy for antipsychotics and stimulants (such as elderly patients with dementia-related psychosis and stimulant abuse)
 - Children without FDA-approved diagnoses or claims history indicating use of non-pharmacological psychosocial services
 - Children less than 5 years of age prescribed a stimulant or antipsychotic
- Develop a prospective safety-edit to ensure appropriate use of antipsychotics for members less than five years old when initiating therapy with an antipsychotic.

Background

Often patients with multiple chronic conditions have an associated increased risk of drug adverse events, polypharmacy, decreased quality of life and greater use of healthcare services. Use of multiple medications can be appropriate to manage patient symptoms and prevent disease progression. However, use of multiple medications can also lead to increased risk of adverse effects and drug-drug interactions. Polypharmacy becomes inappropriate when risk of adverse events outweigh medication benefits. Though definitions in the literature can vary, polypharmacy is most commonly defined as use of 5 or more concomitant medications. The 2018 Scottish Government Polypharmacy Model of Care Group, provide guidelines to identify the patients at highest risk of harm due to polypharmacy and propose approaches to improve outcomes for patients.¹ Patients at highest risk for inappropriate polypharmacy are those with greatest frailty (e.g., elderly or those in resident care homes), those on more medications (≥ 10 drugs), and those taking high-risk medications or risky combinations of medications (e.g, anticholinergics or sedating medications).¹ Current programs which examine polypharmacy in the fee-for-service Medicaid program focus on patients prescribed more than 15 medications.

Many classes of medications for mental health conditions are associated with anticholinergic effects or central nervous system depression, and risk of adverse effects can increase with concomitant use of multiple drugs. Additional drug-disease interactions can occur for patients prescribed stimulants and antipsychotics. For example, current labeling for many stimulants includes warnings and precautions for psychiatric adverse reactions.² Exacerbation of pre-existing psychosis, induction of maniac episodes in patients with bipolar disorder, and new psychotic or maniac symptoms have been documented in patients prescribed drugs to treat ADHD such as methylphenidate or atomoxetine.^{2,3} Stimulant discontinuation should be considered in patients who experience new or worsening hallucinations, delusions, or mania. Because events are primarily derived from post-marketing reports the exact incidence of psychiatric adverse reactions is unknown. Additionally antipsychotics and stimulants may have opposing effects and use of antipsychotics in conjunction with stimulant medications may decrease stimulant efficacy.⁴ Monitoring for efficacy and adverse events is recommended when these agents are used in conjunction. For patients with comorbid ADHD experiencing an acute psychotic or maniac episode, guidelines from NICE recommend discontinuation of any ADHD medication with re-initiation of therapy only after the episode has resolved and after re-assessment of risks and benefits of ADHD treatment.⁵ In adults with ADHD and comorbid aggression, rages or irritability the use of combination stimulants and antipsychotic therapy is not recommended.⁵ No adjustments to ADHD drug regimen are recommended for patients with comorbid anxiety disorder, tic disorder or autism spectrum disorder.⁵ Slower dose titration and more frequent monitoring is recommended for stimulant use in patients with comorbid mental health conditions including schizophrenia, bipolar disorder, and depression.⁵

In children and adolescents especially, the evidence supporting efficacy of combination psychotropic medications or antipsychotics is limited. Primary first-line therapy for many psychiatric conditions in children focuses on non-pharmacological treatment. Pharmacotherapy use in children or adolescents is typically only recommended in conjunction with an assessment and recommendation from a child and adolescent psychiatrist. **Table 1** lists current NICE recommendations for

pharmacotherapy in children and adolescents with mental health conditions. In all cases, use of antipsychotics in children requires frequent reassessment to evaluate treatment efficacy and monitoring for adverse effects.

Table 1. NICE guidance for treatment of mental health conditions in children and adolescents.

Condition	Involvement of child mental health specialists in prescribing	Recommendation for pharmacotherapy
Psychosis or schizophrenia ⁶	Consult upon initiation of any antipsychotic.	<ul style="list-style-type: none"> - Do not use antipsychotics unless there are sufficient symptoms to definitively diagnose psychosis or schizophrenia. - Use antipsychotics only in conjunction with psychological interventions such as CBT.
Bipolar Disorder ⁷	Consult with diagnosis of any patients younger than 14 years of age.	<ul style="list-style-type: none"> - Antipsychotic therapy may be considered to treat mania, hypomania, or moderate to severe depressive symptoms, but is not routinely recommended for longer than 12 weeks.
Depression ⁸	Consult upon initiation of pharmacotherapy. A second consultation is recommended before initiation of second-line antidepressant therapy.	<ul style="list-style-type: none"> - Pharmacotherapy should be considered only after trial and failure of psychosocial therapy. - Fluoxetine is the recommended first-line agent. - Citalopram or sertraline is recommended as a second-line option.
Autism ⁹	Consult with pediatrician or psychiatrist upon initiation of pharmacotherapy	<ul style="list-style-type: none"> - Pharmacotherapy is not routinely recommended. - Antipsychotics are recommended only with severe behavior non-responsive to psychosocial therapy. - Treatment discontinuation is recommended within 6 weeks if efficacy is not established
ADHD ⁵	Consult with 2 specialists before use of ADHD drugs in children under 5 years of age.	<ul style="list-style-type: none"> - Pharmacotherapy is not routinely recommended for children under 5 years of age. - In patients over 5 years of age, ADHD drugs are recommended only with patient and parental education and if ongoing symptoms are present after trial of environmental modifications. - Reassess ongoing need of ADHD drugs at least yearly.
Conduct Disorder or oppositional defiant disorder ¹⁰	Consult upon initiation of risperidone	<ul style="list-style-type: none"> - Routine use of pharmacotherapy is not recommended - Risperidone may be considered for short-term management of severely aggressive behavior - Treatment discontinuation is recommended within 6 weeks if efficacy is not established

Abbreviations: ADHD = attention deficit hyperactivity disorder; CBT = cognitive behavioral therapy

However, despite recommendations, use of multiple medications for mental health conditions is common in children. A recent review of Medicaid claims data from 4 states (California, New York, Illinois, Texas) identified that from 2003 to 2007 approximately 19% of children and adolescents prescribed a long-acting stimulant had concurrent use of a second-generation antipsychotic for at least 14 days.¹¹ The average length of concurrent utilization was 130 days (SD 98).¹¹ Similarly, concomitant use of antipsychotics and antidepressants is common as antipsychotics can be used to augment antidepressant therapy for treatment of depression. In another analysis of Medicaid data from 2004 to 2009 in 4 states (California, Florida, Illinois, New Jersey), approximately 43% of children and adolescents who were prescribed a second-generation antipsychotic had concomitant antidepressant use.¹² A similar proportion (43%) had concomitant stimulant and antipsychotic use.¹²

In Medicaid, several national quality metrics aim to improve use of psychotropic medications in children. Use of 2 concurrent antipsychotics for more than 90 days in children or adolescents is one of the Children’s Health Care Quality Measures for Medicaid programs. On average, 3% of the Medicaid children and adolescents prescribed antipsychotics are prescribed more than one antipsychotic for longer than 90 days.¹³ Similarly, a measure to evaluate the proportion of children and adolescents with use of first-line psychosocial care prior to use of an antipsychotic is included as part of these quality measures.¹³ In Oregon Medicaid, several ongoing programs currently evaluate antipsychotic utilization in children. They include an annual profile review for foster care children prescribed mental health medications and provider consultation for children less than 10 years of age prescribed long-term antipsychotics. The goal of this drug

use evaluation is to assess prescribing patterns for mental health medications in order to identify opportunities to improve and coordinate care for patients prescribed multiple medications.

Methods:

Included patients had a FFS claim for an antipsychotic (oral or injectable) from 1/1/18 to 12/31/18. The first FFS claim in the reporting period was classified as the index event (IE). Subgroup analyses were conducted for patients on concomitant psychotropic medications and concomitant stimulants for at least 90 days. Patients were excluded if they had Medicare Part D coverage or less than 75% of covered days in the 6 months before or after the IE. Baseline characteristics, including patient age, were assessed at the time of the IE.

The following definitions and categories were used for the analysis:

- New start patients were defined as patients without antipsychotic use in the 120 days prior to the IE.
- Prior history of antipsychotic use was evaluated in the 120 days prior to the IE.
- Adherence to antipsychotic therapy was estimated using the proportion of days covered (PDC) in the 6 months following the IE. PDC less than 25% may indicate only short-term therapy and PDC of >75% indicates long-term therapy. PDC of 25-75% may indicate therapy of medium duration, sporadic “as needed” therapy, or low adherence to long-term therapy.
- Diagnoses were identified using ICD-10 codes on medical claims in the 6 months before or after the IE (see **Appendix 1** for relevant ICD-10 codes).
- Combination therapy was defined as an overlapping period of an antipsychotic and other psychotropic medication for at least 90 days with no more than a 14 day gap in coverage. Combination use was assessed in the 6 months following the IE based on both FFS and CCO claims and stratified by PDL class (see **Appendix 1**). In patients with claims for ADHD drugs, therapy was categorized according to stimulant or non-stimulant use.
- Stimulants were defined as drugs in the Other Stimulant PDL class (modafinil, armodafinil, and solriamfetol) and stimulants in the ADHD drugs PDL class (amphetamine, dexamethylphenidate, dextroamphetamine, lisdexamphetamine, methamphetamine, and methylphenidate).
- Duration of combination drug therapy was defined as the time to the first 14 day gap in combination drug use. The number of psychotropic drugs with overlapping therapy was identified based on the number of unique molecular entities or HSNs.
- Provider specialty was identified using the primary provider taxonomy.

Results:Antipsychotic utilization

Table 2 describes characteristics for patients prescribed antipsychotics. Patients were primarily white adults. Approximately 14.5% of identified patients were children or adolescents. The majority of patients (93%) were prescribed a second generation antipsychotic and 63% had a history of antipsychotic use. About half of the identified patients had continued long-term antipsychotic use in the 6 months following the first identified claim.

Table 2. Baseline demographics for patients prescribed antipsychotics

	N=	29,460	%
Age			
Average (min - max)	36.4		(1-91)
0-4	42		0.1%
5-12	1,610		5.5%
13-18	2,627		8.9%
19-64	25,027		85.0%
65+	154		0.5%
Female	15,879		53.9%
Race			
White	17,250		58.6%
Native American	1,589		5.4%
Other	1,903		6.5%
Unknown	8,718		29.6%
Index Antipsychotic Class			
1st Gen	1,346		4.6%
2nd Gen	27,415		93.1%
Parenteral	699		2.4%
Prior Antipsychotic Use			
New start	10,766		36.5%
History of another antipsychotic	18,694		63.5%
Proportion of Days Covered in the 6 months following the IE			
>75%	15,636		53.1%
26-75%	9,221		31.3%
<=25%	4,603		15.6%

Subgroup analysis of combination antipsychotic therapy with other psychotropics

A subgroup analysis was conducted in patients with combination use of an antipsychotic and at least one other psychotropic drug for at least 90 days. Of the 29,460 patients identified with claims for an antipsychotic, 37% (n=10,989) had combination use of at least one other mental health drug (**Table 3**). The most common drug types included antidepressants (84%), benzodiazepines (17%), and stimulants (13%). The majority of prescriptions were for adult patients, though concomitant prescribing was identified in 738 children and 938 adolescents. Use of stimulants and non-stimulants for ADHD was more common in children and adolescents whereas antidepressant and benzodiazepine use was more common for adults. Because patients with Medicare were excluded from this population, only a small proportion of adults over 65 year of age were prescribed concomitant mental health drugs (n=79). About 2% of all patients had claims for 5 or more mental health drugs for more than 90 days (n=237). More than 75% of patients with at least 90 days of concomitant therapy were likely to continue use of combination therapy beyond 150 days. Duration of therapy was similar for all types of psychotropics (data not shown).

Table 3. Combination use of antipsychotics with other psychotropics stratified by age

	All		Age							
	#	%	0-12		13-18		19-64		>=65	
	#	%	#	%	#	%	#	%	#	%
Patients with >=90 day overlap by HSN	10,989		738		938		9,234		79	
Number of mental health drugs with >=90 day overlap by HSN (includes antipsychotics and psychotropics)										
2	6,890	62.7%	471	63.8%	560	59.7%	5,805	62.9%	54	68.4%
3	3,074	28.0%	193	26.2%	278	29.6%	2,584	28.0%	19	24.1%
4	901	8.2%	69	9.3%	79	8.4%	746	8.1%	7	8.9%
5	203	1.8%	8	1.1%	23	2.5%	171	1.9%	1	1.3%
≥6	34	0.3%	0	0.0%	3	0.3%	31	0.3%	0	0.0%
Patients with >=90 day overlap by Class	11,097		778		1,008		9,239		72	
Psychotropic drug type										
Antidepressant	9,329	84.1%	372	47.8%	717	71.1%	8,173	88.5%	67	93.1%
Benzodiazepine	1,826	16.5%	9	1.2%	38	3.8%	1,761	19.1%	18	25.0%
Stimulant (ADHD or other)	1,436	12.9%	411	52.8%	368	36.5%	657	7.1%	0	0.0%
ADHD non-stimulant	801	7.2%	305	39.2%	268	26.6%	228	2.5%	0	0.0%
Sedative	237	2.1%	0	0.0%	7	0.7%	230	2.5%	0	0.0%
Patients with concomitant use for more than 2 antipsychotics >90 days (based on HSN)	82	0.7%	0	0.0%	1	0.1%	80	0.9%	1	1.4%

Combination stimulant and antipsychotic use

Common indications associated with antipsychotic and stimulant use are shown in **Table 4**. Common indications identified via medical claims in patients prescribed antipsychotics in combination with stimulants included depression (35%), bipolar disorder (26%), autism (20%) and conduct disorder (20%). ADHD was diagnosed in 81% of patients. Twenty-one percent of patient did not have an identified indication for antipsychotics, and 16% of patients did not have an identified indication for stimulant based on analysis of their medical claims. However, other common mental health diagnoses present in this population which may be related to prescribing included severe stress reactions/adjustment disorders (such as PTSD), anxiety disorders, disorders of abuse and dependence (including opioid, alcohol, and cannabis), eating disorders (including anorexia), and other developmental or personality disorders. Diagnoses related to box warnings of antipsychotics or stimulants were infrequent and most commonly pertained to suicidal ideation or suicide attempts (n=127; 9%). Diagnoses of stimulant abuse was identified in only 59 patients (4%) prescribed combination antipsychotics and stimulants.

Table 4. Diagnoses in patients with combination stimulant and antipsychotic use. Patients with multiple diagnoses may be counted more than once.

	N	%
	1,436	
Antipsychotic FDA-Approved Indications	1,127	78.5%
Depression	500	34.8%
Bipolar Disorder	374	26.0%
Autism	293	20.4%
Conduct Disorder	293	20.4%
Other Psychotic Disorder*	133	9.3%
Schizophrenia	46	3.2%
Tourette Disorder	27	1.9%
None of the above	309	21.5%
Stimulant FDA-Approved Indications	1,205	83.9%
ADHD	1,164	81.1%
OSA	92	6.4%
Narcolepsy	14	1.0%
Binge Eating Disorder	12	0.8%
None of the above	231	16.1%
Diagnoses related to Black Box Warnings	167	11.6%
Suicidal ideation or suicide attempt	125	8.7%
Stimulant abuse	59	4.1%
Dementia-related psychoses	3	0.2%

* Includes Schizotypal, delusional, brief psychotic, shared psychotic, schizoaffective disorders, and other or unspecified psychotic disorders not due to a known substance or psychological condition. *The most frequent psychiatric diagnosis for patients prescribed stimulants and antipsychotics (top 20) was identified based on ICD-10 codes beginning with F and grouped by category using the first 3 characters of the ICD-10 code.

Prescribers associated with prescription of more than 1% of antipsychotics in patients with concomitant stimulant use are listed in **Table 5**. Antipsychotics were most commonly prescribed from specialists (including mental health nurse practitioners and psychiatrists). In about 55% of patients, antipsychotics and stimulants were prescribed from the same provider (**Table 6**). A small proportion of patients had 4 or more prescribers involved in prescribing stimulants and antipsychotics (n=87, 6%).

Table 5. Most common prescriber types for antipsychotic IE in patients with combination antipsychotic/stimulant use

Patients with overlapping antipsychotic and stimulant		1,436	%
#	Index Prescriber taxonomy		
1	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	479	33.4%
2	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	302	21.0%
3	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CHILD&ADOLESCENT PSYCHIATRY	194	13.5%
4	PHYSICIAN-PEDIATRICS	96	6.7%
5	PHYSICIAN-FAMILY MEDICINE	93	6.5%
6	NURSE PRACTITIONER - FAMILY	67	4.7%
7	PHYSICIAN-INTERNAL MEDICINE	27	1.9%
8	PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVIORAL PEDIATRICS	25	1.7%
9	PHYSICIAN ASSISTANT	25	1.7%
10	PHYSICIAN ASSISTANT - MEDICAL	22	1.5%
11	NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	21	1.5%

Table 6. Number of prescribers involved in concomitant antipsychotic and stimulant therapy

Patients with overlapping antipsychotic and stimulant		1,359	%
Number of prescribers for combination therapy			
1		743	54.7%
2		359	26.4%
3		170	12.5%
4		59	4.3%
≥5		28	2.1%

Limitations:

Data presented in this report is based on Medicaid claims history that has several inherent limitations.

- **Diagnostic accuracy:** Diagnoses based on claims history may be inaccurate or incomplete. Because diagnoses are not associated with prescriptions, it is difficult to determine the intended indication for the drug, particularly when therapy is used off-label. Additionally, many patients in this analysis were enrolled in coordinated care organizations and delays in submission and processing of medical claims data may result in missed diagnoses.
- **Provider specialty:** Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified.
- **Days of coverage:** Estimates of covered days attempts to approximate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately. Days' supply submitted on claims (particularly injectable antipsychotics) may be inaccurate and estimates of PDC do not include medical claims.
- **Definitions for new start patients:** Prior use of mental health medications was only evaluated in the 120 days prior to the IE. Patients may have a remote history of antidepressant use beyond this date which could influence choice in current therapy.

References:

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Appendix 1: Drug Coding

Table A1. Antipsychotic Drug Classes

<u>Class</u>	<u>HSN</u>	<u>Generic</u>
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001661	haloperidol lactate
Antipsychotics, 1st Gen	039886	loxapine
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001667	thiothixene HCl
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine

<u>Class</u>	<u>HSN</u>	<u>Generic</u>
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl
Antipsychotics, Parenteral	024551	aripiprazole
Antipsychotics, Parenteral	042595	aripiprazole lauroxil
Antipsychotics, Parenteral	045050	aripiprazole lauroxil,submicr.
Antipsychotics, Parenteral	001621	chlorpromazine HCl
Antipsychotics, Parenteral	001624	fluphenazine decanoate
Antipsychotics, Parenteral	001626	fluphenazine HCl
Antipsychotics, Parenteral	001660	haloperidol decanoate
Antipsychotics, Parenteral	001661	haloperidol lactate
Antipsychotics, Parenteral	011814	olanzapine
Antipsychotics, Parenteral	036716	olanzapine pamoate
Antipsychotics, Parenteral	036479	paliperidone palmitate
Antipsychotics, Parenteral	008721	risperidone
Antipsychotics, Parenteral	025509	risperidone microspheres
Antipsychotics, Parenteral	001630	trifluoperazine HCl
Antipsychotics, Parenteral	023379	ziprasidone mesylate

Table 2. Combination Psychotropic Drugs

<u>Class</u>	<u>HSN</u>	<u>Generic</u>	<u>Class</u>	<u>HSN</u>	<u>Generic</u>
ADHD Drugs	043652	amphetamine	Antidepressants	040632	levomilnacipran HCl
ADHD Drugs	002064	amphetamine sulfate	Antidepressants	001651	maprotiline HCl
ADHD Drugs (non-stimulant)	024703	atomoxetine HCl	Antidepressants	011505	mirtazapine
ADHD Drugs (non-stimulant)	000113	clonidine HCl	Antidepressants	009612	nefazodone HCl
ADHD Drugs	022987	dexmethylphenidate HCl	Antidepressants	001644	nortriptyline HCl
ADHD Drugs	002065	dextroamphetamine sulfate	Antidepressants	025800	olanzapine/fluoxetine HCl
ADHD Drugs	013449	dextroamphetamine/amphetamine	Antidepressants	007344	paroxetine HCl
ADHD Drugs (non-stimulant)	000120	guanfacine HCl	Antidepressants	025796	paroxetine mesylate
ADHD Drugs	034486	lisdexamphetamine dimesylate	Antidepressants	001639	phenelzine sulfate
ADHD Drugs	002067	methamphetamine HCl	Antidepressants	001646	protriptyline HCl
ADHD Drugs	033556	methylphenidate	Antidepressants	033510	selegiline
ADHD Drugs	001682	methylphenidate HCl	Antidepressants	006324	sertraline HCl
Antidepressants	001643	amitriptyline HCl	Antidepressants	001640	tranylcypromine sulfate
Antidepressants	001648	amoxapine	Antidepressants	001652	trazodone HCl
Antidepressants	045692	brexanolone	Antidepressants	001649	trimipramine maleate
Antidepressants	036156	bupropion HBr	Antidepressants	008847	venlafaxine HCl
Antidepressants	001653	bupropion HCl	Antidepressants	037597	vilazodone HCl
Antidepressants	010321	citalopram hydrobromide	Antidepressants	040637	vortioxetine hydrobromide
Antidepressants	004744	clomipramine HCl	Benzodiazepines	001617	alprazolam
Antidepressants	001645	desipramine HCl	Benzodiazepines	001656	amitriptyline/chlordiazepoxide
Antidepressants	040202	desvenlafaxine	Benzodiazepines	001610	chlordiazepoxide HCl
Antidepressants	040692	desvenlafaxine fumarate	Benzodiazepines	002037	chlordiazepoxide/clidinium Br
Antidepressants	035420	desvenlafaxine succinate	Benzodiazepines	001894	clonazepam
Antidepressants	001650	doxepin HCl	Benzodiazepines	001612	clorazepate dipotassium
Antidepressants	026521	duloxetine HCl	Benzodiazepines	001615	diazepam
Antidepressants	024022	escitalopram oxalate	Benzodiazepines	004846	lorazepam
Antidepressants	041003	esketamine HCl	Benzodiazepines	001616	oxazepam
Antidepressants	001655	fluoxetine HCl	Other Stimulants	034868	armodafinil
Antidepressants	006338	fluvoxamine maleate	Other Stimulants	010865	modafinil
Antidepressants	001641	imipramine HCl	Other Stimulants	045666	solriamfetol HCl
Antidepressants	001642	imipramine pamoate	Sedatives	004480	diphenhydramine HCl
Antidepressants	001638	isocarboxazid	Sedatives	001650	doxepin HCl
			Sedatives	004482	doxylamine succinate

Sedatives	006036	estazolam	Sedatives	040927	tasimelteon
Sedatives	026791	eszopiclone	Sedatives	001592	temazepam
Sedatives	001593	flurazepam HCl	Sedatives	001594	triazolam
Sedatives	001619	midazolam HCl	Sedatives	020347	zaleplon
Sedatives	033126	ramelteon	Sedatives	007842	zolpidem tartrate
Sedatives	041333	suvorexant			

Table 3. ICD-10 codes for relevant psychiatric diagnoses

ICD-10	Diagnosis
F20x	Schizophrenia
F31x	Bipolar Disorders
F32x-F33x	Major Depressive Disorder
F840	Autism
F91x	Conduct Disorders
F952	Tourette's disorder
F21x-F29x	Other Psychotic Disorders
F90x	ADHD
G474x	Narcolepsy
F5081	Binge Eating Disorder
G4733	Obstructive Sleep Apnea
F0281, F0391, F0151	Dementia with behavioral disturbance
R4585x, T1491	Homicidal and suicidal ideations; suicide attempt
F15x	Stimulant abuse