An Open-Label Preliminary Assessment of Aripiprazole Augmentation in the Treatment of Military-Related PTSD with Major Depression

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Abstract:

Background

In this study we attempted to evaluate the benefits of adding aripiprazole in veterans with military-related PTSD with comorbid depression who had been minimally or partially responsive to their existing medications.

Methods:

A retrospective chart review of patients who received an, open-label, flexible-dose, 12-week course of adjunctive aripiprazole was conducted in 27 military veterans meeting DSM-IV criteria for PTSD and comorbid major depression. Concomitant psychiatric medications continued unchanged, except for other antipsychotics which were discontinued prior to initiating aripiprazole. The primary outcome variable was change from baseline in the PTSD checklist-military version (PCL-M) and the Beck Depression Inventory (BDI-II).

Results:

PTSD severity (Total PCL scores) decreased from 56.11 at baseline to 46.85 at study end (p <0.0001 from Wilcoxon signed rank test) and the depression severity decreased from 30.44 at baseline to 20.67 at study end (p <0.0001 from Wilcoxon signed rank test). Thirty seven percent (10/27) were considered responders, as defined by a decrease in total PCL scores of at least 20 percent and 19% (5/27) were considered as responders as
defined by decrease in total BDI score of at least 50%.

**Conclusions:**

The addition of aripiprazole contributed to a reduction in both PTSD and depression symptomatology in a population that has traditionally demonstrated poor pharmacological response. Further investigations, including double-blind, placebo-controlled studies, are essential to confirm and further demonstrate the benefit of aripiprazole augmentation in the treatment of military related PTSD.

Word Count: 2345
Background:

Military-related posttraumatic stress disorder (PTSD) is a serious psychiatric condition often resulting from combat duty in the current wars in Afghanistan and Iraq [1] and past peacekeeping and humanitarian missions. [2-4] Patients with PTSD present with four symptom clusters: re-experience of the traumatic event(s), avoidance of reminders and emotional numbing (which are grouped together as one symptoms cluster in DSM-IV, but are seen as distinct and will likely be denoted as such in DSM-V), and hyperarousal symptoms. [5, 6] Recent estimates of the prevalence of PTSD in various military and veteran populations has varied from a low of 4.8% in UK military members[7] to higher rates of 10.3% in Canadian peacekeeping veterans, [8] and 11.2 – 17.1% in U.S. military members returning from the deployments to Iraq and Afghanistan [9]. Military-related PTSD is associated with severe psychosocial dysfunction. [10, 11]

The response to pharmacological interventions for military-related PTSD are often disappointing. [10, 12-16] PTSD often presents with co-morbidities such as depression and substance abuse and dependence[17, 18] and amongst veterans, the comorbidity rates may be much higher than in other populations. [19, 20] Studies have also demonstrated that veterans with chronic, military-related PTSD often present with significant comorbid psychotic features [21, 22] which may contribute to the severe psychosocial dysfunction in this population. [10, 11]
Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) have the most empirical evidence for efficacy in the treatment of PTSD and are usually considered first-line treatment. [5, 14, 23] SSRIs and SNRIs are also effective agents for the treatment of co-morbid mood and anxiety disorders commonly associated with PTSD. However, the lack of efficacy of antidepressant monotherapy, especially in male combat veterans [24, 25] has led to the frequent use of combination strategies, especially the addition of antipsychotics, in many treatment guidelines for treatment-resistant PTSD. [5, 26]

The benefit of adding a second-generation antipsychotic, such as risperidone, quetiapine, or olanzapine, for the treatment of PTSD in combination with a primary antidepressant has been suggested in numerous small studies, including a few randomized controlled trials. [27-30] These agents appear beneficial in managing hyperarousal symptoms such as hypervigilance and irritability, as well as severe dissociative symptoms. [14] There is also evidence for the addition of aripiprazole, quetiapine, risperidone, and olanzapine for treatment-resistant depression, [31] which often presents as a complicating factor in military-related, chronic PTSD. More recently, the efficacy of aripiprazole in the treatment of PTSD has been demonstrated in three preliminary open-label studies in veteran populations, both as a monotherapy and as an adjunctive treatment. [32-34]

Aripiprazole is a novel antipsychotic with partial agonist activity at D2 receptors and 5HT1A receptors, and antagonist activity at 5-HT2A receptors. [35]
Aripiprazole is reported to have less risk for extrapyramidal side effects than traditional antipsychotics and has been demonstrated to be effective in treatment-resistant depression. [36, 37]

Based on the positive results of aripiprazole for both treatment-resistant depression and treatment-resistant PTSD, and on its unique pharmacology, we hypothesized that aripiprazole would be efficacious for treatment-resistant military-related PTSD with comorbid major depression. To reflect general clinical practice, we conducted a retrospective file review to examine the benefits of adding aripiprazole in veterans with military-related PTSD with comorbid depression who had been minimally or partially responsive to their existing medications. To our knowledge, this is the first study to examine the efficacy of aripiprazole to treat both chronic PTSD and comorbid depression in a sample of veterans with chronic military-related PTSD where 100% of the participants had comorbid major depression.

Methods:

Participants and Procedure:

Participants consisted of a sample of 27 consecutive veterans referred for psychiatric treatment at an outpatient clinic specializing in the treatment of military-
related psychiatric conditions. The study clinic follows a standardized assessment and treatment protocol; the standardized assessments include the PTSD Checklist-Military Version (PCL-M), [38] Beck Depression inventory (BDI), [39] and Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36), [40] administered at intake and at each follow-up appointment over the course of treatment. In addition to providing psychoeducation, the standard psychiatric treatment at the clinic includes symptom management, treatment of comorbid disorders, and management of functional impairment. [5] Participants were prescribed aripiprazole after demonstrating minimal or partial response to their existing antidepressant and/or minimal or partial response to other antipsychotic augmentation strategies. All subjects received a comprehensive psychiatric evaluation and laboratory tests (complete blood count with white count differential, serum electrolytes, glucose, creatinine, blood urea nitrogen, liver function tests, and lipid profile). The initial dose of aripiprazole was 2 to 5 mg daily, with further dose titrations based on tolerability and clinical response, up to a maximum of 30 mg daily. Efficacy and adverse effects were assessed and recorded at each follow-up appointment (bi-weekly for the first month and then monthly). Antidepressants, anxiolytics, and mood stabilizers were allowed but had to be kept at a constant dose during the treatment phase of the study. Other antipsychotics were not allowed during the study, and were discontinued at prior to initiation aripiprazole.

The sample for the study was derived from a retrospective chart review with approval from the Office of Research Ethics of the University of Western Ontario. All patients met the DSM-IV criteria for PTSD and comorbid major depressive disorder. To
maximize the generalizability of this study to usual "clinical practice," all comorbid physical and psychiatric conditions were included in the study.

**Instruments**

To diagnose PTSD, the Clinician-Administered PTSD Scale (CAPS) [41] was administered by a trained clinician and the diagnosis of major depressive disorder was determined using the Patient Health Questionnaire (PHQ-9)[42] and the psychiatric interview according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. [6] To assess change in PTSD symptoms with treatment, the PCL-M[38] was used. Similarly, the BDI [43, 44] was used to assess change in depressive symptoms as a result of treatment. The SF-36 [45] was used to assess health related quality of life (HRQol). The SF-36 measures functional impairment in eight domains or subscales; the mental health sub scales can be collapsed into the Mental Component Summary (MCS) Score reflecting overall mental health [46]. The PCL-M, the BDI, and the SF-36 were all administered at each follow-up appointment including at intake (t1) and at 1-, 2-, and 3-month follow-ups (t2, t3, and t4) over the course of treatment. The PCL-M and the BDI were the primary efficacy variables; the PCL-M re-experiencing, avoidance/numbing, and hyperarousal subscale scores served as secondary efficacy variables.

**Analysis**

The LOCF data for each visit included the data recorded at that visit, or otherwise the data carried forward from the last visit. For the primary outcome, the Wilcoxon signed rank test
and effect sizes (Cohen’s d) was used to determine the statistical significance of the change from baseline in total PCL-M and Total BDI score at each follow-up time point (t2, t3, t4). For the three secondary outcome measures (the PCL-M re-experiencing, avoidance/numbing, and hyperarousal subscale scores), only the effects at t4 were examined.

For each of the two main outcomes, we identified responders on our two outcome measures using criteria established in existing literature. More specifically, on the PCL, we identified those with at least a 20% reduction in their symptom scores as responders;[33] this is in keeping with prior treatment efficacy and more specifically, prior Aripiprazole treatment efficacy studies for PTSD [33]. On the BDI, we identified those with at least a 50% reduction in their symptom scores as responders [47].

Results

Demographics and Clinical Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. Of the 27 participants, almost all were men (n = 26, 96.3%), with an average age of 39.36 (SD=5.98) with an average of 10.26 years (SD = 7.38) with PTSD symptoms. At intake, the majority (n = 20, 74.1%) of the sample had been released from the military. Years of
military service averaged 15.04 ($SD = 7.41$). Almost all ($n = 26$, 96.3%) had exposure to combat or to a war zone during their deployment and the most common deployments reported were Afghanistan ($n = 9$, 33.3%), the former Yugoslavia ($n = 8$, 29.6%), and Africa (Somalia, Rwanda, Eatrea, and Sierra Leone) ($n = 5$, 18.5%). All patients were taking an antidepressant prior to initiating aripiprazole, most commonly an NDRI ($n = 16$, 59.3%) followed by NaSSA ($n = 12$, 44.4%); SNRI ($n = 11$, 41.7%), and SSRI ($n = 10$, 37%). Most patients ($n = 14$, 51.9%) were taking two antidepressant and an additional 14.8% ($n = 4$) were taking three antidepressant. In addition to an antidepressant, 8 patients (30.77%) were prescribed an anticonvulsant, 5 patients (19.23%) were prescribed a stimulant, and 4 patients (15.38%) were prescribed a hypnotic.

Twenty-seven patients had at least one post-baseline efficacy evaluation thus were included in the efficacy analysis. At intake, all participants met full criteria for PTSD based on the CAPS interview. The average duration of PTSD symptoms was 10.26 years ($SD = 7.38$), suggesting a chronic course for this sample. Intake scores on the PCL-M and the BDI averaged 56.11 ($SD = 12.66$) and 30.44 ($SD = 7.86$), respectively. On the PCL-M, a score of 50 is the conventional cut-off score for a positive screen for PTSD in veteran populations; [48] on the BDI, scores above 29 are considered indicative of severe depression [49]. SF-36 MCS and PCS were 20.22 ($SD = 10.11$) and 32.48 ($SD = 15.06$), respectively, indicating significant impairment in scales measuring both mental and physical functioning.

**Dose and Tolerability**
The final average dose of aripiprazole was 12.40 (SD = 4.35) mg daily. The mean value of weight decrease from baseline (mean=99.25 kg, SD=13.35) to the final visit is 1.05 kg (SD= 4.95). Only two patients discontinued the aripiprazole; one patient due to non-response and one due to intolerable restlessness. The remaining 25 patients tolerated the aripiprazole. The improved tolerability was likely related to lower starting doses (e.g., 2 mg daily) and slow titration (increasing the dose by 2-5 mg every two weeks).

Treatment Efficacy

Results from Wilcoxon signed rank tests showed significant decreases between baseline and each of the three follow-ups for the BDI and the PCL, as well as the last visit for the PCL Reexperiencing, Avoidance, and Hyperarousal subscales (Table 2). The total PCL score decreased from 56.11 (SD=12.66) at baseline to 46.85 (SD=13.53) at three months and the total BDI score 30.44 (SD= 7.85) at baseline to 20.67 (SD=10.05) at three months. Effect sizes and changes in the clinical outcome variables from intake to the final visit are reported in Table 3.

The number and percentage of responders at each of the follow-ups are reported in Table 4. Thirty seven percent (10/27) were considered responders, as defined by a
decrease in total PCL scores of at least 20 percent and for depression, 19% (5/27) were considered responders as defined by decrease in total BDI score of at least 50%. Overall, a higher percentage of participants met criteria for being a responder on the PCL than the BDI.

Additional analyses to examine the efficacy of Aripiprazole among those with severe depression (BDI > 29) at intake (n=14) found significant reductions in PCL symptom scores for this subsample as well, with the PCL scores averaging 61.79 (SD=9.60), 51.86 (SD=13.54), 52.14 (SD=15.53), and 48.71 (SD=13.02) at intake and each of the follow-ups respectively. The Wilcoxon signed rank test results showed significant reductions from intake to each of the follow-ups (p=0.0051, p=0.0405, and 0.0010 for each of the follow-ups). The percentages of responders on PCL at each of the follow-ups are 35.71%, 42.86%, and 57.14%, respectively. It is worth noting that at t4, having severe depression was found to be associated with higher percentage of responders on PCL (P=0.0461 from Fisher’s exact test)

Discussion

Consistent with previous studies in veteran, [32-34] the addition of aripiprazole contributed to a reduction in PTSD symptomatology in all symptom clusters (reexperiencing, avoidance/numbing, and hyperarousal) and among those with severe comorbid major depression disorder (baseline BDI ≥ 29). A significant number (37 %) demonstrated a significant reduction in PTSD symptomatology (decrease in total PCL
scores of at least 20%). Although modest, the response rate is particularly encouraging in a population of chronic military related PTSD with comorbid major depression in the severe range which has traditionally demonstrated poor response to pharmacotherapy. The lower response rate observed in this study compared to other augmentation trial by Roberts and colleagues[33] might be related to higher rates of comorbid depression (100%) in this study.

Consistent with studies on treatment resistant depression, [50, 51] the addition of aripiprazole also demonstrated an overall reduction in depression severity from a total BDI score of 30.44 at baseline to 20.67 at three months. However, unlike the study by Berman [52] where 42% met the criteria for significant response, in our study only a minority (19 %) showed decrease in total BDI scores of at least 50%. The lower response rate observed in our study compared to Berman and colleagues [52] study might be related to the fact that in Berman’s study patients with comorbid PTSD were excluded. Also in this study, most (52.9%) reported depression in the severe range and most patients (n =18, 66.7%) in this sample continue to be symptomatic despite being on combination antidepressant prior to initiating aripiprazole suggesting significant treatment resistant.

Due to significant limitations of this study, including a small sample size and a lack of a control group, careful interpretation of the findings is warranted. This was a preliminary, open-label retrospective study, with a small sample size. However, since most patients in our study had PTSD for more than 10 years, with comorbid major depression in
the severe range, the observation that the majority of patients had improved scores for both PTSD and depression severity is noteworthy.

Conclusions:

Military related PTSD often presents with comorbid major depression requiring prompt and effective treatment. This study demonstrates that the addition of aripiprazole can assist in providing symptom relief in a population that has traditionally demonstrated poor pharmacological response. Further studies including double-blind, placebo- controlled studies are necessary to confirm our study findings and further demonstrate the benefit of aripiprazole augmentation in the treatment of military related PTSD.

Competing interests

Drs. Richardson, Fikretoglu and Liu have no disclosures to announce in association with the contents of this issue. Dr. McIntosh has acted as a presenter for, participated on an Advisory Board for, and/or received research funding from Pfizer, AstraZeneca, Eli Lilly, Biovail, Bristol Myers-Squibb, Lundbeck, Forest, Servier, sanofi-aventis, Shire, and Janssen-Ortho.

Authors' contributions

Dr. Richardson conceptualized and designed the study and drafted the manuscript. Dr. Fikretoglu contributed to the statistical analysis and Dr. Liu completed the statistical
analyses. Dr. Richardson, Dr. Fikretoglu and Dr. Liu contributed to the interpretation of the results. All the authors contributed to the preparation of the final

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The views expressed in this manuscript are those of the authors and do not necessarily represent the views of Veterans Affairs Canada.
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*Society for Traumatic Stress Studies: October 1993; San Antonio, Texas.*

International Society for Traumatic Stress Studies; 1993.


46. Ware J, Kosinski M, Bayliss M, McHorney C, Rogers W, Raczek A: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: Summary results from the Medical


Table 1: Baseline characteristics of the sample

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Table 2: Wilcoxon signed rank test between intake and each of the follow-ups

<table>
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<td><strong>BDI</strong></td>
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</tr>
<tr>
<td>– Difference between baseline and t2</td>
<td>0.0179</td>
</tr>
<tr>
<td>– Difference between baseline and t3</td>
<td>0.0042</td>
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<tr>
<td>– Difference between baseline and t4</td>
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<td><strong>PCL</strong></td>
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<tr>
<td>– Difference between baseline and t2</td>
<td>0.0061</td>
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**BDI**: Beck Depression Inventory  
**PCL**: PTSD Checklist
Table 3: Effect sizes and changes in clinical outcome from baseline to final visit (N=27)

<table>
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<tr>
<th></th>
<th>-Intake (t1)</th>
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<td>24.59 (10.53)</td>
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## Open-Label Preliminary Assessment of Aripiprazole

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<tr>
<td><strong>PCL Total</strong></td>
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<td>50.07</td>
<td>0.59</td>
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BDI: Beck Depression Inventory
PCL: PTSD Checklist
Cohon’d was calculated for effect size
Table 4: Frequency of responders at each of the follow-ups

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Responders on the PCL were those with 20% or greater improvement.

Responders on the BDI were those with 50% or greater improvement.
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<tr>
<td>BDI Total</td>
<td>30.44 (7.85)</td>
<td>0.53</td>
<td>24.59 (12.18)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>27.00 (10.51)</td>
<td>0.53</td>
<td>20.67 (10.05)</td>
<td>1.09</td>
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<tr>
<td>PCL Total</td>
<td>56.11 (12.66)</td>
<td>0.59</td>
<td>48.48 (16.40)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>50.07 (13.08)</td>
<td>0.59</td>
<td>46.85 (13.53)</td>
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<tr>
<td>PCL Reexperiencing</td>
<td>15.00 (4.42)</td>
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<td>-</td>
<td>12.61 (4.72)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>21.05 (6.02)</td>
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<tr>
<td>PCL Avoidence</td>
<td>23.40 (5.22)</td>
<td>-</td>
<td>-</td>
<td>13.96 (4.32)</td>
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<tr>
<td>PCL Hyperarousal</td>
<td>16.04 (4.02)</td>
<td>-</td>
<td>-</td>
<td></td>
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</tbody>
</table>

BDI: Beck Depression Inventory
PCL: PTSD Checklist
Cohen’s d was calculated for effect size
An Open-Label Preliminary Assessment of Aripiprazole Augmentation in the Treatment of Military-Related PTSD with Major Depression

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Abstract:

Background

In this study we attempted to evaluate the benefits of adding aripiprazole in veterans with military-related PTSD with comorbid depression who had been minimally or partially responsive to their existing medications.

Methods:

A retrospective chart review of patients who received an, open-label, flexible-dose, 12-week course of adjunctive aripiprazole was conducted in 27 military veterans meeting DSM-IV criteria for PTSD and comorbid major depression. Concomitant psychiatric medications continued unchanged, except for other antipsychotics which were discontinued prior to initiating aripiprazole. The primary outcome variable was change from baseline in the PTSD checklist-military version (PCL-M) and the Beck Depression Inventory (BDI-II).

Results:

PTSD severity (Total PCL scores) decreased from 56.11 at baseline to 46.85 at study end (p <0.0001 from Wilcoxon signed rank test) and the depression severity decreased from 30.44 at baseline to 20.67 at study end (p <0.0001 from Wilcoxon signed rank test).

Thirty seven percent (10/27) were considered responders, as defined by a decrease in total PCL scores of at least 20 percent and 19% (5/27) were considered as responders as
defined by decrease in total BDI score of at least 50%.

**Conclusions:**

The addition of aripiprazole contributed to a reduction in both PTSD and depression symptomatology in a population that has traditionally demonstrated poor pharmacological response. Further investigations, including double-blind, placebo-controlled studies, are essential to confirm and further demonstrate the benefit of aripiprazole augmentation in the treatment of military related PTSD.

Word Count: 2345
Background:

Military-related posttraumatic stress disorder (PTSD) is a serious psychiatric condition often resulting from combat duty in the current wars in Afghanistan and Iraq [1] and past peacekeeping and humanitarian missions. [2-4] Patients with PTSD present with four symptom clusters: re-experience of the traumatic event(s), avoidance of reminders and emotional numbing (which are grouped together as one symptoms cluster in DSM-IV, but are seen as distinct and will likely be denoted as such in DSM-V), and hyperarousal symptoms. [5, 6] Recent estimates of the prevalence of PTSD in various military and veteran populations has varied from a low of 4.8% in UK military members[7] to higher rates of 10.3% in Canadian peacekeeping veterans, [8] and 11.2 – 17.1% in U.S. military members returning from the deployments to Iraq and Afghanistan [9]. Military-related PTSD is associated with severe psychosocial dysfunction. [10,11]

The response to pharmacological interventions for military-related PTSD are often disappointing. [10, 12-16] PTSD often presents with co-morbidities such as depression and substance abuse and dependence[17, 18] and amongst veterans, the comorbidity rates may be much higher than in other populations. [19, 20] Studies have also demonstrated that veterans with chronic, military-related PTSD often present with significant comorbid psychotic features [21, 22] which may contribute to the severe psychosocial dysfunction in this population. [10,11]
Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) have the most empirical evidence for efficacy in the treatment of PTSD and are usually considered first-line treatment. [5, 14, 23] SSRI s and SNRIs are also effective agents for the treatment of co-morbid mood and anxiety disorders commonly associated with PTSD. However, the lack of efficacy of antidepressant monotherapy, especially in male combat veterans [24, 25] has led to the frequent use of combination strategies, especially the addition of antipsychotics, in many treatment guidelines for treatment-resistant PTSD. [5, 26]

The benefit of adding a second-generation antipsychotic, such as risperidone, quetiapine, or olanzapine, for the treatment of PTSD in combination with a primary antidepressant has been suggested in numerous small studies, including a few randomized controlled trials. [27-30] These agents appear beneficial in managing hyperarousal symptoms such as hypervigilance and irritability, as well as severe dissociative symptoms. [14] There is also evidence for the addition of aripiprazole, quetiapine, risperidone, and olanzapine for treatment-resistant depression, [31] which often presents as a complicating factor in military-related, chronic PTSD. More recently, the efficacy of aripiprazole in the treatment of PTSD has been demonstrated in three preliminary open-label studies in veteran populations, both as a monotherapy and as an adjunctive treatment. [32-34]

Aripiprazole is a novel antipsychotic with partial agonist activity at D2 receptors and 5HT1A receptors, and antagonist activity at 5-HT2A receptors. [35]
Aripiprazole is reported to have less risk for extrapyramidal side effects than traditional antipsychotics and has been demonstrated to be effective in treatment-resistant depression. [36, 37]

Based on the positive results of aripiprazole for both treatment-resistant depression and treatment-resistant PTSD, and on its unique pharmacology, we hypothesized that aripiprazole would be efficacious for treatment-resistant military-related PTSD with comorbid major depression. To reflect general clinical practice, we conducted a retrospective file review to examine the benefits of adding aripiprazole in veterans with military-related PTSD with comorbid depression who had been minimally or partially responsive to their existing medications. To our knowledge, this is the first study to examine the efficacy of aripiprazole to treat both chronic PTSD and comorbid depression in a sample of veterans with chronic military-related PTSD where 100% of the participants had comorbid major depression.

Methods:

Participants and Procedure:

Participants consisted of a sample of 27 consecutive veterans referred for psychiatric treatment at an outpatient clinic specializing in the treatment of military-related PTSD.
related psychiatric conditions. The study clinic follows a standardized assessment and
treatment protocol; the standardized assessments include the PTSD Checklist-Military
Version (PCL-M), [38] Beck Depression inventory (BDI), [39] and Medical Outcomes
Study (MOS) 36-item Short-Form Health Survey (SF-36), [40] administered at intake and
at each follow-up appointment over the course of treatment. In addition to providing
psychoeducation, the standard psychiatric treatment at the clinic includes symptom
management, treatment of comorbid disorders, and management of functional
impairment. [5] Participants were prescribed aripiprazole after demonstrating minimal
or partial response to their existing antidepressant and/or minimal or partial response
to other antipsychotic augmentation strategies. All subjects received a comprehensive
psychiatric evaluation and laboratory tests (complete blood count with white count
differential, serum electrolytes, glucose, creatinine, blood urea nitrogen, liver function
tests, and lipid profile). The initial dose of aripiprazole was 2 to 5 mg daily, with
further dose titrations based on tolerability and clinical response, up to a maximum of
30 mg daily. Efficacy and adverse effects were assessed and recorded at each follow-
up appointment (bi-weekly for the first month and then monthly). Antidepressants,
anxiolytics, and mood stabilizers were allowed but had to be kept at a constant dose
during the treatment phase of the study. Other antipsychotics were not allowed during
the study, and were discontinued at prior to initiation aripiprazole.

The sample for the study was derived from a retrospective chart review with
approval from the Office of Research Ethics of the University of Western Ontario. All
patients met the DSM-IV criteria for PTSD and comorbid major depressive disorder. To
maximize the generalizability of this study to usual "clinical practice," all comorbid physical and psychiatric conditions were included in the study.

**Instruments**

To diagnose PTSD, the Clinician-Administered PTSD Scale (CAPS) [41] was administered by a trained clinician and the diagnosis of major depressive disorder was determined using the Patient Health Questionnaire (PHQ-9)[42] and the psychiatric interview according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria. [6] To assess change in PTSD symptoms with treatment, the PCL-M[38] was used. Similarly, the BDI [43, 44] was used to assess change in depressive symptoms as a result of treatment. The SF-36 [45] was used to assess health related quality of life (HRQoL). The SF-36 measures functional impairment in eight domains or subscales; the mental health sub scales can be collapsed into the Mental Component Summary (MCS) Score reflecting overall mental health [46]. The PCL-M, the BDI, and the SF-36 were all administered at each follow-up appointment including at intake (t1) and at 1-, 2-, and 3-month follow-ups (t2, t3, and t4) over the course of treatment. The PCL-M and the BDI were the primary efficacy variables; the PCL-M re-experiencing, avoidance/numbing, and hyperarousal subscale scores served as secondary efficacy variables.

**Analysis**

The LOCF data for each visit included the data recorded at that visit, or otherwise the data carried forward from the last visit. For the primary outcome, the Wilcoxon signed rank test
and effect sizes (Cohen’s d) was used to determine the statistical significance of the change from baseline in total PCL-M and Total BDI score at each follow-up time point (t2, t3, t4). For the three secondary outcome measures (the PCL-M re-experiencing, avoidance/numbing, and hyperaropusal subscale scores), only the effects at t4 were examined.

For each of the two main outcomes, we identified responders on our two outcome measures using criteria established in existing literature. More specifically, on the PCL, we identified those with at least a 20% reduction in their symptom scores as responders;[33] this is in keeping with prior treatment efficacy and more specifically, prior Aripiprazole treatment efficacy studies for PTSD [33]. On the BDI, we identified those with at least a 50% reduction in their symptom scores as responders [47].

Results

Demographics and Clinical Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. Of the 27 participants, almost all were men (n = 26, 96.3%), with an average age of 39.36 (SD=5.98) with an average of 10.26 years (SD = 7.38) with PTSD symptoms. At intake, the majority (n = 20, 74.1%) of the sample had been released from the military. Years of
military service averaged 15.04 ($SD = 7.41$). Almost all ($n = 26, 96.3\%$) had exposure to combat or to a war zone during their deployment and the most common deployments reported were Afghanistan ($n = 9, 33.3\%$), the former Yugoslavia ($n = 8, 29.6\%$), and Africa (Somalia, Rwanda, Eartrea, and Sierra Leone) ($n = 5, 18.5\%$). All patients were taking an antidepressant prior to initiating aripiprazole, most commonly an NDRI ($n = 16, 59.3\%$) followed by NaSSA ($n = 12, 44.4\%$); SNRI ($n = 11, 41.7\%$), and SSRI ($n = 10, 37\%$). Most patients ($n = 14, 51.9\%$) were taking two antidepressant and an additional 14.8% ($n = 4$) were taking three antidepressant. In addition to an antidepressant, 8 patients (30.77%) were prescribed an anticonvulsant, 5 patients (19.23%) were prescribed a stimulant, and 4 patients (15.38%) were prescribed a hypnotic.

Twenty-seven patients had at least one post-baseline efficacy evaluation thus were included in the efficacy analysis. At intake, all participants met full criteria for PTSD based on the CAPS interview. The average duration of PTSD symptoms was 10.26 years ($SD = 7.38$), suggesting a chronic course for this sample. Intake scores on the PCL-M and the BDI averaged 56.11 ($SD = 12.66$) and 30.44 ($SD = 7.86$), respectively. On the PCL-M, a score of 50 is the conventional cut-off score for a positive screen for PTSD in veteran populations; [48] on the BDI, scores above 29 are considered indicative of severe depression [49]. SF-36 MCS and PCS were 20.22 ($SD = 10.11$) and 32.48 ($SD = 15.06$), respectively, indicating significant impairment in scales measuring both mental and physical functioning.

Dose and Tolerability
The final average dose of aripiprazole was 12.40 (SD = 4.35) mg daily. The mean value of weight decrease from baseline (mean=99.25 kg, SD=13.35) to the final visit is 1.05 kg (SD= 4.95). Only two patients discontinued the aripiprazole; one patient due to non-response and one due to intolerable restlessness. The remaining 25 patients tolerated the aripiprazole. The improved tolerability was likely related to lower starting doses (e.g., 2 mg daily) and slow titration (increasing the dose by 2-5 mg every two weeks).

**Treatment Efficacy**

Results from Wilcoxon signed rank tests showed significant decreases between baseline and each of the three follow-ups for the BDI and the PCL, as well as the last visit for the PCL Reexperiencing, Avoidance, and Hyperarousal subscales (Table 2). The total PCL score decreased from 56.11 (SD=12.66) at baseline to 46.85 (SD=13.53) at three months and the total BDI score 30.44 (SD= 7.85) at baseline to 20.67 (SD=10.05) at three months. Effect sizes and changes in the clinical outcome variables from intake to the final visit are reported in Table 3.

The number and percentage of responders at each of the follow-ups are reported in Table 4. Thirty seven percent (10/27) were considered responders, as defined by a
decrease in total PCL scores of at least 20 percent and for depression, 19% (5/27) were considered responders as defined by decrease in total BDI score of at least 50%. Overall, a higher percentage of participants met criteria for being a responder on the PCL than the BDI.

Additional analyses to examine the efficacy of Aripiprazole among those with severe depression (BDI > 29) at intake (n=14) found significant reductions in PCL symptom scores for this subsample as well, with the PCL scores averaging 61.79 (SD=9.60), 51.86 (SD=13.54), 52.14 (SD=15.53), and 48.71 (SD=13.02) at intake and each of the follow-ups respectively. The Wilcoxon signed rank test results showed significant reductions from intake to each of the follow-ups (p=0.0051, p=0.0405, and 0.0010 for each of the follow-ups). The percentages of responders on PCL at each of the follow-ups are 35.71%, 42.86%, and 57.14%, respectively. It is worth noting that at t4, having severe depression was found to be associated with higher percentage of responders on PCL (P=0.0461 from Fisher’s exact test).

Discussion

Consistent with previous studies in veteran, [32-34] the addition of aripiprazole contributed to a reduction in PTSD symptomatology in all symptom clusters (reexperiencing, avoidance/numbing, and hyperarousal) and among those with severe comorbid major depression disorder (baseline BDI ≥ 29). A significant number (37%) demonstrated a significant reduction in PTSD symptomatology (decrease in total PCL...
scores of at least 20%). Although modest, the response rate is particularly encouraging in a population of chronic military related PTSD with comorbid major depression in the severe range which has traditionally demonstrated poor response to pharmacotherapy. The lower response rate observed in this study compared to other augmentation trial by Roberts and colleagues[33] might be related to higher rates of comorbid depression (100%) in this study.

Consistent with studies on treatment resistant depression, [50, 51] the addition of aripiprazole also demonstrated an overall reduction in depression severity from a total BDI score of 30.44 at baseline to 20.67 at three months. However, unlike the study by Berman [52] where 42% met the criteria for significant response, in our study only a minority (19 %) showed decrease in total BDI scores of at least 50%. The lower response rate observed in our study compared to Berman and colleagues [52] study might be related to the fact that in Berman’s study patients with comorbid PTSD were excluded. Also in this study, most (52.9%) reported depression in the severe range and most patients (n =18, 66.7%) in this sample continue to be symptomatic despite being on combination antidepressant prior to initiating aripiprazole suggesting significant treatment resistant.

Due to significant limitations of this study, including a small sample size and a lack of a control group, careful interpretation of the findings is warranted. This was a preliminary, open-label retrospective study, with a small sample size. However, since most patients in our study had PTSD for more than 10 years, with comorbid major depression in
the severe range, the observation that the majority of patients had improved scores for both PTSD and depression severity is noteworthy.

Conclusions:

Military related PTSD often presents with comorbid major depression requiring prompt and effective treatment. This study demonstrates that the addition of aripiprazole can assist in providing symptom relief in a population that has traditionally demonstrated poor pharmacological response. Further studies including double-blind, placebo-controlled studies are necessary to confirm our study findings and further demonstrate the benefit of aripiprazole augmentation in the treatment of military related PTSD.

Competing interests

Drs. Richardson, Fikretoglu and Liu have no disclosures to announce in association with the contents of this issue. Dr. McIntosh has acted as a presenter for, participated on an Advisory Board for, and/or received research funding from Pfizer, AstraZeneca, Eli Lilly, Biovail, Bristol Myers-Squibb, Lundbeck, Forest, Servier, sanofi-aventis, Shire, and Janssen-Ortho.

Authors' contributions

Dr. Richardson conceptualized and designed the study and drafted the manuscript. Dr. Fikretoglu contributed to the statistical analysis and Dr. Liu completed the statistical
analyses. Dr. Richardson, Dr. Fikretoglu and Dr. Liu contributed to the interpretation of the results. All the authors contributed to the preparation of the final

**Acknowledgements**

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of Veterans Affairs Canada.
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Table 1: Baseline characteristics of the sample

<table>
<thead>
<tr>
<th>Demographic and clinical variables</th>
<th>n (%) or mean (sd)</th>
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<tbody>
<tr>
<td>Age</td>
<td>39.36 (6.09)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (96.30%)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (3.70%)</td>
</tr>
<tr>
<td>CF status</td>
<td></td>
</tr>
<tr>
<td>Released</td>
<td>20 (74.07%)</td>
</tr>
<tr>
<td>Still serving</td>
<td>7 (25.93%)</td>
</tr>
<tr>
<td>Current Work Status</td>
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</tr>
<tr>
<td>Unemployed</td>
<td>17 (62.96%)</td>
</tr>
<tr>
<td>Working for Pay</td>
<td>6 (22.22%)</td>
</tr>
<tr>
<td>On Sick Leave from Work</td>
<td>4 (14.81%)</td>
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<tr>
<td>Duration of illness</td>
<td>10.26 (7.38)</td>
</tr>
<tr>
<td>SF-36 Mental component score</td>
<td>20.22 (10.11)</td>
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<tr>
<td>SF-36 Physical component score</td>
<td>32.48 (15.06)</td>
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Table 2: Wilcoxon signed rank test between intake and each of the follow-ups

<table>
<thead>
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<th>p-value</th>
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<td><strong>BDI</strong></td>
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<tr>
<td>Difference between baseline and t2</td>
<td>0.0179</td>
</tr>
<tr>
<td>Difference between baseline and t3</td>
<td>0.0042</td>
</tr>
<tr>
<td>Difference between baseline and t4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>PCL</strong></td>
<td></td>
</tr>
<tr>
<td>Difference between baseline and t2</td>
<td>0.0061</td>
</tr>
<tr>
<td>Difference between baseline and t3</td>
<td>0.0016</td>
</tr>
<tr>
<td>Difference between baseline and t4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Reexperiencing subscale</strong></td>
<td></td>
</tr>
<tr>
<td>Difference between baseline and t4</td>
<td>0.0020</td>
</tr>
<tr>
<td><strong>Avoidance subscale</strong></td>
<td></td>
</tr>
<tr>
<td>Difference between baseline and t4</td>
<td>0.0123</td>
</tr>
<tr>
<td><strong>Hyperarousal subscale</strong></td>
<td></td>
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<tr>
<td>Difference between baseline and t4</td>
<td>0.0043</td>
</tr>
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</table>

BDI: Beck Depression Inventory
PCL: PTSD Checklist
Table 3: Effect sizes and changes in clinical outcome from baseline to final visit (N=27)

<table>
<thead>
<tr>
<th></th>
<th>Intake (t1)</th>
<th>1-month follow-up t2</th>
<th>2-month follow-up t3</th>
<th>3-month follow-up t4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Effect size</td>
<td>Mean (SD)</td>
<td>Effect size</td>
</tr>
<tr>
<td>BDI Total</td>
<td>30.44 (7.85)</td>
<td>27.00 (10.51)</td>
<td>24.59 (12.18)</td>
<td>20.67 (10.05)</td>
</tr>
<tr>
<td>PCL Total</td>
<td>56.11 (12.66)</td>
<td>50.07 (13.08)</td>
<td>48.48 (16.40)</td>
<td>46.85 (13.53)</td>
</tr>
<tr>
<td>PCL Reexperiencing</td>
<td>15.00 (4.42)</td>
<td>-</td>
<td>-</td>
<td>12.61 (4.72)</td>
</tr>
<tr>
<td>PCL Avoidance</td>
<td>23.40 (5.22)</td>
<td>-</td>
<td>-</td>
<td>21.05 (6.02)</td>
</tr>
<tr>
<td>PCL Hyperarousal</td>
<td>16.04 (4.02)</td>
<td>-</td>
<td>-</td>
<td>13.96 (4.32)</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory
PCL: PTSD Checklist
Cohon’d was calculated for effect size
Table 4: Frequency of responders at each of the follow-ups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-month (t2)</td>
</tr>
<tr>
<td></td>
<td>(n=27)</td>
</tr>
<tr>
<td>PCL</td>
<td>7 (25.93%)</td>
</tr>
<tr>
<td>BDI</td>
<td>1 (3.70%)</td>
</tr>
</tbody>
</table>

Responders on the PCL were those with 20% or greater improvement. Responders on the BDI were those with 50% or greater improvement.