CONCURRENT PRESCRIBING OF OPIOIDS AND ANTIPSYCHOTICS

BACKGROUND

Harmful drug interactions may result from the concomitant prescribing of opioids and other central nervous system (CNS) depressants. CNS depression caused by concomitant opioid and CNS depressant use can result in sedation, impaired thoughts, slowed response time, slowed or difficult breathing and death. In 2016 the U.S. Food and Drug Administration issued a drug safety communication warning about serious risks and death when combining opioid pain medicines with other drugs that suppress the CNS. Antipsychotics were listed among the agents associated with potential risk when prescribed along with opioids.[1]

Due to the known potential for abuse associated with opioids, antipsychotics with abuse potential are of particular interest. Among antipsychotics, quetiapine is commonly prescribed off-label to treat sleeplessness or substance abuse withdrawal symptoms. Quetiapine, the most common antipsychotic associated with abuse, has been linked to the street names of "Susie Q," "baby-heroin," and "squirrel." [2] Certain antipsychotics can prolong the QTc interval causing Torsades de Pointes (TdP) which increases the risk of death. These include but are not limited to the antipsychotics aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, olanzapine, paliperidone, perphenazine, pimavanserin, pimozide, quetiapine, risperidone, thioridazine, and ziprasidone.

During the 2018 federal legislative session, the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act received overwhelming approval by the U.S. Congress and was signed into law. The SUPPORT Act's comprehensive legislation addresses various aspects of the opioid epidemic including treatment, prevention, recovery, and enforcement. Section 1004 of the SUPPORT Act contains the Medicaid provisions that pertain to drug review and utilization. This section requires state Medicaid programs to have drug utilization review safety edits for opioid prescription refills and an automated claims review process to identify refills in excess of state limits, monitor concurrent prescribing of opioids and benzodiazepines or antipsychotics, and require managed care plans to have these automated processes in place effective 10/1/19. States also must have a program to monitor and report annually on antipsychotic prescribing for children and a process to identify potential controlled substance fraud or abuse by Medicaid enrollees, providers or pharmacies. States must submit updated state plan amendments (SPAs) incorporating the new SUPPORT Act

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[1] FDA Drug Safety Communication. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016. https://www.fda.gov/media/99761/download. Accessed April 2019.

[2] Kim S, Lee G, Kim E, Jung H, Chang J. Quetiapine Misuse and Abuse: Is it an Atypical Paradigm of Drug Seeking Behavior?. *J Res Pharm Pract*. 2017;6(1):12–15. doi:10.4103/2279-042X.200987

requirements no later than December 31, 2019.[3] Most of the provisions of the SUPPORT Act pertaining to Medicaid drug review and utilization were already established or in development by many state Medicaid programs. As an initial step towards developing the required automatic claims review described in Section 1004 of the SUPPORT ACT, MS-DUR conducted a claims analysis of concomitant opioid and antipsychotic use for the 2018 calendar year.

METHODS

A retrospective analysis was conducted using Mississippi Medicaid pharmacy claims data across Fee-For-Service (FFS) and the three coordinated care organizations (CCO), UnitedHealthcare (UHC), Magnolia Health (MAG), and Molina Healthcare (MOL), for the period of January 2018 through December 2018. Beneficiaries who had at least one antipsychotic (AP) claim in 2018 were included. Beneficiaries who had a diagnosis for cancer or sickle cell disease in 2017-2018 were excluded. Opioid claims were obtained for these beneficiaries in 2018. Concomitant users were identified as beneficiaries who had at least one day of overlapping use between an AP and an opioid. The number of beneficiaries and claims associated with concomitant use were calculated based on the following AP drug classifications:

- quetiapine (≤200mg),
- quetiapine (>200mg),
- QTc prolonging atypical APs (excluding quetiapine),
- QTc prolonging typical APs
- Other atypical APs
- Other typical APs.

Beneficiaries' enrollment information on the date of AP fill was used to assign the corresponding CCO or FFS plan. Chronic concomitant users were identified as those who had at least one day of overlapping use between an AP and an opioid in three or more consecutive months.

RESULTS

Antipsychotics were grouped into categories by potential drug interactions or relevant adverse event profiles when examining concomitant opioid use. Atypical and typical antipsychotics most commonly correlated with higher risk of QTc prolongation were grouped into individual categories. The remaining atypical and typical antipsychotics were placed into respective categories as well.

[3] Federal Legislation to Address the Opioid Crisis: Medicaid Provisions in the SUPPORT Act. Kaiser Family Foundation. October 5, 2018. https://www.kff.org/medicaid/issue-brief/federal-legislation-to-address-the-opioid-crisis-medicaid-provisions-in-the-support-act/. Accessed April 2019.

Characteristics of beneficiaries who concomitantly received opioids and antipsychotics in 2018 are:

- A total of 3962 unique beneficiaries experienced concomitant use of opioids and antipsychotics.
- 93% of beneficiaries with concomitant opioid and antipsychotic use were between the ages of 18-65 years.
- Only 7% of beneficiaries below 18 years of age and < 1% of those beneficiaries > 65 years of age received opioids and antipsychotics concomitantly. These age groups are potentially at higher risk for adverse events due to concomitant use.
- 71% of concomitant use occurred in females.

TABLE 1. Charactersitics of Beneficiaries with Concomitant Use of Antipsychotics and Opioids in Mississippi Medicaid by Plan January 2018 - December 2018

Characteristic	Pharmacy Plan				
	FFS	UHC	Mag	Mol	Total
Age group					
0 to 17 years	80 (10.90%)	88 (6.20%)	114 (6.40%)	1 (3.33%)	283 (7.14%)
18 to 35 years	173 (23.57%)	370 (26.06%)	488 (27.45%)	15 (50.00%)	1046 (26.40%)
36 to 65 years	472 (64.30)	961 (67.68%)	1175 (66.09%)	14 (46.67%)	2622 (66.18%)
66+ years	9 (1.23%)	1 (0.06%)	1 (0.06%)	0 (0.00%)	11 (0.28%)
Gender					
Female	459 (62.53%)	1019 (71.76%)	1325 (74.52%)	23 (76.67%)	2826 (71.33%)
Male	275 (37.47%)	401 (28.24%)	453 (25.48%)	7 (23.33%)	1136 (28.67%)
Race					
Caucasian	410 (55.86%)	690 (48.59%)	835 (46.96%)	13 (43.33%)	1948 (49.16%)
African American	274 (37.33%)	590 (41.55%)	799 (44.94%	16 (53.34%)	1679 (42.38%)
Other	50 (6.81%)	140 (9.86%)	144 (8.10%)	1 (3.33%)	335 (8.46%)

Note:
FFS = Fee-for-service, UHC = United Health Care, Mag = Magnolia, Mol = Molina.
Plan is based on beneficiary enrollment as of the date of antipsychotic fill.

A summary of concomitant use of antipsychotics and opioids in Mississippi Medicaid between January 2018 and December 2018 from Table 2 below is:

- Beneficiaries prescribed multiple antipsychotics who had a concomitant opioid claim could be present in multiple categories.
- A total of 9083 instances of concomitant opioid and antipsychotic use occurred in 2018 impacting 3962 unique beneficiaries.
- Concomitant use of opioids and quetiapine comprised approximately 42% of concomitant events.
- QTc prolonging antipsychotics and opioids accounted for approximately 90% of concomitant claims.

Table 2. Concomitant Use of Antipsychotics (APs) and Opioids in Mississippi Medicaid - Claims and Benes by Plan
January 2018 - December 2018

Drug type	FFS		UHC		Mag		Mol	
	Benes	Claims	Benes	Claims	Benes	Claims	Benes	Claims
Quetiapine (<200mg)	189	323	324	653	392	794	7	10
Quetiapine (>=200mg)	121	244	282	772	361	972	6	7
QTc prolonging atypical APs (excluding quetiapine)	383	789	696	1440	862	1652	13	14
QTc prolonging typical APs	48	100	86	203	96	203	1	2
Other atypical APs	36	93	138	301	151	342	3	3
Other typical APs	16	29	40	52	60	84	0	0

Note:
AP = Antipsychotic, FFS = Fee-for-service, UHC = United Health Care, Mag = Magnolia, Mol = Molina.
Plan is based on beneficiary enrollment as of the date of AP fill.
QTc prolonging atypical APs (excluding quetiapine) include aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, pimavanserin, risperidone, ziprasidone.
QTc prolonging typical APs include chlorpromazine, haloperidol, perphenazine, pimozide, thioridazine.
Other atypical APs include brexpiprazole, cariprazine, lurasidone.
Other typical APs include fluphenazine, loxapine, prochlorperazine, thiothixene, trifluoperazine.

References for AP classification:
1. https://www.accessdata.fda.gov/scripts/cder/daf/
2. https://crediblemeds.org/index.php/drugsearch

Table 3 illustrates claims level analysis of days of overlap in concomitant use of opioids and antipsychotics. This table shows the number of claims and the individual durations of overlap for concomitant use of antipsychotics and opioids.

- 57% of concomitant overlap was for short-term use of opioids defined by ≤ 14 days.
- 43% of overlap occurred for ≥15 days.
- MS-DUR calculated the number of beneficiaries with chronic concomitant use (identified as beneficiaries who had at least one overlapping day of use of opioids and antipsychotics for three or more consecutive months) and identified **258** beneficiaries as chronic concomitant users in 2018.

Table 3. Days of Concomitant Use of Antipsychotics and Opioids in Mississippi Medicaid
January 2018 - December 2018

Drug type	Number of claims				
	Less than 3 days	4 to 7 days	8 to 14 days	15 to 30 days	31+ days
Quetiapine (<200mg)	308	312	297	855	8
Quetiapine (>=200mg)	328	386	332	946	3
QTc prolonging atypical APs (excluding quetiapine)	902	846	635	1499	13
QTc prolonging typical APs	116	99	87	206	0
Other atypical APs	136	124	121	358	0
Other typical APs	47	61	24	33	0

Note:
QTc prolonging atypical APs (excluding quetiapine) include aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, pimavanserin, risperidone, ziprasidone.
QTc prolonging typical APs include chlorpromazine, haloperidol, perphenazine, pimozide, thioridazine.
Other atypical APs include brexpiprazole, cariprazine, lurasidone.
Other typical APs include fluphenazine, loxapine, prochlorperazine, thiothixene, trifluoperazine.
31+ days category was created based on trends observed in data. Corresponding AP claims had greater than 30 days of supply.

References for AP classification:
1. https://www.accessdata.fda.gov/scripts/cder/daf/
2. https://crediblemeds.org/index.php/drugsearch

CONCLUSIONS AND RECOMMENDATIONS

The concomitant use of opioids and antipsychotics may place beneficiaries at higher risk of harmful effects. With the approval of the SUPPORT Act and implementation deadline October 1, 2019, Mississippi DOM plans to establish an automatic claims review process to monitor the concomitant use of opioids and antipsychotics. The MS-DUR claims data indicates nearly 4,000 beneficiaries experienced concomitant therapy with opioids and antipsychotics in 2018. One option is a prospective DUR edit alerting pharmacists of the potential risks associated with concomitant use. Alternatively, a retrospective DUR approach could entail educational mailings to providers targeting all concomitant prescribing, concomitant prescribing of antipsychotics associated with abuse, sedation, CNS depression and /or QTc prolongation. DOM must determine what type of automatic claims monitoring is most appropriate for MS Medicaid beneficiaries.

Recommendations:

1. MS-DUR should work with the DOM to develop an automatic claims review process to monitor concomitant use of opioids and antipsychotics and implement the process prior to October 1, 2019.

2. MS-DUR should implement an educational initiative to notify providers and/or pharmacists, depending on the review process being initiated.