Annals of Clinical Psychiatry, 18[1]:1–7, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230500464588

A Regional Comparison of Developing Diabetes among VA Patients Exposed to Typical and Atypical Antipsychotics Relative to Corticosteroids and Proton Pump Inhibitors

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Background. *Metabolic changes, including weight gain and onset of diabetes, have been associated with both systemic corticosteroid use and atypical antipsychotic drugs. The purpose of this study was to quantify and compare the risk of new-onset diabetes mellitus in a Veterans Affairs population receiving antipsychotics and corticosteroids, using persons taking proton pump inhibitors as a control group.*

Methods. *This study included data from subjects treated within Veterans Integrated Service Network 23 who had received an outpatient prescription in fiscal years (FY) 1999 or 2000 for a corticosteroid (CS), a proton pump inhibitor (PPI), a typical antipsychotic, or an atypical antipsychotic. Patients receiving prescriptions in more than one class were not excluded. Subjects were excluded if they had a documented diagnosis of diabetes either in the previous FY year (1998) or prior to their index prescription date.*

Results. *Thirteen percent of the population had a new diagnosis for diabetes during the two-year study. Cox-regression analysis using time dependent covariates determined a significantly higher risk of developing diabetes (RR = 1.21) in users of CS relative to PPIs. Demographic variables including age, race, gender, marital status, and VA financial classification as well as a marker for schizophrenia, were also included in the model. Comparison of both typical and atypical antipsychotics to PPIs found an increased but nonsignificant risk of developing diabetes (RR = 1.18 and RR = 1.19 respectively).*

Conclusions. *The diabetogenic risk associated with atypical antipsychotics was found to be less than that of corticosteroids when compared to controls. Periodic monitoring of blood glucose should be considered with chronic use of an agent from either class.*

Keywords Diabetes, Corticosteroid, Antipsychotic, Proton Pump Inhibitors

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INTRODUCTION

Atypical antipsychotics (AAP) agents are widely utilized in the treatment of schizophrenia as they have been shown to be

clinically effective while carrying a much lower risk of EPS than typical antipsychotic (TAP) agents (1). However, a growing body of evidence has implicated the role of treatment with certain AAP agents with an increased risk of DMII (23–67). Clinical trials and post-marketing surveillance of the use of AAP agents have elucidated substantial weight increases, particularly with clozapine and olanzapine (8). Weight gain secondary to AAP treatment is likely a mode by which metabolic changes, such as diabetes, hyperlipidemia and metabolic syndrome may occur. Continued study has focused on determining how treatment with AAP may impact pancreatic β-cell functioning, release of insulin, peripheral insulin sensitivity, as well as central hypothalamic regulation of glucose (9,10).

Atypical antipsychotics are not alone in their ability to precipitate diabetes. In fact, corticosteroids (CS), which are frequently used for maintenance or remission of a variety of respiratory, endocrinological, rheumatic, neoplastic, and autoimmune diseases, have long been associated with glucose dysregulation and development of DMII (11–14). Incidence rates of diabetes in patients on corticosteroid therapy have been reported to range from 1% to 46% (11). As with the antipsychotic agents, the exact pathophysiological mechanism by which corticosteroid therapy increases blood glucose levels is not certain. Similar to AAP, weight gain often accompanies extended corticosteroid therapy, and corticosteroids have been shown to promote gluconeogenesis and insulin resistance, and raise insulin levels (15–17).

Several studies have looked at the development of diabetes in patients exposed to AAPs relative to typical antipsychotics (TAPs); however clinical interpretation of these studies is often difficult. DMII has been shown to be more prevalent in patients with schizophrenia than the general population (18). Also, AP use is often coupled with weight gain, which makes it hard to separate possible metabolic liabilities of AP agents due to direct effects on cellular functioning. Further, only one study to date has examined the rate of diabetes associated with AAPs relative to CS and a control group; however this study was limited to an elderly Canadian population in a long-term care setting (19). The purpose of this study was to quantify and compare the risk of new-onset diabetes mellitus in a Veterans Affairs (VA) population receiving antipsychotics and corticosteroids, using persons taking proton pump inhibitors (PPIs) as a control group.

METHODS

Data Sources

The study utilized computerized patient information from three VA databases: the Pharmacy Benefits Management (PBM) database, maintained by the VA information Resource Center at the Hines VA Medical Center in Oak Brook, IL, and the Patient Treatment File (PTF) and the Outpatient Care File (OPC) databases maintained by the VA Automation Center in Austin, TX. The PBM contains patient-level information on all outpatient prescriptions filled in an outpatient VA pharmacy (20). The PTF and OPC are a set of linked databases that provide patient-level information on all outpatient and inpatient encounters from VA facilities and have been used extensively in health services research (21,22).

Data Elements

Data elements that were extracted from the PTF and OPC included: age, gender, race, marital status, social security number (to link PTF/OPC and PBM data); primary service facility; VA financial class; dates of admission and discharge for inpatient hospitalizations; dates of all outpatient visits; and all primary and secondary diagnoses captured on inpatient and outpatient encounters, as based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) taxonomy. VA financial class was categorized into three mutually exclusive groups: patients with chronic medical conditions attributable to military service (i.e., service-connected conditions) or patients who were financially indigent (based on VA income thresholds), and patients who were neither service-connected condition nor indigent. Data elements specifically captured from the PBM included the names, classes, and dates of all medications dispensed on an outpatient basis, from October 1, 1998 through September 30, 2000. VA medication names and classification are based upon nomenclature developed by the United States Pharmacopoeia.

Patients

The study population was drawn from a pool of 57,628 patients who received an outpatient prescription in fiscal years (FY) 1999 or 2000 from the VAMC. Of these patients, 17,887 received at least one prescription for either a CS, a PPI, a TAP, or an AAP; patients receiving prescriptions in more than one class were not excluded. PPIs were chosen as a control group because of their widespread use and the lack of an association with onset of diabetes.

The date of the first prescription for one of these four classes was assigned as the patient's index date. Next, we excluded 4,758 patients who were in a class, but did not receive at least a 30-day supply. Finally, we excluded 3,424 patients who had a primary or secondary (inpatient or outpatient) ICD-9-CM diagnosis code (250.xx) associated with diabetes either in the previous FY year (1998), or prior to their index date. These exclusions left a final analytical cohort of 9,705 patients.

Analytic Strategy

Patients were defined as developing diabetes if they had an inpatient or outpatient encounter with a primary or secondary

diabetes ICD-9-CM code (250.xx) after their index date. Diabetes was coded to a particular medication class (CS, PPI, TAP, AAP) if it occurred while the patient was on the medication, or within 60 days of discontinuation of a medication class. Comparisons between diabetic and non-diabetic patients were made using Chi-square tests for categorical variables and T-tests for continuous variables.

To examine the effect of medication class on the development of diabetes, we utilized a Cox-regression model using time dependent covariates. This approach is similar to the one developed by Fuller and colleagues to address the deficiencies of previous atypical antipsychotic and diabetes studies (3,23). Specifically, we sought to control for switching between classes of medication as well as the possibility of concomitant therapy within the four classes. This method allowed preservation of the patient's drug history while giving more weight to medication classes occurring closer in time to the development of diabetes. Because of this approach however, the interpretation of differences between medication groups becomes difficult. That is the classification by index group is counter intuitive because the importance of the index group decreases over time, while the reporting of all patients who were in a group results in non-independent observations.

Because of the importance of age in the development of diabetes, age was expressed as a continuous variable as well as one of thirteen indicator variables, which allowed for a better fitting model. Race and gender were expressed using an indicator variable, as was marital status, and VA financial category. As schizophrenia has been implicated as an independent risk factor for diabetes (25), an indicator variable for schizophrenia was included in the model if the patient had a diagnosis (ICD-9-CM codes of 295.00–295.90) during the study period. Coefficients associated with medication classes were used to determine relative risks. In Cox regression analyses, patients not developing diabetes were censored. The proportional hazards model met the assumption that the hazard was similar over time and the assumption that diabetes and censoring were independent events (26). Finally, to determine whether the results were consistent for each of the individual agents within the AAP class, follow up analyses were performed separating the four AAP (clozapine, olanzapine, quetiapine, and risperidone) agents and running a final Cox regression model. All analyses were conducted using SAS for Windows, Version 8.1 (SAS Institute; Cary, NC).

RESULTS

The mean age of the 9,975 study patients was 63 years. Ninty-six percent of patients were male and a similar proportion were white (Table 1). Slightly under two-thirds of the patients were married, while nearly one-third of the patients had a service-connected medical condition and nearly one-half were indigent. We found that 13% (N = 1,283) of our study population had a new diagnosis for diabetes during our two-year study. The percentage of patients in our sample having a least a 30 day exposure to corticosteroids was 18% (N = 1,839), PPIs 73% (N = 7,292), while exposure to typical and atypical antipsychotic was 8% (N = 883) and 12% (N = 1,201), respectively.

Table 1 Baseline Characteristics of Regional VAMC Patients Receiving Corticosteroids, Proton Pump Inhibitors, Typical Antipsychotics or Atypical Antipsychotics (n = 9,975)

Mean Age ± SD (years)	62.7 ± 13.5
Male, number, (%)	9,536 (95.6%)
White, number, (%)	9,625 (96.5%)
Married, number, (%)	6,121 (61.4%)
Schizophrenia diagnosis	996 (9.9%)
VA Classification	
Indigent, number, (%)	4,780 (47.9%)
Service Connected, number, (%)	3,026 (30.3%)
Other, number, (%)	2,169 (21.7%)
Diabetes encounter, number, (%) (At least one during follow up period)	1,283 (12.9%)
Medication Classes (numbers add up to more than 9,975 because patients may have received more than one class during the follow up period)	
Corticosteroids, number, (%)	1,839 (18.4%)
Proton Pump Inhibitors, number, (%)	7,292 (73.1%)
Typical Antipsychotics, number, (%)	833 (8.2%)
Atypical Antipsychotics, number, (%)	1,201 (12.0%)

Patient characteristics for patients who were in each of the four medication classes are shown in Table 2, although it should be stressed that these groups are not independent, because a single patient may be in one, two, three, or all four groups depending on their medication history over the two year time period. Patients receiving antipsychotics, both typical and atypical, were noticeably younger than patients in the corticosteroid and PPI groups. Patients receiving antipsychotics were also less likely to be married and were more likely to have a service-connected condition. As expected, a diagnosis of schizophrenia was much higher in the antipsychotic groups. Incidence of diabetes was relatively consistent across the groups. Classification of patients into mutually exclusive categories by index medication group resulted in similar findings (results not shown).

As mentioned previously, 1,283 (12.9%) patients developed a diagnosis for diabetes, as defined as having a new encounter for diabetes care, after their index prescription date. Differences in patient characteristics for those with and without new diabetes encounters are shown in Table 3. The mean time until diagnosis was 415 days and the median time was 384 days. In the multivariate Cox regression model using time dependent covariates and controlling for the previously mentioned factors, only corticosteroids relative to PPIs were associated with a significantly higher risk of developing diabetes (RR = 1.21; 95% CI, 1.09 – 1.33; P = .03), (Table 4). We also found a higher, although non-significant, increased risk of developing diabetes for both typical and atypical antipsychotics relative to PPIs (RR = 1.18; 95% CI, 0.80 – 1.62; P = .52 RR = 1.19; 95% CI, 0.90 – 1.49; P = .66,

Table 2 Differences in Characteristics Between Patients Receiving: Corticosteroids, Proton Pump Inhibitors, Typical Antipsychotics, or Atypical Antipsychotics

	Corticosteroids (n = 1,839)	Proton Pump Inhibitors (n = 7,292)	Typical Antipsychotics (n = 833)	Atypical Antipsychotics (n = 1,201)
Mean Age ± SD (years)	66.3 ± 12.5	63.8 ± 13.0	54.2 ± 12.8	51.4 ± 13.0
Male, number, (%)	1,764 (95.9%)	7,000 (96.0%)	775 (93.0%)	1,115 (92.8%)
White, number, (%)	1,780 (96.8%)	7,089 (97.2%)	770 (92.4%)	1,096 (91.3%)
Married, number, (%)	1,251 (68.0%)	4,821 (66.1%)	225 (27.0%)	379 (31.6%)
Schizophrenia diagnosis	26 (1.4%)	172 (2.4%)	549 (65.9%)	665 (55.4%)
VA Classification				
Indigent, number, (%)	885 (48.1%)	3,518 (48.2%)	380 (45.6%)	582 (48.5%)
Service Connected, number, (%)	488 (26.5%)	2,097 (28.8%)	381 (45.7%)	528 (44.0%)
Other, number, (%)	466 (25.3%)	1,677 (23.0%)	72 (8.6%)	91 (7.6%)
Diabetes encounter, number, % (At least one during follow up period)	279 (15.2%)	933 (12.8%)	124 (14.2%)	160 (13.3%)

Table 3 Differences in Characteristics between Patients Not Developing Diabetes and Those Developing Diabetes

	No Diabetes Encounter (n = 8,692)	At Least One Diabetes Encounter (n = 1,283)	P Value
Mean Age ± SD (years)	62.4 ± 13.7	64.3 ± 12.6	<.001
Male, number, (%)	8,310 (95.6%)	1,226 (95.6%)	=.93
White, number, (%)	8,392 (96.5%)	1,233 (96.1%)	=.67
Married, number, (%)	5,324 (61.3%)	797 (62.1%)	=.71
Schizophrenia diagnosis	846 (9.7%)	150 (11.7%)	=.02
VA Classification			<.001
Indigent, number, (%)	4,173 (48.0%)	607 (47.3%)	
Service Connected, number, (%)	2,525 (29.1%)	501 (39.1%)	
Other, number, (%)	1,994 (22.9%)	175 (13.6%)	

Table 4 Relative Risk of Developing Diabetes in Users According to Exposure of Medication Groups Using a Time Dependent Covariant and Adjusting for Age, Schizophrenia, Gender, Race, Marital Status and VA Service Connection

	Relative Risk	95% CI	P Value
Corticosteroids vs. PPIs	1.21	1.09 – 1.33	=.03
Antipsychotics vs. PPIs	1.18	0.87 – 1.52	=.52
Typical Antipsychotics vs. PPIs	1.18	0.80 – 1.62	=.43
Atypical Antipsychotics vs. PPIs	1.19	0.90 – 1.49	=.66
Typical Antipsychotics vs. Corticosteroids	0.90	0.62 – 1.20	=.88
Atypical Antipsychotics vs. Corticosteroids	0.94	0.61 – 1.27	=.91
Atypical Antipsychotics vs. Typical Antipsychotics	1.03	0.77 –1.28	=.89

respectively). However, we found a decreased risk of diabetes when comparing typical and atypical antipsychotics to corticosteroids, (RR = 0.90; 95% CI, 0.62 – 1.20; P = .88, RR = 0.94; 95% CI, 0.61 – 1.27; P = .91, respectively). Further, we found almost no increase in risk when examining atypical antipsychotics relative to typical antipsychotics relative to typical antipsychotics (RR = 1.03; 95% CI, 0.77 – 1.28; P = .89)

Table 5 Relative Risk of Developing Diabetes in Atypical Antipsychotic Users According to Individual Agents Using a Time Dependent Covariant and Adjusting for Age, Schizophrenia, Gender, Race, Marital Status and VA Service Connection

	Relative Risk	95% CI	P Value
Atypical Antipsychotics vs. PPIs			
Olanzapine vs. PPIs	1.17	0.93 – 1.41	=.33
Risperidone vs. PPIs	1.10	0.81 – 1.38	=.51
Clozapine vs. PPIs	1.63	0.49 – 2.77	=.34
Quetiapine vs. PPIs	1.04	0.11 – 1.97	=.94
Atypical Antipsychotics vs. Corticosteroids			
Olanzapine vs. Corticosteroids	0.96	0.54 – 1.35	=.69
Risperidone vs. Corticosteroids	0.90	0.56 – 1.22	=.42
Clozapine vs. Corticosteroids	1.32	0.13 – 2.51	=.67
Quetiapine vs. Corticosteroids	0.86	0.21 – 1.55	=.72
Atypical Antipsychotics vs. Typical Antipsychotics			
Olanzapine vs. Typical Antipsychotics	1.03	0.75 – 1.31	=.95
Risperidone vs. Typical Antipsychotics	0.96	0.47 – 1.45	=.81
Clozapine vs. Typical Antipsychotics	1.42	0.04 – 2.82	=.50
Quetiapine vs. Typical Antipsychotics	0.92	0.12 – 1.73	=.85

As mentioned earlier, we sought to disentangle the association of diabetes among the specific atypical agents. However, because of the relatively few number of clozapine (N = 44) and quetiapine (N = 107) encounters relative to olanzapine (N = 681) and risperidone (N = 910), only results for the later two agents are discussed. Specifically, we found a higher, but non-significant, increase in risk for diabetes among both olanzapine and risperidone agents relative to PPIs (RR = 1.17; 95% CI, 0.93 – 1.41; P = .33, RR = 1.10; 95% CI, 0.81 – 1.38; P = .51, respectively) (Table 5). We also found a slight decrease in risk for both agents relative to corticosteroids (RR = 0.96; 95% CI, 0.54 – 1.35; P = .69, RR = 0.90; 95% CI, 0.56 – 1.22; P = .42, olanzapine and risperidone, respectively). Finally, we observed almost no difference between the individual atypicals relative to typical agents (RR = 1.03; 95% CI, 0.75 – 1.31; P = .95, RR = 0.96; 95% CI, 0.47 – 1.45; P = .81, olanzapine and risperidone, respectively).

DISCUSSION

The current study represents the first direct comparisons of typical and atypical antipsychotic medications relative to a widely used class of medications known to be associated with diabetes, corticosteroids, as well as a widely used class of medications with no known relationship to diabetes, proton pump inhibitors. We found patients receiving antipsychotics to be younger, less likely to be married, more likely to have a diagnosis of schizophrenia, and more likely to have a service-connected classification compared to patients receiving corticosteroids and PPIs. Patients were relatively similar in other measures, that is, gender, race, and incidence of diabetes. Among patients acquiring a diagnosis of diabetes, we found these to be slightly older and more likely to have a service-connected condition and more likely to have a diagnosis of schizophrenia relative to non-diabetes, but similar in regards to other measures. Using a multivariate Cox-regression to analyze VAMC claims over a two-year period for an entire region, we found that VA patients with exposure to typical antipsychotics as a whole, had higher, although nonsignificant ($P < .05$), increased risk of developing diabetes relative to PPIs; but a lower, nonsignificant risk, relative to corticosteroids. When analyzing the two major atypical antipsychotics (olanzapine and risperidone) separately, we found consistently higher risks for olanzapine compared to risperidone, relative to PPIs, corticosteroids, and typical antipsychotics, although again, all results were nonsignificant.

Several studies have directly examined the correlation between diabetes and antipsychotic use; however the study designs have differed considerably with regards to exclusion and inclusion criteria, basis of comparison, length of follow-up. Using a nationwide VA sample, Sernyak and colleagues compared patients with a diagnosis of schizophrenia who had received either AAPs or TAPs (7). Using TAPs as the comparison group, the authors found that patients whose last prescription was written for an atypical antipsychotic were 9% more likely to have diabetes than those who received typical antipsychotics. Also, the prevalence of diabetes was increased for those persons receiving clozapine, olanzapine, and quetiapine, but not risperidone. However, this analysis was limited by the fact that pre-existing diabetes was not excluded when determining the prevalence of diabetes.

A second study used a nested case control design to assess the risk of diabetes among schizophrenic patients taking olanzapine and risperidone (6). Patients on conventional antipsychotic therapies, as well as patients that were non-users of antipsychotics served as comparators. Subjects with a previous diagnosis of diabetes were excluded and the mean follow-up period was 5.2 years. Compared with conventional antipsychotic use, olanzapine was associated with a significantly increased risk of diabetes (OR = 4.2, p = 0.008), while risperidone was not (OR = 1.2, p = 0.290). Compared to those with no antipsychotic use, significant increased risk of diabetes was found with both olanzapine (OR = 5.8, p = 0.001) and conventional agents (OR = 1.4, p = 0.004).

Similarly, increased rates of diabetes with olanzapine and clozapine use have been reported in other studies (2,3,4,24). Caro and colleagues compared relative risk of diabetes among patients with one prescription for either risperidone or olanzapine (2). Follow-up continued for a period up to three years, and persons with a previous diabetes diagnosis were excluded. The authors reported a 20% increased risk of diabetes with olanzapine relative to risperidone (P = 0.05) after adjustments were made for potential confounders.

Increased odds of diabetes were also found when considering an exposure period of 12 months in patients with psychosis treated with olanzapine, clozapine, and high and low potency typical agents, when compared to untreated patients (24). No significant increase in risk was found with risperidone use. However, in a separate analysis, using a more stringent criteria for evidence of diabetes, only olanzapine remained as having a significant increase in odds for diabetes (OR = 1.42, 95% CI = 1.05 – 2.0).

A recent study examining only atypical antipsychotics found that among a large group of VA patients on stable monotherapy, that clozapine and olanzapine patients had a greater risk of developing diabetes relative to quetiapine and risperidone. However the authors estimated that the overall risk of diabetes with the atypicals was minimal, ranging from 0.05% for risperidone to 2.3% for clozapine (27).

Similar to our study design, Fuller and colleagues utilized Veterans Affairs databases to assess risk of developing diabetes in patients taking APs, particularly olanzapine, risperidone, haloperidol, and fluphenazine (3). Additionally, they incorporated antipsychotic therapy as a time dependent covariate to account for switching to or concomitant treatment. A diagnosis of diabetes was noted by either the presence of ICD-9 codes or claims for hypoglycemic therapy. Persons with a previous diagnosis of diabetes were excluded. One important difference in their analysis was the use of the risperidone cohort as the basis for comparison, while our methods involved comparisons to CS's and PPI's. The overall rate of developing diabetes was 6.3%, which is significantly lower than we report here (12.9%). Fuller and colleagues also reported a 37% increased risk of developing diabetes compared to risperidone (p = 0.016), while no differences were found when comparing either fluphenazine or haloperidol to risperidone.

The increased risk of diabetes associated with AAPs that we report is slightly higher than what was reported in a similar study Caro and colleagues, and may reflect differences in study design and ability to measure and adjust for potential confounders (2). In addition, our study may more closely reflect real world conditions in which patients are exposed to a wide range of medications over time, and may more closely estimate the true risk of exposure.

In interpreting our findings, it is important to consider several potential limitations. First, the study involved a single regional VA network. The generalizability to VA hospitals serving other markets is uncertain, as is the generalizability to the larger population of all patients receiving these classes of medications.

Second, as we did not attempt to adjust for comorbidity in the study population. Our results may be confounded by unmeasured comorbidity, as previous studies have shown that VA patients have more comorbid conditions than the general population (28,29).

Third, while diagnosis-based methods have been found to explain a large proportion of resource utilization, such methods are dependent on the accuracy of capturing diagnosis codes from patient encoutners and may be subject to systematic variations between practitioners and facilities (30,31). We also had no clinical data to monitor serum glucose levels, weight gain or other potential markers for diabetes. A measure such as weight or BMI would have allowed us to adjust or stratify based on these potential risk factors.

Fourth, pharmacy data has its own set of potential limitations. Specifically, automated pharmacy databases require significant human effort to maintain congruence with medications that patients are actually taking. Patients may have obtained medications from providers and pharmacies outside the VA. Indeed, a recent analysis of the agreement between VA computerized medication lists obtained from a detailed history by a clinical pharmacist found complete agreement for less than 5% of patients (32).

Also, another important limitation of our analysis is the potential for dual utilization of care in the private sector by Veterans who use VA services (33,34). Thus, our estimates of diabetes are likely underestimates and may introduce systematic bias, as private sector utilization is likely to vary according to specific factors, including the availability of private health insurance. Finally, our study sample size may have limited our ability to detect statistically significant differences in our Cox regression analyses that may have been of clinical significance.

Nonetheless, if generalizable, our findings suggest that previous studies may have over estimated the true risk of diabetes associated with antipsychotics, particularly with regards to the atypical agents olanzapine and risperidone. While some clinicians have suggested more stringent guidelines and monitoring with atypical antipsychotics, we are not aware of any such calls for similar measures associated with corticosteroids, a class of medications which are clearly linked to the development of diabetes. Moreover, in the absence of long-term follow-up data, our results highlight the potential bias that can be introduced by an artificial assignment to medication classes, and the need to use analytical methods that consider the duration of patient observation and control for the time of exposure.

ACKNOWLEDGMENTS

Dr. Barnett is a researcher in the Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP) at the Iowa City VA Medical Center, which is funded through the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

We would like to recongnize the contributions of the Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP) staff at the Iowa City VAMC, especially those of Jon Yankey for statistical assistance.

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