AWARD NUMBER: W81XWH-16-1-0210

TITLE: Improving Care for Veterans with PTSD: Comparing Risks and Benefits of Antipsychotics versus Other Medications to Augment First-line Pharmacologic Therapy

PRINCIPAL INVESTIGATOR: Beth Cohen, MD, MAS

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education Inc. (NCIRE)

REPORT DATE: January 2020

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
January 2020	Final Report	30 Sept 2016 – 29 Sept 2019

4. TITLE AND SUBTITLE
Improving Care for Veterans with PTSD: Comparing Risks and Benefits of Antipsychotics versus other Medications to Augment First-line Pharmacologic Therapy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0210

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Beth Cohen, MD, MAS; Thomas Neylan, MD; Nancy Bernary, PhD, Karen Seal, MD, MPH;

W. John Boscardin, PhD; Shira Maguen, PhD

E-Mail: Beth.Cohen@ucsf.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Northern California Institute
for Research and Education Inc.
4150 Clement Street (151NC)
San Francisco, CA 94121-1545

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The goal of this project was to use national Veterans Affairs (VA) healthcare data to determine the benefits and risks of use of antipsychotic medications to augment first-line medication therapy in patients with posttraumatic stress disorder (PTSD). We found that patients prescribed antipsychotics or a variety of non-antipsychotic psychiatric medications had small but similar improvements in PTSD symptoms. They had larger improvements in mental health emergency room visits and hospitalizations, suggesting these medications may be of most benefit to those with worsening symptoms/instability. We also found several of these medications, particularly antipsychotics and mirtazapine, were associated with weight gain and other metabolic harms. Though our findings are from observational data and cannot prove causal associations, they suggest patients prescribed these augmenting medications should be carefully observed for treatment response and potential harms. They also highlight the importance of clinical trials dedicated to comparing treatment options in patients who do not have an adequate response to first-line therapy.

15. SUBJECT TERMS
PTSD, treatment augmentation, antipsychotic medication, mental health hospitalization, suicidality screening, metabolic disease, cardiovascular disease

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	69	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:**

The goal of this project was to use national Veterans Affairs (VA) healthcare data to determine the benefits and risks of use of antipsychotic medications to augment first-line medication therapy in patients with posttraumatic stress disorder (PTSD). To date, over 2.5 million American men and women have served in support of the military operations in Iraq and Afghanistan (OEF/OIF/OND). PTSD is the most commonly diagnosed mental health disorder in Veterans, with nearly 1 in 3 returning Iraq and Afghanistan Veterans seen in VA care receiving this diagnosis. In addition to counseling therapies, several medications are effective in treating PTSD symptoms.

Serotonin reuptake inhibitors (SRIs), such as paroxetine and venlafaxine are considered first-line medications for PTSD. However, clinical trials show less than 30% of patients will achieve remission of PTSD symptoms with these treatments. Therefore, providers and patients will look for additional medications to augment therapy. Antipsychotic medications are FDA-approved and beneficial for the treatment of bipolar disorder and psychotic disorders, such as schizophrenia. However, they have been increasingly prescribed “off-label” for non-approved conditions, such as PTSD. In a prior study, we found that 1 in 5 returning Iraq and Afghanistan Veterans with PTSD seen in VA care were receiving an antipsychotic medication in the absence of one of the approved conditions. This is occurring despite the VA/DoD Clinical Practice Guideline that discourages the use of antipsychotics for PTSD treatment because there is still considerable debate about whether antipsychotic medications are safe and effective in PTSD.

This project used the VA healthcare data of Iraq and Afghanistan Veteran’s with PTSD to compare the effects of antipsychotics versus other types of psychiatric medications to compare metabolic and mental health outcomes, as well as gender and racial/ethnic differences in the risks and benefits of antipsychotic use. Our overall goal is to provide more information for patients and providers about the comparative effectiveness and harms of these medications as they make treatment decisions.

2. **KEYWORDS:**

   PTSD, treatment augmentation, antipsychotic medication, mental health hospitalization, suicidality screening, metabolic disease, cardiovascular disease

3. **ACCOMPLISHMENTS:**

a. **What were the major goals of the project?**

i. **Aim 1:** To determine the metabolic impact of augmentation of first-line serotonin reupdate inhibitor (SRI) treatment with antipsychotics versus other psychiatric medications in OEF/OIF/OND Veterans with posttraumatic stress disorder (PTSD)
   a. Application Timeline: Complete at 12 months
   b. Revised Timeline for EWOF: Complete at 23 months
   c. Actual Completion Timeline: Completed at 23 months

ii. **Aim 2:** To determine the impact of augmentation of first-line SRI treatment with antipsychotics versus other psychiatric medications on PTSD symptoms and mental health outcomes in OEF/OIF/OND Veterans with PTSD
   a. Application Timeline: Complete at 16 months
   b. Revised Timeline for EWOF: Complete at 16 months
   c. Actual Completion Timeline: Completed at 16 months

iii. **Aim 3:** To examine variations in the risks and benefits of augmentation of first-line SRI treatment with antipsychotics versus other psychiatric medications in specific demographic subgroups
   a. Application Timeline: Complete at 22 months
   b. Revised Timeline for EWOF: Complete at 32 months
   c. Actual Completion Timeline: Completed at 32 months

b. **What was accomplished under these goals?**

Summary of Methods

We used VA data to select all OEF/OIF/OND Veterans seen in VA care from 2007 to 2015 with a diagnosis of PTSD. We excluded patients with comorbid bipolar or psychotic disorders as these would have been specific indications for some of the medications in our study. To examine augmentation, we required patients take at least 30 days of an SRI then have an augmenting medication added and take it for at least 60 of 120 days. The date the augmenting medication was filled was considered the “index date” for the study. We then divided patients into groups based on the class of augmenting medication they filled. To compare the potential benefits and risks of the medications we evaluated the change in a number of outcomes from the year prior to the year after the index date. Below we will present our results and summarize the main findings from our study.

As shown in Table 1 below, we examined a number of characteristics of patients and the facilities where they received care that could potentially affect the type of augmenting

medication they received and/or our outcomes of interest. Given our large sample size, we found many statistically significant differences in these characteristics. However, the majority of these differences were small and not clinically significant. Those prescribed antipsychotics were more likely to be white and to have comorbid major depressive disorder and alcohol abuse/dependence. Also, as expected from our prior research, in this population of patients with PTSD, we observed rates of cardiovascular risk factors that are higher that we would expect given the young age of the population. However, rates were similar in those prescribed antipsychotics or other augmenting medications. Prescribing facility and service utilization factors were also similar except for mental health utilization where those prescribed antipsychotics had on average 5 more mental health visits in the year prior to treatment augmentation than those prescribed non-antipsychotics. Despite the relatively small magnitude of these differences, as planned, in addition to analyses adjusting for the covariates in Table 1 using a traditional regression approach, we also used a propensity score matching approach to select groups of patients taking antipsychotic and non-antipsychotics that had similar characteristics. Results from both approaches are presented in the analyses below. We present results for potential mental health benefits (Aim 2) first followed by results for metabolic harms (Aim 1) and heterogeneity by sex and race/ethnicity (Aim 3).

Table 1: Characteristics by augmenting medication group

Variable	**Antipsychotics (N=24,131)**		**Non-Antipsychotics (N=96,383)**		**P-value**
Sociodemographics					
Age, Mean ± SD	35.1	± 8.9	35.7	± 9.0	<.0001
Birth sex					<.0001
Male	21,823	(90.4)	85,822	(89.0)	
Female	2,308	(9.5)	10,561	(11.0)	
Race					<.0001
White	18,581	(77.0)	71,091	(73.8)	
Black	3,537	(14.7)	16,089	(16.7)	
Other	2013	(8.3)	9,203	(9.6)	
Ethnicity					0.0202
Hispanic	2,645	(11.0)	10,865	(11.3)	
Non-Hispanic	20,931	(86.7)	83,046	(86.2)	

Unknown	555	(2.3)	2,472	(2.6)	
Marital Status					0.0051
Married	13,066	(54.2)	53,275	(55.3)	
Never Married	5,399	(22.4)	20,854	(21.6)	
Other	5,666	(23.5)	22,254	(23.1)	
Comorbidities					
Major Depressive Disorder	9,013	(37.6)	31,672	(32.9)	<.0001
Personality Disorder	1,579	(6.5)	3,850	(4.0)	<.0001
Generalized Anxiety Disorder	1,869	(7.6)	6,921	(7.2)	0.0026
Insomnia	5,931	(24.6)	23,326	(24.2)	0.2219
Substance abuse/dependence	9,697	(40.2)	33,545	(43.8)	<.0001
Alcohol abuse/dependence	8,079	(33.5)	28,468	(29.5)	<.0001
Traumatic Brain Injury	4,193	(17.4)	15,514	(16.1)	<.0001
Obesity	5,487	(22.7)	22,092	(22.9)	0.5458
Dyslipidemia	7,994	(33.1)	32,027	(33.2)	0.7649
Diabetes	1,156	(4.8)	4,995	(5.2)	0.0134
Hypertension	6,393	(26.5)	25,352	(26.3)	0.5501
Heart disease (myocardial infarction or ischemic heart disease or unstable angina)	164	(0.7)	585	(0.6)	0.1989
Congestive Heart Failure	77	(0.3)	291	(0.3)	0.6655
Cerebrovascular disease	47	(0.2)	205	(0.2)	0.5857
Charlson Comorbidity Index score	0.303	± 0.7	0.296	± 0.7	0.1439
Prescribing Facility Factors					
VA Prescribing Site					0.0286
Medical Center	14,956	(62.0)	58,997	(61.2)	
Community-Based Outpatient Clinics	9,175	(38.0)	37,386	(38.8)	
Service Utilization factors					

Primary Care utilization (# visits in pre-index year)	3.2	± 3.2	3.0	± 2.9	<.0001
Mental Health utilization (# visits in pre-index year)	21.7	± 33.9	16.88	± 28.0	<.0001
Drive time to nearest VA at time of index Rx (minutes)*	22.9	± 17.9	22.8	± 24.3	0.4890
VA Service Connection % Mean ± SD	54.1	± 35.0	52.7	± 34.7	<.0001

* Results are shown as N (%) or mean +/- standard deviation

**Numbers for the individual non-antipsychotics are: Buspirone 9,211, Mirtazapine 11,232, Mood Stabilizers 12,260, Nefazodone 39, Prazosin 28,571, Trazodone 30,243, and Tricyclics 4,827

Summary of Results for Aim 2: Mental Health Outcomes

We found that patients had statistically significant but clinically small improvements (1-2% decline) in their PTSD symptoms and endorsement of suicidal thoughts after receiving augmenting medications, and that the effect was similar in antipsychotic and other classes of augmenting medications. However, we observed more dramatic reductions in rates of emergency room visits and hospitalizations for mental health conditions (15-30% decline). Notably, the groups prescribed tricyclic antidepressants and trazodone had significantly smaller improvements in these outcomes. The more dramatic declines in hospitalizations and emergency room visits without a substantial change in PTSD symptoms may indicate that these medications are useful in a select population of patients with particularly severe symptoms, comorbid conditions, or those in crisis situations and may not be as beneficial for the broader population of patients with more moderate and/or stable PTSD symptoms. Below we provide further detail on the results for individual mental health outcomes.

Changes in PTSD symptom scores by augmenting medication type

We found that patients in all augmenting medication groups had minimal improvement in their PTSD symptoms from the year prior to receiving the augmenting medication to the year after (Table 2a). Improvements in PTSD symptoms did not differ between those on antipsychotics versus non-antipsychotics (Tables 2b and c). Adjusting for the factors shown in Table 1 did not substantially change our findings (Table 2c) and we found individual types of antipsychotics had similar effects. From our prior work and published studies of these medications, we expected to find no or modest improvement in PTSD symptoms given these are patients that are not

responding to first line therapies and may be more difficult to treat. However, documenting the minimal average change in PTSD symptoms is extremely important as the cardiovascular and metabolic consequences may therefore outweigh potential benefits for some patients.

Table 2a: Changes in PTSD Checklist scores by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	62.72	61.88	-0.83	<0.0001	-1.33%
Non-antipsychotics	60.98	60.14	-0.84	<0.0001	-1.38%
Individual Medications/Classes					
Quetiapine	62.80	62.43	-0.37	0.06	-0.59%
Aripiprazole	62.29	61.04	-1.25	<0.0001	-2.01%
Risperidone	63.29	61.84	-1.45	<0.0001	-2.29%
Buspirone	60.91	60.30	-0.61	0.005	-1.00%
Mirtazapine	61.73	60.97	-0.76	<0.0001	-1.24%
Mood Stabilizers	62.37	61.52	-0.85	<0.0001	-1.36%
Prazosin	61.98	61.01	-0.96	<0.0001	-1.55%
Trazodone	60.65	59.82	-0.83	<0.0001	-1.37%
Tricyclics	62.08	61.13	-0.95	0.002	-1.53%

***Note we have removed nefazodone as the group size was very small**

Table 2b: Propensity Matching 1 to 1

Changes in PTSD Checklist by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	62.71	61.88	-0.83	<0.0001	-1.32%
Non-antipsychotics	61.71	60.66	-1.05	<0.0001	-1.70%

Table 2c: Unadjusted and adjusted models for change in PTSD Checklist symptom scores in non-antipsychotic vs. antipsychotic medications.

Table shows the coefficient for the difference in changes from the pre- to post-index year compared to the reference group of antipsychotics with p-value in ().

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-0.04 (0.76)	-0.03 (0.79)	-0.04 (0.74)	-0.04 (0.74)	-0.05 (0.69)	-0.20 (0.21)
By Class						
Buspirone	0.26 (0.28)	0.25 (0.28)	0.23 (0.32)	0.23 (0.32)	0.23 (0.34)	NA
Mirtazapine	0.05 (0.83)	0.06 (0.77)	0.06 (0.77)	0.06 (0.77)	0.05 (0.81)	NA
Mood Stabilizers	0.02(0.90)	0.03 (0.90)	0.19 (0.92)	0.02 (0.92)	0.01 (0.95)	NA
Prazosin	-0.15 (0.36)	-0.13 (0.45)	-0.14 (0.39)	-0.15 (0.36)	-0.15 (0.34)	NA
Trazodone	-0.01 (0.94)	-0.005 (0.98)	-0.02 (0.92)	-0.02 (0.91)	-0.03 (0.86)	NA
Tricyclics	-0.19 (0.55)	-0.17 (0.60)	-0.17 (0.55)	-0.19 (0.55)	-0.20 (0.52)	NA

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

As a secondary mental health outcome, we examined changes in the Primary Care PTSD screen (a 4-item questionnaire that is mandated in periodic assessments in VA). Similar to the PTSD checklist, we found small improvements in most groups from the pre- to post-index year without differences in antipsychotics versus non-antipsychotic medications. Of note, among the antipsychotics, those on quetiapine did not have significant changes in their PTSD symptom score.

Table 2d: Changes in Primary Care PTSD Screen scores by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	3.22	3.14	-0.07	0.0006	-2.27%
Non-antipsychotics	3.10	3.07	-0.03	0.004	-1.05%
Individual Medications/Classes					
Quetiapine	3.24	3.24	-0.001	0.97	-0.04%
Aripiprazole	3.15	2.99	-0.16	0.0009	-5.00%
Risperidone	3.22	3.06	-0.16	0.007	-5.03%
Buspirone	2.99	2.92	-0.07	0.06	-2.39%
Mirtazapine	3.09	3.02	-0.07	0.03	-2.32%
Mood Stabilizers	3.18	3.13	-0.05	0.07	-1.72%
Prazosin	3.22	3.24	0.03	0.18	0.82%
Trazodone	2.99	2.97	-0.03	0.22	-0.84%
Tricyclics	3.10	3.01	-0.10	0.05	-3.09%

Table 2e: Propensity Matching 1 to 1

Changes in Primary Care PTSD by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	3.22	3.14	-0.07	0.0006	-2.26%
Non-antipsychotics	3.11	3.09	-0.02	0.37	-0.63%

Table 2f: Unadjusted and adjusted models for change in Primary Care PTSD Screen scores in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	0.04 (0.11)	0.04 (0.12)	0.04 (0.14)	0.04 (0.15)	0.03 (0.18)	0.05 (0.09)
By Class						
Buspirone	0.002 (0.93)	0.005 (0.99)	0.006 (0.96)	0.005 (0.97)	0.007 (0.95)	NA
Mirtazapine	0.001 (0.97)	-0.0008 (0.93)	-0.004 (0.87)	-0.004 (0.87)	-0.005 (0.85)	NA
Mood Stabilizers	0.02 (0.64)	0.02 (0.63)	0.02 (0.64)	0.02 (0.64)	0.02 (0.62)	NA
Prazosin	0.10 (0.001)	0.10 (0.002)	0.09 (0.002)	0.09 (0.003)	0.08 (0.007)	NA
Trazodone	0.05 (0.12)	0.05 (0.14)	0.04 (0.16)	0.04 (0.18)	0.04 (0.20)	NA
Tricyclics	-0.02 (0.61)	-0.02 (0.66)	-0.02 (0.72)	-0.02 (0.71)	-0.02 (0.67)	NA

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Changes in mental health emergency room visits and hospitalizations by augmenting medication type

We used ICD-9 and 10 codes to identify emergency room visits and hospitalizations with a primary diagnosis that was for a mental health condition. For each medication group, we determined the difference between the rate in the pre- and post-index years. We found patients in the antipsychotic group had the greatest number of mental health emergency room visits in the pre-index year, followed by mood stabilizers and mirtazapine (Table 3a). All groups apart from tricyclics had significant declines in their rates of hospitalization. In fully adjusted models, patients augmented with trazodone or tricyclic antidepressants had significantly smaller

improvements in mental health emergency room visits than patients augmented with antipsychotics (Table 3c). Among the individual antipsychotics, quetiapine had lower declines in rate of emergency room visits. Findings for mental health hospitalizations were similar with the highest burden of hospitalizations pre-augmentation in the antipsychotic group (Table 3d) and all groups except those prescribed tricyclic antidepressants having significantly lower rates of hospitalization in the post-index year. In fully adjusted models, patients receiving augmentation with prazosin, trazodone, or tricyclic antidepressants had significantly smaller improvements in hospitalization than those prescribed antipsychotics (Table 3f).

Table 3a Changes in Mental Health Emergency Room visits by augmenting medication group. Rates are shown as # visits/100 person years

Medications	**Pre-Index Year**	**Post-Index Year**	**Absolute Change (post minus pre)**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	24.18	18.62	-5.56	<0.0001	-23.00%
Non-antipsychotics	16.49	13.42	-3.07	<0.0001	-18.60%
Individual Medications/Classes					
Quetiapine	25.69	20.29	-5.40	<0.0001	-21.01%
Aripiprazole	20.62	14.27	-6.34	<0.0001	-30.77%
Risperidone	22.10	18.39	-3.70	0.005	-16.76%
Buspirone	18.27	14.82	-3.45	0.0002	-18.89%
Mirtazapine	19.71	15.93	-3.78	<0.0001	-19.19%
Mood Stabilizers	19.85	14.42	-5.42	<0.0001	-27.33%
Prazosin	16.32	13.41	-2.91	<0.0001	-17.84%
Trazodone	14.54	12.29	-2.25	<0.0001	-15.46%
Tricyclics	9.82	9.16	-0.66	0.45	-6.75%

Table 3b: Propensity Matching 1 to 1
Changes in Mental Health Emergency Room visits by augmenting medication group
Rates are shown as # visits/100 person years

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	24.17	18.62	-5.55	<0.0001	-22.96%
Non-antipsychotics	21.15	16.76	-4.39	<0.0001	-20.75%

Table 3c: Unadjusted and adjusted models for change in Mental Health Emergency Room visits in non-antipsychotic vs. antipsychotic medications

Table shows the coefficient for the difference in changes from the pre- to post-index year compared to the reference group of antipsychotics with p-value in ().

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	2.50 (0.12)	1.78 (0.10)	1.05 (0.07)	0.91 (0.07)	0.82 (0.05)	1.16 (0.53)
By Class						
Buspirone	2.11 (0.42)	1.55 (0.40)	0.97 (0.35)	0.77 (0.34)	0.71 (0.30)	NA
Mirtazapine	1.78 (0.40)	1.30 (0.38)	0.77 (0.33)	0.67 (0.33)	0.56 (0.29)	NA
Mood Stabilizers	0.14 (0.31)	0.06 (0.29)	-0.17 (0.24)	-0.11 (0.24)	-0.18 (0.20)	NA
Prazosin	2.65 (0.15)	1.90 (0.14)	1.13 (0.10)	0.99 (0.10)	0.88 (0.07)	NA
Trazodone	3.31 (0.04)	2.41 (0.03)	1.49 (0.02)	1.29 (0.02)	1.23 (0.01)	NA
Tricyclics	4.90 (0.07)	3.68 (0.06)	2.52 (0.04)	2.21 (0.04)	2.18 (0.02)	NA

Table 3d Mental Health Hospitalizations by augmenting medication group

Rates are shown as # visits/100 person years

Medications	Pre-Index Year	Post-Index Year	Absolute Change	P-value	Percent Change (post minus pre)

			(post minus pre)		
Antipsychotics	29.13	21.99	-7.14	<0.0001	-24.51%
Non-antipsychotics	18.99	15.51	-3.49	<0.0001	-18.36%
Individual Medications/Classes					
Quetiapine	31.00	25.00	-6.00	<0.0001	-19.35%
Aripiprazole	27.00	17.00	-10.00	<0.0001	-37.04%
Risperidone	26.00	20.00	-6.00	<0.0001	-23.08%
Buspirone	20.50	15.57	-4.93	<0.0001	-24.04%
Mirtazapine	22.62	17.86	-4.76	<0.0001	-21.05%
Mood Stabilizers	24.05	18.15	-5.91	<0.0001	-24.55%
Prazosin	19.17	15.68	-3.49	<0.0001	-18.21%
Trazodone	16.02	14.09	-1.93	<0.0001	-12.04%
Tricyclics	12.14	10.90	-1.24	0.17	-10.24%

Table 3e: Propensity Matching 1 to 1

Mental Health Hospitalizations by augmenting medication group

Rates are shown as # visits/100 person years

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	24.17	18.62	-5.55	<0.0001	-22.96%
Non-antipsychotics	21.15	16.76	-4.39	<0.0001	-20.75%

Table 3f: Unadjusted and adjusted models for change in Mental Health Hospitalizations in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	3.65 (0.006)	2.63 (0.005)	1.48 (0.002)	1.29 (0.002)	1.19 (0.0008)	0.89 (0.55)

By Class						
Buspirone	2.21 (0.91)	1.59 (0.90)	0.84 (0.90)	0.64 (0.90)	0.59 (0.87)	NA
Mirtazapine	2.37 (0.34)	1.74 (0.33)	0.96 (0.28)	0.82 (0.28)	0.75 (0.24)	NA
Mood Stabilizers	1.24 (0.99)	0.90 (0.99)	0.37 (0.99)	0.36 (0.99)	0.23 (0.97)	NA
Prazosin	3.65 (0.03)	2.64 (0.02)	1.47 (0.01)	1.29 (0.01)	1.19 (0.007)	NA
Trazodone	5.21 (<.0001)	3.85 (<.0001)	2.33 (<.0001)	2.02 (<.0001)	1.96 (<0.0001)	NA
Tricyclics	5.90 (0.04)	4.37 (0.04)	2.68 (0.02)	2.35 (0.02)	2.27 (0.01)	NA

Changes in suicidal ideation and plan

We used responses on the VA-mandated annual suicidality screen to examine the proportion of patients screening positive for suicidal ideation in each augmenting group over time. Patients prescribed antipsychotics had the highest rates of suicidal ideation in the pre-index year, with nearly one in four endorsing suicidal thoughts (Table 4a). Most groups had small improvements in suicidal ideation after treatment augmentation, though in adjusted models, the improvements did not differ between those prescribed antipsychotics versus other types of psychiatric medications (Table 4c). We also examined the proportion screened who endorsed having a suicidal plan. This was highest among those augmented with antipsychotics. In contrast to suicidal ideation, none of the groups had significant reductions in endorsement of suicidal plan after treatment augmentation (Tables 4d-f).

Table 4a: Changes in Proportion of those Screened with Positive Suicidal Ideation by augmenting medication group.

Medications	Pre-Index Year	Post-Index Year	Absolute Change (post minus pre)	P-value
Antipsychotics	22.48%	20.88%	-1.60%	0.009
Non-antipsychotics	18.14%	16.86%	-1.28%	<0.0001

Individual Medications/Classes				
Quetiapine	20.89%	19.32%	-1.57%	0.07
Aripiprazole	24.27%	23.95%	-0.32%	0.81
Risperidone	23.34%	20.14%	-3.20%	0.02
Buspirone	17.37%	15.29%	-2.09%	0.02
Mirtazapine	19.26%	18.80%	-0.47%	0.59
Mood Stabilizers	19.63%	18.32%	-1.31%	0.11
Prazosin	18.50%	17.20%	-1.30%	0.01
Trazodone	17.04%	15.69%	-1.35%	0.009
Tricyclics	17.04%	16.32%	-0.73%	0.41

Table 4b: Propensity Matching 1 to 1

Changes in Proportion of those Screened with Positive Suicidal Ideation by augmenting medication group.

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	22.47%	20.88%	-1.60%	0.009	-7.11%
Non-antipsychotics	19.81%	18.28%	-1.54%	0.009	-7.75%

Table 4c: Unadjusted and adjusted models for change in Positive Suicidal Ideation in non-antipsychotic vs. antipsychotic medications.

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	0.32 (0.89)	0.29 (0.92)	0.25 (0.90)	0.24 (0.93)	0.17 (0.99)	0.06 (0.91)
By Class						
Buspirone	-0.49 (0.44)	-0.47 (0.45)	-0.41 (0.51)	-0.39 (0.52)	-0.39 (0.54)	NA
Mirtazapine	1.13 (0.34)	1.14 (0.33)	1.14 (0.31)	1.09 (0.33)	0.97 (0.38)	NA
Mood Stabilizers	0.29 (0.89)	0.25 (0.92)	0.24 (0.91)	0.24 (0.91)	0.12 (0.99)	NA

Prazosin	0.30 (0.91)	0.24 (0.96)	0.15 (0.99)	0.14 (0.97)	0.04 (0.88)	NA
Trazodone	0.25 (0.93)	0.22 (0.92)	0.21 (0.97)	0.17 (0.93)	0.14 (0.92)	NA
Tricyclics	0.58 (0.82)	0.54 (0.83)	0.36 (0.90)	0.36 (0.91)	0.32 (0.91)	NA

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 4d: Changes in Proportion of those Screened with Positive Suicidal Plan by augmenting medication group.

Medications	**Pre-Index Year**	**Post-Index Year**	**Absolute Change (post minus pre)**	**P-value**
Antipsychotics	12.06%	10.80%	-1.26%	0.14
Non-antipsychotics	10.24%	10.05%	-0.19%	0.65
Individual Medications/Classes				
Quetiapine	12.54%	10.72%	-1.81%	0.15
Aripiprazole	12.13%	11.40%	-0.73%	0.67
Risperidone	11.26%	12.03%	0.77%	0.68
Buspirone	9.05%	8.02%	-1.03%	0.41
Mirtazapine	11.21%	10.28%	-0.94%	0.45
Mood Stabilizers	11.31%	9.65%	-1.65%	0.15
Prazosin	10.18%	10.79%	0.61%	0.43
Trazodone	9.67%	10.04%	0.37%	0.63
Tricyclics	10.84%	9.74%	-1.10%	0.55

Table 4e: Propensity Matching 1 to 1

Changes in Proportion of those Screened with Positive Suicidal Plan by augmenting medication group.

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	12.07%	10.82%	-1.25%	0.14	-10.35%
Non-antipsychotics	11.06%	10.31%	-0.74%	0.37	-6.71%

Table 4f: Unadjusted and adjusted models for % change in Positive Suicidal Plan in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	1.06 (0.28)	1.09 (0.28)	0.93 (0.32)	0.86 (0.34)	0.81 (0.37)	0.51 (0.70)
By Class						
Buspirone	0.22 (0.96)	0.24 (0.97)	-0.01 (0.87)	-0.03 (0.88)	-0.09 (0.27)	NA
Mirtazapine	0.32 (0.86)	0.31 (0.87)	0.33 (0.84)	0.27 (0.86)	0.11 (0.86)	NA
Mood Stabilizers	-0.40 (0.73)	-0.43 (0.72)	-0.59 (0.64)	-0.55 (0.65)	-0.64 (0.95)	NA
Prazosin	1.86 (0.11)	1.91 (0.11)	1.72 (0.13)	1.57 (0.15)	1.52 (0.61)	NA
Trazodone	1.62 (0.17)	1.69 (0.16)	1.58 (0.17)	1.51 (0.18)	1.50 (0.17)	NA
Tricyclics	0.15 (0.98)	0.16 (0.98)	-0.18 (0.92)	-0.17 (0.92)	-0.21 (0.18)	NA

Model 1: Adjusted for sociodemographics (see Table 1)

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

<u>Summary of Results for Aim 1: Metabolic and Cardiovascular Outcomes</u>

As detailed below, we found consistent, significant evidence of adverse metabolic effects of PTSD treatment augmentation, particularly with antipsychotics and mirtazapine and to a lesser degree with mood stabilizers and tricyclic antidepressants. Effects were most pronounced in weight gain and increases in triglycerides though we also found worsening of HDL-cholesterol and substantial use of new or intensified medications to treat metabolic complications. Given in

our analyses of mental health outcomes we did not find substantial reductions in PTSD symptoms with augmentation, our results raise concern that some patients may be being put at metabolic risk without benefit, particularly if they are not in an acute crisis and are kept on these medications for long periods of time without improvement in symptoms of functioning.

Changes in Weight

We found that patients augmented with antipsychotics gained significantly more weight than those prescribed non-antipsychotics (see Table 5a). Of the antipsychotics, those on quetiapine had slightly less weight gain than those prescribed aripiprazole or risperidone. Among the non-antipsychotic medications, mirtazapine and mood stabilizers were associated with the largest weight gain. In analyses adjusting for sociodemographics, clinical comorbidities, and service utilization, patients prescribed antipsychotics had significantly higher weight gain than those prescribed all other medications, with the exception of mirtazapine. The propensity matched analysis yielded similar results.

Table 5a: Changes in weight by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	205.77	210.22	4.45	<0.0001	2.16%
Non-antipsychotics	206.21	209.45	3.24	<0.0001	1.57%
Individual Medications/Classes					
Quetiapine	202.81	206.57	3.76	<0.0001	1.85%
Aripiprazole	211.80	217.42	5.62	<0.0001	2.65%
Risperidone	206.90	211.83	4.93	<0.0001	2.38%
Buspirone	206.71	209.93	3.22	<0.0001	1.56%
Mirtazapine	201.09	206.14	5.05	<0.0001	2.51%
Mood Stabilizers	207.97	211.83	3.86	<0.0001	1.86%
Prazosin	208.75	211.94	3.19	<0.0001	1.53%

Trazodone	207.05	209.58	2.53	<0.0001	1.22%
Tricyclics	203.51	206.85	3.34	<0.0001	1.64%

Table 5b: Propensity Matching 1 to 1

Changes in weight by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	205.76	210.21	4.45	<0.0001	2.16%
Non-antipsychotics	206.94	210.34	3.40	<0.0001	1.64%

Table 5c: Unadjusted and adjusted models for change in weight in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-1.20 (<0.0001)	-1.21 (<0.0001)	-1.21 (<0.0001)	-1.21 (<0.0001)	-1.21 (<0.0001)	-1.05 (<0.0001)
By Class						
Buspirone	-1.27 (<0.0001)	-1.29 (<0.001)	-1.29 (<0.0001)	-1.29 (<0.0001)	-1.28 (<0.0001)	NA
Mirtazapine	0.57 (0.0003)	0.57 (0.0002)	0.57 (0.0002)	0.57 (0.0002)	0.57 (0.0002)	NA
Mood Stabilizers	-0.60 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)	NA
Prazosin	-1.29 (<0.0001)	-1.30 (<0.0001)	-1.31 (<0.0001)	-1.31 (<0.0001)	-1.31 (<0.0001)	NA
Trazodone	-2.04 (<0.0001)	-2.05 (<0.0001)	-2.05 (<0.0001)	-2.06 (<0.0001)	-2.06 (<0.0001)	NA
Tricyclics	-1.13 (<0.0001)	-1.12 (0.0001)	-1.12 (<0.0001)	-1.12 (<0.0001)	-1.12 (<0.0001)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Changes in blood pressure

Though weight increased in patients after augmenting medications were added, we found small but significant improvements in systolic blood pressure in most groups. This may be due to the large number of patients who were started on new blood pressure medications or had existing blood pressure medications increased following augmentation (see Table 10a). This suggests that several augmenting medications did have an adverse impact on blood pressure but providers responded appropriately. Of note, those prescribed mirtazapine and tricyclics did have small increases in blood pressure despite escalating use of blood pressure medications, highlighting the need for ongoing monitoring in patients prescribed these medications. Results for diastolic blood pressure were more variable, with some groups increasing and others decreasing but no group had a clinically significant change.

Table 6a: Changes in systolic blood pressure by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	127.07	126.78	-0.29	<0.0001	-0.23%
Non-antipsychotics	127.14	126.88	-0.26	<0.0001	-0.20%
Individual Medications/Classes					
Quetiapine	127.04	126.93	-0.11	0.24	-0.09%
Aripiprazole	126.96	126.61	-0.35	0.004	-0.28%
Risperidone	127.42	126.63	-0.79	<0.0001	-0.62%
Buspirone	127.15	126.99	-0.16	0.12	-0.13%
Mirtazapine	126.80	127.04	0.24	0.01	0.19%

Mood Stabilizers	126.95	126.67	-0.28	0.0006	-0.22%
Prazosin	127.75	127.37	-0.38	<0.0001	-0.30%
Trazodone	127.15	126.70	-0.45	<0.0001	-0.35%
Tricyclics	126.44	126.75	0.31	0.01	0.25%

Table 6b: Propensity Matching 1 to 1

Changes in systolic blood pressure by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	127.07	126.78	-0.29	<0.0001	-0.23%
Non-antipsychotics	127.30	126.98	-0.32	<0.0001	-0.25%

Table 6c: Unadjusted and adjusted models for change in systolic blood pressure in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	0.02 (0.72)	0.02 (0.72)	0.02 (0.72)	0.02 (0.72)	0.03 (0.70)	-0.03 (0.74)
By Class						
Buspirone	0.12 (0.30)	0.12 (0.31)	0.12 (0.30)	0.12 (0.31)	0.12 (0.28)	NA
Mirtazapine	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)	NA
Mood Stabilizers	0.01 (0.90)	0.01 (0.89)	0.01 (0.90)	0.01 (0.90)	0.02 (0.88)	NA
Prazosin	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.21)	NA

Trazodone	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.04)	NA
Tricyclics	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 6d: Changes in diastolic blood pressure by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	79.17	79.36	0.19	<0.0001	0.24%
Non-antipsychotics	79.26	79.25	-0.01	<0.0001	-0.01%
Individual Medications/Classes					
Quetiapine	79.10	79.54	0.44	<0.0001	0.56%
Aripiprazole	79.54	79.52	-0.02	0.79	-0.03%
Risperidone	79.17	79.03	-0.14	0.22	-0.18%
Buspirone	79.38	79.37	0.00	0.96	0.00%
Mirtazapine	79.14	79.60	0.46	<0.0001	0.58%
Mood Stabilizers	79.08	79.10	0.02	0.72	0.03%
Prazosin	79.79	79.67	-0.12	0.007	-0.16%

Trazodone	79.23	78.99	-0.23	<0.0001	-0.30%
Tricyclics	78.96	79.72	0.76	<0.0001	0.97%

Table 6e: Propensity Matching 1 to 1

Changes in diastolic blood pressure by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	79.17	79.36	0.19	<0.0001	0.24%
Non-antipsychotics	79.38	79.40	0.02	0.6556	0.03%

Table 6f: Unadjusted and adjusted models for change in diastolic blood pressure in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.21 (<0.0001)	--0.17 (0.009)
By Class						
Buspirone	-0.20 (0.03)	-0.20 (0.02)	-0.20 (0.02)	-0.20 (0.02)	-0.20 (0.02)	NA
Mirtazapine	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.001)	NA
Mood Stabilizers	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)	NA
Prazosin	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)	NA
Trazodone	-0.42 (<0.0001)	-0.42 (<0.0001)	-0.42 (<0.0001)	-0.43 (<0.0001)	-0.43 (<0.0001)	NA

Tricyclics	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Changes in Hemoglobin A1c and Glucose

We found significant increases in hemoglobin A1c that were more pronounced in patients prescribed antipsychotics (see Tables 7a and b). In fully adjusted analyses, only patients prescribed mirtazapine had greater increases in A1c than those prescribed antipsychotics (see Table 7c). Findings for glucose were similar with significant increases from pre- to post-augmentation in both groups with the greatest increases in those prescribed antipsychotics or mirtazapine (see Tables 7d and e). Similar to our findings for weight, among the antipsychotics, quetiapine had a smaller metabolic impact.

Table 7a: Changes in Hemoglobin A1c by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	5.61	5.68	0.07	0.001	1.18%
Non-antipsychotics	5.66	5.72	0.05	<0.0001	0.91%
Individual Medications/Classes					
Quetiapine	5.56	5.62	0.06	<0.0001	1.08%
Aripiprazole	5.68	5.78	0.10	<0.0001	1.76%
Risperidone	5.63	5.70	0.07	0.0003	1.24%
Buspirone	5.67	5.73	0.07	<0.0001	1.16%
Mirtazapine	5.64	5.75	0.11	<0.0001	1.87%

Mood Stabilizers	5.63	5.71	0.07	<0.0001	1.30%
Prazosin	5.69	5.74	0.05	<0.0001	0.84%
Trazodone	5.71	5.74	0.03	<0.0001	0.57%
Tricyclics	5.67	5.76	0.09	<0.0001	1.55%

Table 7b: Propensity Matching 1 to 1

Changes in hemoglobin A1c by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	5.61	5.68	0.07	<0.0001	1.19%
Non-antipsychotics	5.67	5.72	0.05	<0.0001	0.86%

Table 7c: Unadjusted and adjusted models for change in hemoglobin A1c in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	-0.01 (0.15)	-0.01 (0.07)	-0.02 (0.07)	-0.02 (0.07)	-0.020 (0.06)	-0.02 (0.06)
By Class						
Buspirone	-0.004 (0.81)	-0.006 (0.66)	-0.009 (0.55)	-0.009 (0.55)	-0.009 (0.52)	NA
Mirtazapine	0.03 (0.04)	0.03 (0.05)	0.03 (0.04)	0.03 (0.04)	0.03 (0.04)	NA
Mood Stabilizers	-0.004 (0.79)	-0.006 (0.66)	-0.006 (0.63)	-0.006 (0.63)	-0.007 (0.58)	NA
Prazosin	-0.02 (0.08)	-0.02 (0.04)	-0.02 (0.03)	-0.02 (0.03)	-0.02 (0.02)	NA

Trazodone	-0.03 (0.002)	-0.04 (0.0005)	-0.03 (0.0008)	-0.03 (0.0008)	-0.04 (0.0006)	NA
Tricyclics	0.01 (0.52)	0.007 (0.72)	0.007 (0.71)	0.007 (0.70)	0.007 (0.71)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 7d: Changes in glucose by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	98.41	100.80	2.39	<0.0001	2.43%
Non-antipsychotics	98.90	100.62	1.72	<0.0001	1.74%
Individual Medications/Classes					
Quetiapine	97.44	99.19	1.75	<0.0001	1.80%
Aripiprazole	99.94	103.67	3.73	<0.0001	3.73%
Risperidone	98.71	101.21	2.50	<0.0001	2.53%
Buspirone	99.65	101.35	1.70	<0.0001	1.70%
Mirtazapine	98.57	101.33	2.76	<0.0001	2.80%
Mood Stabilizers	98.51	99.83	1.33	<0.0001	1.35%
Prazosin	99.47	101.54	2.07	<0.0001	2.08%

Trazodone	99.58	100.98	1.40	<0.0001	1.40%
Tricyclics	99.14	100.75	1.61	<0.0001	1.63%

Table 7e: Propensity Matching 1 to 1

Changes in glucose by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	98.40	100.79	2.39	<0.0001	2.43%
Non-antipsychotics	99.18	101.00	1.82	<0.0001	1.83%

Table 7f: Unadjusted and adjusted models for change in glucose in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-0.59 (0.006)	-0.60 (0.005)	-0.58 (0.006)	-0.59 (0.006)	-0.59 (0.005)	-0.55 (0.045)
By Class						
Buspirone	-0.69 (0.06)	-0.70 (0.05)	-0.68 (0.06)	-0.68 (0.06)	-0.69 (0.06)	NA
Mirtazapine	0.40 (0.24)	0.44 (0.22)	0.44 (0.19)	0.44 (0.19)	0.44 (0.19)	NA
Mood Stabilizers	-0.98 (0.003)	-0.97 (0.003)	-0.96 (0.003)	-0.96 (0.003)	-0.97 (0.003)	NA
Prazosin	-0.32 (0.22)	-0.34 (0.19)	-0.33 (0.21)	-0.33 (0.21)	-0.33 (0.20)	NA
Trazodone	-0.99 (0.0001)	-1.004 (0.0001)	-0.98 (0.0001)	-0.99 (0.0001)	-0.99 (0.0001)	NA

Tricyclics	-0.77 (0.10)	-0.77 (0.09)	-0.77 (0.09)	-0.77 (0.09)	-0.76 (0.10)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Changes in Lipids

We found that most augmenting medications were associated with small improvements in LDL-cholesterol (see Tables 8a-c). However, as with blood pressure, this must be interpreted in light of increasing use of medications to treat cholesterol, which was started or intensified in over 10% of patients (see Table 10d). These lipid-lowering medications largely act on LDL-cholesterol. Indeed, we found while LDL improved, HDL-cholesterol and triglycerides worsened after augmenting medications were added, providing a better reflection of their metabolic impact. Again, antipsychotics and mirtazapine had the worst metabolic outcomes, with the largest decreases in protective HDL-cholesterol (see Tables 8d-f) and the largest increases in triglycerides (see Tables 8g-i).

Table 8a: Changes in LDL-cholesterol by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	118.02	117.38	-0.64	0.007	-0.54%
Non-antipsychotics	118.16	117.17	-0.99	<0.0001	-0.84%
Individual Medications/Classes					
Quetiapine	117.63	117.30	-0.33	0.36	-0.28%
Aripiprazole	119.47	117.77	-1.70	0.0003	-1.42%
Risperidone	117.83	117.54	-0.29	0.59	-0.25%
Buspirone	116.85	116.98	0.13	0.74	0.11%

Mirtazapine	116.36	117.05	0.69	0.06	0.59%
Mood Stabilizers	118.55	117.85	-0.70	0.04	-0.59%
Prazosin	118.96	117.58	-1.38	<0.0001	-1.16%
Trazodone	118.52	116.78	-1.74	<0.0001	-1.47%
Tricyclics	118.93	117.43	-1.50	0.007	-1.26%

Table 8b: Propensity Matching 1 to 1

Changes in LDL by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	118.00	117.37	-0.63	0.0070	-0.53%
Non-antipsychotics	117.93	116.68	-1.25	<0.0001	-1.06%

Table 8c: Unadjusted and adjusted models for change in LDL-cholesterol in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-0.41 (0.09)	-0.42 (0.09)	-0.42 (0.09)	-0.42 (0.09)	-0.42 (0.09)	-0.56 (0.08)
By Class						
Buspirone	0.70 (0.09)	0.69 (0.10)	0.67 (0.11)	0.67 (0.11)	0.68 (0.11)	NA
Mirtazapine	1.20 (0.002)	1.20 (0.002)	1.19 (0.002)	1.19 (0.002)	1.19 (0.002)	NA
Mood Stabilizers	-0.15 (0.69)	-0.15 (0.68)	-0.16 (0.68)	-0.16 (0.68)	-0.17 (0.65)	NA
Prazosin	-0.76 (0.01)	-0.76 (0.01)	-0.75 (0.01)	-0.75 (0.01)	-0.75 (0.01)	NA

Trazodone	-1.14 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)	NA
Tricyclics	-0.65 (0.23)	-0.66 (0.22)	-0.64 (0.23)	-0.64 (0.23)	-0.64 (0.23)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 8d: Changes in HDL-cholesterol by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	43.32	42.85	-0.48	<0.0001	-1.10%
Non-antipsychotics	43.98	43.69	-0.29	<0.0001	-0.66%
Individual Medications/Classes					
Quetiapine	43.89	43.19	-0.70	<0.0001	-1.59%
Aripiprazole	42.15	41.85	-0.30	0.03	-0.71%
Risperidone	42.97	42.62	-0.35	0.03	-0.81%
Buspirone	43.87	43.72	-0.15	0.23	-0.35%
Mirtazapine	43.95	43.41	-0.54	<0.0001	-1.23%
Mood Stabilizers	42.25	41.80	-0.45	<0.0001	-1.06%
Prazosin	43.80	43.51	-0.29	<0.0001	-0.65%
Trazodone	44.12	43.86	-0.26	0.0002	-0.59%

Tricyclics	43.69	43.41	-0.28	0.09	-0.63%

Table 8e: Propensity Matching 1 to 1

Changes in HDL by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	43.32	42.85	-0.47	<0.0001	-1.10%
Non-antipsychotics	43.37	42.98	-0.39	<0.0001	-0.91%

Table 8f: Unadjusted and adjusted models for change in HDL-cholesterol in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)	0.11 (0.28)
By Class						
Buspirone	0.38 (0.004)	0.39 (0.003)	0.39 (0.003)	0.39 (0.003)	0.39 (0.003)	NA
Mirtazapine	-0.01 (0.92)	-0.004 (0.97)	-0.005 (0.97)	-0.005 (0.97)	-0.007 (0.95)	NA
Mood Stabilizers	0.05 (0.66)	0.05 (0.67)	0.05 (0.67)	0.05 (0.66)	0.05 (0.66)	NA
Prazosin	0.21 (0.02)	0.21 (0.02)	0.21 (0.02)	0.21 (0.02)	0.22 (0.02)	NA
Trazodone	0.24 (0.009)	0.25 (0.007)	0.25 (0.007)	0.25 (0.007)	0.25 (0.007)	NA
Tricyclics	0.20 (0.23)	0.20 (0.22)	0.21 (0.21)	0.21 (0.21)	0.21 (0.22)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 8g: Changes in triglycerides by augmenting medication group

Medications	**Pre-Index Year mean**	**Post-Index Year mean**	**Mean change**	**P-value**	**Percent Change (post minus pre)**
Antipsychotics	178.18	190.99	12.81	<0.0001	7.19%
Non-antipsychotics	174.09	181.65	7.56	<0.0001	4.34%
Individual Medications/Classes					
Quetiapine	173.78	190.43	16.65	<0.0001	9.58%
Aripiprazole	192.16	202.90	10.74	<0.0001	5.59%
Risperidone	177.78	186.82	9.04	0.0002	5.08%
Buspirone	177.63	186.68	9.05	<0.0001	5.09%
Mirtazapine	174.59	191.18	16.59	<0.0001	9.50%
Mood Stabilizers	184.27	195.12	10.85	<0.0001	5.89%
Prazosin	179.62	185.10	5.48	<0.0001	3.05%
Trazodone	174.23	179.52	5.29	<0.0001	3.04%
Tricyclics	182.03	192.07	10.04	<0.0001	5.52%

Table 8h: Propensity Matching 1 to 1

Changes in triglycerides by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	178.14	190.98	12.84	<0.0001	7.21%
Non-antipsychotics	179.27	187.83	8.56	<0.0001	4.77%

Table 8i: Unadjusted and adjusted models for change in triglycerides in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-5.04 (<0.0001)	-5.17 (<0.0001)	-5.18 (<0.0001)	-5.19 (<0.0001)	-5.25 (<0.0001)	-4.43 (0.004)
By Class						
Buspirone	-4.05 (0.04)	-4.25 (0.03)	-4.25 (0.03)	-4.25 (0.03)	-4.27 (0.03)	NA
Mirtazapine	2.92 (0.11)	2.76 (0.13)	2.78 (0.13)	2.78 (0.13)	2.75 (0.13)	NA
Mood Stabilizers	-2.22 (0.21)	-2.24 (0.20)	-2.24 (0.20)	-2.24 (0.20)	-2.36 (0.18)	NA
Prazosin	-7.27 (0.0001)	-7.37 (<0.0001)	-7.40 (<0.0001)	-7.40 (<0.0001)	-7.47 (<0.0001)	NA
Trazodone	-7.67 (<0.0001)	-7.84 (<0.0001)	-7.85 (<0.0001)	-7.86 (<0.0001)	-7.93 (<0.0001)	NA
Tricyclics	-3.87 (0.13)	-4.00 (0.11)	-4.02 (0.10)	-4.06 (0.11)	-4.06 (0.11)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 8j: Changes in total cholesterol by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	193.08	193.72	0.64	0.02	0.33%
Non-antipsychotics	193.16	192.76	-0.40	0.003	-0.21%
Individual Medications/Classes					
Quetiapine	192.43	193.94	1.51	0.0004	0.78%
Aripiprazole	195.81	195.13	-0.68	0.22	-0.35%
Risperidone	192.57	193.12	0.55	0.38	0.29%
Buspirone	192.36	193.15	0.79	0.08	0.41%
Mirtazapine	191.47	193.90	2.43	<0.0001	1.27%
Mood Stabilizers	193.68	193.87	0.19	0.65	0.10%
Prazosin	194.44	193.38	-1.06	<0.0001	-0.55%
Trazodone	193.85	192.37	-1.48	<0.0001	-0.76%
Tricyclics	194.95	194.39	-0.56	0.39	-0.29%

Table 8k: Propensity Matching 1 to 1

Changes in total cholesterol by augmenting medication group

Medications	Pre-Index Year mean	Post-Index Year mean	Mean change	P-value	Percent Change (post minus pre)
Antipsychotics	193.06	193.72	0.66	0.0173	0.34%
Non-antipsychotics	193.03	192.38	-0.65	0.0206	-0.34%

Table 8l: Unadjusted and adjusted models for change in total cholesterol in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Non-antipsychotics	-1.08 (0.0002)	-1.10 (0.0001)	-1.09 (0.0001)	-1.09 (0.0001)	-1.09 (0.0001)	-1.24 (0.0009)
By Class						
Buspirone	0.19 (0.70)	0.16 (0.75)	0.16 (0.75)	0.16 (0.75)	0.17 (0.73)	NA
Mirtazapine	1.531 (0.0008)	1.52 (0.0009)	1.52 (0.0009)	1.52 (0.0009)	1.56 (0.0009)	NA
Mood Stabilizers	-0.56 (0.20)	-0.57 (0.19)	-0.57 (0.19)	-0.57 (0.19)	-0.58 (0.19)	NA
Prazosin	-1.66 (<0.0001)	-1.68 (<0.0001)	-1.67 (<0.0001)	-1.67 (<0.0001)	-1.67 (<0.0001)	NA
Trazodone	-2.14 (<0.0001)	-2.16 (<0.0001)	-2.15 (<0.0001)	-2.15 (<0.0001)	-2.15 (<0.0001)	NA
Tricyclics	-1.19 (0.06)	-1.21 (0.05	-1.20 (0.05)	-1.20 (0.06)	-1.20 (0.06)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Incident Diagnoses of Cardiovascular Risk Factors

To complement our analyses of vital sign and laboratory data, we also compared rates of incident diagnoses of cardiovascular risk factors (using ICD-9 and 10 diagnostic codes) among the medication groups. Incident dyslipidemia and obesity were significantly higher for antipsychotics with no differences for hypertension and diabetes (See Table 9a). In terms of individual drug classes, antipsychotics, mirtazapine, mood stabilizers, and tricyclics had the highest rates of cardiovascular risk factor diagnoses (see Tables 9c-g).

Table 9a: Rate of new diagnosis of metabolic conditions in post-augmentation year

Medication Group	Antipsychotics Count per 100 person years	Non-Antipsychotics Count per 100 person years	p-value

Hypertension	7.04	6.75	0.07
Dyslipidemia	13.11	11.88	<0.0001
Obesity	10.55	10.01	0.01
Diabetes	1.80	1.75	0.54

Table 9b: Propensity Matching 1 to 1

New diagnoses of metabolic conditions in post-augmentation year by augmenting medication group

Medication Group	**Antipsychotics Count per 100 person years**	**Non-Antipsychotics Count per 100 person years**	**p-value**
Hypertension	6.89	6.73	0.48
Dyslipidemia	12.51	11.36	<0.0001
Obesity	10.10	9.72	0.14
Diabetes	1.81	1.69	0.27

9c: Rate of new diagnosis of metabolic conditions for individual antipsychotics vs. non-antipsychotics

Medications	**Hypertension**	**Dyslipidemia**	**Obesity**	**Diabetes**
Quetiapine	7.09	12.61	9.79	1.49
Aripiprazole	7.39	13.92	12.15	2.28
Risperidone	6.55	13.18	10.39	1.62
Buspirone	6.63	11.98	9.96	1.82
Mirtazapine	7.05	11.98	10.11	1.75
Mood Stabilizers	7.06	12.63	10.33	1.82
Prazosin	6.83	11.86	10.14	1.76
Trazodone	6.40	11.45	9.71	1.66
Buspirone	6.63	11.98	9.96	1.82

Table 9d: Unadjusted and adjusted models for rates of new diagnoses of diabetes in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**

Non-antipsychotics	-0.05 (0.53)	-0.22 (0.01)	-0.20 (0.02)	-0.20 (0.02)	-0.18 (0.04)	-0.17 (0.15)
By Class						
Buspirone	-0.13 (0.42)	-0.13 (0.40)	-0.11 (0.47)	-0.11 (0.48)	-0.09 (0.55)	NA
Mirtazapine	-0.24 (0.12)	-0.30 (0.04)	-0.29 (0.04)	-0.29 (0.04)	-0.28 (0.04)	NA
Mood Stabilizers	-0.16 (0.29)	-0.13 (0.37)	-0.13 (0.34)	-0.14 (0.33)	-0.14 (0.32)	NA
Prazosin	-0.13 (0.26)	-0.24 (0.03)	-0.22 (0.04)	-0.22 (0.04)	-0.19 (0.07)	NA
Trazodone	-0.13 (0.25)	-0.27 (0.01)	-0.25 (0.02)	-0.25 (0.02)	-0.21 (0.05)	NA
Tricyclics	0.19 (0.37)	0.06 (0.76)	0.03 (0.87)	0.03 (0.88)	0.006 (0.98)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 9e: Unadjusted and adjusted models for rates of new diagnoses of obesity in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	-0.52 (0.007)	-0.68 (0.0008)	-0.93 (0.0002)	-0.92 (0.0002)	-0.82 (0.0008)	-0.62 (0.04)
By Class						
Buspirone	-1.09 (0.008)	-1.33 (0.002)	-1.30 (0.003)	-1.23 (0.004)	-1.17 (0.006)	NA

Mirtazapine	-0.93 (0.01)	-1.03 (0.009)	-1.04 (0.009)	-1.01 (0.009)	-0.97 (0.01)	NA
Mood Stabilizers	-0.47 (0.21)	-0.53 (0.18)	-0.54 (0.17)	-0.59 (0.13)	-0.54 (0.16)	NA
Prazosin	-0.57 (0.05)	-0.76 (0.01)	-0.76 (0.01)	-0.76 (0.01)	-0.64 (0.03)	NA
Trazodone	-0.86 (0.003)	-1.15 (0.0001)	-1.14 (0.0001)	-1.11 (0.0002)	-0.95 (0.001)	NA
Tricyclics	-0.23 (0.67)	-0.67 (0.22)	-0.72 (0.19)	-0.77 (0.16)	-0.74 (0.17)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 9f: Unadjusted and adjusted models for rates of new diagnoses of dyslipidemia in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	-1.24 (<0.0001)	-1.46 (<0.0001)	-1.45 (<0.0001)	-1.45 (<0.0001)	-1.40 (<0.0001)	-1.57 (0.0002)
By Class						
Buspirone	-1.56 (0.001)	-1.39 (0.001)	-1.38 (0.001)	-1.36 (0.001)	-1.33 (0.002)	NA
Mirtazapine	-1.46 (0.001)	-1.46 (0.0002)	-1.43 (0.0002)	-1.42 (0.0002)	-1.42 (0.0002)	NA
Mood Stabilizers	-0.60 (0.18)	-0.76 (0.05)	-0.73 (0.06)	-0.74 (0.05)	-0.70 (0.07)	NA

Prazosin	-1.65 (<0.0001)	-1.72 (<0.0001)	-1.71 (<0.0001)	-1.70 (<0.0001)	-1.64 (<0.0001)	NA
Trazodone	-1.71 (<0.0001)	-1.65 (<0.0001)	-1.66 (<0.0001)	-1.64 (<0.0001)	-1.59 (<0.0001)	NA
Tricyclics	-0.79 (0.22)	-0.85 (0.12)	-0.85 (0.13)	-0.85 (0.12)	-0.82 (0.14)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Table 9g: Unadjusted and adjusted models for rates of new diagnoses of hypertension in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Non-antipsychotics	-0.59 (0.003)	-0.37 (0.01)	-0.63 (0.0008)	-0.61 (0.0009)	-0.55 (0.002)	-0.53 (0.21)
By Class						
Buspirone	-0.60 (0.09)	-0.54 (0.10)	-0.49 (0.14)	-0.41 (0.20)	-0.38 (0.24)	NA
Mirtazapine	-0.32 (0.33)	-0.43 (0.16)	-0.37 (0.22)	-0.34 (0.25)	-0.32 (0.28)	NA
Mood Stabilizers	-0.42 (0.19)	-0.47 (0.11)	-0.42 (0.15)	-0.46 (0.11)	-0.44 (0.12)	NA
Prazosin	-0.49 (0.05)	-0.67 (0.004)	-0.60 (0.01)	-0.59 (0.008)	-0.52 (0.02)	NA
Trazodone	-0.95 (<0.0001)	-1.06 (<0.0001)	-0.98 (<0.0001)	-0.94 (<0.0001)	-0.86 (<0.0001)	NA

Tricyclics	0.03 (0.95)	-0.15 (0.73)	-0.04 (0.92)	-0.07 (0.86)	-0.11 (0.80)	NA

Model 1: Adjusted for sociodemographics

Model 2: Adjusted for above plus comorbidities

Model 3: Adjusted for above plus prescribing facility factors

Model 4: Adjusted for above plus service utilization factors

Model 5: Propensity score match 1 to 1

Use of New or Intensified Medications to Treat Metabolic Complications

We recognize that as providers may respond to metabolic complications, such as increases in blood pressure, lipids, or blood sugar, with medications. Examining only vital sign and laboratory data would yield an incomplete picture of the metabolic effects of augmenting medications. Therefore, we also used pharmacy data to determine the proportion of patients started on new metabolic medications in the year after augmentation and the proportion already taking these medications who had their regimen intensified by increasing the dose or potency of medication. We found that nearly one in 5 patients on augmenting medications had a blood pressure medication started or intensified with rates being highest in those on mood stabilizers, buspirone, and mirtazapine (see Tables 10a and b).

We also found approximately 1 in 10 patients added or intensified a cholesterol medication, which is concerning given the overall young age of this population of returning Veterans. Rates were highest for tricyclics, antipsychotics, and mirtazapine (see Tables 10d-g). Finally, diabetes, as expected, was rare, and we did not see significant differences in new use/intensification of diabetes regimen by augmenting medication category (see Tables 10h and i).

Table 10a: Percent of patients with addition or increase in blood pressure medications during post-augmentation year

Medications	% prescribed new medication	% with dose/potency increase	% with new medication or dose increase	p-value
Antipsychotics	11.69	10.97	17.93	0.50
Non-antipsychotics	11.39	10.71	18.10	

Individual Medications/Classes				
Buspirone	11.04	10.97	19.46	<0.0001
Mirtazapine	10.74	11.02	19.17	
Mood Stabilizers	11.37	11.46	19.71	
Prazosin	11.11	10.56	19.04	
Trazodone	10.94	10.26	18.67	
Tricyclics	10.80	10.52	18.46	

Table 10b: Propensity Matching 1 to 1

Percent of patients with addition or increase in medications during post-augmentation year

Condition	**Antipsychotics**	**Non-Antipsychotics**	**p-value**
Blood Pressure Medications- all types combined	18.58	18.67	0.77
Cholesterol Medications- all types combined	13.37	12.60	0.006
Cholesterol Medications- all statins	10.85	10.41	0.09
Diabetes Medications- all types combined	2.92	2.98	0.65

Table 10c: Unadjusted and adjusted models for addition and/or increase in blood pressure medications in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**
Non-antipsychotics	0.17 (0.50)	-0.61 (0.02)	-0.41 (0.12)	0.10 (0.77)
By Class				
Buspirone	-0.29 (0.55)	0.09 (0.85)	0.23 (0.62)	NA
Mirtazapine	0.25 (0.58)	0.01 (0.98)	0.12 (0.78)	NA

Mood Stabilizers	-0.42 (0.33)	-0.43 (0.30)	-0.44 (0.28)	NA
Prazosin	-0.79 (0.02)	-1.02 (0.002)	-0.78 (0.02)	NA
Trazodone	-1.00 (0.003)	-1.15 (0.0003)	-0.79 (0.01)	NA
Tricyclics	2.69 (<0.0001)	1.89 (0.002)	1.54 (0.009)	NA

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors

Model 2: Adjusted for above plus service utilization factors

Model 3: Propensity score match 1 to 1

Table 10d: Percent of patients with addition and/or increase in cholesterol (all types combined) medications during post-augmentation year

Medications	**% prescribed new medication**	**% with dose/potency increase**	**% with new medication or dose increase**	**p-value**
Antipsychotics	10.70	4.25	12.98	0.06
Non-antipsychotics	10.35	4.12	12.57	
Individual Medications/Classes				
Quetiapine	10.47	4.24	12.80	0.13
Aripiprazole	11.24	4.37	13.52	
Risperidone	10.52	4.02	12.52	
Buspirone	9.73	3.94	11.74	0.0003
Mirtazapine	10.65	4.41	12.96	
Mood Stabilizers	10.48	4.80	12.79	
Prazosin	10.09	4.13	12.31	
Trazodone	10.54	4.35	12.66	

Tricyclics	10.95	5.26	13.68	

Table 10e: Unadjusted and adjusted models for addition and/or increase in cholesterol medications (all types combined) in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**
Non-antipsychotics	-0.41 (0.06)	-0.99 (<0.0001)	-0.88 (<0.0001)	-0.77 (0.006)
Individual Medications/Classes				
Buspirone	-1.25 (0.0009)	-1.44 (<0.0001)	-1.35 (0.0001)	NA
Mirtazapine	-0.02 (0.94)	-0.76 (0.02)	-0.67 (0.04)	NA
Mood Stabilizers	-0.20 (0.56)	-0.26 (0.43)	-0.28 (0.38)	NA
Prazosin	-0.67 (0.01)	-1.55 (<0.0001)	-1.41 (<0.0001)	NA
Trazodone	-0.32 (0.23)	-0.88 (0.0004)	-0.67 (0.007)	NA
Tricyclics	0.69 (0.16)	-0.08 (0.86)	-0.24 (0.60)	NA

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors

Model 2: Adjusted for above plus service utilization factors

Model 3: Propensity score match 1 to 1

Table 10f: Percent of patients with addition and/or increase in cholesterol (statins only) medications during post-augmentation year

Medications	**% prescribed new medication**	**% with dose/potency increase**	**% with new medication or dose increase**	**p-value**
Antipsychotics	8.32	3.82	10.62	0.33
Non-antipsychotics	8.13	3.75	10.42	
Individual Medications/Classes				

Quetiapine	8.02	3.82	10.37	0.67
Aripiprazole	8.44	3.97	10.84	
Risperidone	8.78	3.50	10.68	
Buspirone	7.83	3.59	10.12	<0.0001
Mirtazapine	8.39	3.98	10.90	
Mood Stabilizers	8.82	4.27	11.59	
Prazosin	8.21	3.77	10.58	
Trazodone	8.83	3.97	11.21	
Tricyclics	9.07	4.79	12.24	

Table 10g: Unadjusted and adjusted models for addition and/or increase in cholesterol medications (statins only) in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3
Non-antipsychotics	-0.20 (0.12)	-0.63 (0.0006)	-0.57 (0.002)	-0.44 (0.09)
By Class	-1.21 (0.002)	-1.01 (0.002)	-0.97 (0.002)	
Buspirone	-0.44 (0.23)	-0.64 (0.03)	-5.79 (0.04)	NA
Mirtazapine	0.26 (0.47)	0.17 (0.56)	0.17 (0.57)	NA
Mood Stabilizers	-0.76 (0.006)	-1.10 (<0.0001)	-1.03 (<0.0001)	NA
Prazosin	-0.12 (0.65)	-0.55 (0.01)	-0.42 (0.06)	NA
Trazodone	0.91 (0.07)	0.18 (0.65)	0.08 (0.85)	NA
Tricyclics	-1.21 (0.002)	-1.01 (0.002)	-0.97 (0.002)	NA

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors

Model 2: Adjusted for above plus service utilization factors

Model 3: Propensity score match 1 to 1

Table 10h: Percent of patients with addition and/or increase in diabetes medications during post-augmentation year

Medications	**% prescribed new medication**	**% with dose/potency increase**	**% with new medication or dose increase**	**p-value**
Antipsychotics	2.51	1.15	2.86	0.35
Non-antipsychotics	2.58	1.10	2.96	
Individual Medications/Classes				
Quetiapine	2.25	0.99	2.58	0.03
Aripiprazole	2.83	1.32	3.23	
Risperidone	2.64	1.25	2.99	
Buspirone	2.62	1.16	3.04	0.63
Mirtazapine	2.80	1.26	3.24	
Mood Stabilizers	2.46	1.13	2.90	
Prazosin	2.74	1.21	3.15	
Trazodone	2.71	1.15	3.17	
Tricyclics	3.05	0.93	3.36	

Table 10i: Unadjusted and adjusted models for addition and/or increase in diabetes medications in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**
Non-antipsychotics	0.09 (0.46)	-0.04 (0.64)	-0.02 (0.81)	0.06 (0.65)

By Class				
Buspirone	-0.002 (0.99)	0.02 (0.88)	0.05 (0.71)	NA
Mirtazapine	0.20 (0.32)	0.04 (0.80)	-0.01 (0.91)	NA
Mood Stabilizers	-0.14 (0.47)	-0.07 (0.59)	-0.07 (0.60)	NA
Prazosin	0.11 (0.47)	-0.03 (0.79)	-0.01 (0.91)	NA
Trazodone	0.13 (0.40)	-0.07 (0.50)	-0.03 (0.79)	NA
Tricyclics	0.31 (0.25)	-0.12 (0.52)	-0.14 (0.42)	NA

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors

Model 2: Adjusted for above plus service utilization factors

Model 3: Propensity score match 1 to 1

AIM 3 Summary of Results

Given the extensive number of subgroup analyses and comparisons, we highlight here only the differences that appear statistically significant (using $p \leq .005$ to adjust for multiple comparisons) and clinically significant. Complete analyses are provided in Appendix Spreadsheets 1 and 2 Regarding mental health symptoms, the only heterogeneity by sex or racial/ethnic group was a difference in effect of tricyclics on the change in Primary Care PTSD symptom score. In men, tricyclics were associated with a decline in PC-PTSD score that was similar to that observed for other medications (Table 11a). However, women prescribed tricyclics had an increase in PC-PTSD score (Table 11b). This may indicate that tricyclics are being used for other conditions such as chronic neuropathic pain, fibromyalgia, and irritable bowel syndrome that are more common in women and not being titrated to relief of PTSD symptoms. Tricyclics were also associated with a decrease in PC-PTSD symptoms in patients of White race and Hispanic ethnicity but not of Black or Other category of race (Tables 11c-f). Again, this may reflect the heterogeneity of indication for these medications rather than differential efficacy for PSTD symptoms, particularly as we did not observe differences in other mental health outcomes. We also found that while prazosin was associated with a reduction in mental health emergency department visits in all racial/ethnic groups, the reduction was most dramatic in Black patients (Tables 12a-d).

For our primary metabolic outcome of weight, we observed greater changes in weight for White patients for both the antipsychotic and non-antipsychotic medication classes than for all other racial/ethnic groups (Tables 13a-d). White patients also had small increases in total cholesterol on antipsychotics while other racial/ethnic groups had decreases or no change (Tables 14a-d). For the non-antipsychotic medication classes, weight differed specifically in mood stabilizers and trazodone. For hemoglobin A1c and glucose, we did not find differences by race/ethnicity but did find that men prescribed antipsychotics had a greater increase in these measures of insulin resistance/blood sugar than women, though the absolute changes were modest (Tables 15a-b and 16a-b).

MALE

Table 11a: Changes in PC-PTSD score by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	3.24	3.20	-0.04	0.07	-1.10%	0.72
Non-antipsychotics	3.12	3.12	0.002	0.86	0.05%	0.26
By Class						
Antipsychotics	3.24	3.20	-0.04	0.07	-1.10%	0.72
Buspirone	3.03	2.98	-0.05	0.21	-1.55%	0.38
Mirtazapine	3.12	3.09	-0.03	0.30	-1.06%	0.43
Mood Stabilizers	3.21	3.18	-0.02	0.43	-0.71%	0.97
Prazosin	3.23	3.26	0.04	0.07	1.09%	0.61
Trazodone	3.03	3.04	0.01	0.79	0.18%	1.00
Tricyclics	3.17	3.05	-0.11	0.02	-3.56%	0.003

FEMALE

Table 11b: Changes in PC-PTSD score by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	2.99	2.97	-0.01	0.82	-0.41%	0.72
Non-antipsychotics	2.86	2.89	0.03	0.20	1.12%	0.26

By Class						
Antipsychotics	2.99	2.97	-0.01	0.82	-0.41%	0.72
Buspirone	2.81	2.85	0.04	0.65	1.38%	0.38
Mirtazapine	2.87	2.77	-0.10	0.24	-3.62%	0.43
Mood Stabilizers	2.92	2.90	-0.02	0.84	-0.58%	0.97
Prazosin	3.13	3.13	-0.002	0.97	0.08%	0.61
Trazodone	2.77	2.77	-0.005	0.92	0.18%	1.00
Tricyclics	2.83	3.04	0.22	0.03	7.60%	0.003

WHITE

Table 11c: Changes in PC-PTSD score by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	3.22	3.20	-0.01	0.50	-0.46%	0.10
Non-antipsychotics	3.09	3.10	0.01	0.42	0.29%	0.01
By Class						
Antipsychotics	3.22	3.20	-0.01	0.50	-0.46%	0.10
Buspirone	3.00	2.99	-0.01	0.89	-0.20%	0.61
Mirtazapine	3.08	3.04	-0.04	0.29	-1.25%	0.83
Mood Stabilizers	3.19	3.17	-0.01	0.70	-0.39%	0.55
Prazosin	3.21	3.27	0.06	0.01	1.80%	0.26
Trazodone	3.01	3.01	-0.002	0.93	-0.07%	0.06
Tricyclics	3.13	2.99	-0.14	0.01	-4.53%	0.005

BLACK

Table 11d: Changes in PC-PTSD score by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	3.24	3.18	-0.06	0.24	-1.86%	0.10
Non-antipsychotics	3.04	3.08	0.04	0.11	1.26%	0.01

By Class						
Antipsychotics	3.24	3.18	-0.06	0.24	-1.86%	0.10
Buspirone	3.00	2.87	-0.13	0.23	-4.20%	0.61
Mirtazapine	3.15	3.14	0.00	0.97	-0.08%	0.83
Mood Stabilizers	3.12	3.09	-0.03	0.70	-0.97%	0.55
Prazosin	3.19	3.19	0.01	0.89	0.21%	0.26
Trazodone	2.93	2.98	0.05	0.28	1.66%	0.06
Tricyclics	3.01	3.27	0.26	0.02	8.53%	0.005

HISPANIC

Table 11e: Changes in PC-PTSD score by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	3.13	2.98	-0.15	0.01	-4.85%	0.10
Non-antipsychotics	3.09	3.02	-0.08	0.01	-2.48%	0.01
By Class						
Antipsychotics	3.13	2.98	-0.15	0.01	-4.85%	0.10
Buspirone	2.96	2.87	-0.08	0.42	-2.75%	0.61
Mirtazapine	3.08	3.00	-0.07	0.46	-2.34%	0.83
Mood Stabilizers	3.20	3.06	-0.14	0.11	-4.34	0.55
Prazosin	3.25	3.21	-0.04	0.50	-1.18%	0.26
Trazodone	3.00	2.90	-0.10	0.07	-3.37%	0.06
Tricyclics	3.17	3.02	-0.16	0.30	-4.91%	0.005

OTHER

Table 11f: Changes in PC-PTSD score by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	3.29	3.29	0.001	0.98	0.05	0.10
Non-antipsychotics	3.13	3.15	0.01	0.67	0.46	0.01

By Class						
Antipsychotics	3.29	3.29	0.001	0.98	0.05	0.10
Buspirone	3.10	2.98	-0.12	0.40	-3.77	0.61
Mirtazapine	3.17	3.04	-0.12	0.27	-3.88	0.83
Mood Stabilizers	3.23	3.26	0.02	0.83	0.68	0.55
Prazosin	3.30	3.27	-0.03	0.62	-1.01	0.26
Trazodone	3.03	3.14	0.11	0.10	3.64	0.06
Tricyclics	3.06	3.22	0.16	0.30	5.12	0.005

WHITE

Table 12a: Changes in mental health emergency room visits by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	26.02	20.36	-6.00	<.0001	-21.75%	0.12
Non-antipsychotics	17.05	13.79	-3.00	<.0001	-19.15%	0.001
By Class						
Antipsychotics	26.02	20.36	-6.00	<.0001	-21.75%	0.12
Buspirone	20.41	16.98	-3.00	0.0004	-16.78%	0.57
Mirtazapine	22.12	18.68	-3.00	0.0001	-15.53%	0.08
Mood Stabilizers	21.39	15.59	-6.00	<.0001	-27.14%	0.45
Prazosin	18.89	15.72	-3.00	<.0001	-16.81%	0.003
Trazodone	17.25	14.22	-3.00	<.0001	-17.59%	0.18
Tricyclics	11.19	10.05	-1.00	0.23	-10.20%	0.84

BLACK

Table 12b: Changes in mental health emergency room visits by augmenting medication group

Medications	**pre**	**post**	**Mean Change**	**p-value**	**Percent Change**	**p-value for Interaction**
Antipsychotics	15.16	9.55	-6.00	<.0001	-37.03%	0.12

Non-antipsychotics	10.06	6.86	-3.00	<.0001	-31.75%	0.001
By Class						
Antipsychotics	15.16	9.55	-6.00	<.0001	-37.03%	0.12
Buspirone	11.94	7.71	-4.00	0.01	-35.40%	0.57
Mirtazapine	15.39	9.46	-6.00	<.0001	-38.52%	0.08
Mood Stabilizers	14.43	9.75	-5.00	0.002	-32.41%	0.45
Prazosin	11.08	6.66	-4.00	<.0001	-39.85%	0.003
Trazodone	8.44	6.81	-2.00	0.01	-19.41%	0.18
Tricyclics	7.31	8.05	1.00	0.64	10.11%	0.84

HISPANIC

Table 12c: Changes in mental health emergency room visits by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	17.35	13.25	-4.00	0.00	-23.59%	0.12
Non-antipsychotics	11.74	10.30	-1.00	0.01	-12.28%	0.001
By Class						
Antipsychotics	17.35	13.25	-4.00	0.002	-23.59%	0.12
Buspirone	14.12	11.40	-3.00	0.16	-19.29%	0.57
Mirtazapine	13.89	11.45	-2.00	0.18	-17.59%	0.08
Mood Stabilizers	17.58	11.59	-6.00	0.0006	-34.09%	0.45
Prazosin	12.55	12.10	-0.45	0.69	-3.57%	0.003
Trazodone	11.97	11.58	-0.39	0.70	-3.26%	0.18
Tricyclics	6.19	5.97	-0.23	0.91	-3.63%	0.84

OTHER

Table 12d: Changes in mental health emergency room visits by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	20.16	15.19	-5.00	0.004	-24.66%	0.12
Non-antipsychotics	12.13	10.55	-2.00	0.02	-12.97%	0.001
By Class						
Antipsychotics	20.16	15.19	-5.00	0.004	-24.66%	0.12
Buspirone	15.58	11.93	-4.00	0.14	-23.43%	0.57
Mirtazapine	15.49	11.56	-4.00	0.06	-25.39%	0.08
Mood Stabilizers	14.89	13.02	-2.00	0.35	-12.56%	0.45
Prazosin	12.82	11.27	-2.00	0.23	-12.16%	0.003
Trazodone	11.97	11.49	-0.48	0.69	-4.00%	0.18
Tricyclics	8.86	8.61	-0.25	0.92	-2.80%	0.84

WHITE

Table 13a: Changes in Weight by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	206.49	211.49	5.00	<.0001	2.42%	<.0001
Non-antipsychotics	207.18	210.73	3.55	<.0001	1.71%	<.0001
By Class						
Antipsychotics	206.49	211.49	5.00	<.0001	2.42%	<.0001
Buspirone	207.52	211.02	3.50	<.0001	1.68%	0.01
Mirtazapine	202.08	207.52	5.44	<.0001	2.69%	<.0001
Mood Stabilizers	208.88	213.07	4.19	<.0001	2.00%	0.0006
Prazosin	210.09	213.59	3.50	<.0001	1.67%	<.0001
Trazodone	207.64	210.27	2.63	<.0001	1.27%	0.0001
Tricyclics	205.31	208.72	3.41	<.0001	1.66%	0.50

BLACK

Table 13b: Changes in Weight by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	205.94	208.93	2.99	<.0001	1.45%	<.0001
Non-antipsychotics	206.70	209.21	2.51	<.0001	1.22%	<.0001
By Class						
Antipsychotics	205.94	208.93	2.99	<.0001	1.45%	<.0001
Buspirone	205.43	207.64	2.21	<.0001	1.07%	0.01
Mirtazapine	200.36	204.67	4.31	<.0001	2.15%	<.0001
Mood Stabilizers	208.06	211.38	3.32	<.0001	1.59%	0.0006
Prazosin	208.18	210.61	2.43	<.0001	1.17%	<.0001
Trazodone	206.85	208.62	1.77	<.0001	0.85%	0.0001
Tricyclics	202.00	204.93	2.93	<.0001	1.45%	0.50

HISPANIC

Table 13c: Changes in Weight by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	203.28	206.69	3.40	<.0001	1.67%	<.0001
Non-antipsychotics	203.12	205.90	2.78	<.0001	1.37%	<.0001
By Class						
Antipsychotics	203.28	206.69	3.40	<.0001	1.67%	<.0001
Buspirone	205.91	208.71	2.81	<.0001	1.36%	0.01
Mirtazapine	200.01	203.85	3.85	<.0001	1.92%	<.0001
Mood Stabilizers	203.93	206.93	3.00	<.0001	1.47%	0.0006
Prazosin	205.51	208.32	2.81	<.0001	1.37%	<.0001
Trazodone	203.24	205.51	2.27	<.0001	1.12%	0.0001
Tricyclics	199.51	202.57	3.06	<.0001	1.53%	0.50

OTHER

Table 13d: Changes in Weight by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	202.56	206.55	3.99	<.0001	1.97%	<.0001
Non-antipsychotics	202.15	205.12	2.96	<.0001	1.46%	<.0001
By Class						
Antipsychotics	202.56	206.55	3.99	<.0001	1.97%	<.0001
Buspirone	202.61	205.64	3.03	<.0001	1.50%	0.010
Mirtazapine	195.67	200.53	4.86	<.0001	2.48%	<.0001
Mood Stabilizers	205.18	208.14	2.95	<.0001	1.44%	0.0006
Prazosin	204.52	207.35	2.83	<.0001	1.39%	<.0001
Trazodone	203.70	205.86	2.17	<.0001	1.06%	0.0001
Tricyclics	196.58	200.45	3.86	<.0001	1.96%	0.50

WHITE

Table 14a: Changes in Total Cholesterol by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	193.59	195.02	1.44	<.0001	0.74%	0.0005
Non-antipsychotics	193.53	193.32	-0.21	0.22	-0.11%	0.21
By Class						
Antipsychotics	193.59	195.02	1.44	<.0001	0.74%	0.0005
Buspirone	192.92	193.74	0.82	0.14	0.43%	0.98
Mirtazapine	192.28	195.05	2.77	<.0001	1.44%	0.17
Mood Stabilizers	194.01	194.51	0.50	0.30	0.26%	0.65
Prazosin	195.09	194.00	-1.09	0.00	-0.56%	0.98
Trazodone	194.44	193.04	-1.40	<.0001	-0.72%	0.39
Tricyclics	195.40	195.92	0.52	0.52	0.27%	0.05

BLACK

Table 14b: Changes in Total Cholesterol by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	189.71	188.19	-1.52	0.03	-0.80%	0.0005
Non-antipsychotics	189.37	188.40	-0.97	0.00	-0.51%	0.21
By Class						
Antipsychotics	189.71	188.19	-1.52	0.03	-0.80%	0.00
Buspirone	185.91	186.59	0.68	0.60	0.36%	0.98
Mirtazapine	188.41	189.52	1.11	0.28	0.59%	0.17
Mood Stabilizers	190.24	189.90	-0.34	0.76	-0.18%	0.65
Prazosin	189.20	188.06	-1.14	0.08	-0.60%	0.98
Trazodone	190.47	188.36	-2.11	0.00	-1.11%	0.39
Tricyclics	189.30	188.29	-1.01	0.52	-0.53%	0.05

HISPANIC

Table 14c: Changes in Total Cholesterol by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	194.55	193.89	-0.66	0.41	-0.34%	0.0005
Non-antipsychotics	195.35	194.79	-0.56	0.15	-0.29%	0.21
By Class						
Antipsychotics	194.55	193.89	-0.66	0.41	-0.34%	0.0005
Buspirone	193.86	194.44	0.58	0.64	0.30%	0.98
Mirtazapine	191.76	192.76	1.00	0.45	0.52%	0.17
Mood Stabilizers	194.39	193.43	-0.95	0.41	-0.49%	0.65
Prazosin	197.30	196.55	-0.76	0.32	-0.38%	0.98
Trazodone	195.21	194.62	-0.59	0.42	-0.30%	0.39
Tricyclics	200.99	195.45	-5.54	0.01	-2.75%	0.05

OTHER

Table 14d: Changes in Total Cholesterol by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	192.79	192.85	0.06	0.95	0.03%	0.0005
Non-antipsychotics	194.92	194.53	-0.38	0.42	-0.20%	0.21
By Class						
Antipsychotics	192.79	192.85	0.06	0.95	0.03%	0.00
Buspirone	194.81	196.24	1.43	0.38	0.74%	0.98
Mirtazapine	190.83	195.36	4.53	0.00	2.37%	0.17
Mood Stabilizers	195.19	195.19	0.00	1.00	0.00%	0.65
Prazosin	195.80	194.78	-1.02	0.27	-0.52%	0.98
Trazodone	195.33	193.34	-1.99	0.03	-1.02%	0.39
Tricyclics	195.68	193.79	-1.90	0.39	-0.97%	0.05

MALE

Table 15a: Changes in A1C by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	5.62	5.69	0.07	<.0001	1.20%	0.79
Non-antipsychotics	5.68	5.74	0.06	<.0001	0.99%	0.004
By Class						
Antipsychotics	5.62	5.69	0.07	<.0001	1.20%	0.79
Buspirone	5.68	5.75	0.07	<.0001	1.25%	0.35
Mirtazapine	5.65	5.76	0.11	<.0001	1.92%	0.54
Mood Stabilizers	5.64	5.72	0.08	<.0001	1.39%	0.16
Prazosin	5.71	5.76	0.05	<.0001	0.88%	0.43
Trazodone	5.73	5.77	0.04	<.0001	0.67%	0.10
Tricyclics	5.70	5.79	0.09	<.0001	1.63%	0.54

FEMALE

Table 15b: Changes in A1C by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	5.54	5.60	0.06	0.02	1.08%	0.79
Non-antipsychotics	5.54	5.55	0.02	0.24	0.28%	0.004
By Class						
Antipsychotics	5.54	5.60	0.06	0.02	1.08%	0.79
Buspirone	5.58	5.60	0.03	0.55	0.48%	0.35
Mirtazapine	5.54	5.62	0.08	0.11	1.40%	0.54
Mood Stabilizers	5.50	5.51	0.01	0.81	0.20%	0.16
Prazosin	5.54	5.57	0.03	0.35	0.48%	0.43
Trazodone	5.57	5.57	-0.01	0.77	-0.14%	0.10
Tricyclics	5.52	5.58	0.06	0.22	1.09%	0.54

MALE

Table 16a: Changes in glucose by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction
Antipsychotics	98.93	101.23	2.30	<.0001	2.33%	0.14
Non-antipsychotics	99.56	101.41	1.85	<.0001	1.86%	0.001
By Class						
Antipsychotics	98.93	101.23	2.30	<.0001	2.33%	0.14
Buspirone	100.39	102.38	1.99	<.0001	1.98%	0.03
Mirtazapine	99.06	101.93	2.87	<.0001	2.90%	0.24
Mood Stabilizers	98.91	100.45	1.54	<.0001	1.56%	0.006
Prazosin	100.09	102.23	2.15	<.0001	2.14%	0.26
Trazodone	100.38	101.87	1.49	<.0001	1.49%	0.27
Tricyclics	100.23	102.00	1.77	0.00	1.77%	0.42

FEMALE

Table 16b: Changes in glucose by augmenting medication group

Medications	pre	post	Mean Change	p-value	Percent Change	p-value for Interaction

Antipsychotics	93.58	96.85	3.27	<.0001	3.50%	0.14
Non-antipsychotics	93.74	94.51	0.77	0.01	0.82%	0.001
By Class						
Antipsychotics	93.58	96.85	3.27	<.0001	3.50%	0.14
Buspirone	94.87	94.76	-0.11	0.90	-0.12%	0.03
Mirtazapine	94.27	96.00	1.73	0.06	1.83%	0.24
Mood Stabilizers	94.03	93.11	-0.93	0.28	-0.99%	0.006
Prazosin	93.52	94.93	1.41	0.02	1.51%	0.26
Trazodone	94.13	94.96	0.83	0.14	0.88%	0.27
Tricyclics	93.77	94.66	0.89	0.37	0.95%	0.42

Sensitivity Analyses

Polypharmacy is common among patients with PTSD, particularly those who have an inadequate response to initial medication trials. In our primary analyses, a patient had to have a new prescription for a specific augmenting medication but may have continued chronic prescriptions for other classes. Therefore, we also conducted sensitivity analyses that required patients not to be taking other classes of augmenting medications during the two-year evaluation period. These are presented in Appendix Spreadsheet 3 Our findings were similar with small changes in PTSD symptoms that did not differ by medication class and larger reductions in mental health emergency room visits and hospitalizations. We also found similar worsening of metabolic parameters that were most pronounced for the antipsychotics and mirtazapine. As with our primary analyses, the increase in use of medications to treat metabolic problems was common and the differences were most apparent in parameters that are more challenging to treat, such as weight.

c. **What opportunities for training and professional development has the project provided?**

Though training and professional development opportunities were not specific objectives of the project, we have provided mentorship to several trainees through the project. These include Nicholas Holder, a MIRECC post-doctoral fellow at the San Francisco VA Medical Center and Kaylin Nguyen, an internal medicine resident at UCSF. Both have

written first-author manuscripts based on their work and Dr. Holder is currently developing a VA HSR&D career development award application.

d. **How were the results disseminated to communities of interest?**
We are currently in the dissemination phase of this project. The PI has made numerous presentations of the results to local and national groups. These are detailed in Section 6 but include local grand rounds and VA research presentations that are open to clinical and research staff as well as patients. She has also presented the work at annual meetings of relevant national and international organizations, including the International Society of Traumatic Stress Studies and the Military Health Research Symposium. She is working with members of the National Center for PTSD to discuss opportunities to present findings on their widely used website for patients and providers.

e. **What do you plan to do during the next reporting period to accomplish the goals?**
Nothing to Report

4. **IMPACT:**

a. **What was the impact on the development of the principal discipline(s) of the project?**

How to treat the large number of patients with PTSD who do not have an adequate response to first-line serotonin reuptake inhibitors has been a great controversy in the field. Very few trials have specifically examined augmentation of first-line medications though it is a common practice. In addition, no trials have compared strategies for augmentation. Our findings that the impact of augmentation on PTSD symptoms is relatively small at a population level suggest that providers should not automatically add these medications. Given the more profound decrease in rates of mental health emergency room visits and hospitalizations, these medications may be most effective in patients who have a serious increase in PTSD symptoms or a comorbid mental health issue that causes instability. As expected, we also found that several medications, particularly antipsychotics and mirtazapine were associated with metabolic harms. While this might be a reasonable “cost” in a person in crisis or with a substantial improvement in PTSD symptoms, it may outweigh the benefit in other patients.

Taken together, our findings suggest that providers should be thoughtful in not only patient selection for augmentation but also in monitoring for treatment response and side

effects. The VA has instituted guidelines and clinical reminders to improve rates of monitoring for metabolic consequences in antipsychotics. Our findings of high rates of metabolic medication use suggest that providers are noticing and responding to these adverse outcomes. However, less attention has been paid to monitoring primary PTSD symptom response. Our results indicate that some patients will have minimal benefit with these medications. Therefore, it would be helpful to have systems in place to have regular reassessments of PTSD symptom scores and check ins with patients on their perception of improvements after augmentation. If there is no substantial improvement after a reasonable time frame, monitored titration off the medication could be considered to prevent potential metabolic harms.

We recognize that given our findings are from observational data and did not include a control group, clinical trial evidence would be important to provide clearer guidance on these situations. Indeed, a large trial of strategies for augmentation with medication and/or psychotherapy in patients with treatment resistant PTSD was just funded by the Patient-Centered Outcomes Research Institute. In the meantime, as we disseminate our findings, we hope that they will allow patients and providers to have more informed discussions about treatment options and closer monitoring of outcomes of treatment trials.

b. **What was the impact on other disciplines?**

This project is focused on PTSD and therefore results are most relevant for mental health providers. However, within the VA and many other settings, many patients are reluctant to seek specialty mental health care and are often treated by primary care providers. In addition, the metabolic consequences of these medications and potential for subsequent worsening or development of hypertension, diabetes, and obesity are firmly in the domain of primary care. Therefore, as we focus on disseminating our results, we have given presentations for primary care and internal medicine audiences and are targeting some of our manuscripts for publication in general medical journals.

c. **What was the impact on technology transfer?**

As noted in Section 6d, the analyst working on this project and another using VA pharmacy data developed a method to code the data that saved storage space and time. She shared the method at a poster presentation at the American Medical Informatics

Association annual meeting and intends to publish a manuscript in a statistical journal. She has also shared it with members of the VA Informatics and Computing Infrastructure (VINCI) team in the hopes that it will be useful for other projects and types of VA data. The VA Technology Transfer Program filed a Patent Cooperation Treaty application and is awaiting a review response to determine whether filing a patent in the US or other countries is warranted.

d. **What was the impact on society beyond science and technology?**

We hope that these findings will provide valuable information for patients and providers and contribute to the shared decision-making process for PTSD treatment. Selection of medications is a complex process, particularly for patients who have already had an inadequate response to first-line medications. There is very little information to guide patients and providers in these situations as no trials have specifically compared options for augmenting medications in patients with PTSD. Therefore, though our findings are observational, they may provide some context for expected benefits and risks that can guide discussions. This may help prevent exposure to unnecessary cardiovascular and metabolic harms through selection of medications with similar benefits but improved side effect profiles or from de-escalation/discontinuation of medications if they do not lead to substantial improvements in symptoms. In addition, there is growing interest in the field in conducting trials specifically in treatment-resistant PTSD and our results can be useful in selection of medications for further study.

5. **CHANGES/PROBLEMS:**

a. **Changes in approach and reasons for change**

Due to additional time required to clean the data for Aim 1, we reversed the order of Aims 1 and 2. We found errors in coding and classification within the VA data that needed to be corrected. It therefore took longer than expected to complete some sensitivity analyses for our examination of mental health outcomes but did not delay the overall project completion. We informed the Science Officer of this change via email in August 2017.

b. **Actual or anticipated problems or delays and actions or plans to resolve them**

i. As stated above, we reversed the order of Aims 1 and 2 due to additional time required for data cleaning for Aim 1. We informed the Science Officer of this change

via email in August 2017. This problem and the resulting change did not cause any delays in overall completion.

ii. We requested and received a one-year no-cost extension to allow more time extract additional PTSD symptom checklist scores by using a natural language processing (NLP) algorithm. We completed the NLP extraction and conducted validation studies comparing extracted scores with those that were available within our electronic system. We also examined text snippets for scores that were out of the PCL scoring range. In all cases, the algorithm extracted the score correctly and the error was made by the provider entering the score. After eliminating these scores, using the NLP increased our total number of available scores for analysis by 10%. We repeated our analyses examining average change in PCL score from the pre- to post-index year for each of the augmenting medication groups. Our findings were similar to our prior analyses.

c. **Changes that had a significant impact on expenditures**

None

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

None

e. **Significant changes in use or care of human subjects**

None

f. **Significant changes in use or care of vertebrate animals.**

None

g. **Significant changes in use of biohazards and/or select agents**

None

6. **PRODUCTS:**

a. **Publications, conference papers, and presentations**

i. Journal publications.

1. Anne Woods, Craig Meyer, Beth Cohen. Mining Time-Stamped Electronic Health Records Data Using Referenced Sequences. *Under review.*

ii. Books or other non-periodical, one-time publications.

Nothing to report

iii. Other publications, conference papers, and presentations.

Manuscripts

1. Kaylin Nguyen, Anne Woods, Janet Tang, Thomas Neylan, Shira Maguen, Karen Seal, Nancy Bernardy, Ilse Weichers, Annie Ryder, W. John Boscardin, Beth Cohen. Comparison of Metabolic and Cardiovascular Risk Outcomes with Adjunctive Medications for PTSD: A National Department of Veterans Affairs Study. (In preparation)
2. Nicholas Holder, Anne Woods, Thomas Neylan, Shira Maguen, Karen Seal, Nancy Bernardy, Ilse Weichers, Janet Tang, Annie Ryder, Beth Cohen. Trends in Prescribing of Pharmacotherapy for posttraumatic Stress Disorder within the Department of Veterans Affairs from 2009 to 2018. (In preparation)

Meeting Abstracts

1. Cohen BE, Woods A, Seal KH, Maguen S, Bernardy N, Neylan T. Patterns of PTSD Medication Augmentation: An Analysis of National VA Data. (Oral Presentation at International Society for Traumatic Stress Studies 33nd Annual Meeting; Chicago, 2017).*
2. Cohen BE, Tang J, Woods A, Maguen S, Seal KH, Bernardy N, Weichers I, Neylan T. Impact of Antipsychotic vs. Non-Antipsychotic Medications to Augment First-Line PTSD Medications in Returning Iraq & Afghanistan Veterans: A National VA Data Study. (Poster Presentation at the Military Health System Research Symposium; Kissimmee, 2018)*
3. Woods AS, Cohen BE. Representing Patient Medication History with Symbols. (Poster Presentation at the American Medical Informatics Association Annual Symposium; San Francisco, 2018).*
4. Cohen BE, Woods A, Tang J, Seal KH, Maguen S, Neylan T. Comparing the Effects of Medications to Augment Serotonin Reuptake Inhibitors in Patients with PTSD: A National VA Data Study. (Oral Presentation at the International Society for Traumatic Stress Studies 34th Annual Meeting; Washington, DC, 2018).*
5. Nguyen K, Woods A, Maguen S, Seal K, Neylan T, Cohen B. Comparison of Metabolic and Cardiovascular Risk with PTSD Medication Augmentation Strategies: A National VA Study. (Oral Presentation at the International Society for Traumatic Stress Studies 35th Annual Meeting; Boston, 2019)*

Invited Presentations

1. “Comparing the Effectiveness of Medications to Augment First-line PTSD

Therapy: A National VA Data Study"
Research Presentation, San Francisco VA Medical Center; February, 2018

2. "Risks and Benefits of Second-line Medications for PTSD Treatment"
Research Presentation, San Francisco VA Medical Center; May, 2019
3. "Updates in PTSD Diagnosis and Treatment"
Department of Medicine, Grand Rounds, San Francisco VA Medical Center; December 2019

b. **Website(s) or other Internet site(s)**

Nothing to report

c. **Technologies or techniques**

Nothing to report

d. **Inventions, patent applications, and/or licenses**

During data cleaning for this and another project that used VA data, the project analyst, Ms. Anne Woods used a technique where she represented complex VA pharmacy data with a series of strings that identified for each calendar day whether or not a patient was taking each medication under study. This allowed for more efficient storage of data and quicker verification of whether participants met our inclusion/exclusion criteria based on use of specific medication types at set intervals. She believed this technique could be applied to a variety of other types of electronic health records data and assist with the data cleaning and analysis process. She presented her method at that 2018 American Medical Informatics Association Annual Symposium and a manuscript describing the method has been submitted for publication (see above). She contacted the VA Technology Transfer Program since the method was developed at the VA using VA data. Ms. Woods informed the VA that the DoD was the funder of one of the projects. The VA filed a Patent Cooperation Treaty application (PCT/US19/59696) in November 2019 and is awaiting a review response to determine whether filing a patent in the US or other countries is warranted.

e. **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **What individuals have worked on the project?**

Name:	*Beth Cohen, MD, MAS*

Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	eRA Commons: COHENBETH
Nearest person month worked:	2.4
Contribution to Project:	*Dr. Cohen has overall scientific and administrative responsibility for this project and supervises all project staff.*
Funding Support:	*VA, PCORI, UCSF, TRDRP*

Name:	*Karen Seal, MD, MPH*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	eRA Commons: KASEAL
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Seal has assisted with planning data analyses and interpreting findings for the proposed project.*
Funding Support:	*NCIRE, UCSF*

Name:	*Thomas Neylan, MD*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	eRA Commons: TNEYLAN
Nearest person month worked:	1.2

Contribution to Project:	*Dr. Neylan has provided guidance on coding of metabolic outcomes as well as examination of specific psychiatric medication classes and doses.*
Funding Support:	*VA, UCSF*

Name:	*Shira Maguen, PhD*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	eRA Commons: SMAGUEN
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Maguen has assisted in data cleaning, coding, and interpretation for these outcomes.*
Funding Support:	*VA, UCSF*

Name:	*Anne Woods*
Project Role:	*Data Analyst/Data Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	*Ms. Woods is responsible for data extraction, cleaning and error checking and running all study analyses.*

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Dr. Cohen has added the follow grants as other support:

T30IR0988 (PI: Cohen) 09/02/19 – 09/01/22 2.16 calendar mos

Tobacco Related Disease Research Program $250,000 direct/year
"The Impact of Recreational Marijuana Legalization on Tobacco and Marijuana Co-Use"
The goal of this project is to examine changes in rates and forms of marijuana and tobacco use and public perceptions of safety following recreational legalization of marijuana in California compared to temporal trends in non-legal and medical-legal states.
Role: Principal Investigator

T29IP0511 (PI: Keyhani) 04/01/2019-03/31/2021 0.6 calendar mos
Tobacco Related Disease Research Program $149,193 direct/yr
"The Effect of Combined Tobacco and Marijuana Use of Pulmonary Function: A Pilot Study"
This study proposes a pilot study of Veterans in Northern California to lay the foundation for a larger cross-sectional cohort study. We will examine the effect of smoking marijuana and combined marijuana and tobacco smoking on lung health.
Role: Co-Investigator

R01 AG058678 (PI: Keyhani) 04/01/19-03/31/24 2.4 calendar mos
NIH: National Institute on Aging $499,948 direct/yr
"Marijuana Use in Older Adults: Health, Function and Fall-Related Injury"
There is evidence of increasing use of marijuana among older adults in the US; however, the physical harms of marijuana have not been studied in this population. This proposal will provide insight into the potential harms associated with marijuana use among older adults.
Role: Co-Investigator

c. **What other organizations were involved as partners?**

Nothing to report

8. **SPECIAL REPORTING REQUIREMENTS**

a. **COLLABORATIVE AWARDS:** Not applicable.

b. **QUAD CHARTS:** Not applicable.

9. **APPENDICES**

See attached excel files.