Association of Hospitalization With First-Line Antidepressant Polypharmacy Among Veterans of Iraq and Afghanistan With Post-Traumatic Stress Disorder: Examining the Influence of Methodological Approaches

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ABSTRACT Objective: To compare the influence of various statistical analysis approaches while assessing the marginal effect of polypharmacy (prescription of multiple psychotropics including a first-line antidepressant) on all-cause hospital admission among veterans diagnosed with post-traumatic stress disorder. Methods: Data were obtained on 398 Iraq/Afghanistan veterans being followed in a southwestern U.S. health care system from October 2005 through September 2009, diagnosed with post-traumatic stress disorder and receiving first-line antidepressants (serotonin selective or serotonin norepinephrine reuptake inhibitors). High-dimensional propensity score (hd-PS) approaches were considered, examining both covariate adjustment per PS deciles and propensity weighting, with results compared to those of standard multivariable logistic regression. Results: Veterans prescribed polypharmacy did not appear to have increased odds of admission in either the decile-adjusted hd-PS model (odds ratio [OR] = 2.1; 95% confidence interval [CI]: 0.9–4.9, not significant [ns]) or traditional covariate-adjusted logistic model (OR = 2.1; 0.9–5.0, ns). Inverse probability of treatment (OR = 2.1; 1.3–3.3) and standardized-morbidity-ratio-weighted (OR = 2.2; 1.3–3.6) hd-PS models estimated similar odds of admission with narrower CIs. Conclusions: Future research should incorporate alternate analytical methods for observational data and investigate their respective biases relative to clinician treatment decision-making. For several analytical approaches, greater risk of admission among patients prescribed antidepressant-related polypharmacy was observed despite recommended guidelines, suggesting the need to investigate why clinicians may deviate from guidelines.

INTRODUCTION

More than 2 million U.S. military service personnel have been deployed to combat areas in Iraq and Afghanistan since September 2001.[1,2] Individuals involved in Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND), are at high risk for exposure to combat-related trauma.[3] Postdeployment, these service men and women may develop a broad range of long-term negative health problems, including functional impairments, psychiatric disorders, and physical health issues.[4] Discharged OIF/OEF/OND military personnel needing medical and psychiatric care can receive treatment from the Department of Veterans Affairs (VA) health care system. Among OIF/OEF/OND veterans seeking care in the VA since 2002, more than half (56%) are diagnosed with a mental disorder, with post-traumatic stress disorder (PTSD) being the most common (30%).[5]

Given the high prevalence of PTSD among returning veterans, a clear understanding of the comparative effectiveness of treatments for PTSD is needed. The volume of returning veterans and the acuity of their mental distress has generated intense research into best treatment practices.[6] According to VA and Department of Defense Clinical Practice Guidelines,[7] first-line interventions for PTSD include pharmacological treatment with a single antidepressant and/or psychotherapy. For antidepressant monotherapy, a serotonin selective reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI) is recommended.[7] Despite the guidelines, veterans with PTSD are often prescribed multiple psychotropic medications, presumably to treat refractory symptoms of PTSD or a comorbid mental disorder.[8,9]

Polypharmacy is generally a pejorative term referring to the inappropriate use of multiple medications for the same illness or in a manner that poses more risk than benefit and is not in line with community medical standards.[10,11] Polypharmacy has been linked to an increased risk of adverse drug reactions with detrimental effects to patients.[12] In turn, hospital admissions have been linked to adverse drug reactions, with higher rates of admission found in patients who are likely to be receiving multiple medications for long-term illnesses.[13,14] Among Veterans with schizophrenia seeking care in the VA, antipsychotic polypharmacy had an observed prevalence of 20 to 22% with risk of admission double that

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of patients receiving monotherapy.[15] For that reason, it is important we understand the degree to which polypharmacy in returning war veterans with PTSD plays a role in their being hospitalized medically or psychiatrically. The answer has the potential to drive clinical and policy decisions about the care of our veterans. Although the guidelines acknowledge a tendency to use polypharmacy in the treatment of PTSD, they note that studies examining the efficacy of these combined treatments are lacking.[7]

Randomized control trials have long been recognized as the gold standard in drug development when comparing pharmacological treatments.[16] In randomized trials, measurable and nonmeasurable differences between exposure groups are minimized, leaving only group assignment as the likely cause for differences in the observed outcome (high internal validity). Randomized trials, however, are expensive and lack generalizability because of narrow inclusion criteria (low external validity). On the other hand, observational studies may reflect real-world practices (high external validity), but have limited ability to assess causality (low internal validity) as a result of selection bias and confounding.[16]

Research results of observational studies are generally derived from some variant of multiple regression analysis. These results inform policy and treatment decisions. Because policy and treatment decisions require understanding of the causal processes involved, it is critically important that the methods chosen best address issues of confounding and selection bias and produce the best estimates of the causal effect of interest. The purpose of this study was to assess the influence of the selected analytical approach when examining the marginal clinical effect of concurrent psychotropics prescribed with first-line antidepressant monotherapy of a SSRI/SNRI on all-cause hospital admission among OIF/OEF/OND veterans diagnosed with PTSD.

METHODS

Sample and Study Design

This retrospective observational study assembled data on 398 OIF/OEF/OND veterans diagnosed with PTSD (*International Classification of Diseases*, 9th Revision, Clinical Modification [ICD-9] code 309.81) and prescribed a SSRI/SNRI in a southwestern VA medical center during fiscal year 2006 (FY06: October 2005–September 2006). These participants were part of a larger study of all OIF/OEF/OND veterans using the medical center in FY06 (N = 2,470), the baseline year for cohort definition; the next 3 years provided follow-up data (through FY09).[17] Patients with a hospital admission during FY06 were excluded because their covariates could not be assessed before the outcome.

Data Sources and Measures

Data were obtained from administrative extracts of the VA's all-electronic medical records system, assured for quality through extensive data processing routines.[18,19] Data included patient demographics, diagnosis and procedure codes, outpatient visit dates, inpatient admission/discharge dates, and outpatient prescriptions containing drug name, dispense date, and days' supply. One primary diagnosis, up to 9 additional diagnoses, up to 20 Current Procedural Terminology (CPT) procedure codes, and clinic type stop codes characterized each outpatient visit.

Covariate measures included age, gender, comorbidities, and VA Priority status. VA Priority status indicates eligibility for VA health care per service-connected disability and other factors, serving as a proxy for socioeconomic status and disease severity.[20] An indicator of Priority 1 status was created to contrast highly disabled veterans who incurred no copays for prescriptions or care with those with copays for medications (Priority 2–6) or for care and medications (Priority 7–8).[21,22] Co-occurring conditions were captured using the Selim Physical Comorbidity Index, which sums 30 chronic medical conditions (range, 0–30), and the Selim Mental Comorbidity Index accounting for 6 mental conditions including alcohol abuse disorders, anxiety, and depression (range, 0–6).[22–24] In addition, dichotomous indicators for baseline diagnoses of major depressive disorders (ICD-9 296.2x-296.3x, 311), substance use disorders including alcohol and other drug abuse (291.xx, 292.xx, 303.xx–305.xx, excluding 305.1), and anxiety/phobias (300.xx) were created.[25]

Patients were classified into one of two groups on the basis of their pharmacological treatment: (1) first-line monotherapy and (2) polypharmacy. Monotherapy consisted of patients following pharmacological guidelines for the treatment of PTSD with a single SSRI/SNRI during the year before outcome (or end of study). Polypharmacy included patients concurrently using any psychotropic in addition to a SSRI/SNRI. The primary outcome measure was a dichotomous variable representing all-cause (psychiatric or medical) hospital admission during follow-up.

Analysis Plan

Recognizing the potential clinical implications of corresponding findings, several analytical approaches were considered in examining the association between pharmacological treatment with SSRI/SNRI monotherapy versus polypharmacy and hospitalization, including multivariable logistic regression as the traditional method.[26] In addition, high-dimensional propensity score (hd-PS) model approaches were investigated, examining both covariate adjustment per PS deciles and propensity weighting. Each approach is detailed below.

Conventional Approach

Multivariable logistic regression was employed to assess the relationship between pharmacological treatment (SSRI/SNRI polypharmacy vs. monotherapy) and hospitalization, adjusting for 7 other predictors including demographics (age, gender, and Priority 1), mental illnesses (depression, substance use, and anxiety/phobias), and physical comorbidities per Selim

Physical. This resulted in a total of 8 predictors. Some simulation analyses recommend an event-per-covariate ratio of 8 to 10 as logistic regression loses power and becomes biased if fewer events-per-covariate are available.[27,28] This means we are limited to one predictor (covariate) for every 8 to 10 hospital admissions (event) observed. Given the rarity of our outcome (15%; $n = 59$), it would be recommended to include approximately 6 (59/10) to 7 (59/8) predictors in our model. As 8 variables may be slightly more than recommended, treatment was similarly assessed when the predictors for depression, substance use, and anxiety/phobia disorders were replaced with a single score, Selim Mental. This led to the inclusion of 6 predictors, satisfying the recommended event-per-covariate ratio of 8 to 10. Results were reported as odds ratios (OR) with their 95% confidence intervals (CI).

Unweighted hd-PS

When conventional analytical approaches have limitations imposed from too many covariates, small sample size, or few observed events, a PS approach may be preferred. Appropriate situations for their use include those where dozens or hundreds of potential predictors are available. This is a common situation in studies utilizing health care administrative data of high dimensionality.[29] Using hd-PS methods, we were able to adjust for patient characteristics as well as incorporate an abundance of additional information including diagnoses, procedures, and clinic types. The included covariates (empirical covariates) were chosen through the analytical process and were expected to improve the control of potential confounders.

Following the algorithm (Fig. 1) proposed by Schneeweiss et al,[30] hd-PS models were constructed incorporating covariates derived from baseline outpatient diagnoses, procedure codes, and clinic types. For the baseline temporal window of 12 months, four data dimensions, p, were considered (1) primary diagnosis (ICD-9 codes; granularity 5 digits), (2) secondary diagnoses, (3) procedures (CPT codes; granularity 5 digits), and (4) clinic type (granularity 3 digits). Within each data dimension, the n most prevalent codes were selected (up to $p \times n$ covariates) from which three additional binary covariates were created on the basis of its frequency: (1) ever observed; (2) observed more than its median; and (3) observed in the fourth quartile.[31] The larger cutoff variable was dropped if any quartile values were equal, resulting in up to $3 \times n \times p$ candidate binary covariates.

Across data dimensions, candidate binary covariates were prioritized by their potential for controlling confounding that was not conditional on exposure or other covariates using Schlesselman's bias formula.[32,33] Then, the top k empirical covariates contributing the most bias were selected for use in the PS model, modeling patients' propensity for receiving polypharmacy. Along with these prioritized covariates, predictors proposed for the traditional logistic regression models were used, including demographics (age, gender, and Priority 1) and both Selim measures, totaling $k + 5$ covariates.

From the estimated PS, patients were grouped into PS deciles. Representing 10 dichotomous variables, these deciles were used for covariate adjustment in the final logistic model. Using deciles may improve control for confounding when using claims data and a large number of proxy covariates for PS estimation compared to models with fewer covariates.[30] They have the potential advantage of reducing the influence of extreme values while still capturing the majority of the information in continuous measures. Thus, logistic regression was used to model admission as a function of polypharmacy (vs. monotherapy), unweighted and adjusted for deciles.

Weighted hd-PS

PS weighting may eliminate a greater degree of systematic differences between exposure groups compared to covariate-adjusted PS methods.[34] In some cases, combining regression adjustment with weighting to remove bias rather than relying solely on one of these methods may be beneficial.[35] Weighted hd-PS models entailed weighting each observation to further adjust for baseline differences. Two PS weighting methods were considered, standardized morbidity ratio (SMbR) and inverse probability of treatment (IPT). SMbR weighting estimates the treatment effect in a population whose distribution of risk factors equals that found in the treated subjects only. This method assigns weights of 1 to patients treated with polypharmacy ($p = 1$) and the propensity odds to patients prescribed monotherapy ($p = 0$).[36] This approach may be most appropriate when study populations in the two treatment groups are very different.[37] IPT weighting estimates the treatment effect in a population whose distribution of risk factors is equal to that found in all subjects, and it uses as weights the inverse PS for those with polypharmacy and the inverse of the difference from 1 for monotherapy.[36–38] A major drawback of weighted PS approaches is their sensitivity to extreme PS values, a problem that can be addressed through trimming.[38,39]

To summarize, in addition to the unweighted decile-adjusted hd-PS model, two weighting approaches were considered in the current study, SMbR and IPT (Fig. 1, Step 7). In addition, we used PS decile adjustment in combination with weights. Finally, given the possibility of influential weights, the extreme 5% of the weights were trimmed, reducing the sample to 360 patients. For reporting, we used the specific case of $n = 10$ and $k = 30$. That is, within each of the four data dimensions ($p = 4$), the 10 ($n = 10$) most prevalent codes were selected (up to $p \times n = 40$ covariates) from which up to three additional binary covariates were created on the basis of each code's frequency (up to $3 \times n \times p = 120$ candidate binary covariates). Then, the top 30 ($k = 30$) empirical covariates contributing the most bias were selected for use in the PS model, modeling patients' propensity for receiving polypharmacy (Table I), along with demographics (age, gender, and Priority 1) and both Selim measures for a total of 35 ($k + 5$) covariates (Fig. 1, Steps 5 and 6). Given

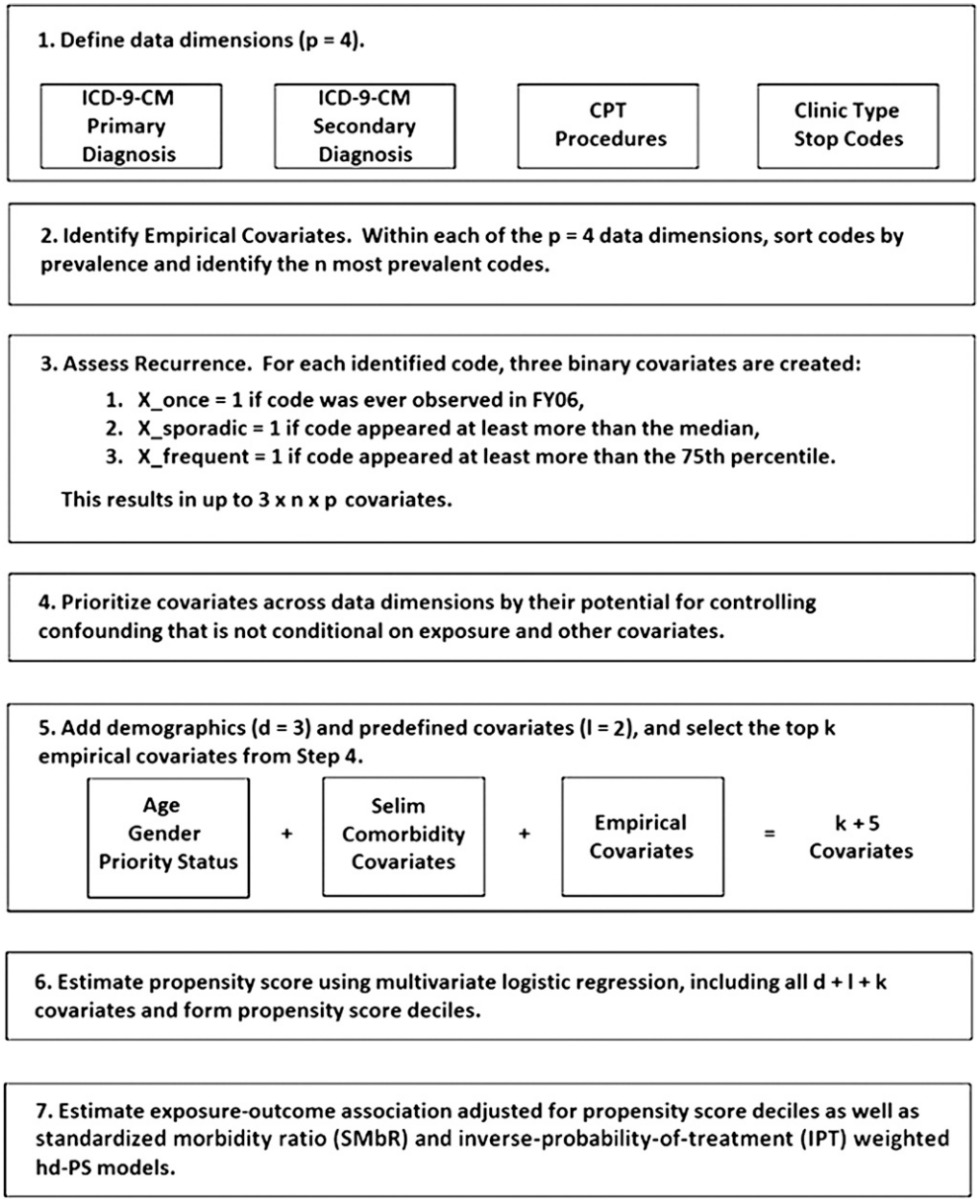

FIGURE 1. High-dimensional propensity score algorithm (reproduced with permission from Schneeweiss et al 2009).[30]

the ambiguity of selecting values for n and k, we also examined OR estimates for varying n and k (Figs. 2 and 3). All analyses were performed using SAS, Version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Cohort Characteristics

In the sample of 398 OIF/OEF/OND veterans, 86% were male with a mean age of 34 years (standard deviation = 10; Table II). About half were VA Priority 1 (55%), and 15% had an inpatient admission during follow-up with just over half of these for psychiatric reasons (32 of 59; 8% overall). About one-fourth (22%) of patients had major depressive disorder, 7% substance use disorder, and 6% anxiety/phobia. We observed 91 patients (23%) with SSRI/SNRI monotherapy and 307 (77%) with polypharmacy. Compared to monotherapy, those treated with concurrent psychotropics had significantly higher proportions of VA Priority 1 status ($\chi^2 = 4.5$; $p = 0.03$), comorbid mental disorders per Selim Mental, and hospital admissions ($\chi^2 = 4.8$; $p = 0.03$). These patients were also more likely to have major depressive disorder ($\chi^2 = 5.2$; $p = 0.02$).

Attrition Analysis

Several differences were observed between patients with PTSD on SSRI/SNRI therapy ($N = 398$) and patients with PTSD excluded from this study for not receiving

TABLE I. Empirical Covariates (Diagnoses, Procedures, and Clinic Types) Prioritized for Inclusion as Indicators in Estimating the Propensity Score for Patients

Baseline Empirical Covariates	Occurrence	Code
Primary ICD-9		
Depressive Disorder	Frequent	311
Lumbago (Lower Back Pain)	Frequent	724.2
Depressive Disorder	Once	311
Lumbago (Lower Back Pain)	Once	724.2
Other Hyperlipidemia	Once	272.4
Unspecified Hypertension	Once	401.9
Accretions on Teeth	Once	523.6
Other Suspected Mental Condition	Once	V710.9
Secondary ICD-9		
Depressive Disorder	Frequent	311
Other Hyperlipidemia	Frequent	272.4
PTSD	Frequent	309.81
Depressive Disorder	Once	311
Other Hyperlipidemia	Once	272.4
Lumbago (Lower Back Pain)	Once	724.2
Unspecified Hypertension	Once	401.9
Tobacco Use	Once	305.1
Esophageal Reflux	Once	530.81
CPT Procedures		
New Office/Outpatient Visit	Once	99205
Group Psychotherapy	Once	90853
Emergency Department Visit	Once	99282
Glycosylated Hemoglobin Test	Once	83036
Flu Vaccine	Once	90658
Office Psychotherapy Treatment, 20–30 min	Once	90804
Assay of PSA, Total	Once	84153
Clinic Types		
Telephone/PTSD	Frequent	542
Psychiatrist–Individual	Frequent	509
Telephone/PTSD	Once	542
PTSD–Individual	Once	562
Audiology	Once	203
Magnetic Resonance Imaging	Once	151

PSA, Prostate Specific Antigen.

SSRI/SNRIs ($N = 394$). Compared to excluded patients, the study sample was composed of generally older patients with a mean age of 34 vs. 30 years (median = 31 vs. 26; $p < 0.01$ per Mann–Whitney test). The study sample had more physical and mental comorbidities per Selim Physical and Mental indices ($p < 0.01$ and $p = 0.02$, respectively) and included more depressed patients (22% vs. 13%; $\chi^2 = 10.3$; $p < 0.01$). They were also more likely to have VA Priority 1 status (55% vs. 35%; $\chi^2 = 32.9$; $p < 0.01$). Patients did not differ on gender, substance use, or anxiety/phobia diagnoses. Consistent with their generally greater comorbidity burden, patients included in the study were nearly twice as likely to have an admission as those excluded (15% vs. 8% all-cause, $\chi^2 = 9.5$, $p < 0.01$; 8% vs. 5% psychiatric, $\chi^2 = 4.0$, $p = 0.04$).

Logistic Regression Models

The unadjusted OR suggested increased odds of admission for polypharmacy compared to guideline-concordant antidepressant monotherapy (OR = 2.4, 95% CI: 1.1–5.6). However, this association did not persist in the traditional logistic regression model (OR = 2.1; 95% CI: 0.9–4.9), adjusting for demographics, other mental illnesses, and physical comorbidity per Selim Physical (Table III). Similarly, no treatment effect persisted after adjusting for the Selim Mental (OR = 2.1; 95% CI: 0.9–5.0). Multicollinearity was not observed after performing checks with variance inflation factors (1.0–1.1), variance contributions, and the Durbin–Watson test ($D = 2.0$).

hd-PS-Adjusted Models

For the unweighted, decile-adjusted hd-PS model, no effect was observed for polypharmacy (OR = 2.1; 95% CI: 0.9–4.9) after incorporating demographics, both Selim indices, and empirical covariates. This estimate closely resembled that of the traditional models. Empirical covariates derived from baseline procedures and treatments prioritized for inclusion in the hd-PS models comprised indicators of office psychotherapy, emergency department use, and group psychotherapy. Diagnoses included depressive disorder, lower back pain, and hyperlipidemia. Clinic encounter types included psychiatry visits, PTSD telephone calls, and individual PTSD counseling.

Similar OR estimates were observed for the weighted hd-PS models (OR = 2.1; 95% CI: 1.3–3.3 for IPT; OR = 2.2; 95% CI: 1.3–3.6 for SMbR). These effects were significant as both weighting methods produced narrower 95% CIs compared to unweighted models, with IPT weighting producing the narrowest. Employing both decile adjustment and IPT weighting produced a larger treatment effect (OR = 2.5; 95% CI: 1.5–3.9). The estimated effect decreased after trimming 5% of the weights (OR = 2.2; 95% CI: 1.4–3.6). PS decile adjustment with SMbR weighting also produced larger effects than either approach alone (OR = 2.6; 95% CI: 1.5–4.4), which was similarly reduced after trimming (OR = 2.3; 95% CI: 1.3–3.9).

DISCUSSION

This article demonstrates how the analytical approach taken may lead to varying results, possibly with contradictory or challenging clinical implications. The novel hd-PS approach was applied in a mental health context accounting for these patients' complex health care utilization patterns that made use of psychiatric patients' tendency to use VA services more often than their nonmental illness counterparts.[40,41] In multivariable logistic regression, multicollinearity, model overfitting/underfitting, or a small event-per-covariate ratio may introduce bias and reduce power.[27,42] In PS analysis, a multitude of observable characteristics can be balanced across treatment groups, potentially minimizing bias from observable factors and increasing internal validity,[39,43] although large PS values may introduce bias and should probably be trimmed. As the quality of large claims databases has improved, health outcomes studies using these data have become increasingly common. The most appropriate approach to handling baseline

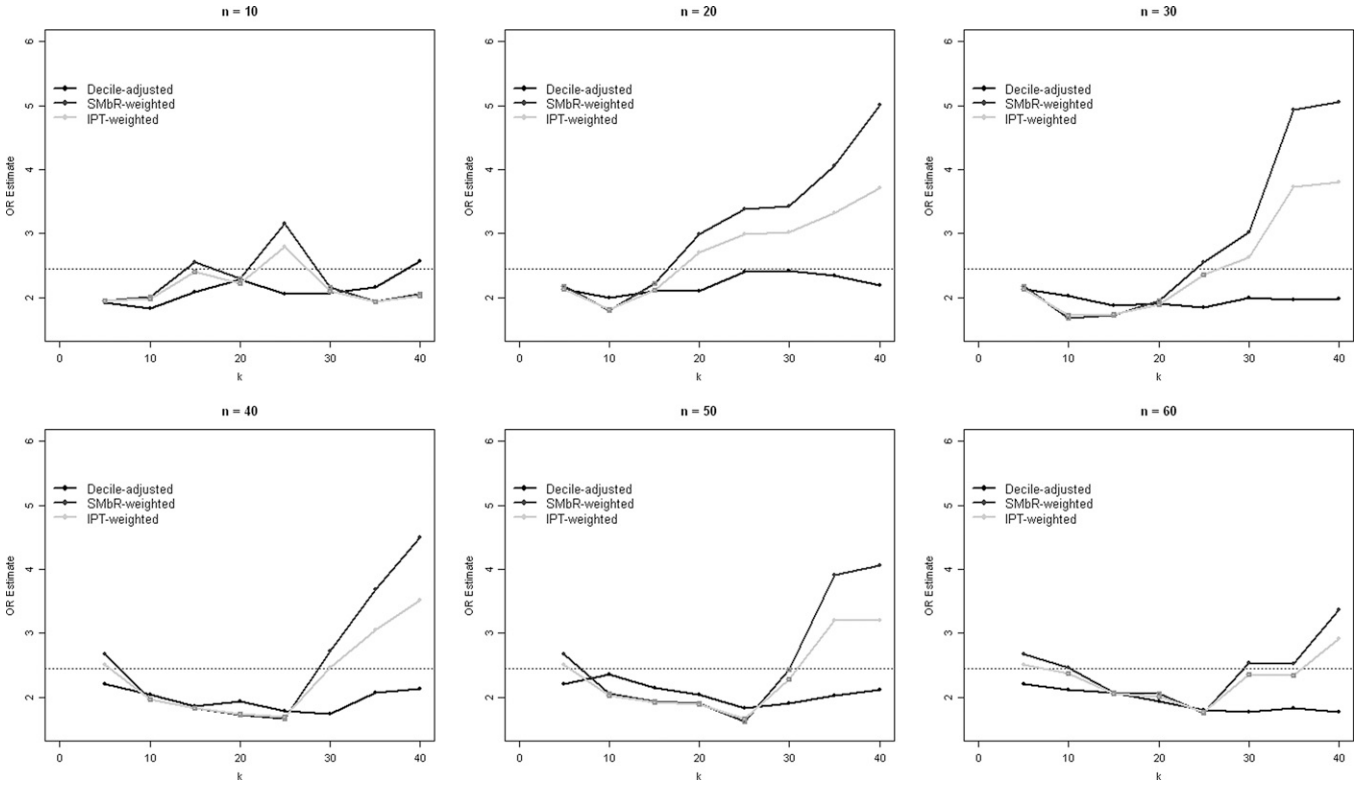

FIGURE 2. Odds ratio estimates for the unweighted, decile-adjusted, IPT-weighted, and SMbR-weighted hd-PS models for various values of n and k (crude, unadjusted odds ratio marked by dashed horizontal line with estimates above this line considered biased; circled estimates denote significance).

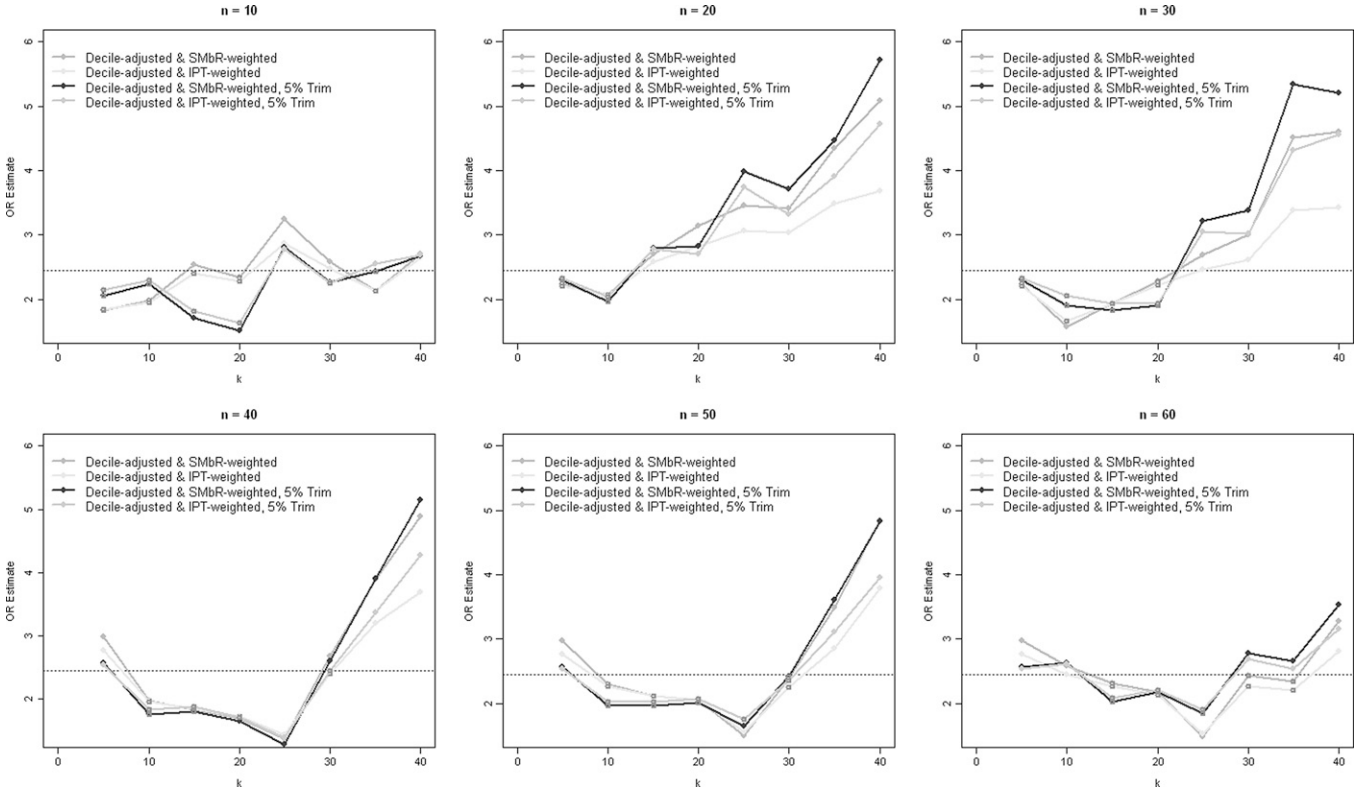

FIGURE 3. Odds ratio estimates for the hd-PS double-adjustment models with deciles and weighting for various values of n and k (crude, unadjusted odds ratio marked by dashed horizontal line with estimates above this line considered biased; circled estimates denote significance).

TABLE II. Patient Characteristics for OIF/OEF/OND Veterans Seeking Care in a Southwestern VA in Fiscal 2006 ($N = 398$) by PTSD Pharmacological Treatment

Patient Characteristics	PTSD Sample	Monotherapy $N = 91$ (23%)	Polypharmacy $N = 307$ (77%)	p Value[a]
Age				
Mean (SD)	33.6 (9.9)	33.1 (10.4)	33.7 (9.8)	0.38
Median (Minimum–Maximum)	30.6 (19–61)	27.9 (21–59)	31.4 (19–61)	
Female	57 (14.3%)	11 (12.1%)	46 (15.0%)	0.49
VA Priority 1	218 (54.8%)	41 (45.1%)	177 (57.7%)	0.03
Selim Physical				
Mean (SD)	0.73 (0.9)	0.65 (0.9)	0.76 (0.9)	0.24
Median (Minimum-Maximum)	0 (0–4)	0 (0–4)	1 (0–4)	
Major Depressive Disorder	87 (21.9%)	12 (13.2%)	75 (24.4%)	0.02
Substance Use Disorder	27 (6.8%)	4 (4.4%)	23 (7.5%)	0.3
Anxiety/Phobia	25 (6.3%)	2 (2.2%)	23 (7.5%)	0.07
All-Cause Admission	59 (14.8%)	7 (7.7%)	52 (16.9%)	0.03
Psychiatric Admission	32 (8.0%)	1 (1.1%)	31 (10.1%)	<0.01

[a]Significant at $\alpha = 0.05$ for comparing treatment groups using Mann–Whitney U test and χ^2 analyses. SD, standard deviation.

differences of samples culled from medical records systems must still be debated. hd-PS methods have the ability to incorporate additional utilization characteristics obtained from health care data that are normally unaccounted for in traditional models of analyses.

Significance of Analytical Approach

Multivariable logistic regression is a fairly common and simple approach to employ with the advantage of studying specific predictors. In our example, this model produced an estimated effect of similar magnitude as other approaches, but with a very wide CI leading to a finding of no significant treatment effect for polypharmacy; we suspect low power accounts for the nonsignificance. Similar results were observed for the unweighted hd-PS model. Although OR estimates were similar across all models (including double adjustment methods after trimming), the weighted hd-PS methods employed in this article elicited narrower CIs and thus significant differences between treatment groups, with an increased risk of hospitalization observed for polypharmacy.

TABLE III. Variations in Covariate-Adjusted and Weighted Models Examining First-Line Polypharmacy Versus Monotherapy for All-Cause Admission ($N = 398$)

All-Cause Admissions[a]	Polypharmacy vs. Monotherapy OR (95% CI)
Unadjusted	2.45 (1.07, 5.59)
Standard Multivariable Logistic Regression	
Variables Entered	
Demographics[b] + Selim Physical[c] + Comorbidities[d]	2.10 (0.90, 4.92)
Demographics + Selim Physical + Selim Mental	2.12 (0.91, 4.95)
PS Decile Adjustment[e]	
Variables in PS	
Demographics + Selim Physical + Selim Mental + Empirical	2.07 (0.88, 4.90)
PS IPT-Weighted	
Variables in PS	
Demographics + Selim Physical + Selim Mental + Empirical	2.10 (1.35, 3.28)
PS SMbR-Weighted	
Variables in PS	
Demographics + Selim Physical + Selim Mental + Empirical	2.16 (1.31, 3.57)
PS Decile Adjustment and IPT-Weighted	
Variables in PS	
Demographics + Selim Physical + Selim Mental + Empirical	2.47 (1.55, 3.94)
Demographics + Selim Physical + Selim Mental + Empirical–5% Trim[f]	2.25 (1.39, 3.63)
PS Decile Adjustment and SMbR-Weighted	
Variables in PS	
Demographics + Selim Physical + Selim Mental + Empirical	2.58 (1.53, 4.38)
Demographics + Selim Physical + Selim Mental + Empirical–5% Trim	2.27 (1.33, 3.88)

PS, Propensity Score. [a]91 first-line monotherapy; 307 polypharmacy; 59 total all-cause admissions. [b]Demographics include age, gender, and VA Priority 1 status. [c]Selim Physical, Selim Physical Comorbidity Index; Selim Mental, Selim Mental Comorbidity Index. [d]Comorbidities include major depressive disorder, substance use disorder, and anxiety/phobia disorder indicators. [e]hd-PS model, adjusted for PS deciles formed from demographics, Selim indices, and empirical covariates. [f]A trim of 5% reduced the sample size to 360 patients.

The hd-PS models appeared to offer a more flexible approach by incorporating more patient detail for a small sample. Although we did not have all the data to adequately address criteria needed for establishing causality, internal validity may have been improved. A disadvantage of the hd-PS approach is choosing appropriate parameterization for the model. The highly variable results from different values for n and k are a concern as they reduce the validity of our results and suggest the need for additional comparative studies. Although not appropriate for this study, a k value larger than n was selected in Schneeweiss et al.[30] The variability observed may be an artifact of our data or sample size. Further exploration of suitable parameterization in the hd-PS algorithm for varying sample sizes is needed. Between weighting schemas, the SMbR-weighted approach would seem more appropriate over IPT as risk factors among patients receiving monotherapy may be very different from those patients on polypharmacy (e.g., nonresponse to first-line SSRI/SNRI, comorbidities).

Clinical Implications

There has been limited clinical research examining the effectiveness of VA/Department of Defense guideline-recommended first-line pharmacological treatment for PTSD among OIF/OEF/ONDveterans in observational studies. Many patients with psychiatric disorders also suffer from co-occurring conditions that may complicate their PTSD treatment. In fact, because of co-occurring conditions, possible nonresponse to treatment, or side effects, clinicians may explore various psychotropics or combinations of drugs for these patients.[7] The guidelines are based largely on randomized trials but acknowledge the paucity of knowledge regarding best practices for veterans with PTSD and co-occurring mental illnesses. Thus, this study's findings may be more generalizable to the broader patient population with PTSD receiving SSRI/SNRI therapy.

For polypharmacy associated with a higher risk of hospitalization, as found in the weighted hd-PS models, it is possible that the polypharmacy per se contributed to the likelihood of admission. Alternatively, the observed association may primarily signal that the more intractable the illness, the greater the likelihood of polypharmacy and equally, the greater the risk of hospital admission: polypharmacy becomes a proxy for severity of illness. Including measures of symptom severity in future research might tease out contributions attributable to treatment per se vs. treatment serving as a proxy for severity. Interestingly, depression was identified as an empirical covariate for receipt of polypharmacy in the hd-PS models. For depressed patients with PTSD, an antidepressant aimed at addressing both conditions should be prescribed. This would entail a first-line SSRI/SNRI or a second-line antidepressant. However, further exploration of these patients may reveal why this group of patients with PTSD and comorbid major depression are receiving multiple psychotropic medications when it is possible that one might treat both conditions.

Limitations

All methodological approaches have the disadvantage of limited information on patients' medication history, including any care received elsewhere outside of the VA.[25] It is also difficult to fully capture the complexity of the prescribing patterns as patients may switch from one antidepressant (or treatment group) to another. In administrative data, tapering off one medication onto another may be so gradual as to appear to be polypharmacy. We lack information on whether patients were new to pharmacotherapy for PTSD at the time the study began, although the proportion with polypharmacy did not vary by prior use of the VA (55% mono vs. 58% poly; results not shown). Although multicollinearity was checked for the traditional logistic regression model, methods are yet to be developed for hd-PS methods. In a model where PS are calculated, the PS will be correlated with the treatment variable, resulting in multicollinearity and some loss of power.

In addition, guidelines for treating PTSD recommend antidepressants and/or psychotherapy, and note that the most effective forms of psychotherapy are trauma-focused therapies such as prolonged exposure. This form of therapy, however, is difficult to undergo such that many veterans refuse it. Failure to use optimal psychotherapy may be a strong predictor of psychiatric hospitalization, yet our data sources do not distinguish among therapy types; in fact, this was a factor in our decision not to include psychotherapy among our predictors. Only the PS models included psychotherapy visits (undifferentiated with respect to type of therapy). Also, as the VA/Department of Defense clinical practice guideline for PTSD recommends the use of an SSRI/SNRI, we examined their effect collectively rather than by drug. If a patient does not respond to the initial dose of an SSRI/SNRI, a recommendation includes increasing dose or switching to another SSRI/SNRI. Although a limitation in this study, further exploration of the effect of both drug and dose on adverse outcomes such as hospitalization should be conducted in a larger sample of patients.

Patients with PTSD not prescribed a first-line antidepressant should be further studied to assess reasons for their nonuse of SSRI/SNRI. These patients may have chosen to opt out of all types of treatment including psychotherapy, or perhaps only out of pharmacological treatment. Alternatively, they may be taking second-line or other antidepressants. The decision not to be prescribed first-line antidepressants may have been made for multiple reasons (e.g., contraindications, opted out of all treatments, and first-line ineffective). Thus, this study's findings are limited to patients receiving first-line pharmacotherapy for PTSD only and are not generalizable to all patients with PTSD.

CONCLUSIONS

Different analytical approaches for the analysis of observational data may lead to varying results, influencing clinical decision-making. Investigating alternative methods and their respective biases for the estimation of causal relationships will help inform policy and treatment decisions. Much of the information available on pharmacological treatments for PTSD is derived from randomized control trials, whose samples may not be representative of the population of OIF/OEF/OND veterans, a key drawback to making clinical inferences from study populations. However, after performing an observational study utilizing multiple analytical approaches, there appears to be a trend toward first-line pharmacotherapy being associated with fewer hospitalized events compared to the use of antidepressants with additional psychotropics. Similar findings have recently been found in veterans and other patients with schizophrenia.[15] As OIF/OEF/OND veterans are fairly young and are expected to be utilizing services in the VA health care system for many years, it is vital to provide them with the best care possible. In pursuing this goal, providing appropriate treatment guided by substantial empirically based evidence may lead to a reduction in PTSD symptoms and serve as a preventative measure to reduce adverse events such as hospitalization. Health care providers and patients may consider this study's findings when making treatment decisions for PTSD or formulating revisions to treatment guidelines for complex patients with PTSD, considering how the presence of co-occurring psychiatric and physical conditions and associated drug treatments might alter or hinder treatment outcomes. This in turn can help to improve veterans' health, functioning, and quality of life.

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