An Evaluation of Relapse with Regards to Dose and Concomitant Use of Sedating Medications in a Veteran Population Prescribed Buprenorphine/Naloxone: A Retrospective Cohort Study  
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Background

- 8 million people worldwide dependent on opioids  
- Multitude of health problems  
- Opioid maintenance treatment programs  
  - Substitute drug of dependence with prescribed opioid agonist, antagonist, or combination  
  - Ultimate goal is drug free state

Background: Maintenance Therapy

- Methadone  
  - Full opioid agonist  
- Naloxone/Naltrexone  
  - Opioid antagonists  
- Buprenorphine  
  - Synthetic partial opioid agonist

Background: Suboxone Clinic

- Initiated in 2009  
- 138 patients  
- Prior to enrollment  
  - Sign a consent form  
  - Sign opioid agreement  
  - Lab work  
- Once enrolled  
  - Weekly visits which may be increased to every other week or monthly  
  - UDS at each follow up  
  - Once weekly group sessions and aftercare appointments through VA  
  - At least 3 community support groups

Literature Review

- It is known that 80-90% of receptors need to be inactivated to block effects of heroin  
- Study by Zubieta found a dose-dependent difference in mu opioid receptor availability with buprenorphine  
  - 2mg bound 36-50%  
  - 16mg bound 79-95%  
- Therefore, questioned if higher doses may produce better outcomes


Literature Review

- Currently, there is no literature specifically evaluating relapse rates of patients prescribed buprenorphine/naloxone as well as concomitant sedating medications  
  - A study by Amass, et al. examined the use of medications for insomnia, anxiety, arthralgias, and other common complaints during withdrawal  
  - Showed benefit during the detoxification period, but their role in the maintenance period is questionable

Objective

• Two-fold
  – First, to determine if buprenorphine/naloxone dosed at 8mg or less daily compared to higher doses affected relapse rates
  – Second, to assess if concomitant sedating medications affected relapse rates

Methods

• Retrospective cohort study
• Inclusion criteria: All veterans enrolled in Suboxone Clinic, at least 18 years old, and followed in clinic for at least 6 months unless relapsed
• Collected data through CPRS including gender, age, race, psychiatric diagnosis, pain diagnosis, date enrolled in Suboxone Clinic, most recent dose, date most recent dose initiated, concomitant sedating medications, relapse*, date of relapse, graduated from clinic, or continued in clinic
  – *Lost to follow up considered relapse
  – Sedating medications: Cyproheptadine, hydroxyzine, quetiapine, trazodone

Methods: Outcomes

• Primary outcome
  – Relapse within 6 months
• Secondary outcome
  – Time to relapse

Methods: Statistics

• Primary outcome assessed with Fishers Exact
• Secondary outcome calculated using paired T test
• Preset alpha 0.05
• With 95% CI and assuming dropout rate of 70% +/- 10%, calculated that 29 patients needed in each arm to reach statistical significance
• No controls for gender, ethnicity, past medical history, or current medications

Results: Enrollment

• 132 patients included
  – 163 patient encounters due to multiple enrollments

Results: Baseline Demographics

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Dose &lt;8mg</th>
<th>Dose &gt;8mg</th>
<th>Sedating Medication</th>
<th>No Sedating Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>79 (94.0%)</td>
<td>78 (98.7%)</td>
<td>84 (97.7%)</td>
<td>72 (94.7%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>82</td>
<td>77</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>37.5</td>
<td>38.7</td>
<td>37.7</td>
<td>38.9</td>
</tr>
<tr>
<td>Psychiatric Diagnosis</td>
<td>76 (90.5%)</td>
<td>70 (88.6%)</td>
<td>79 (91.9%)</td>
<td>66 (85.7%)</td>
</tr>
<tr>
<td>Pain Diagnosis</td>
<td>60 (71.4%)</td>
<td>69 (87.3%)</td>
<td>P=0.0198*</td>
<td>70 (81.4%)</td>
</tr>
</tbody>
</table>
Results: Most Efficacious Dose

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Relapse Within 6 Months</th>
<th>Dose ≤8mg</th>
<th>Dose &gt;8mg</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (%)</td>
<td>51 (60.7%)</td>
<td>26 (32.9%)</td>
<td></td>
<td>0.0005*</td>
</tr>
<tr>
<td>No (%)</td>
<td>33 (39.3%)</td>
<td>53 (67.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Average Time Until Relapse</th>
<th>Dose ≤8mg</th>
<th>Dose &gt;8mg</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>5.1</td>
<td>8.4</td>
<td></td>
<td>0.0017*</td>
</tr>
</tbody>
</table>

Results: Sedating Medications

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Relapse Within 6 Months</th>
<th>Sedating Med</th>
<th>No Sedating Med</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (%)</td>
<td>37 (43.0%)</td>
<td>40 (51.9%)</td>
<td></td>
<td>0.2746</td>
</tr>
<tr>
<td>No (%)</td>
<td>49 (57.0%)</td>
<td>37 (48.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Average Time Until Relapse</th>
<th>Sedating Med</th>
<th>No Sedating Med</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>6.8</td>
<td>5.3</td>
<td></td>
<td>0.2209</td>
</tr>
</tbody>
</table>

Comparison of Relapse Rate in Patients Receiving >8mg Dose

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Sedating Med</th>
<th>No Sedating Med</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (%)</td>
<td>13</td>
<td>14</td>
<td>0.1555</td>
</tr>
<tr>
<td>No (%)</td>
<td>34</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

- Statistically greater number of patients given buprenorphine/naloxone 8mg or less relapsed within 6 months as compared to higher doses
- If relapse did occur, time was prolonged with higher doses

Discussion

- More patients in the higher dose group continue to be enrolled in clinic. Some theories that may support this are:
  - Lower doses may not control cravings, leading to relapse
  - Higher doses control cravings causing fear to discontinue due to potential for relapse
  - Due to partial mu opioid activity, there could be pain control leading patients to no longer self-medicate
  - This is supported by statistically more patients in the higher dose group having a pain diagnosis

Discussion

- The use of concomitant sedating medications did not appear to have an impact on relapse rates within 6 months.
- Time until relapse was approximately 1.5 months longer in patients receiving a concomitant sedating medication, but this was not statistically significant
- Prompted a change in practice

Discussion

- When use of concomitant sedating medications was analyzed separately in patients receiving at least 8mg buprenorphine/naloxone, the concomitant use resulted in lower rates of relapse, though this was not statistically significant
  - Possible beta error due to low number of patients to analyze
**Limitations**

- Retrospective chart review
- Majority of patients included in this study were Caucasian males
- No evaluation of individual or specific combinations of sedating medications

**Conclusions**

- Buprenorphine/naloxone dosed above 8mg daily helped prevent relapse and prolonged the time until relapse compared to smaller doses
- Concomitant use of sedating medications did not have a statistically significant effect on relapse rate or time to relapse

**Self-assessment Question #1**

- Based on the data presented here, which dose of buprenorphine/naloxone would be most effective at reducing relapse rates?
  - a. 2mg (2mg/0.5mg)
  - b. 4mg (4mg/1mg)
  - c. 8mg (8mg/2mg)
  - d. 12mg (12mg/3mg)

**Self-assessment Question #2**

2. Concomitant use of sedating medications was shown to have which effect on relapse?
   - a. A statistically significant increase in relapse rates at 6 months
   - b. A statistically significant decrease in relapse rates at 6 months
   - c. A statistically significant decrease in time to relapse
   - d. No statistically significant effect on relapse rates at 6 months