Veterans, Antidepressants, and Suicide:
A Systematic Review of Adverse Events

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Abstract

Background: Military veterans represent a disproportionate number of suicides that occur in the U.S. Antidepressants have been associated with increased risk of suicidal thoughts/behaviors and completed suicide. Given the high number of psychotropic medications prescribed to the veteran population, it is salient that any relationship between veteran suicide and antidepressants be explored. Method: A preregistered systematic review was conducted of empirical studies from 1988-2018. Studies were identified through electronic bibliographic databases. Results: A total of 25 studies met eligibility criteria. Studies reviewed only *minimally* explored adverse effects of antidepressants. Conclusion: Rigorous evidence is urgently needed, but lacking. Further research will need to explore the frequency of adverse effects (e.g. suicidality, aggression, akathisia) among veteran users of antidepressants.

Keywords: Veterans, Suicide, Antidepressants, Akathisia, Aggression, Agitation, Mental Health Policy

Background

According to the American Foundation for Suicide Prevention (ASFP), the prevalence of suicide deaths around the world have increased by more than 30 percent from 1999 – 2016 (ASFP, Suicide Statistics, 2019). Additionally, the Center for Disease Control (CDC) estimates that for each individual who dies by suicide, between 20-30 people have attempted to take their own life (2018). This results in a global suicide rate of 16/100,000 – making it the second leading cause of death among 15-34 year olds (CDC, 2018). In 2016, over 45,000 suicides were reported in the United States (U.S.), making it the 10th leading cause of death (CDC, 2018) and the 2nd leading cause of death among individuals ages 15-29 (Klonsky, May, & Saffer, 2016). This statistic shows that suicide deaths are more than double the number of homicide deaths per year (19,362 in 2016; 112 suicides per day) (ASFP, Suicide Statistics, 2018).

Compared to the general population, veterans die by suicide at exceptionally high rates. Military suicide rates in the U.S. have been increasing over the last two decades. The number of active duty troops dying by suicide has more than doubled, rising from 145 in 2001 to 321 in 2012 (Kemp & Bossarte, 2013). Though comprising only 8.5% of the U.S. population in 2014, they accounted for 22.2% of total suicides that occur every year (U.S. Department of Veterans Affairs, 2016); a rate of about 20 deaths per day. While risk factors associated with suicide for veterans mirror that of the general population, the unique characteristics veterans face while in active duty as well as post-service put them at a higher risk for suicide than their civilian peers. The higher risk has been substantiated by the rate of military and veteran suicide deaths surpassing the civilian rate and remaining elevated since 2012 (Thompson & Gibbs, 2012).

Mental disorders such as anxiety, depression, and posttraumatic stress disorder (PTSD), interpersonal issues, non-suicidal self-injury (NSSI), and exposures to traumatic events are all

predictors of veteran suicide. Veterans are exposed to physical and psychological trauma that manifests in similar, though perhaps more severe, ways than the general population. An estimated 42,000 returning veterans from Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF) and Operation New Dawn (OND) have been physically wounded. Further, it is estimated that an additional 40% of troops reintegrating into civilian life meet the criteria for the diagnosis of PTSD (Reisman, 2016). The rates of PTSD are higher for veterans returning from modern conflicts (OEF, OIF, and OND) are higher than in previous conflicts (i.e. Vietnam, Korean War, Gulf War, Desert Storm etc.). This prevalence has given PTSD the label as one of the ‘signature injuries’ of the Middle Eastern conflict. PTSD symptomatology is characterized by irritable behavior and angry outbursts, with little to no provocation, of physical or verbal aggression towards people or objects, reckless or self-destructive behavior, hypervigilance, exaggerated startle response and problems concentrating (American Psychological Association, 2013).

A recent study conducted on soldiers returning from deployment in the Middle East found that 14% screened positive for difficulties associated with PTSD, 14% screened positive for major depressive disorder (MDD), and 19% reported probable traumatic brain injury (TBI) related to injuries sustained while deployed (Hosek, Kavanaugh, & Miller, 2006). Current estimates suggest that over 320,000 combat veterans suffer from PTSD or TBI, with roughly 5-10% of them suffering from both (Hosek et al., 2006; Schell & Marshall, 2008).

Military personnel are at an increased risk for TBI due to combat exposure and occupational hazards, for example, IEDs and parachuting (Ommaya et al., 1996). TBIs are also considered a signature injury of the conflicts in the Middle East (Pickett, Stevens, Pai, & Pastorek, 2018). TBIs affect 56,998 or 9.6% of returning OEF/OIF veterans, predominantly from

blast injuries or injuries sustained from being near an explosion. A third of veterans with the diagnosis of a mild TBI have a comorbid diagnosis of depression or PTSD (Tanielian & Jaycox, 2008). Many complications associated with recovery of a TBI that are known to be risk factors of suicide ideation and attempts, such as a comorbid diagnosis of depression or PTSD. These complications include emotional problems like anger, lowered frustration tolerance, anxiety, depression, and low self-esteem, irritability/loss of temper, weakened inhibition (impulse control issues), apathy, mania, psychosis, socially inappropriate behavior(s), agitation, excessive use of profanity, aggression, physical and cognitive deficiencies, potentially destructive behaviors, and impaired judgment (Albanese et al., 2017).

In a study conducted on 88 veterans with a TBI diagnosis and current suicide ideation, 52.3% had comorbid MDD, 50% had an anxiety disorder other than PTSD, and 45.9% had PTSD (Tsaousides et al., 2011). The presence of a TBI suggests a 2-4 time increased the risk of death by suicide than the general population (Silver et al., 2001). Veterans are at a higher risk for the development of PTSD than that of the general population (30% versus 7-8% respectively (Clemans, 2012).

Suicide amongst America's veterans can, therefore, be considered both an epidemic and a significant public health issue. This has prompted calls from a variety of sources (i.e. politicians, public health officials, veterans and their caregivers, and the public at large) for additional mental health treatment services and a reevaluation of current standards of care for veterans (Government Accountability Office, 2014; Hester, 2017; Steinhauer, 2019; see also Public Law 114-2, 2015; U.S. Department of Veterans Affairs, 2019). This includes considering the role of psychotropic medications, like antidepressants (ADs), in treating complex behavioral health

conditions (e.g. PTSD, depression, anxiety, substance use disorders) common among military veterans (Trivedi et al., 2015; Whitaker & Blumke, 2019).

Antidepressants and adverse effects

Suicide prevention and intervention are urgent public health priorities, particularly for the veteran population, however the current mainstay treatment of prescribed psychiatric medications is known, in some cases, to cause iatrogenic harms. Antidepressants, in particular, are associated with abnormal mood states (e.g. aggression, akathisia, suicidal thoughts), self-harm and attempted suicide (Creaney, Murray, & Healy, 1991; Healy, 1994, 2003, 2011, 2012; Healy, Herxheimer, & Menkes, 2006; Hengartner & Plöderl, 2019; Hoehn-Saric, Lipsey, & McLeod, 1990; LaPorta, 1993; Sharma, Guski, Freund, Gøtzsche, 2016; Stone et al., 2008; Teicher, Glod, & Cole, 1993; Wirshing et al., 1992), and extreme behavioural states, including violence (Bielefeldt, Danborg, Gøtzsche, 2016; Molero, Lichtenstein, Zetterqvist, Gumpert, & Fazel, 2015; Moore, Glenmullen, & Furberg, 2010). In their re-analysis of FDA safety summaries, Hengartner & Plöderl (2019) found that suicide rates were approximately 2.5 times higher for those on an antidepressant, compared to those on placebo. Likewise, polypharmacy and overmedication, as highlighted by the late Senator John McCain (S.992, 2017), also contribute to iatrogenic harm among veteran populations and may increase the likelihood of suicide (Collett et al., 2016). The use of psychotropic drugs with those experiencing trauma and PTSD, TBI, and exposure to violence, is hypothesized by some (e.g. Breggin, 2010, 2014) to be a particularly dangerous combination of factors. While ample evidence exists on the iatrogenic harm potential of conventional psychotropic drugs, the possible connection between high rates of psychotropic medication use and high rates of suicide among veteran populations is both highly concerning and woefully underexplored.

The aim of this systematic review is to investigate what evidence exists about suicide and related behavioral adverse effects in studies of antidepressant use¹ among veterans. While a meta-analysis was considered, as noted below, the quality and type of studies included were too heterogeneous to permit such an analysis.

Methods

Literature Search

Preregistered electronic searches were performed (*Systematic Review Registration No.: PROSPERO CRD42019118017*) to identify relevant studies between 1988 and 2018 using the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, MEDLINE, PubMed, PsycINFO. A non-systematic search of Google Scholar (using the first 50 relevant results) was also undertaken. Neither reference lists, nor the grey literature (conference papers, unpublished works, etc.) was reviewed, beyond that which may have been indexed by Google Scholar. Three keyword search terms were used to identify studies among veteran populations, using an antidepressant, and reporting a suicide-related outcome. Figure 1 details the specific combinations of search terms used.

Article Selection and Evaluation Criteria

All published reports written in English since 1988 were eligible for inclusion. No restrictions were placed on the type of study design employed. Study participants had to be military veterans and age 18 or older. Study samples of active military members or non-military

¹ Antidepressants are used to treat a variety of conditions, including but not limited to, Major Depressive Disorder, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, Chronic Pain, Fibromyalgia. Though colloquially referred to as “antidepressants,” these substances are best conceptualized as *psychoactive* substances that cause *global* cognitive/behavioural changes (Jacobs & Cohen, 1999; Moncrieff & Cohen, 2006); rather than targeted treatments with *disease-specific* mechanisms of action (see Lacasse & Leo, 2005; and McHenry, 2006).

personnel were excluded. If it was unclear whether the sample was comprised *solely* of military veterans, it was included in the analysis.²

Additionally, studies were only included if they reported on use of antidepressants and included mention of relevant suicide-related adverse effects. Antidepressant efficacy studies that did not report on adverse effects (described in Figure 1) were excluded from the review.

Study titles and abstracts were screened by two independent raters (DD and CO) using Covidence reviewing software. After studies were screened out in this first phase, both raters then independently reviewed the full-text of studies and came to agreement about their inclusion in the final sample. Disagreements were resolved by discussion; with the second author (JL) serving as arbitrator as needed. Given the heterogeneity of the results (i.e. in terms of study design, population sampled from, sample size, treatment, outcomes, etc.) no meta-analysis was attempted.

The first author (DD) extracted data from the final group of studies along the following domains: 1) suicide and related harms, 2) agitation, irritability, and anger, 3) akathisia and restlessness, and 4) aggression and violent behaviors; in accordance with the search terms employed. Ambiguous cases were discussed with the third author (CO). Articles were reviewed, one by one, and relevant data/text was extracted into a spreadsheet for review.

Data Availability

Materials (Protocol, PDFs, figures, and spreadsheets) are publicly available at: <https://osf.io/bydfa>. As this study involved only use of secondary data, it was exempt from IRB review.

² It was unclear in 10 studies (Bailey, Makela, & Asberg, 2016; Ciraulo et al., 2005; Forrester, 2017; Mayo, Cahill, & Lott, 2005; McCarthy et al., 2015; Mohamed et al., 2017; Prochazka et al., 1998; Roy, 2010; Tsai et al., 2007), whether *all* participants were veterans (i.e. whether family-members or active-duty military personnel were included).

Results

This search strategy yielded a total of 324 references for screening (see Figure 2). Study titles/abstracts were screened first (232 studies screened after 92 duplicates were removed). The full-text of studies that were not immediately excluded in the screening phase were then reviewed (102 full-text studies reviewed; 120 were determined to be unrelated to this topic). 25 studies were determined eligible for inclusion in this systematic review (77 having been excluded). A flow chart depicting the literature search process is displayed in Figure 2.

Study Characteristics

Of the 25 studies, five were randomized controlled trials (RCTs) (Chung et al., 2004; Ciraulo et al., 2005; Mohamed et al., 2017; Naylor et al., 2013; Prochazka et al., 1998). The remaining 20 studies used a variety of methodologies, including: cohort studies (n=8), retrospective chart reviews (n=3), case-control studies (n=3), case series studies (n=2), cross-sectional analyses (n=2), open-label (n=1), and the predictive modelling of administrative data (n=1). All but two studies were conducted in the United States (i.e. Chung et al., 2004; Tsai, Tsai, Yang, & Hwang, 2007). Sample sizes varied substantially, in line with the type of methodology employed, ranging from *n* of 7 (Tsai et al., 2007) to *n* of 502,179 (Valenstein et al., 2012). As some overlap may occur between the samples across studies, it is unclear how many unique cases exist within this review.

Study Outcomes

Suicide and Related Harms. 19 studies included results related to suicide or suspected suicide, suicide ideation/thoughts or behaviors (e.g. self-injury/harm). A subset of these studies finds that antidepressant prescriptions are prevalent in advance of suicide, but do not offer estimates of any risk conferred by such prescriptions. For example, Basham et al. (2011)

reviewed VA administrative data linked to cases in the Oregon Violent Death Reporting System. Of the veterans who completed suicide in Oregon between 2000 and 2005 and received care at a VA facility ($n = 212$), 44.8% ($n = 95$) had an antidepressant prescription within past 12 months and 3.3% ($n = 7$) had an antidepressant prescription within 30 days prior to suicide. Similarly, Smith, Craig, Ganoczy, Walters, & Valenstein (2011) performed a retrospective cohort study, using Veterans Health Administration data from 1999-2004. Of their sample ($n = 1843$), 69.9% had been received an antidepressant, of any type at last treatment visit ($n = 656$) and 47.4% had received an antidepressant that was characterized as being prescribed at an adequate (i.e. high enough) dose ($n = 445$).

Denneson, Williams, Jacobson, Nguyen, & Dobscha (2017) used a qualitative analysis, as part of a case-control study, to explore the quality and type of healthcare and psychosocial care received by veterans who would go on to complete suicide. Their analysis included 38 veterans, across 11 states. Most (68.4%, $n = 26$) had an antidepressant prescription in the 6 months prior to suicide, while 23.7% ($n = 9$) had 90+ days on an antidepressant in the 6 months prior to suicide. A larger study (McCarthy et al., 2015) used Veterans Health Administration/National Death Index data in an effort to validate a predictive model that would help in identifying future high-risk patients. From the data used to test the model ($n = 2,138$; comprised of suicide decedents from 2008-2011) 42.3% ($n = 905$) of cases of completed suicide had a prescription of an antidepressant in past 24 months.

Yerevanian, Koek, Mintz, & Akiskal (2007) performed a retrospective chart review of veterans ($n = 405$) with a diagnosis of bipolar disorder, using California VA healthcare data. Treatment was divided into three categories: antidepressant monotherapy ($n = 192$), mood stabilizer monotherapy ($n = 192$), and mood stabilizer and antidepressant combination therapy.

Here, we only compare the two conditions that use an antidepressant. Antidepressant monotherapy had zero recorded suicides, but seven suicide attempts. 20 patients were hospitalized for suicidal ideation or intent. The combination group had one completed suicide and five attempted suicides. There were 18 cases of hospitalization for suicidal ideation or intent.

Studies in this category confirm the common sensical association between treatment and suicidal behaviour without the ability to disentangle the presenting psychiatric issues from possible iatrogenic effects of the medication, and without attempts to estimate any risks of treatment. However, in a very small study, Tsai et al. (2007) screened patients with dementia ($n=7$), who had been admitted after a suicide attempt, at a Chinese veteran's hospital ($n = 7$). Antidepressants and atypical antipsychotics were prescribed in all seven cases, with clinical improvement resulting among all the patients, and with no known suicidal ideation at discharge. In a similarly-sized study, Ramaswamy et al. (2015) investigated the effects of escitalopram on OEF/OIF veterans ($n = 11$), with PTSD, in an open-label study, reporting one case of suicidal ideation while on escitalopram.

Another subset of studies does attempt to estimate the relationship between antidepressant prescriptions and risk of suicide. Some studies do find an increased risk. Copeland et al. (2014) used VA administrative data to retrospectively investigate the prevalence of suicidality among Hispanic and African American veterans post-surgery. They reported that within the 3 years after surgery antidepressant use had a hazard ratio (HR) of 1.90 (95% CI: 1.73, 2.09) for suicidal behaviour(s) and ideation. Denneson et al. (2016) used a case-control design ($n = 236$) to examine the type of care provided to veterans who had mental health symptoms and died by suicide. They reported no statistically significant difference between cases (death by suicide; $n=118$) and controls ($n = 118$) for antidepressant prescription ($p = 0.36$) or for having

90 or more consecutive days on an antidepressant ($p = 0.47$). There was a statistically significant difference between cases and controls with regard to having 90 or more total days on an antidepressant ($p = 0.02$) (only 71.4% of cases vs. 87% of controls).³ Roy (2010) interviewed 527 opioid dependent patients, selected from a treatment program at the New Jersey Department of Veterans Affairs ($n = 377$) and a local community mental health clinic. Roy reported that treatment with an antidepressant was a statistically significant predictor of a suicide attempt ($p < 0.013$; OR 3.261, 95% CI [1.283, 8.288]), having the highest odds ratio of all analysed predictors (see p. 419). Seyfried, Kales, Ignacio, Conwell, & Valenstein (2011) performed a national, retrospective cohort study of patients with dementia and analyzed potential predictors of suicide. The sample ($n = 294,952$) was restricted to veterans aged 60 and up. They reported an increase risk of suicide with the prescription of an antidepressant ($p < 0.0001$, OR 2.11, 95% CI: 1.57, 2.84).

Other observational studies found either a neutral, positive or mixed effect of antidepressants on suicide. Gibbons et al. (2007) performed one of the most explicit investigations into suicide and antidepressants, among veterans. Using administrative data ($n = 226,866$) they reported an inverse relationship between suicide and the prescription of an antidepressant. There was a statistically significant difference, indicating lower rates of suicide prior to treatment initiation, than after treatment (i.e. for those on SSRI monotherapy [$p < 0.001$, RR 0.56, CI 0.44, 0.71] and non-SSRI monotherapy [$p < 0.001$, RR 0.51, CI 0.39-0.68]). Tricyclic monotherapy suicide rates did not diverge, statistically, before or after treatment was initiated ($p < 0.53$, RR 0.57, CI 0.17, 1.95). Pfeiffer, Kim, Ganoczy, Zivin, & Valenstein (2013)

³ It is believed that this data-source overlaps with those described above in Denneson et al. (2017). It is unclear how many cases of suicide are repeated here. A problem that may affect numerous studies here, which rely on national or state administrative data.

also used Veterans Health Administration/National Death Index data to evaluate whether different treatment stages (as measured by the Massachusetts General Hospital staging method) in patients with treatment-resistant depression (TRD) had an association with risk of suicide. Case of suicide (n = 499) were matched with non-suicide controls (n = 1994). They reported that the stage of intervention (i.e. the intensiveness of treatment and the number of antidepressant trials) was not statistically significant with regard to suicide, when controlling for demographic factors. In other words, whether patients had a higher level of treatment intensity was not a statistically significant predictor of suicide. Valenstein et al. (2012) performed a cohort study, analyzing a national sample of veterans with a diagnosis of depression and an antidepressant prescription (n = 502,179). Hazard ratios ranged from reduced to increased risk, depending on this antidepressant: Citalopram (1.0), bupropion (0.45), fluoxetine (0.63), venlafaxine (0.89), sertraline (0.70), paroxetine (1.06), and mirtazapine (1.11) According to the authors, an instrumental variable analyses did not find statistically significant differences across antidepressants for suicide.

There were three interventional studies which contained relevant data. Ciraulo et al. (2005) performed a double-blind RCT, comparing nefazodone (n = 34) to placebo (n = 35), for patients diagnosed with cocaine dependence with comorbid depressive symptoms. There was one case of reported suicide ideation in the treatment group. Mohamed et al. (2017) performed a multi-site randomized controlled trial compared patients with Treatment-Resistant Depression across three conditions (switching to bupropion [n = 511]; antidepressant with bupropion augmentation [n = 506]; and augmentation with an atypical antipsychotic [ariprazole] [n = 505]). Here, we will only focus on the first two treatment arms. Suicidal ideation was lower in the bupropion switch group (n = 8, 1.6%) than the bupropion augmentation group (n = 11, 2.2%).

Suicide attempts and completed suicide were higher in the switch group compared to the augmentation group ([n = 3, 0.6% vs. n = 1, 0.2%]) and [n = 1, 0.2% vs. n = 0, 0%] respectively). Prochazka et al. (1998) investigated the use of nortriptyline as a treatment for smoking cessation. While suicidal ideation was not explicitly reported, there was a statistically significant difference between the treatment and placebo groups for drop-out due to drug discontinuation, although the causes for discontinuation were not explained.

Finally, there were two studies using reports of poisonings which reported data relevant to antidepressants and suicide. Forrester (2017) performed a retrospective analysis of reports on poisonings made to military and VA hospitals in Texas, U.S. There were 4,353 reports made to military hospitals and 1,676 reports made to VA hospitals. Of these, there were 814 (18.7% of cases) and 330 (19.7% of cases) reports of antidepressant poisoning, respectively. It is unclear how many of antidepressant poisonings were intentional; however, 57.3% of military hospital reports and 47.7% of VA hospital reports were suspected attempted suicide (p. 53). Similar to Forrester (2017), Johnson et al. (2015) examined reports of poisonings from the Florida Poisoning Control Information Network (FPCIN). Of 601 reports, antidepressants were present in 120 instances (12.4%). Antidepressants also showed the strongest association with intentional-suspected suicide (Odds Ratio [OR] = 6.737).

Agitation, Irritability, and Anger. Of the 25 studies in this review, six included results related to agitation, irritability, or anger (See Table 2 for an overview). RCTs were performed by Chung et al. (2004), Mohamed et al. (2017), Naylor et al. (2013), and Prochazka et al. (1998). Chung et al. (2004) performed a randomized open-label trial comparing two different antidepressants, mirtazapine (n = 51) and sertraline (n = 49), in Korean veterans. There was one reported case (2%) of agitation in the sertraline group at 6 weeks. The lack of placebo-control

makes it difficult to distinguish within this particular study, whether there are higher rates of agitation in the sertraline group than would have otherwise been observed.

Mohamed et al. (2017) performed a multi-site randomized controlled trial compared patients with Treatment-Resistant Depression across three conditions (switching to bupropion [$n = 511$]; antidepressant with bupropion augmentation [$n = 506$]; and augmentation with an atypical antipsychotic [aripiprazole] [$n = 505$]). Again, we will only focus on the first two treatment arms. All three adverse events discussed in this section were more common in the bupropion switch group: agitation occurred in 7 cases of bupropion (1.4%) vs. 4 cases (0.8%) of bupropion augmentation; irritability in 32 cases (6.3%) vs. 15 (3%); and anger in cases 7 (1.4%) vs. 4 cases (0.8%). It is unclear whether these higher rates of adverse events are caused by the treatment itself, the effects of discontinuation syndromes (Haddad & Anderson, 2007), random variation, or some other cause. Again, a more ideal design would include treatment without augmentation, treatment with augmentation, treatment as usual, and a placebo control group.

Naylor et al. (2013) performed a pilot RCT on OEF/OIF veterans with subthreshold PTSD. Five patients received paroxetine; while seven received placebo. There was one reported case of excitement/agitation on placebo vs. zero in the paroxetine group. The particularly small sample size in this study ($n = 12$) precludes us from drawing firm conclusions about rates of agitation, irritability, and anger among those taking paroxetine or placebo.

Prochazka et al. (1998), investigated the use of nortriptyline as a treatment for smoking cessation. In 108 patients randomized to the treatment arm (nortriptyline vs. 106 on placebo), the authors reported lower mean rates of irritability/anger (1.2 [1.3 SD] vs. 1.8 [1.4 SD] in placebo) and anxiousness/tension (1.2 [1.4 SD] vs. 2.1 [1.7 SD] in placebo) within the treatment arm, on a self-report, 5-point scale, after 8 days of smoking cessation. While this gives credence to the

belief that nortriptyline may decrease or prevent irritability/anger and anxiousness/tension, firm conclusions are difficult, as such symptoms are consistent with, and to be expected during, nicotine withdrawal.

Mayo et al. (2005) performed a retrospective chart review of 103 patients in a Veterans Affairs clinic to determine the tolerability and cost-effectiveness of converting patients from sustained release to immediate-release bupropion. They reported 2 cases of agitation/anxiety (2%) among patients in the study. The lack of control-comparison, and relatively small sample size, precludes any firm conclusions from being drawn.

Ramaswamy, et al. (2015) investigated the effects of escitalopram on OEF/OIF veterans ($n = 11$), as noted above. There was one reported case of irritability while the subject was on escitalopram; however, the authors cast doubt as to whether it was related to the treatment (p. 16). As with Naylor et al. (2013), the small sample size of Ramaswamy et al. (2015) precludes us from drawing firm conclusions based on their results.

Akathisia and Restlessness. Of the 25 studies in this review, five included results related to akathisia and/or restlessness (including Restless Leg Syndrome [RLS]) (See Table 3 for an overview). Mohamed et al. (2017) performed the most extensive assessment of akathisia and restlessness in this review. To reiterate, this multi-site randomized controlled trial compared patients with Treatment-Resistant Depression across three conditions (switching to bupropion [$n = 511$]; antidepressant with bupropion augmentation [$n = 506$]; and augmentation with an atypical antipsychotic [aripiprazole] [$n = 505$]). Again, we will only focus on the first two treatment arms. Barnes Akathisia scores (of mild, moderate, or severe) were more common in the bupropion augmentation group (8.5%, $n = 43$) vs. the bupropion switch group (6.3%, $n = 32$). Cases of akathisia were reported as being more common in the augmentation group ($n = 32$,

6.3%) vs. the switch group ($n = 24$, 4.7%). Reported cases of restlessness were disproportionate with the bupropion augmentation group having more cases of restlessness ($n = 10$, 2.0%) vs. 1 case in the bupropion switch group (0.2%). While these results provide the most robust support for investigating any relation between antidepressant use and akathisia, restlessness, etc. it is unclear how many cases in the augmentation treatment group are being driven by the addition of an antipsychotic drug; drugs that are also known to cause akathisia (Kumar & Sachdev, 2009). Again, a more ideal design would include treatment without augmentation, treatment with augmentation, treatment as usual, and a placebo control group.

Naylor et al. (2013), described above, reported 2 cases of restlessness (1, mild, 1 moderate) out of five patients on paroxetine. This, compared to zero cases out of seven patients in the placebo group. Though the only instances of restlessness were found in the treatment group, the small sample size in this study ($n = 12$, total) precludes us from drawing conclusions.

Prochazka et al. (1998) investigated the use of nortriptyline as a treatment for smoking cessation, as described above. In 108 patients randomized to the treatment arm (nortriptyline vs. 106 on placebo) there were lower mean rates of restlessness on a 5-point scale (1.0 [1.3 SD] vs. 1.9 [1.6 SD] in placebo), after 8 days of smoking cessation. While this gives credence to the belief that nortriptyline may decrease or prevent restlessness, firm conclusions are difficult, as such symptoms are consistent with, and to be expected during, nicotine withdrawal.

Two studies specifically looked at the relationship between antidepressants and RLS (Bailey et al., 2016; Baughman, Bourguet, & Ober, 2009). The first study (Bailey et al., 2016), a retrospective chart review of 254 patients, found no relationship between SSRI/SNRI use and RLS. Only 14 patients on an antidepressant (5.5%) had a diagnosis of RLS; with 3 patients developing RLS prior to drug initiation. The second study (Baughman et al., 2009), a cross-

sectional study of 1,693 veterans, found no relationship between RLS and antidepressant use for women (Relative Risk [RR] = 0.79, CI = 0.43, 1.47); though associations were found between RLS and fluoxetine (RR = 2.47, CI = 1.33, 4.56). There was an association between antidepressants and RLS in men (RR = 1.77, CI = 1.26, 2.48), with citalopram, paroxetine, and amitriptyline having the largest associations. It is unclear from these two studies alone, whether there is a relationship between antidepressant use and RLS. While RLS is a distinct condition from akathisia proper, it is included here, given the difficulty researchers and clinicians have of distinguishing RLS from akathisia and related disorders (e.g. postencephalitic parkinsonism) (Sachdev, 1995a, 1995b).

Aggression/Violent Behaviors. None of the 25 studies in this review (Table 4) included information related to aggression or violent behaviors.

Discussion

The results of this review do not provide sufficient evidence of whether a connection exists between antidepressant use and high suicide rates among veterans. The quality of the present data precludes us from drawing any firm conclusions, as no trials have rigorously examined this issue. Thus, it remains an open question as to what extent antidepressants might contribute to veteran suicide or acts of aggression or self-harm. This is problematic given the frequency with which antidepressants are prescribed and evidence from other meta-analyses of antidepressant studies in civilian populations that suggests a link to suicide. A vast number of veterans require treatment, but the rational provision of treatment must be informed by a clear

understanding of benefits and harms (Dunleavy, 2018; Fava, 2014). The results of the above systematic review suggest that we do not have such evidence.⁴

Considering the substantial amount of evidence in the extant literature of the adverse effects of the anti-depressant medications, as well as the similarity that those adverse effects have with the experienced symptomatology of veterans with significant mental health issues, more rigorous study needs to be conducted on how these medications may exacerbate these issues that are known to increase the risk of suicide. While caution with the usage of these medications should be taken for all individuals, adherence to best-practice guidelines and treatment protocols for clinicians who prescribe and monitor the usage of these medications is arguably more critical for those working with the veteran population. Further, reporting rates and treatment utilization is also important to consider with regard to veterans. Understanding the complex dynamics that military culture and the stigma that that culture imposes on veterans is crucial to understanding the ways this population discusses, seeks out treatment for, and perceives mental health as a whole.

One future direction for researchers and agencies to take would be to implement more rigorous randomized controlled trials;⁵ though such designs may be limited. Selective reporting of results, lack of data transparency, the use of statistically underpowered studies, and conflicts of interest all contribute to the overestimation of drug benefits and the minimization of drug harms in these trials (see especially Stegenga, 2017; and Chan, Hróbjartsson, Haahr, Gøtzsche, & Altman, 2004; Cohen & Jacobs 2010; Hengartner, 2017; Hughes, Cohen, & Jaggi, 2014;

⁴ It is especially concerning that no studies reviewed here reported on instances of aggression or violent behavior, given that veterans are more likely than the general population to own a firearm (Cleveland, Azrael, Simonetti, & Miller, 2017).

⁵ While RCTs are often touted as the “gold standard” for establishing causality (though see Cartwright, 2010; Fuller, 2018; Stegenga, 2014; Worrall, 2007) for philosophical discussion of this argument), a number of factors undermine their use for identifying harms (see Stegenga 2017).

Hughes, Cohen, & Johnson, 2016; Ioannidis, 2009; Jacobs & Cohen, 2010; Maund et al., 2014; Mayo-Wilson et al., 2019a, 2019b; Moncrieff, 2016; Tsang, Colley, & Lynd, 2009). Further, even under ideal conditions, the common practice of maximizing the statistical power to detect a drug benefit may actually decrease the available statistical power to detect a drug harm (Stegenga, 2016). In other words, as statistical power to detect beneficial effects of an antidepressant are increased, the power to detect potential harms (e.g. akathisia, aggression, suicide) is decreased (see also Cai, Parast, & Ryan, 2010). On a practical level, this means that if one is to accurately capture the frequency in which veterans experience harms on antidepressants, and to establish causality, one would seemingly have to create large trials, that intentionally focus on harm prevalence, and then accurately measure them (see Mayo-Wilson et al., 2019a, 2019b). Given these considerations, funnelling money into expensive, large-scale RCTs may not be the best use of resources.

A more dynamic solution would require triangulation among a diverse set of related data sources and methodologies (e.g. Rutherford et al., 2010); including but not limited to the use of RCTs, non-randomized studies (e.g. observational trials), qualitative analyses, spontaneous reporting systems, online support communities (see generally Hughes & Cohen, 2010, 2011; Hughes, Lacasse, Fuller, and Spaulding-Givens, 2017; Osimani, 2014; Papanikolaou, Christidi, Ioannidis, 2006; Silverman, 2009; Vandenbroucke, 2006), and listening to the feedback, perspectives, preferences, and stories of veterans themselves (Caplan, 2014).

Conclusion

This systematic review attempted to answer, “What evidence is there about suicide and other adverse effects, with regard to veteran antidepressant users?”. Our conclusion, based on the

results of this review, is that there is minimal evidence by which to answer this question. More rigorous, dynamic, research methods should be employed to explore this pressing issue.

Contributor Roles

Contributor roles are assigned in accordance with [CRediT](#). DD was responsible for conceptualization, funding acquisition, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, and writing/reviewing. JL was responsible for conceptualization, funding acquisition, reviewing, and supervision. CO was responsible for investigation. SH was responsible for writing/reviewing. MW was responsible for conceptualization, writing/reviewing.

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**Denotes Inclusion in Systematic Review*

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Figure 1. Search Terms Utilized

Search Term 1 (Location: abstract)	<i>Veteran*</i>
Search Term 2 (Location: anywhere in text)	<i>Antidepressant OR SSRI OR Selective Serotonin Reuptake Inhibitor OR Citalopram OR Escitalopram OR Fluoxetine OR Paroxetine OR Fluvoxamine OR Sertraline OR SNRI OR Serotonin and Norepinephrine Reuptake Inhibitor OR Desvenlafaxine OR Duloxetine OR Levomilnacipran OR Milnacipran OR Venlafaxine OR SARI OR Serotonin Antagonist and Reuptake Inhibitor OR Nefazodone OR Trazodone OR NDRI OR Norepinephrine Dopamine Reuptake Inhibitor OR Lisdexamfetamine OR Reboxetine OR Teniloxazine OR Viloxazine OR NRI OR Norepinephrine Reuptake Inhibitor OR Amineptine OR Bupropion OR TCA OR Tricyclic Antidepressant OR Amitriptyline OR Amitriptylinoxide OR Clomipramine OR Desipramine OR Dibenzepin OR Dimetracine OR Dosulepin OR Doxepin OR Imipramine OR Lofepramine OR Melitracen OR Nitroxazepine OR Nortriptyline OR Noxiptiline OR Opipramol OR Protriptyline OR Trimipramine OR TeCA OR Tetracyclic Antidepressant OR Amoxapine OR Maprotiline OR Mianserin OR Mirtazapine OR Setiptiline OR MAOI OR Monoamine Oxidase Inhibitor OR Isocarboxazid OR Phenelzine OR Tranylcypromine OR Selegiline OR Caroxazone OR Moclobemide OR Pirlindole OR Toloxatone OR Tranylcypromine OR SMS OR Serotonin Modulator and Stimulator OR Vilazodone OR Vortioxetine</i>
Search Term 3 (Location: anywhere in text)	<i>Suic* OR Aggress* OR Agitat* OR Self-Injur* OR Self-Harm OR Akathisia OR Irritab* OR Restless*.</i>

Figure 2. Flow Chart

Table 1. Suicide and related harms (e.g. ideation, self-injury/harm)

Study /Year	Antidepressant /Sample Size	Adverse Event Findings
Basham et al., 2011	Antidepressants (n = 968)	Of veterans who completed suicide in Oregon, between 2000 and 2005, and received care at a VA facility (n = 212), 44.8% (n = 95) had an antidepressant prescription within past 12 months and 3.3% (n = 7) had an antidepressant prescription within 30 days prior to suicide
Ciraulo et al., 2005	Nefazadone (n = 34) vs. Placebo (n = 35)	There was one case of reported suicidal ideation in the treatment group
Copeland et al., 2014	Antidepressants (n = 89,995)	Within the 3 years after surgery, antidepressant use had a hazard ratio (HR) of 1.90 (95% CI: 1.73, 2.09) for suicidal behaviour(s) and ideation.
Denneson et al. 2017	Antidepressants (n = 38)	68.4% (n = 26) had an antidepressant prescription in the 6 months prior to suicide; while 23.7% (n = 9) had 90+ days on an antidepressant in the 6 months prior to suicide
Denneson et al., 2016	Antidepressants (n = 236)	There was no statistically significant difference between cases (death by suicide; n = 118) and controls (n = 118) for antidepressant prescription (p = 0.36) or for having 90 or more consecutive days on an antidepressant (p = 0.47). There was a statistically significant difference between cases and controls with regard to having 90 or more total days on an antidepressant (p = 0.02) (only 71.4% of cases vs. 87% of controls)
Forrester, 2017	Antidepressants (n = 4,353)	In military and VA hospitals, there were 814 (18.7%) reports and 330 (19.7%) reports of antidepressant poisoning, respectively. It is unclear how many of antidepressant poisonings were intentional; 57.3% of military hospital reports and 47.7% of VA hospital reports were suspected attempted suicide
Gibbons et al., 2007	Antidepressants (n = 226,866)	There was an an inverse relationship between suicide and the prescription of an antidepressant. There was a statistically significant difference, indicating lower rates of suicide prior to treatment initiation, than after treatment (i.e. for those on SSRI monotherapy [p <

		0.001, RR 0.56, CI 0.44, 0.71] and non-SSRI monotherapy [$p < 0.001$, RR 0.51, CI 0.39-0.68]). Tricyclic monotherapy suicide rates did not diverge, statistically, before or after treatment was initiated ($p < 0.53$, RR 0.57, CI 0.17, 1.95)
Johnson et al., 2015	Antidepressants (n = 601)	Of the 601 poisonings reported to the Florida Poisoning Control Information Network (FPCIN) antidepressants were present in 120 instances (12.4%). Antidepressants also showed the strongest association with intentional-suspected suicide (Odds Ratio [OR] = 6.737)
McCarthy et al., 2015	Antidepressants (n = 2,138)	From the data used to test the predictive model, an antidepressant was prescribed within the past 24 months in 42.3% of suicide cases (n = 905)
Mohamed et al., 2017	Switch to Bupropion vs. Augment w/Bupropion vs. Augment w/Aripiprazole (latter not included in table) (n = 511 vs. n = 506 vs. n = 505)	Suicidal ideation was lower in the bupropion switch group (n = 8, 1.6%) than the bupropion augmentation group (n = 11, 2.2%). Suicide attempts and completed suicide were higher in the switch group compared to the augmentation group ([n = 3, 0.6% vs. n = 1, 0.2%]) and [n = 1, 0.2% vs. n = 0, 0%] respectively)
Pfeiffer, Kim, Ganoczy, Zivin, & Valenstein, 2013	Antidepressants (n = 499 [suicide] vs. n = 1994 [non-suicide])	The stage of intervention (i.e. the intensiveness of treatment and the number of antidepressant trials) was not statistically significant with regard to suicide, when controlling for demographic factors. In other words, whether patients had a higher level of treatment intensity was not a statistically significant predictor of suicide
Prochazka et al., 1998	Nortriptyline (n = 108) vs. Placebo (n = 106)	Though suicidal ideation was not explicitly reported, there was a statistically significant difference between the treatment and placebo groups for drop-out due to drug discontinuation (9 vs. 3). It is unknown the cause(s) for discontinuation
Ramaswamy et al., 2015	Escitalopram (n = 11)	There was one reported case of suicidal ideation while on escitalopram
Roy, 2010	Antidepressants (n = 527)	It was reported that treatment with an antidepressant was a statistically significant predictor of a suicide attempt ($p < 0.013$; OR 3.261, 95% CI [1.283, 8.288]), having the highest odds ratio of all analysed predictors

Seyfried, Kales, Ignacio, Conwell, & Valenstein, 2011	Antidepressants (n = 294,952)	There was an increased risk of suicide with the prescription of an antidepressant ($p < 0.0001$, OR 2.11, 95% CI: 1.57, 2.84)
Smith, Craig, Ganoczy, Walters, & Valenstein, 2011	Antidepressants (n = 1,843)	69.9% of cases of suicide had received an antidepressant, of any type at last treatment visit (n = 656) and 47.4% had received an antidepressant that was characterized as being prescribed at an adequate (i.e. high enough) dose (n = 445)
Tsai, Tsai, Yang, & Hwang, 2007	Antidepressants (n = 7)	All patients reported as improving. No suicidal ideation was reported at discharge. All patients received antidepressant and antipsychotic during hospitalization
Valenstein et al., 2012	Citalopram, Bupropion, Fluoxetine, Venlafaxine, Sertraline, Paroxetine, Mirtazapine (n = 502,179)	The authors reported the raw number of suicides for those on antidepressants as follows: citalopram (n = 77), bupropion (12), fluoxetine (26), venlafaxine (15), sertraline (57), paroxetine (45), and mirtazapine (15). Hazard ratios were reported as follows: citalopram (1.0), bupropion (0.45), fluoxetine (0.63), venlafaxine (0.89), sertraline (0.70), paroxetine (1.06), mirtazapine (1.11) According to the authors, an instrumental variable analyses did not find statistically significant differences across antidepressants for suicide
Yerevanian, Koek, Mintz, & Akiskal, 2007	Antidepressants (n = 405 [Mood Stabilizer Monotherapy = 192; Antidepressant Monotherapy = 112; MS+AD Therapy = 202])	Antidepressant monotherapy resulted in zero recorded suicides, and seven suicide attempts. 20 patients were hospitalized for suicidal ideation or intent. The combination treatment group (MS+AD) had one completed suicide and five attempted suicides. There were 18 cases of hospitalization for suicidal ideation or intent.

Table 2. Agitation, irritability, and anger

Study /Year	Antidepressant /Sample Size	Adverse Event Findings
Chung et al., 2004	Mirtazipine (n = 51) vs. Sertraline (n = 49)	There was one reported case (2%) of agitation in the sertraline group at 6 weeks
Mayo et al., 2005	Bupropion [Immediate Release] (n = 103)	They reported 2 cases of agitation/anxiety (2%) among patients in the study
Mohamed et al., 2017	Switch to Bupropion vs. Augment w/Bupropion vs. Augment w/Aripiprazole (latter not included in table) (n = 511 vs. n = 506 vs. n = 505)	All three adverse events discussed in this section were more common in the bupropion switch group: agitation occurred in 7 cases of bupropion vs. 4 cases (0.8%) of bupropion augmentation; irritability in 32 cases (6.3%) vs. 15 (3%); and anger in cases 7 (1.4%) vs. 4 cases (0.8%)
Naylor et al. (2013)	Paroxetine (n = 5) vs. Placebo (n = 7)	There was one reported case of excitement/agitation on placebo vs. zero in the paroxetine group
Prochazka et al., 1998	Nortryptaline (n = 108) vs. Placebo (n = 106)	There were reported lower mean rates of irritability/anger (1.2 [1.3 SD] vs. 1.8 [1.4 SD] in placebo) and anxiousness/tension (1.2 [1.4 SD] vs. 2.1 [1.7 SD] in placebo) within the treatment arm, on a self-report, 5-point scale, after 8 days of smoking cessation.
Ramaswamy et al., 2015	Escitalopram (n = 11)	There was one reported case of irritability while the subject was on escitalopram; however, the authors cast doubt as to whether it was related to the treatment (p. 16)

Table 3. Akathisia and restlessness

Study /Year	Antidepressant /Sample Size	Adverse Event Findings
Bailey, Makela, & Asberg, 2016	SSRIs/SNRIs (n = 254)	There was no relationship between SSRI/SNRI use and RLS found. 14 patients on an antidepressant (5.5%) had a diagnosis of RLS; with 3 patients developing RLS prior to drug initiation
Baughman, Bourguet, & Ober, 2009	Antidepressants (n = 1693)	No relationship was found between RLS and antidepressant use in women (Relative Risk [RR] = 0.79, CI = 0.43, 1.47); though associations were found between RLS and fluoxetine (RR = 2.47, CI = 1.33, 4.56). There was an association between antidepressants and RLS in men (RR = 1.77, CI = 1.26, 2.48), with citalopram, paroxetine, and amitriptyline having the largest associations
Mohamed et al., 2017	Switch to Bupropion vs. Augment w/Bupropion vs. Augment w/Aripiprazole (latter not included in table) (n = 511 vs. n = 506 vs. n = 505)	Barnes Akathisia scores (of mild, moderate, or severe) were more common in the bupropion augmentation group (8.5%, n = 43) vs. the bupropion switch group (6.3%, n = 32). Cases of akathisia were reported as being more common in the augmentation group (n = 32, 6.3%) vs. the switch group (n = 24, 4.7%). Reported cases of restlessness were disproportionate with the bupropion augmentation group having more cases of restlessness (n = 10, 2.0%) vs. one case in the bupropion switch group (0.2%)
Naylor et al. (2013)	Paroxetine (n = 5) vs. Placebo (n = 7)	There were 2 reported cases of restlessness (1, mild, 1 moderate) out of five patients on paroxetine. This, compared to zero cases out of seven patients on placebo
Prochazka et al., 1998	Nortriptyline (n = 108) vs. Placebo (n = 106)	There were lower mean rates of restlessness on a 5-point scale (1.0 [1.3 SD] vs. 1.9 [1.6 SD] in placebo), within the treatment arm, after 8 days of smoking cessation.

Table 4. Aggression/violent behaviors

Study /Year	Antidepressant /Sample Size	Adverse Event Findings
N/A	N/A	Zero studies reported results related specifically to aggression and antidepressant use