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14. ABSTRACT

The goal of this project is 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. 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. 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 VA and DoD guidelines that discourage 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 uses the VA healthcare data of Veteran's with PTSD to compare the effects of antipsychotics versus other types of psychiatric medications to determine metabolic and mental health outcomes, as well as gender and racial differences in the risks and benefits of antipsychotic use.

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1. INTRODUCTION:

The goal of this project is 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. 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. 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 VA and DoD guidelines that discourage 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 uses 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 determine metabolic and mental health outcomes, as well as gender and racial differences in the risks and benefits of antipsychotic use.

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

  The overall Aims for this project are:

  - 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)

- 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
- 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

The specific tasks from the Statement of Work relevant to this reporting period include:

Task 5: Complete sensitivity analyses for Aim 1. Timeline: Months 12-14 Status: Complete

Task 6: Complete primary analyses and hypothesis testing for Aim 1, including comparing effects of augmentation of first-line therapy with antipsychotics versus other psychiatric medications on metabolic outcomes. Timeline: Months 17-21 Status: Complete

Task 7: Complete sensitivity analyses for Aim 1. Timeline: Months 22-23 Status: Complete

Task 8: Complete primary analyses and hypothesis testing for Aim 3. Timeline: Months 24-25 Status: Analyses begun.

- **What was accomplished under these goals?**

Having already completed analyses for Aim 2, this year, we focused on completing all analyses for Aim 1, which compared cardiovascular and metabolic outcomes in patients prescribed specific augmenting medications for PTSD in addition to first line serotonin reuptake inhibitor therapy. Our analyses involved vital sign, laboratory, diagnostic, and pharmacy data. Below, we group results by metabolic outcome and summarize findings for each category. For our analyses, we define the date the patient started the augmenting medication as the index date. For most outcomes, we are comparing changes from the year prior to augmentation (pre-index) to the year following start of the augmenting medication (post-index).

Summary of Results

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 kept on these medications for long periods of time.

Changes in Weight

We found that patients augmented with antipsychotics gained significantly more weight than those prescribed non-antipsychotics (see Table 1a). 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.

Table 1a: 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%
By Class					
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 1b: Unadjusted and adjusted models for change in weight in non-antipsychotic vs. antipsychotic medications

Medications	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Non-antipsychotics	-1.20 (<0.0001)	-1.21 (<0.0001)	-1.21 (<0.0001)	-1.21 (<0.0001)	-1.21 (<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)
Mirtazapine	0.57 (0.0003)	0.57 (0.0002)	0.57 (0.0002)	0.57 (0.0002)	0.57 (0.0002)
Mood Stabilizers	-0.60 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)	-0.61 (<0.0001)
Prazosin	-1.29 (<0.0001)	-1.30 (<0.0001)	-1.31 (<0.0001)	-1.31 (<0.0001)	-1.31 (<0.0001)
Trazodone	-2.04 (<0.0001)	-2.05 (<0.0001)	-2.05 (<0.0001)	-2.06 (<0.0001)	-2.06 (<0.0001)
Tricyclics	-1.13 (<0.0001)	-1.12 (0.0001)	-1.12 (<0.0001)	-1.12 (<0.0001)	-1.12 (<0.0001)

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

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 prescribers 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.

Table 2a: 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%
By Class					
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 2b: 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
Non-antipsychotics	0.02 (0.72)	0.02 (0.72)	0.02 (0.72)	0.02 (0.72)	0.03 (0.70)
By Class					
Buspirone	0.12 (0.30)	0.12 (0.31)	0.12 (0.30)	0.12 (0.31)	0.12 (0.28)
Mirtazapine	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)	0.53 (<0.0001)
Mood Stabilizers	0.01 (0.90)	0.01 (0.89)	0.01 (0.90)	0.01 (0.90)	0.02 (0.88)
Prazosin	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.20)	-0.10 (0.21)
Trazodone	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.03)	-0.17 (0.04)
Tricyclics	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)	0.61 (<0.0001)

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

Table 3a: 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%
By Class					
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 3b: 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**
Non-antipsychotics	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.20 (<0.0001)	-0.21 (<0.0001)
By Class					
Buspirone	-0.20 (0.03)	-0.20 (0.02)	-0.20 (0.02)	-0.20 (0.02)	-0.20 (0.02)
Mirtazapine	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.0008)	0.27 (0.001)
Mood Stabilizers	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)
Prazosin	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)	-0.32 (<0.0001)

Trazodone	-0.42 (<0.0001)	-0.42 (<0.0001)	-0.42 (<0.0001)	-0.43 (<0.0001)	-0.43 (<0.0001)
Tricyclics	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)	0.58 (<0.0001)

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

Changes in Hemoglobin A1c and Glucose:

We found significant increases in hemoglobin A1c that were more pronounced in patients prescribed antipsychotics. In fully adjusted analyses, only patients prescribed mirtazapine had greater increases in A1c than those prescribed antipsychotics (see Table 4b). 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 5 a and b).

Table 4a: 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%
By Class					
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 4b: 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
Non-antipsychotics	-0.01 (0.15)	-0.01 (0.07)	-0.02 (0.07)	-0.02 (0.07)	-0.020 (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)
Mirtazapine	0.03 (0.04)	0.03 (0.05)	0.03 (0.04)	0.03 (0.04)	0.03 (0.04)
Mood Stabilizers	-0.004 (0.79)	-0.006 (0.66)	-0.006 (0.63)	-0.006 (0.63)	-0.007 (0.58)
Prazosin	-0.02 (0.08)	-0.02 (0.04)	-0.02 (0.03)	-0.02 (0.03)	-0.02 (0.02)
Trazodone	-0.03 (0.002)	-0.04 (0.0005)	-0.03 (0.0008)	-0.03 (0.0008)	-0.04 (0.0006)
Tricyclics	0.01 (0.52)	0.007 (0.72)	0.007 (0.71)	0.007 (0.70)	0.007 (0.71)

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

Table 5a: 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%
By Class					
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 5b: Unadjusted and adjusted models for change in glucose in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2	Model 3	Model 4
Non-antipsychotics	-0.59 (0.006)	-0.60 (0.005)	-0.58 (0.006)	-0.59 (0.006)	-0.59 (0.005)
By Class					
Buspirone	-0.69 (0.06)	-0.70 (0.05)	-0.68 (0.06)	-0.68 (0.06)	-0.69 (0.06)
Mirtazapine	0.40 (0.24)	0.44 (0.22)	0.44 (0.19)	0.44 (0.19)	0.44 (0.19)
Mood Stabilizers	-0.98 (0.003)	-0.97 (0.003)	-0.96 (0.003)	-0.96 (0.003)	-0.97 (0.003)
Prazosin	-0.32 (0.22)	-0.34 (0.19)	-0.33 (0.21)	-0.33 (0.21)	-0.33 (0.20)
Trazodone	-0.99 (0.0001)	-1.004 (0.0001)	-0.98 (0.0001)	-0.99 (0.0001)	-0.99 (0.0001)
Tricyclics	-0.77 (0.10)	-0.77 (0.09)	-0.77 (0.09)	-0.77 (0.09)	-0.76 (0.10)

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

Changes in Lipids

We found that most augmenting medications were associated with small improvements in LDL cholesterol (see Tables 6a and b). 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 10c). These lipid-lowering medications largely act on LDL, and indeed, we found while LDL improved, HDL 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 7a and b) and the largest increases in triglycerides (see Tables 8a and b).

Table 6a: 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%
By Class					
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 6b: 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**
Non-antipsychotics	-0.41 (0.09)	-0.42 (0.09)	-0.42 (0.09)	-0.42 (0.09)	-0.42 (0.09)
By Class					
Buspirone	0.70 (0.09)	0.69 (0.10)	0.67 (0.11)	0.67 (0.11)	0.68 (0.11)
Mirtazapine	1.20 (0.002)	1.20 (0.002)	1.19 (0.002)	1.19 (0.002)	1.19 (0.002)

Mood Stabilizers	-0.15 (0.69)	-0.15 (0.68)	-0.16 (0.68)	-0.16 (0.68)	-0.17 (0.65)
Prazosin	-0.76 (0.01)	-0.76 (0.01)	-0.75 (0.01)	-0.75 (0.01)	-0.75 (0.01)
Trazodone	-1.14 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)	-1.15 (0.0001)
Tricyclics	-0.65 (0.23)	-0.66 (0.22)	-0.64 (0.23)	-0.64 (0.23)	-0.64 (0.23)

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

Table 7a: 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%
By Class					
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 7b: 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**

Non-antipsychotics	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)	0.19 (0.01)
By Class					
Buspirone	0.38 (0.004)	0.39 (0.003)	0.39 (0.003)	0.39 (0.003)	0.39 (0.003)
Mirtazapine	-0.01 (0.92)	-0.004 (0.97)	-0.005 (0.97)	-0.005 (0.97)	-0.007 (0.95)
Mood Stabilizers	0.05 (0.66)	0.05 (0.67)	0.05 (0.67)	0.05 (0.66)	0.05 (0.66)
Prazosin	0.21 (0.02)	0.21 (0.02)	0.21 (0.02)	0.21 (0.02)	0.22 (0.02)
Trazodone	0.24 (0.009)	0.25 (0.007)	0.25 (0.007)	0.25 (0.007)	0.25 (0.007)
Tricyclics	0.20 (0.23)	0.20 (0.22)	0.21 (0.21)	0.21 (0.21)	0.21 (0.22)

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

Table 8a: 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%
By Class					
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 8b: Unadjusted and adjusted models for change in triglycerides in non-antipsychotic vs. antipsychotic medications

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

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

Incident Diagnoses of Cardiovascular Risk Factors

To complement our analyses of vital sign and laboratory data, we also compared rates of new provider diagnoses of cardiovascular risk factors (using ICD9 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 9a-e).

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	6.47	5.94	0.21
Dyslipidemia	11.79	10.22	0.0002
Obesity	9.53	8.92	0.04
Diabetes	1.74	1.57	0.15

Medications	Hypertension	Dyslipidemia	Obesity	Diabetes
Antipsychotics	6.47	11.79	9.53	1.74
Buspirone	5.87	10.23	8.44	1.61
Mirtazapine	6.15	10.33	8.60	1.51
Mood Stabilizers	6.05	11.19	9.07	1.59
Prazosin	5.98	10.14	8.96	1.61
Trazodone	5.52	10.08	8.67	1.61
Tricyclics	6.50	11.00	9.30	1.93
p-value	0.006	<.0001	0.004	0.47

Table 9b: 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
Non-antipsychotics	-0.05 (0.53)	-0.22 (0.01)	-0.20 (0.02)	-0.20 (0.02)	-0.18 (0.04)
By Class					
Buspirone	-0.13 (0.42)	-0.13 (0.40)	-0.11 (0.47)	-0.11 (0.48)	-0.09 (0.55)
Mirtazapine	-0.24 (0.12)	-0.30 (0.04)	-0.29 (0.04)	-0.29 (0.04)	-0.28 (0.04)
Mood Stabilizers	-0.16 (0.29)	-0.13 (0.37)	-0.13 (0.34)	-0.14 (0.33)	-0.14 (0.32)
Prazosin	-0.13 (0.26)	-0.24 (0.03)	-0.22 (0.04)	-0.22 (0.04)	-0.19 (0.07)

Trazodone	-0.13 (0.25)	-0.27 (0.01)	-0.25 (0.02)	-0.25 (0.02)	-0.21 (0.05)
Tricyclics	0.19 (0.37)	0.06 (0.76)	0.03 (0.87)	0.03 (0.88)	0.006 (0.98)

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

Table 9c: 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
Non-antipsychotics	-0.52 (0.007)	-0.68 (0.0008)	-0.93 (0.0002)	-0.92 (0.0002)	-0.82 (0.0008)
By Class					
Buspirone	-1.09 (0.008)	-1.33 (0.002)	-1.30 (0.003)	-1.23 (0.004)	-1.17 (0.006)
Mirtazapine	-0.93 (0.01)	-1.03 (0.009)	-1.04 (0.009)	-1.01 (0.009)	-0.97 (0.01)
Mood Stabilizers	-0.47 (0.21)	-0.53 (0.18)	-0.54 (0.17)	-0.59 (0.13)	-0.54 (0.16)
Prazosin	-0.57 (0.05)	-0.76 (0.01)	-0.76 (0.01)	-0.76 (0.01)	-0.64 (0.03)
Trazodone	-0.86 (0.003)	-1.15 (0.0001)	-1.14 (0.0001)	-1.11 (0.0002)	-0.95 (0.001)
Tricyclics	-0.23 (0.67)	-0.67 (0.22)	-0.72 (0.19)	-0.77 (0.16)	-0.74 (0.17)

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

Table 9d: 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

Non-antipsychotics	-1.24 (<0.0001)	-1.46 (<0.0001)	-1.45 (<0.0001)	-1.45 (<0.0001)	-1.40 (<0.0001)
By Class					
Buspirone	-1.56 (0.001)	-1.39 (0.001)	-1.38 (0.001)	-1.36 (0.001)	-1.33 (0.002)
Mirtazapine	-1.46 (0.001)	-1.46 (0.0002)	-1.43 (0.0002)	-1.42 (0.0002)	-1.42 (0.0002)
Mood Stabilizers	-0.60 (0.18)	-0.76 (0.05)	-0.73 (0.06)	-0.74 (0.05)	-0.70 (0.07)
Prazosin	-1.65 (<0.0001)	-1.72 (<0.0001)	-1.71 (<0.0001)	-1.70 (<0.0001)	-1.64 (<0.0001)
Trazodone	-1.71 (<0.0001)	-1.65 (<0.0001)	-1.66 (<0.0001)	-1.64 (<0.0001)	-1.59 (<0.0001)
Tricyclics	-0.79 (0.22)	-0.85 (0.12)	-0.85 (0.13)	-0.85 (0.12)	-0.82 (0.14)

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

Table 9e: 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
Non-antipsychotics	-0.59 (0.003)	-0.37 (0.01)	-0.63 (0.0008)	-0.61 (0.0009)	-0.55 (0.002)
By Class					
Buspirone	-0.60 (0.09)	-0.54 (0.10)	-0.49 (0.14)	-0.41 (0.20)	-0.38 (0.24)
Mirtazapine	-0.32 (0.33)	-0.43 (0.16)	-0.37 (0.22)	-0.34 (0.25)	-0.32 (0.28)
Mood Stabilizers	-0.42 (0.19)	-0.47 (0.11)	-0.42 (0.15)	-0.46 (0.11)	-0.44 (0.12)
Prazosin	-0.49 (0.05)	-0.67 (0.004)	-0.60 (0.01)	-0.59 (0.008)	-0.52 (0.02)
Trazodone	-0.95 (<0.0001)	-1.06 (<0.0001)	-0.98 (<0.0001)	-0.94 (<0.0001)	-0.86 (<0.0001)

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

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

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 10c and d). 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 10e and f).

Table 10a: Proportion 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**	**Propensity matched p-value**
Antipsychotics	11.69	10.97	17.93	0.77
Non-antipsychotics	11.39	10.71	18.10	
By Class				
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: 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
Non-antipsychotics	0.17 (0.50)	-0.61 (0.02)	-0.41 (0.12)
By Class			
Buspirone	-0.29 (0.55)	0.09 (0.85)	0.23 (0.62)
Mirtazapine	0.25 (0.58)	0.01 (0.98)	0.12 (0.78)
Mood Stabilizers	-0.42 (0.33)	-0.43 (0.30)	-0.44 (0.28)
Prazosin	-0.79 (0.02)	-1.02 (0.002)	-0.78 (0.02)
Trazodone	-1.00 (0.003)	-1.15 (0.0003)	-0.79 (0.01)
Tricyclics	2.69 (<0.0001)	1.89 (0.002)	1.54 (0.009)

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors
Model 2: Adjusted for above plus service utilization factors

Table 10c: Proportion of patients with addition or increase in cholesterol medications during post-augmentation year

Medications	% prescribed new medication	% with dose/potency increase	% with new medication or dose increase	Propensity matched p-value
Antipsychotics	10.70	4.25	12.98	0.006

Non-antipsychotics	10.35	4.12	12.57	
By Class				
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 10d: Unadjusted and adjusted models for addition and/or increase in cholesterol medications in non-antipsychotic vs. antipsychotic medications

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

Model 1: Adjusted for sociodemographics, comorbidities, prescribing facility factors
Model 2: Adjusted for above plus service utilization factors

Table 10e: Proportion of patients with addition or increase in diabetes medications during post-augmentation year

Medications	% prescribed new medication	% with dose/potency increase	% with new medication or dose increase	Propensity matched p-value
Antipsychotics	2.51	1.20	2.86	0.65
Non-antipsychotics	2.58	1.17	2.96	
By Class				
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 10f: Unadjusted and adjusted models for addition and/or increase in diabetes medications in non-antipsychotic vs. antipsychotic medications

Medications	Unadjusted	Model 1	Model 2
Non-antipsychotics	0.09 (0.46)	-0.04 (0.64)	-0.02 (0.81)
By Class			
Buspirone	-0.14 (0.47)	-0.07 (0.59)	-0.07 (0.60)
Mirtazapine	0.11 (0.47)	-0.03 (0.79)	-0.01 (0.91)
Mood Stabilizers	0.13 (0.40)	-0.07 (0.50)	-0.02 (0.79)
Prazosin	0.31 (0.25)	-0.12 (0.52)	-0.14 (0.42)
Trazodone	-0.14 (0.47)	-0.07 (0.60)	-0.07 (0.60)
Tricyclics	0.11 (0.47)	-0.03 (0.79)	-0.01 (0.91)

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

Model 2: Adjusted for above plus service utilization factors

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

  Nothing to report at this time though we plan to involve trainees in dissemination of study findings and are currently working on our first manuscript.

- **How were the results disseminated to communities of interest?**

  We have presented our work at national conferences and have upcoming presentations as well (see Section 6). We collaborated with the National Center for PTSD and VA Psychotropic Drug Safety Initiative and have informed them of interim results.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  During the next reporting period, we will complete our analyses for Aim 3 (examination of demographic subgroups), which we have already begun. This will allow us to provide more tailored recommendations for prescribing that can be disseminated by our partners. We will also complete our NLP algorithm to obtain additional PTSD Checklist scores and repeat analyses involving these.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
  Nothing to report
- **What was the impact on other disciplines?**
  Nothing to report
- **What was the impact on technology transfer?**
  Nothing to report
- **What was the impact on society beyond science and technology?**
  Nothing to report

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

Nothing to report

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  We requested and received a no cost extension to allow more time to get additional PTSD symptom checklist scores by using an NLP algorithm. We have now constructed a database of relevant mental health notes from the cohort that may have symptom scores and are working with the NLP group to arrange analysis of PCL scores from these notes.
- **Changes that had a significant impact on expenditures**
  None
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  None
- **Significant changes in use or care of human subjects**
  None
- **Significant changes in use or care of vertebrate animals.**
  None
- **Significant changes in use of biohazards and/or select agents**
  None

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  - We presented data from this project at the Military Health Research Symposium on August 23, 2018 in a poster entitled Impact of Antipsychotic versus Non-Antipsychotic Medications to Augment First-Line PTSD Medications in Returning Iraq and Afghanistan Veterans: A National VA Data Study.
  - We will be presenting data from this project at the International Society of Traumatic Stress Studies annual meeting on November 10, 2018 in an oral presentation entitled Comparing the Effects of Medications to Augment Serotonin Reuptake Inhibitors in Patients with PTSD: A National VA Data Study.
  - The biostatistician for this project, Anne Woods, will be presenting a poster on our use of intermediate data objects (binary strings) in the process of cleaning pharmacy data for this project at the American Medical Informatics Association annual meeting on November 5, 2018.
- **Journal publications.**

Nothing to report

- **Books or other non-periodical, one-time publications.**
  Nothing to report
- **Other publications, conference papers, and presentations.**
  Nothing to report
- **Website(s) or other Internet site(s)**
  None
- **Technologies or techniques**
  None
- **Inventions, patent applications, and/or licenses**
  None
- **Other Products**
  None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	*Beth Cohen, MD, MAS*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
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*

Name:	*Karen Seal, MD, MPH*

Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
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):	
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):	

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.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Nothing to Report
- **What other organizations were involved as partners?**
  Not applicable

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**
  Not applicable
- **QUAD CHARTS:**
  Not applicable

9. APPENDICES:

Not applicable