Appendix Methods 1. Diagnostic Codes Used for Cause of Death Classification

Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine Pharmacotherapy and Associations with Mortality in the VHA, 2008-2017

Appendix Table 2. Follow-up Time, Deaths, and Incidence Rates by Type of MOUD among Veterans Initiating Buprenorphine Pharmacotherapy in the VHA, 2008-2017 (N=29,054)

Appendix Table 3. Association between Receipt of Buprenorphine Pharmacotherapy and Death with up to 5 Years of Follow-Up from Buprenorphine Pharmacotherapy Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Appendix Table 4. Association between Receipt of Buprenorphine Pharmacotherapy and Death with up to 1 Year of Follow-Up from Buprenorphine Pharmacotherapy Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Appendix Table 5. Association between Receipt of Buprenorphine Pharmacotherapy and Death with up to 2 Years of Follow-Up from Buprenorphine Pharmacotherapy Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Appendix Table 6. Association between Receipt of Buprenorphine Pharmacotherapy and Death with up to 3 Years of Follow-Up from Buprenorphine Pharmacotherapy Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Appendix Table 7. Association between Receipt of Buprenorphine Pharmacotherapy and Death with up to 4 Years of Follow-Up from Buprenorphine Pharmacotherapy Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Receipt of Buprenorphine Pharmacotherapy and Mortality with up to 5 Year

Appendix Figure 1. Evaluation of Multiplicative Effect Modification of Buprenorphine Pharmacotherapy and Mortality by Select Variables

Appendix Figure 2. Association between Receipt of Buprenorphine Pharmacotherapy and Mortality by Year of Follow-up
## Appendix Methods 1. ICD-10 Diagnostic Codes Used in Classifying Cause-Specific Mortality Outcomes

<table>
<thead>
<tr>
<th>Cause-Specific Outcome</th>
<th>ICD-10 Codes</th>
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<tr>
<td>Opioid-specific</td>
<td>T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6</td>
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## Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine and Associations with Mortality in the VHA, 2008-2017

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<th>Demographics and Clinical Measures</th>
<th>Suicide/Overdose</th>
<th>Suicide</th>
<th>Overdose</th>
<th>Opioid-Related Death</th>
<th>All-Cause Death</th>
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<td>0.84 0.75, 0.93</td>
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<th>Suicide/Overdose</th>
<th>Suicide</th>
<th>Overdose</th>
<th>Opioid-Related Death</th>
<th>All-Cause Death</th>
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<td>95% CI</td>
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<td>≥ 30 minutes</td>
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<td>Diabetes (with complications)</td>
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<td>Diabetes (without)</td>
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<td>0.86, 1.35</td>
<td>0.83</td>
<td>0.42, 1.63</td>
<td>1.12</td>
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</table>
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<th>All-Cause Death</th>
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<tbody>
<tr>
<td></td>
<td>uHR</td>
<td>95% CI</td>
<td>uHR</td>
<td>95% CI</td>
<td>uHR</td>
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<td>uHR</td>
<td>95% CI</td>
<td>uHR</td>
<td>95% CI</td>
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<tr>
<td>Hypertension (without complications)</td>
<td>1.08</td>
<td>0.94, 1.23</td>
<td>0.89</td>
<td>0.60, 1.30</td>
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<td>0.97, 1.28</td>
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<td>0.92, 1.29</td>
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<td>0.82, 2.56</td>
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<td>0.68, 2.72</td>
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<td>1.94</td>
<td>1.63, 2.30</td>
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</tbody>
</table>

### Psychiatric Co-morbidities

| Attention-deficit/ | Hyperactivity disorder | 1.41  | 1.11, 1.81 | 2.07  | 1.17, 3.67 | 1.39  | 1.07, 1.81 | 1.45  | 1.07, 1.96 | 0.89  | 0.74, 1.09 |
| Adjustment         | 1.26  | 1.07, 1.48 | 0.96  | 0.58, 1.58 | 1.30  | 1.09, 1.55 | 1.25  | 1.02, 1.54 | 1.06  | 0.95, 1.19 |
| Anxiety disorder   | 1.47  | 1.28, 1.68 | 1.24  | 0.87, 1.78 | 1.50  | 1.30, 1.73 | 1.57  | 1.32, 1.85 | 1.08  | 0.99, 1.17 |
| Bipolar disorder   | 1.51  | 1.31, 1.75 | 0.78  | 0.49, 1.26 | 1.61  | 1.39, 1.87 | 1.60  | 1.34, 1.91 | 1.16  | 1.05, 1.29 |
| Depression         | 1.55  | 1.33, 1.82 | 1.60  | 1.03, 2.47 | 1.50  | 1.31, 1.83 | 1.47  | 1.21, 1.78 | 1.24  | 1.13, 1.37 |
| Personality disorder | 1.49  | 1.22, 1.81 | 1.77  | 1.06, 2.94 | 1.47  | 1.19, 1.82 | 1.43  | 1.11, 1.84 | 1.36  | 1.19, 1.55 |
| Post-traumatic stress disorder             | 1.32  | 1.16, 1.50 | 1.39  | 0.98, 1.97 | 1.32  | 1.15, 1.51 | 1.36  | 1.16, 1.59 | 1.05  | 0.96, 1.14 |
| Schizophrenia                | 1.34  | 1.06, 1.70 | 0.91  | 0.42, 1.95 | 1.40  | 1.10, 1.78 | 1.30  | 0.96, 1.75 | 1.36  | 1.17, 1.58 |

### Other Substance Use

| Dependence | Alcohol | 1.50  | 1.32, 1.71 | 1.16  | 0.81, 1.65 | 1.52  | 1.33, 1.74 | 1.48  | 1.26, 1.74 | 1.43  | 1.32, 1.55 |
|            | Stimulants | 1.27  | 1.09, 1.47 | 0.68  | 0.42, 1.11 | 1.37  | 1.15, 1.56 | 1.43  | 1.20, 1.71 | 1.13  | 1.02, 1.24 |
|            | Cannabis | 1.14  | 0.94, 1.37 | 0.77  | 0.43, 1.40 | 1.15  | 0.94, 1.40 | 1.14  | 0.90, 1.43 | 0.98  | 0.87, 1.12 |
|            | Cocaine | 1.50  | 1.30, 1.73 | 0.44  | 0.24, 0.80 | 1.63  | 1.41, 1.89 | 1.72  | 1.44, 2.05 | 1.37  | 1.25, 1.51 |
|            | Hallucinogen | 1.71  | 0.81-3.60 | ***   | ***    | 1.91  | 0.91, 4.01 | 2.30  | 1.03, 5.15 | 0.83  | 0.41, 1.66 |
|            | Nicotine | 1.28  | 1.13, 1.45 | 1.01  | 0.71, 1.43 | 1.30  | 1.14, 1.49 | 1.27  | 1.08, 1.49 | 1.28  | 1.18, 1.40 |
|            | Sedative | 1.70  | 1.42, 2.05 | 1.01  | 0.54, 1.87 | 1.79  | 1.48, 2.17 | 1.74  | 1.39, 2.19 | 1.35  | 1.19, 1.54 |
### Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine and Associations with Mortality in the VHA, 2008-2017

<table>
<thead>
<tr>
<th>Demographics and Clinical Measures</th>
<th>Suicide/Overdose</th>
<th>Suicide</th>
<th>Overdose</th>
<th>Opioid-Related Death</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>uHR</td>
<td>95% CI</td>
<td>uHR</td>
<td>95% CI</td>
<td>uHR</td>
</tr>
<tr>
<td>Recent Medication Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.41</td>
<td>1.23, 1.62</td>
<td>1.61</td>
<td>1.08, 2.39</td>
<td>1.39</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.62</td>
<td>1.41, 1.85</td>
<td>1.48</td>
<td>1.02, 2.15</td>
<td>1.64</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>1.29</td>
<td>1.14, 1.47</td>
<td>1.63</td>
<td>1.15, 2.30</td>
<td>1.27</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>1.57</td>
<td>1.38, 1.78</td>
<td>1.27</td>
<td>0.89, 1.82</td>
<td>1.58</td>
</tr>
<tr>
<td>Opioids</td>
<td>1.05</td>
<td>0.93, 1.20</td>
<td>0.97</td>
<td>0.68, 1.39</td>
<td>1.09</td>
</tr>
<tr>
<td>Stimulants</td>
<td>1.45</td>
<td>1.08, 1.96</td>
<td>1.98</td>
<td>0.97, 4.05</td>
<td>1.48</td>
</tr>
<tr>
<td>Healthcare Utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any reason</td>
<td>1.71</td>
<td>1.50, 1.94</td>
<td>1.32</td>
<td>0.94, 1.87</td>
<td>1.74</td>
</tr>
<tr>
<td>Mental Health</td>
<td>1.71</td>
<td>1.50, 1.94</td>
<td>1.30</td>
<td>0.92, 1.84</td>
<td>1.75</td>
</tr>
<tr>
<td>Suicide or Self harm</td>
<td>1.59</td>
<td>1.33, 1.90</td>
<td>2.18</td>
<td>1.40, 3.39</td>
<td>1.53</td>
</tr>
<tr>
<td>Substance Use</td>
<td>1.70</td>
<td>1.50, 1.93</td>
<td>1.33</td>
<td>0.94, 1.88</td>
<td>1.74</td>
</tr>
<tr>
<td>Urgent Care Use</td>
<td>1.45</td>
<td>1.25, 1.70</td>
<td>1.04</td>
<td>0.65, 1.66</td>
<td>1.51</td>
</tr>
<tr>
<td>Emergency Department Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide or Self harm</td>
<td>1.58</td>
<td>1.29, 1.94</td>
<td>2.00</td>
<td>1.20, 3.33</td>
<td>1.55</td>
</tr>
<tr>
<td>Substance Use</td>
<td>1.44</td>
<td>1.26, 1.64</td>
<td>1.89</td>
<td>1.33, 2.67</td>
<td>1.40</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; uHR = unadjusted hazard ratio; *** = Unable to compute hazard ratios due to small sample size
### Appendix Table 2. Follow-up Time, Deaths, and Incidence Rates by Type of MOUD among Veterans Initiating Buprenorphine Pharmacotherapy in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Type of Death</th>
<th>Methadone</th>
<th>Naltrexone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Person-Days = 258,355</td>
<td>Total Person-Days = 177,339</td>
<td>Total Person-Days = 15,094,978</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>IR</td>
<td>n</td>
</tr>
<tr>
<td>Suicide/Overdose</td>
<td>11</td>
<td>4.26</td>
<td>13</td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
<td>0.39</td>
<td>2</td>
</tr>
<tr>
<td>Overdose</td>
<td>10</td>
<td>3.87</td>
<td>11</td>
</tr>
<tr>
<td>Opioid-Related</td>
<td>7</td>
<td>2.71</td>
<td>10</td>
</tr>
<tr>
<td>All Cause Death</td>
<td>28</td>
<td>10.84</td>
<td>19</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; MOUD = Medications for OUD
### Appendix Table 3. Association between Treatment Status and Death with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

#### Treatment Status and Suicide/Overdose (n=964 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>142</td>
<td>0.94</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>20,191,645</td>
<td>822</td>
<td>4.07</td>
<td>4.61 (3.84, 5.54)</td>
<td>4.33 (3.60, 5.21)</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>142</td>
<td>0.94</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified ≤7 days since last treatment</td>
<td>543,673</td>
<td>28</td>
<td>5.15</td>
<td>5.13 (3.40, 7.75)</td>
<td>4.56 (3.01, 6.90)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>388,091</td>
<td>28</td>
<td>7.21</td>
<td>7.47 (4.95, 11.28)</td>
<td>6.54 (4.32, 9.91)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>708,080</td>
<td>26</td>
<td>3.67</td>
<td>3.95 (2.59, 6.04)</td>
<td>3.45 (2.25, 5.29)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>18,551,801</td>
<td>740</td>
<td>3.99</td>
<td>4.51 (3.74, 5.43)</td>
<td>4.29 (3.55, 5.17)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Suicide (n=128 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>25</td>
<td>0.17</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>20,191,645</td>
<td>103</td>
<td>0.51</td>
<td>3.53 (2.24, 5.58)</td>
<td>3.57 (2.25, 5.66)</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>25</td>
<td>0.17</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified ≤7 days since last treatment</td>
<td>543,673</td>
<td>3</td>
<td>0.55</td>
<td>2.95 (0.88, 9.95)</td>
<td>2.79 (0.82, 9.46)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>388,091</td>
<td>5</td>
<td>1.29</td>
<td>6.11 (2.26, 16.54)</td>
<td>5.83 (2.15, 15.85)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>708,080</td>
<td>3</td>
<td>0.42</td>
<td>2.78 (0.83, 9.32)</td>
<td>2.56 (0.76, 8.70)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>18,551,801</td>
<td>92</td>
<td>0.50</td>
<td>3.46 (2.16, 5.55)</td>
<td>3.55 (2.21, 5.70)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Overdose (n=867 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>121</td>
<td>0.80</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>20,191,645</td>
<td>746</td>
<td>3.69</td>
<td>4.83 (3.97, 5.89)</td>
<td>4.58 (3.75, 5.59)</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>121</td>
<td>0.80</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified ≤7 days since last treatment</td>
<td>543,673</td>
<td>25</td>
<td>4.60</td>
<td>5.40 (3.49, 8.38)</td>
<td>4.82 (3.10, 7.49)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>388,091</td>
<td>24</td>
<td>6.18</td>
<td>7.73 (4.96, 12.04)</td>
<td>6.81 (4.35, 10.65)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>708,080</td>
<td>24</td>
<td>3.39</td>
<td>4.24 (2.72, 6.61)</td>
<td>3.73 (2.38, 5.83)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>18,551,801</td>
<td>673</td>
<td>3.63</td>
<td>4.73 (3.87, 5.78)</td>
<td>4.53 (3.70, 5.55)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Opioid-Related Death (n=616 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>87</td>
<td>0.58</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>20,191,645</td>
<td>529</td>
<td>2.62</td>
<td>4.84 (3.84, 6.12)</td>
<td>4.59 (3.62, 5.80)</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>87</td>
<td>0.58</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
### Appendix Table 3. Association between Treatment Status and Death with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>380</td>
<td>2.52</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>20,191,645</td>
<td>1,894</td>
<td>9.38</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>380</td>
<td>2.52</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>543,673</td>
<td>20</td>
<td>3.68</td>
<td>5.95 (3.62, 9.76)</td>
<td>5.18 (3.14, 8.52)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>388,091</td>
<td>19</td>
<td>4.90</td>
<td>8.70 (5.27, 14.39)</td>
<td>7.46 (4.49, 12.39)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>708,080</td>
<td>15</td>
<td>2.12</td>
<td>3.60 (2.07, 6.28)</td>
<td>3.08 (1.76, 5.40)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>18,551,801</td>
<td>475</td>
<td>2.56</td>
<td>4.72 (3.72, 5.99)</td>
<td>4.54 (3.57, 5.77)</td>
</tr>
</tbody>
</table>

**VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD**

---

### Treatment Status and All-Cause Death (n=2,274 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>n</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>380</td>
<td>2.52</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>20,191,645</td>
<td>1,894</td>
<td>9.38</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Treated</td>
<td>15,094,978</td>
<td>380</td>
<td>2.52</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>543,673</td>
<td>57</td>
<td>10.48</td>
<td>4.21 (3.18, 5.58)</td>
<td>4.25 (3.20, 5.65)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>388,091</td>
<td>65</td>
<td>16.75</td>
<td>6.90 (5.28, 9.01)</td>
<td>6.94 (5.30, 9.07)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>708,080</td>
<td>71</td>
<td>10.03</td>
<td>4.16 (3.22, 5.38)</td>
<td>4.17 (3.22, 5.41)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>18,551,801</td>
<td>1,701</td>
<td>9.17</td>
<td>3.67 (3.27, 4.12)</td>
<td>3.68 (3.28, 4.14)</td>
</tr>
</tbody>
</table>

# Appendix

**Association Between Buprenorphine for Opioid Use Disorder and Mortality Risk**

Vakkalanka et al.

*American Journal of Preventive Medicine*
### Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

#### Treatment Status and Suicide/Overdose (n=265 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>50</td>
<td>0.88</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4,163,150</td>
<td>215</td>
<td>5.16</td>
<td>6.31 (4.58, 8.69)</td>
<td>6.01 (4.34, 8.30)</td>
</tr>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>50</td>
<td>0.88</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>296,722</td>
<td>19</td>
<td>6.40</td>
<td>6.75 (3.93, 11.60)</td>
<td>6.03 (3.50, 10.40)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>209,264</td>
<td>14</td>
<td>6.69</td>
<td>7.52 (4.10, 13.79)</td>
<td>6.62 (3.59, 12.21)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>380,269</td>
<td>9</td>
<td>2.37</td>
<td>2.85 (1.39, 5.88)</td>
<td>2.52 (1.22, 5.21)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3,276,895</td>
<td>173</td>
<td>5.28</td>
<td>6.67 (4.75, 9.36)</td>
<td>6.53 (4.63, 9.21)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Suicide (n=40 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>9</td>
<td>0.16</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4,163,150</td>
<td>31</td>
<td>0.74</td>
<td>5.87 (2.65, 13.01)</td>
<td>5.64 (2.52, 12.63)</td>
</tr>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>9</td>
<td>0.16</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>296,722</td>
<td>3</td>
<td>1.01</td>
<td>5.89 (1.52, 22.75)</td>
<td>5.02 (1.28, 19.70)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>209,264</td>
<td>3</td>
<td>1.43</td>
<td>6.79 (1.73, 26.67)</td>
<td>5.85 (1.47, 23.23)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>380,269</td>
<td>1</td>
<td>0.26</td>
<td>2.17 (0.27, 17.73)</td>
<td>1.70 (0.20, 14.18)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3,276,895</td>
<td>24</td>
<td>0.73</td>
<td>6.28 (2.63, 15.04)</td>
<td>6.43 (2.66, 15.56)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Overdose (n=229 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>42</td>
<td>0.74</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4,163,150</td>
<td>187</td>
<td>4.49</td>
<td>6.40 (4.52, 9.04)</td>
<td>5.95 (4.19, 8.46)</td>
</tr>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>42</td>
<td>0.74</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>296,722</td>
<td>16</td>
<td>5.39</td>
<td>6.68 (3.70, 12.03)</td>
<td>5.86 (3.24, 10.61)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>209,264</td>
<td>12</td>
<td>5.73</td>
<td>7.93 (4.12, 15.26)</td>
<td>6.89 (3.56, 13.32)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>380,269</td>
<td>8</td>
<td>2.10</td>
<td>2.90 (1.34, 6.25)</td>
<td>2.54 (1.17, 5.50)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3,276,895</td>
<td>151</td>
<td>4.61</td>
<td>6.79 (4.71, 9.81)</td>
<td>6.48 (4.46, 9.42)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Opioid-Related Death (n=162 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>32</td>
<td>0.56</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

---

*Vakkalanka et al.*

*American Journal of Preventive Medicine*
## Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Treated Overall</td>
<td>4,163,150</td>
<td>130</td>
<td>3.12</td>
<td>6.08 (4.07, 9.09)</td>
<td>5.55 (3.68, 8.35)</td>
</tr>
<tr>
<td>Treated</td>
<td>5,663,738</td>
<td>32</td>
<td>0.56</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>296,722</td>
<td>12</td>
<td>4.04</td>
<td>6.50 (3.29, 12.81)</td>
<td>5.56 (2.81, 11.02)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>209,264</td>
<td>10</td>
<td>4.78</td>
<td>9.11 (4.41, 18.83)</td>
<td>7.69 (3.69, 16.00)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>380,269</td>
<td>4</td>
<td>1.05</td>
<td>1.82 (0.64, 5.23)</td>
<td>1.54 (0.54, 4.45)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3,276,895</td>
<td>104</td>
<td>3.17</td>
<td>6.51 (4.24, 10.01)</td>
<td>6.12 (3.95, 9.47)</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

a Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

b Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

c Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrrhythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

d Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrrhythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

e Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disorders, mental health disorders, other CHD, other neurological disorders, diabetes, other CHD, other neurological disorders, diabetes, other CHD)
Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median dose of buprenorphine, other MOUD, healthcare utilization (urgent care visit, overdose in ED)
### Appendix Table 5. Association between Treatment Status and Death with up to 2 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

#### Treatment Status and Suicide/Overdose (n=488 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>9,187,970</td>
<td>77</td>
<td>0.84</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>8,948,410</td>
<td>411</td>
<td>4.59</td>
<td>5.90 (4.58, 7.58)</td>
<td>5.61 (4.35, 7.22)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Suicide (n=65 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>9,187,970</td>
<td>15</td>
<td>0.16</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>8,948,410</td>
<td>50</td>
<td>0.56</td>
<td>4.17 (2.27, 7.67)</td>
<td>4.15 (2.24, 7.68)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Overdose (n=434 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>9,187,970</td>
<td>64</td>
<td>0.70</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>8,948,410</td>
<td>370</td>
<td>4.13</td>
<td>6.25 (4.76, 8.22)</td>
<td>5.96 (4.53, 7.86)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Opioid-Related Death (n=310 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>9,187,970</td>
<td>46</td>
<td>0.50</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated</td>
<td>8,948,410</td>
<td>264</td>
<td>2.95</td>
<td>6.37 (4.61, 8.80)</td>
<td>6.07 (4.38, 8.42)</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Hazard ratio adjusted for age, sex, race, income quintile, and calendar year

<sup>b</sup> Hazard ratio adjusted for age, sex, race, income quintile, and calendar year

<sup>c</sup> Hazard ratio adjusted for age, sex, race, income quintile, and calendar year

<sup>d</sup> Hazard ratio adjusted for age, sex, race, income quintile, and calendar year
Appendix Table 5. Association between Treatment Status and Death with up to 2 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>9,187,970</td>
<td>210</td>
<td>2.29</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>8,948,410</td>
<td>882</td>
<td>9.86</td>
<td>4.49 (3.84, 5.25)</td>
<td>4.49 (3.83, 5.26)</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>401,255</td>
<td>41</td>
<td>10.22</td>
<td>4.48 (3.19, 6.30)</td>
<td>4.53 (3.22, 6.37)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>284,364</td>
<td>42</td>
<td>14.77</td>
<td>6.71 (4.79, 9.41)</td>
<td>6.73 (4.79, 9.45)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>517,880</td>
<td>47</td>
<td>9.08</td>
<td>4.20 (3.05, 5.80)</td>
<td>4.20 (3.04, 5.81)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>7,744,911</td>
<td>752</td>
<td>9.71</td>
<td>4.39 (3.74, 5.16)</td>
<td>3.73 (5.17)</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

a Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)
b Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)
c Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrhythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)
d Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrhythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)
e Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)
### Appendix Table 6. Association between Treatment Status and Death with up to 3 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

#### Treatment Status and Suicide/Overdose (n=684 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>111</td>
<td>0.94</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>13,328,049</td>
<td>573</td>
<td>4.30</td>
<td>4.84 (3.92, 5.96)</td>
<td>4.59 (3.72, 5.67)</td>
</tr>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>111</td>
<td>0.94</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>467,075</td>
<td>25</td>
<td>5.35</td>
<td>5.35 (3.44, 8.32)</td>
<td>4.80 (3.08, 7.48)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>332,087</td>
<td>26</td>
<td>7.83</td>
<td>8.17 (5.29, 12.63)</td>
<td>7.25 (4.68, 11.25)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>605,231</td>
<td>22</td>
<td>3.63</td>
<td>3.96 (2.49, 6.30)</td>
<td>3.51 (2.20, 5.60)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>11,923,656</td>
<td>500</td>
<td>4.19</td>
<td>4.70 (3.79, 5.83)</td>
<td>4.52 (3.65, 5.62)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Suicide (n=92 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>21</td>
<td>0.18</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>13,328,049</td>
<td>71</td>
<td>0.53</td>
<td>3.46 (2.07, 5.76)</td>
<td>3.47 (2.07, 5.81)</td>
</tr>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>21</td>
<td>0.18</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>467,075</td>
<td>3</td>
<td>0.64</td>
<td>3.19 (0.93, 10.94)</td>
<td>2.94 (0.85, 10.12)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>332,087</td>
<td>4</td>
<td>1.20</td>
<td>5.20 (1.72, 15.74)</td>
<td>4.87 (1.60, 14.78)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>605,231</td>
<td>2</td>
<td>0.33</td>
<td>2.06 (0.48, 8.93)</td>
<td>1.84 (0.42, 8.06)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>11,923,656</td>
<td>62</td>
<td>0.52</td>
<td>3.45 (2.02, 5.87)</td>
<td>3.54 (2.07, 6.05)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Overdose (n=611 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>93</td>
<td>0.79</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>13,328,049</td>
<td>518</td>
<td>3.89</td>
<td>5.13 (4.09, 6.44)</td>
<td>4.89 (3.89, 6.15)</td>
</tr>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>93</td>
<td>0.79</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>467,075</td>
<td>22</td>
<td>4.71</td>
<td>5.63 (3.51, 9.03)</td>
<td>5.08 (3.16, 8.17)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>332,087</td>
<td>23</td>
<td>6.93</td>
<td>8.90 (5.60, 14.15)</td>
<td>7.97 (5.00, 12.72)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>605,231</td>
<td>21</td>
<td>3.47</td>
<td>4.45 (2.75, 7.21)</td>
<td>3.99 (2.46, 6.47)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>11,923,656</td>
<td>452</td>
<td>3.79</td>
<td>4.98 (3.95, 6.28)</td>
<td>4.80 (3.80, 6.07)</td>
</tr>
</tbody>
</table>

#### Treatment Status and Opioid-Related Death (n=435 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>65</td>
<td>0.55</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>13,328,049</td>
<td>370</td>
<td>2.78</td>
<td>5.36 (4.08, 7.03)</td>
<td>5.13 (3.90, 6.75)</td>
</tr>
<tr>
<td>Treated</td>
<td>11,753,066</td>
<td>65</td>
<td>0.55</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>
### Appendix Table 6. Association between Treatment Status and Death with up to 3 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th></th>
<th>Not Treated Stratified</th>
<th>Treatment Status and All-Cause Death (n=1,538 Deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤7 days since last treatment</td>
<td>≥7 days since last treatment</td>
</tr>
<tr>
<td></td>
<td>467,075</td>
<td>3,64</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>6.11 (3.54, 10.54)</td>
</tr>
<tr>
<td></td>
<td>5.48 (3.17, 9.48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>332,087</td>
<td>5.42</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>10.23 (6.02, 17.37)</td>
</tr>
<tr>
<td></td>
<td>9.09 (5.33, 15.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>605,231</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3.85 (2.10, 7.05)</td>
</tr>
<tr>
<td></td>
<td>3.42 (1.86, 6.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11,923,656</td>
<td>2.70</td>
</tr>
<tr>
<td></td>
<td>322</td>
<td>5.21 (3.94, 6.88)</td>
</tr>
<tr>
<td></td>
<td>5.06 (3.82, 6.71)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7 days since last treatment</td>
<td>≥7 days since last treatment</td>
</tr>
<tr>
<td></td>
<td>467,075</td>
<td>9.85</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>4.03 (2.94, 5.52)</td>
</tr>
<tr>
<td></td>
<td>4.07 (2.96, 5.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>332,087</td>
<td>16.86</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>7.11 (5.32, 9.51)</td>
</tr>
<tr>
<td></td>
<td>7.15 (5.33, 9.58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>605,231</td>
<td>9.25</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>3.94 (2.95, 5.27)</td>
</tr>
<tr>
<td></td>
<td>3.95 (2.95, 5.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11,923,656</td>
<td>9.15</td>
</tr>
<tr>
<td></td>
<td>1,091</td>
<td>3.81 (3.32, 4.36)</td>
</tr>
<tr>
<td></td>
<td>3.83 (3.34, 4.39)</td>
<td></td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

\[a\] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

\[b\] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

\[c\] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median buprenorphine dose, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

\[d\] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

\[e\] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)
Appendix Table 7. Association between Treatment Status and Death with up to 4 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Treatment Status and Suicide/Overdose (n=847 Deaths)</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>130</td>
<td>0.95</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>17,099,344</td>
<td>717</td>
<td>4.19</td>
<td>4.67 (3.85, 5.66)</td>
<td>4.41 (3.64, 5.36)</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>130</td>
<td>0.95</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>511,921</td>
<td>28</td>
<td>5.47</td>
<td>5.43 (3.58, 8.23)</td>
<td>4.83 (3.18, 7.34)</td>
<td>a</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>364,604</td>
<td>27</td>
<td>7.41</td>
<td>7.64 (5.01, 11.65)</td>
<td>6.72 (4.39, 10.27)</td>
<td></td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>665,247</td>
<td>25</td>
<td>3.76</td>
<td>4.04 (2.62, 6.23)</td>
<td>3.54 (2.28, 5.48)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>15,557,572</td>
<td>637</td>
<td>4.09</td>
<td>4.54 (3.73, 5.52)</td>
<td>4.35 (3.47, 5.30)</td>
<td></td>
</tr>
<tr>
<td>Treatment Status and Suicide (n=111 Deaths)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>23</td>
<td>0.17</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>17,099,344</td>
<td>88</td>
<td>0.51</td>
<td>3.54 (2.19, 5.73)</td>
<td>3.56 (2.20, 5.79)</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>23</td>
<td>0.17</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>511,921</td>
<td>3</td>
<td>0.59</td>
<td>3.05 (0.90, 10.37)</td>
<td>2.86 (0.84, 9.76)</td>
<td>b</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>364,604</td>
<td>4</td>
<td>1.10</td>
<td>5.00 (1.67, 14.98)</td>
<td>4.73 (1.57, 14.22)</td>
<td></td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>665,247</td>
<td>3</td>
<td>0.45</td>
<td>2.95 (0.87, 9.98)</td>
<td>2.68 (0.78, 9.18)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>15,557,572</td>
<td>78</td>
<td>0.50</td>
<td>3.52 (2.14, 5.79)</td>
<td>3.60 (2.18, 5.95)</td>
<td></td>
</tr>
<tr>
<td>Treatment Status and Overdose (n=758 Deaths)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>110</td>
<td>0.81</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>17,099,344</td>
<td>648</td>
<td>3.79</td>
<td>4.91 (3.99, 6.04)</td>
<td>4.68 (3.80, 5.77)</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>110</td>
<td>0.81</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>511,921</td>
<td>25</td>
<td>4.88</td>
<td>5.75 (3.70, 8.95)</td>
<td>5.15 (3.30, 8.04)</td>
<td>c</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>364,604</td>
<td>24</td>
<td>6.58</td>
<td>8.27 (5.28, 12.94)</td>
<td>7.33 (4.67, 11.51)</td>
<td></td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>665,247</td>
<td>23</td>
<td>3.46</td>
<td>4.34 (2.75, 6.84)</td>
<td>3.84 (2.42, 6.08)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>15,557,572</td>
<td>576</td>
<td>3.70</td>
<td>4.77 (3.86, 5.89)</td>
<td>4.60 (3.72, 5.70)</td>
<td></td>
</tr>
<tr>
<td>Treatment Status and Opioid-Related Death (n=542 Deaths)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>78</td>
<td>0.57</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>17,099,344</td>
<td>464</td>
<td>2.71</td>
<td>5.04 (3.94, 6.45)</td>
<td>4.82 (3.76, 6.18)</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>78</td>
<td>0.57</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

American Journal of Preventive Medicine
## Appendix Table 7. Association between Treatment Status and Death with up to 4 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>511,921</td>
<td>20</td>
<td>3.91</td>
<td>6.42 (3.89, 10.59)</td>
<td>5.64 (3.41, 9.34)</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>364,604</td>
<td>19</td>
<td>5.21</td>
<td>3.64 (2.04, 6.48)</td>
<td>8.20 (4.91, 13.71)</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>665,247</td>
<td>14</td>
<td>2.10</td>
<td>9.46 (5.69, 15.72)</td>
<td>3.16 (1.76, 5.65)</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>15,557,572</td>
<td>411</td>
<td>2.64</td>
<td>4.88 (3.79, 6.27)</td>
<td>4.75 (3.68, 6.12)</td>
</tr>
</tbody>
</table>

### Treatment Status and All-Cause Death (n=1,951 Deaths)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Person Days at Risk</th>
<th>N</th>
<th>IR</th>
<th>uHR (95% CI)</th>
<th>aHR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>346</td>
<td>2.53</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>17,099,344</td>
<td>1,605</td>
<td>9.39</td>
<td>3.79 (3.34, 4.28)</td>
<td>3.81 (3.38, 4.30)</td>
</tr>
<tr>
<td>Treated</td>
<td>13,660,680</td>
<td>346</td>
<td>2.53</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

---

a Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

b Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

c Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrhythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

---

d Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrhythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

e Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)
# Appendix

## Association Between Buprenorphine for Opioid Use Disorder and Mortality Risk

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### Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Treatment Status and Mortality with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Main Analysis&lt;sup&gt;a&lt;/sup&gt; N=29,054</th>
<th>SA 1: Excluding Low Utilizers&lt;sup&gt;b&lt;/sup&gt; N=26,404</th>
<th>SA 2: Excluding Infrequent Buprenorphine Utilizers&lt;sup&gt;c&lt;/sup&gt; N=24,405</th>
<th>SA 3: E-Values&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicide/Overdose Deaths</strong></td>
<td>n=964</td>
<td>n=899</td>
<td>n=731</td>
<td></td>
</tr>
<tr>
<td>Treatment Status</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4.33 (3.60, 5.21)</td>
<td>4.15 (3.44, 5.02)</td>
<td>3.92 (3.23, 4.76)</td>
<td>8.15/6.66</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>4.56 (3.01, 6.90)</td>
<td>4.23 (2.75, 6.50)</td>
<td>4.16 (2.53, 6.83)</td>
<td>8.59/5.47</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>6.54 (4.32, 9.91)</td>
<td>6.30 (4.12, 9.63)</td>
<td>6.66 (4.18, 10.62)</td>
<td>12.56/8.11</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>3.45 (2.25, 5.29)</td>
<td>3.19 (2.05, 4.98)</td>
<td>3.27 (2.01, 5.32)</td>
<td>6.36/3.93</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>4.29 (3.55, 5.17)</td>
<td>4.12 (3.40, 5.00)</td>
<td>3.87 (3.18, 4.71)</td>
<td>8.05/6.56</td>
</tr>
<tr>
<td><strong>Suicide Deaths</strong></td>
<td>n=128</td>
<td>n=120</td>
<td>n=97</td>
<td></td>
</tr>
<tr>
<td>Treatment Status</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>3.57 (2.25, 5.66)</td>
<td>3.61 (2.23, 5.83)</td>
<td>3.05 (1.87, 4.96)</td>
<td>6.60/3.93</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>2.79 (0.82, 9.46)</td>
<td>2.89 (0.85, 9.88)</td>
<td>2.87 (0.67, 12.31)</td>
<td>5.02/1.00</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>5.83 (2.15, 15.85)</td>
<td>4.77 (1.58, 14.35)</td>
<td>3.92 (0.91, 16.88)</td>
<td>11.14/3.72</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>2.56 (0.76, 8.70)</td>
<td>2.71 (0.79, 9.29)</td>
<td>2.10 (0.49, 9.08)</td>
<td>4.56/1.00</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3.55 (2.21, 5.70)</td>
<td>3.64 (2.22, 5.99)</td>
<td>3.08 (1.88, 5.05)</td>
<td>6.56/3.85</td>
</tr>
<tr>
<td><strong>Overdose Deaths</strong></td>
<td>n=867</td>
<td>n=807</td>
<td>n=657</td>
<td></td>
</tr>
<tr>
<td>Treatment Status</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4.58 (3.75, 5.59)</td>
<td>4.34 (3.54, 5.31)</td>
<td>4.20 (3.40, 5.17)</td>
<td>8.63/6.96</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>4.82 (3.10, 7.49)</td>
<td>4.39 (2.78, 6.93)</td>
<td>4.39 (2.59, 7.45)</td>
<td>9.11/5.65</td>
</tr>
<tr>
<td>Opioid-Related Deaths</td>
<td>n=616</td>
<td>n=578</td>
<td>n=459</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Treatment Status</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>4.59 (3.62, 5.80)</td>
<td>4.27 (3.36, 5.41)</td>
<td>4.03 (3.14, 5.16)</td>
<td>8.89/6.86</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>5.18 (3.14, 8.52)</td>
<td>4.53 (2.69, 7.63)</td>
<td>4.46 (2.42, 8.24)</td>
<td>8.65/6.70</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>7.46 (4.49, 12.39)</td>
<td>7.27 (4.37, 12.10)</td>
<td>7.61 (4.34, 13.33)</td>
<td>14.40/8.45</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>3.08 (1.76, 5.40)</td>
<td>2.61 (1.44, 4.73)</td>
<td>2.76 (1.42, 5.37)</td>
<td>5.61/2.92</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>4.54 (3.57, 5.77)</td>
<td>4.25 (3.33, 5.42)</td>
<td>3.98 (3.09, 5.11)</td>
<td>8.55/6.60</td>
</tr>
<tr>
<td>All-Cause Deaths</td>
<td>n=2,274</td>
<td>n=2,138</td>
<td>n=1,737</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treatment Status</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>aHR (95% CI)</td>
<td>E-Value/CI</td>
</tr>
<tr>
<td>Treated</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Not Treated Overall</td>
<td>3.82 (3.41, 4.28)</td>
<td>3.74 (3.32, 4.20)</td>
<td>3.58 (3.17, 4.04)</td>
<td>7.10/6.28</td>
</tr>
<tr>
<td>Not Treated Stratified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 days since last treatment</td>
<td>4.25 (3.20, 5.65)</td>
<td>3.73 (2.75, 5.05)</td>
<td>4.17 (3.03, 5.74)</td>
<td>7.97/5.85</td>
</tr>
<tr>
<td>8-14 days since last treatment</td>
<td>6.94 (5.30, 9.07)</td>
<td>6.88 (5.23, 9.05)</td>
<td>7.19 (5.37, 9.62)</td>
<td>13.36/10.07</td>
</tr>
<tr>
<td>15-30 days since last treatment</td>
<td>4.17 (3.22, 5.41)</td>
<td>4.04 (3.09, 5.27)</td>
<td>4.13 (3.10, 5.49)</td>
<td>7.81/5.89</td>
</tr>
<tr>
<td>&gt;30 days since last treatment</td>
<td>3.68 (3.28, 4.14)</td>
<td>3.62 (3.21, 4.08)</td>
<td>3.43 (3.04, 3.88)</td>
<td>6.82/6.01</td>
</tr>
</tbody>
</table>

VHA = Veterans Health Administration; N = Total Sample Population; n = Number of deaths; IR = Incidence rate (deaths per 100,000 person days); SA = Sensitivity analysis; uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio

a Main Analysis: Represents the results from the final models for each mortality outcome over five years of follow-up, as seen in Table 3.

b SA 1: Represents results from excluding Veterans who had ≤14 outpatient encounters within the VHA system in the two years preceding initial buprenorphine prescription. The purpose of this analysis was to assess whether there was potential unmeasured confounding from those who might not have had the opportunity to have co-morbidities documented to the same extent as routine VHA users.
Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Treatment Status and Mortality with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017

- **SA 2**: Represents results from excluding Veterans who had a total of ≤30 days on buprenorphine treatment over five years of follow up from the initial buprenorphine prescription. The purpose of this analysis was to account for potential misclassification of exposure, specifically among those who might have received treatment outside of the VHA but have been documented as not being on treatment in our main analysis.

- **SA 3**: Represents an assessment of unmeasured confounding and bias by evaluating the E-values, the minimum strength of association that an unmeasured confounder would need to fully explain away the observed association, conditioned on covariates that are measured. For example, for the primary suicide/overdose composite outcome over 5 years of follow-up, the observed hazard ratio of 4.34 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a hazard ratio of 8.15-fold each, above and beyond the measured confounders, but weaker confounding could not do so. The confidence interval could be moved to include the null by an unmeasured confounder that was associated with both the treatment and the outcome by a hazard ratio of 6.66-fold each, above and beyond the measured confounders, but weaker confounding could not do so.
Appendix Figure 1. Evaluation of Multiplicative Effect Modification of Buprenorphine Pharmacotherapy and Mortality by Select Variables

- **A. Gender**
  - p=0.747

- **B. Age**
  - p=0.979

- **C. Urban/Rural Designation**
  - p=0.836

- **D. Race**
  - p=0.080

- **E. Peak Initial Dose**
  - p=0.292

*Reference group = Those on buprenorphine treatment*
*P-values indicate multiplicative interaction term value from final adjusted models*
Appendix Figure 2. Association between Receipt of Buprenorphine Pharmacotherapy and Morality by Year of Follow-Up

* Reference group = On buprenorphine pharmacotherapy