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ONLINE SUPPLEMENT CONTENT

Supplemental Methods Notes

Study Population and Design

The MAX data, extracted from the states' Medicaid Statistical Information System (MSIS), and the Medicare data, contain information on eligibility, demographic characteristics, diagnoses, and service and pharmacy utilization.

Medicaid and Medicare data for dual eligibles were linked through a common identifier. Only beneficiaries with full dual Medicaid-Medicare coverage were described as dual eligibles, a population for whom Medicare is the main payer. Continuous enrollment was evaluated during the 12-month period surrounding the SGA prescription, and defined as enrolled for at least five of the six months preceding the SGA fill and five of the six months following the month of the SGA fill. Continuous enrollment for Medicare and dually eligible beneficiaries was defined based on Parts A, B, and D enrollment.

Ascertainment of Mental Illness

We ascertained serious mental illness (SMI) diagnoses by requiring at least one primary inpatient discharge or two primary or secondary outpatient ICD-9 diagnosis in claims from two different days indicating *schizophrenia* (295.0–295.9), *bipolar I disorder* (296.0, 296.1, 296.4–296.7), or *severe MDD* (296.2x and 296.3x, with 5th digit indicating severe subtype with or without psychosis) during the 12-month period surrounding the SGA prescription. Beneficiaries lacking 5th digit codes met criteria if MDD codes were observed as primary discharge diagnosis in ≥ 2 occasions, or if ≥ 1 claim with electroshock therapy, trans-cranial magnetic stimulation, or suicide-related injury codes were observed during the 12-month period. Although SGAs are FDA-approved only for augmentation of antidepressant treatment, we did not require observation of a concurrent antidepressant because we might have missed antidepressant drugs prescribed prior to the six-months preceding the SGA fill and discontinued due to inefficacy or intolerance. Beneficiaries qualifying for more than one of these diagnoses were assigned a single primary diagnosis based on phenomenological hierarchy (schizophrenia highest and severe MDD lowest), frequency, and recency of diagnosis.[1] Because the MAX data restrict the number of diagnoses per claim to a maximum of two while Medicare claims can have up to 25 diagnoses, our analyses restricted the number of Medicare diagnoses to those observed in the first two diagnostic slots to balance the amount of observable information among the payers. We repeated all analyses making full use of the 25 diagnosis slots available in the Medicare data.

We captured diagnostic information from FFS claims indicating face-to-face inpatient or outpatient encounters. If inpatient admissions were observed, we looked for on-label diagnoses in claims found in the Medpar (Medicare) and Inpatient (MAX/Medicaid) files. For outpatient encounters, we looked for on-label diagnoses in Part A outpatient claims found in the Outpatient file and Part B professional claims found in the Carrier file (Medicare), and claims found in the Other Therapy file (MAX/Medicaid).

We defined *other mental illness* as one or more claims with other mental illness ICD-9 codes in any position during the 12-month period (codes 290-319 except for the above mentioned SMI diagnosis codes); *no mental illness* implied the absence of ICD-9 codes 290-319.

Covariates

FFS Payer (time-varying). Person-months were classified as Medicaid, Medicare, or dual eligible. Because we distributed utilization over the period covered by the days supply of the prescription, for beneficiaries switching payers from month to month, person-months might include utilization and costs covered by more than one payer. In those instances, we assigned the person-month to the payer covering the largest share of the average monthly standardized dose.

Race/ethnicity (time-invariant). We focused on non-Latino whites, Blacks, and Latinos, excluding subjects of other race/ethnicity due to small numbers. Medicaid and Medicare largely collect self-reported race/ethnicity data. Much of the demographic data on Medicaid beneficiaries is collected through a paper or online application during the eligibility determination and enrollment processes, with additional data collected during the renewal or redetermination processes in some states. Although states vary in the completeness of the race/ethnicity data as several states do not require applicants to self-report race/ethnicity in their Medicaid applications, CA, the largest contributor to Medicaid beneficiaries in our study, does collects race and ethnicity information.[2] Because the MAX data includes an "Unknown" category often used for individuals with Latino ethnicity,[3] we employed a previously developed algorithm[4] to reclassify race/ethnicity for individuals having unknown race/ethnicity in some but not all years. The Medicare program obtains race/ethnicity information from the Social Security Administration (SSA), collected at the time of application for a Social Security Number and transferred to the Centers for Medicare & Medicaid Services' (CMS's) Medicare program's enrollment database. Despite multiple efforts by CMS to fill in missing data, the race/ethnicity information is particularly incomplete for beneficiaries of race/ethnicity other than white and black. As a result, the program also includes a race/ethnicity variable developed at the Research Triangle Institute (RTI) that improves classification of Latinos (Hispanics) and Asians/Pacific Islanders through an imputation algorithm based on names from the US Census and geography to;[5] this variable was recently found to perform quite well relative to the gold standard (self-reported race/ethnicity).[6] We used the RTI variable to ascertain race/ethnicity just like CMS, which uses the RTI variable to report on racial/ethnic disparities among Medicare beneficiaries.[7]

Age in months at study entry (time invariant): For each subject, we determined their age at their index SGA prescription fill, measured in months, and centered their age by subtracting the average age at entry for all subjects in the state.

Neuropsychiatric Morbidity variables (most time-varying). These variables were operationalized similarly as the SMI diagnoses. We focused on anxiety disorders including

generalized anxiety disorder, phobias, and panic disorder; obsessive compulsive disorder; post-traumatic stress disorder; and cognitive disorders including intellectual disability. The cognitive disorders variable was the only time-invariant variable as we assumed unremitting chronicity for this morbidity.

Time variables. We separated time into a cross-sectional component (fiscal year of index SGA prescription for each subject) and a longitudinal component operationalized as the subject's age (in months) at each SGA prescription fill centered at the subject's age at index prescription, effectively quantifying months from the index fill. We denote the variable quantifying the longitudinal component as "aging." The coefficient of the cross-sectional component quantifies the association between year of the index SGA prescription fill (relative to the baseline year) and the log-odds of an off-label prescription whereas the coefficient of the longitudinal component (aging) quantifies the monthly change in the log-odds of an off-label SGA prescription.

Statistical Analysis

Off-Label utilization analyses: Generalized estimating equations linked the log-odds of an off-label SGA prescription fill to race/ethnicity, payer, sex, age at index SGA fill, neuropsychiatric morbidity variables, year of index SGA fill (cross-sectional component), and aging (longitudinal component). We used an AR(1) error structure to account for repeated monthly observations for each person. Because both age at entry and aging are measured in months, we report estimates for a 60-month [5-year] increase of age at index SGA fill and a 12-month temporal (aging) change.

*Payer*Race Interaction tests:* We tested interaction terms using chi-square tests — given 4 states having 1 interaction term each and an overall type I error 0.05, we required p-values of 0.0125 or smaller to meet statistical significance. For significant interaction terms, we calculated marginal means for each subgroup by averaging over all other model covariates and determined corresponding 95% confidence intervals of the probability of a monthly off-label SGA prescription.

Dose-Related analyses: Generalized estimating equations linked average monthly standardized dose to off-label status and other model variables using a log-link, normal between-person error, and AR(1) within-person error.

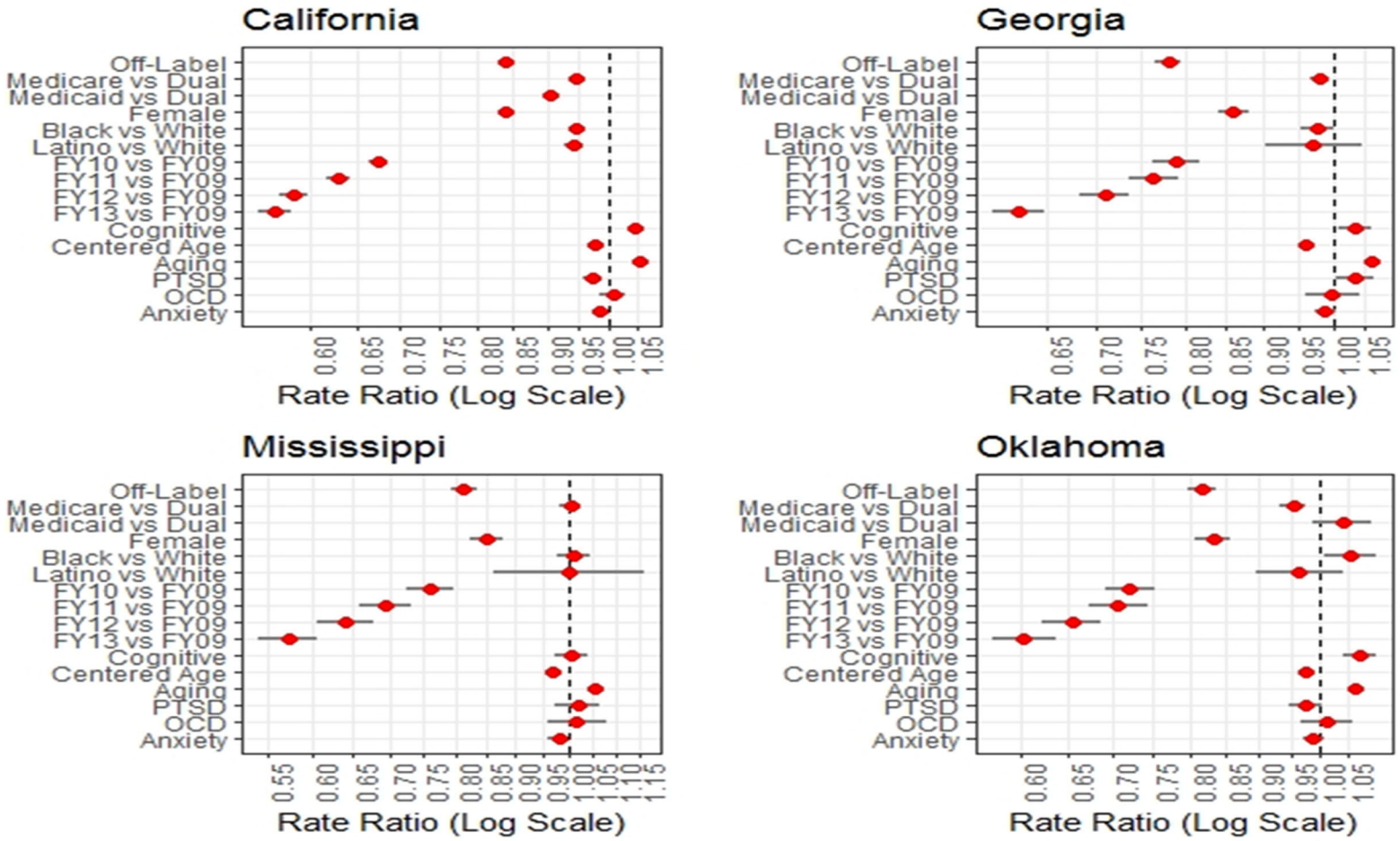
Multiplicity: Confidence intervals are not adjusted for multiplicity of estimation. Tests of the payer by race interactions within state were adjusted for multiple testing.

Sensitivity Analyses

Drug class effects: Unadjusted person-level rates were re-estimated after removing the assumption of class effects and reclassifying person-months as off-label if the specific SGA was not FDA-approved for observed diagnosis. Rates of always off-label utilization were 2% to 4% higher compared to unadjusted rates when class effects were ignored.

Variable number of diagnoses available in Medicare versus Medicaid: Unadjusted rates models were re-estimated utilizing all the diagnosis slots in the Medicare care data. As expected, the percent of beneficiaries within each state categorized as always off-label decreased compared to only using the first 2 diagnosis slots. The size of the reduction varied by the state-specific Medicare penetration. However, the percentages of always off-label utilization remained high (Supplemental Table 1).

Supplemental Figure. Rate (95% CI) of average monthly standardized dose (expressed as Defined Daily Dose) relative to the reference category. We report estimates for a 60-month [5-year] increase of age at entry and a 12-month temporal (aging) change.



Supplemental Table. **Percentages of Study Cohorts Characterized by Off-Label Status Using Two (Primary Analysis) versus All Diagnosis Slots, by State.** [^] Rates were estimated without assuming class SGA effects, i.e., SGA deemed on-label only if FDA-approved for the specific disorder.

State	California		Georgia		Mississippi		Oklahoma	
Unit	People	Person-Months	People	Person-Months	People	Person-Months	People	Person-Months
Off-label status using 2 Dx, %								
Off-label		38.6		32.8		38.4		38.8
Never Off-label [^]	44.2 [41.2]		52.3 [46.9]		47.4 [42.3]		49.2 [43.3]	
Always Off-label [^]	41.4 [43.5]		36.5 [40.6]		41.9 [45.2]		39.9 [43.5]	
Off-to-On Label [^]	14.4 [15.3]		11.2 [12.5]		10.7 [12.5]		10.8 [13.2]	
Off-label status using all Dx, %								
Off-label		39.9		29.0		35.7		32.8
Never Off-label [^]	37.6 [35.3]		56.0 [50.6]		50.1 [45.0]		55.6 [49.6]	
Always Off-label [^]	40.7 [42.7]		33.0 [37.1]		38.9 [42.2]		33.3 [37.1]	
Off-to-On Label [^]	21.0 [22.0]		11.0 [12.3]		11.1 [12.8]		11.1 [13.3]	

Supplemental Table. Annualized SGA Costs, mean $ (SD), by State, Year, and Payer, Inflation-adjusted to June 2013.

California										
	FY09		FY10		FY11		FY12		FY13	
Off-label	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Medicare	4871 (4844)	6117 (5542)	4295 (4410)	5758 (5419)	4242 (4496)	5958 (5861)	4067 (4769)	5798 (6095)	2631 (3643)	3930 (5054)
Medicaid	5796 (4789)	7898 (5798)	5266 (4911)	7227 (5837)	5159 (4870)	7393 (6045)	5167 (4957)	7447 (6511)	5368 (5106)	8428 (7269)
Dual eligible	6057 (5277)	7780 (5995)	5758 (5424)	7670 (6330)	5753 (5688)	7881 (6818)	5550 (5739)	7890 (7137)	3612 (4411)	5620 (6126)
Georgia (No FFS Medicaid)										
	FY09		FY10		FY11		FY12		FY13	
Off-label	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Medicare	4031 (3824)	5545 (4653)	3782 (3944)	5456 (5127)	3811 (4126)	5528 (5361)	3897 (4215)	5526 (5553)	2336 (3195)	3624 (4543)
Dual eligible	4613 (4094)	6508 (5142)	4159 (4231)	6304 (5662)	4062 (4355)	6419 (6040)	4075 (4694)	6485 (6422)	2384 (3508)	4188 (5147)
Mississippi (No FFS Medicaid)										
	FY09		FY10		FY11		FY12		FY13	
Off-label	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Medicare	4981 (4533)	6155 (4926)	4632 (4572)	5869 (5155)	4434 (4377)	6142 (5836)	4470 (4411)	6179 (5714)	3039 (3441)	4183 (4708)
Dual eligible	4938 (4183)	6577 (4971)	4741 (4390)	6437 (5343)	4795 (4663)	6660 (5804)	4728 (4803)	6777 (6192)	3250 (3835)	4802 (5364)
Oklahoma										
	FY09		FY10		FY11		FY12		FY13	
Off-label	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Medicare	4166 (3504)	5440 (4548)	4051 (3706)	5569 (5082)	3880 (3933)	5549 (5373)	3812 (4079)	5510 (5370)	2617 (3199)	3971 (4853)
Medicaid	6833 (6199)	8942 (6801)	5974 (5873)	7068 (6401)	6248 (6166)	7682 (6940)	5778 (6377)	6860 (6433)	3357 (5244)	5163 (5599)
Dual eligible	5715 (4637)	7125 (5271)	5490 (4885)	7048 (5648)	5362 (5164)	6918 (5902)	5278 (5244)	7098 (6367)	3530 (3949)	5482 (5690)

Supplemental References

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