

# Impact of a Program Encouraging the Use of Generic Antipsychotics

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Second-generation antipsychotics (SGAs) have become the most prescribed psychopharmacologic treatment for schizophrenia.<sup>1</sup> However, a growing body of evidence from several large, government-funded trials, such as VA Cooperative Study 451, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), and the Cost Utility of The Latest Antipsychotics in Severe Schizophrenia (CUTLASS), have failed to find an advantage for SGAs, other than clozapine, over first-generation antipsychotics (FGAs) on measures of effectiveness, side effects, or cost-effectiveness.<sup>2-5</sup> SGAs had been thought to represent an advantage due to their decreased risk of neurologic side effects<sup>6,7</sup> but these advantages have not been confirmed in recent comparative large-scale trials which more closely approximate real-world practice.<sup>8,9</sup> In addition, several SGAs are now known to be associated with significant weight gain, impairment of glucose metabolism, and lipid abnormalities.<sup>10,11</sup>

SGA use has also increased beyond US Food and Drug Administration (FDA)-approved applications, which include, among others, schizophrenia, acute and maintenance treatment of bipolar disorder, and as an adjunct to other depression treatments. Common off-label uses include the treatment of posttraumatic stress disorder (PTSD), anxiety disorders, and insomnia.<sup>12-14</sup> In 2010, SGAs accounted for over \$18 billion in sales<sup>15</sup> with 75% of US expenditures paid through Medicaid.<sup>16</sup> These high costs stem from the fact that most SGAs are still “on patent” and cost up to \$10 a day in the United States, 10 to 100 times the cost of FGAs and off-patent SGAs.<sup>17</sup> Much of the overwhelming prescriber preference for SGAs is thought to be linked to early impressions of efficacy created through industry-sponsored trials and marketing.<sup>18-20</sup>

The expense associated with SGAs has led payers to consider diverse strategies for modifying their practice, ranging from more limited measures such as formulary restrictions and prior authorization to less limited measures such as educational outreach.<sup>21</sup> Educational strategies, termed academic detailing, link information dissemination activities with 1-on-1 practice reviews and provide alternative information regarding evidence-based prescribing practices to that presented by pharmaceutical manufacturers.<sup>22</sup> These interventions, which are sometimes combined with

other management strategies,<sup>23</sup> provide more balanced evidence-based information to physicians, pharmacists, and patients in order to promote more cost-effective

**Objective:** Recent research suggests that second-generation antipsychotics (SGAs) may be used more often than clinically warranted. An intervention consisting of academic detailing and a prescriber survey was employed to encourage the reduction of newly prescribed on-patent SGAs.

**Design:** Quasi-experimental quality improvement trial.

**Methods:** Academic detailing consisted of educational lectures and a pocket guide on the latest effectiveness, safety, and cost data for SGAs and first-generation antipsychotics. Detailing was coupled with a required 20-item survey of provider decision making completed prior to prescriptions for on-patent SGAs at a Veterans Health Administration medical center between October 2007 and May 2009. The survey identified the medication, treated diagnosis, comorbid psychiatric and medical diagnoses, reasons for the medication, prior medications, and provider professional status. The outcome was the number of new SGA prescriptions per month.

**Results:** The sample included 2176 surveys. The Spearman correlation between the number of prescriptions and the intervention month (range = 1-18) was 0.25 ( $P = .31$ ), indicating no reduction. The most common medication prescribed was quetiapine (55.8%). The distributions of diagnoses were fairly even among schizophrenia, bipolar disorder, other affective disorders, and posttraumatic stress disorder (17.0, 28.2, 25.8, and 20.4%, respectively). The 3 most common reasons for prescribing an SGA were to improve efficacy (49.8%), reduce side effects (29.1%), and increase sleep or sedation (34.5%).

**Conclusions:** Academic detailing coupled with a provider survey did not decrease the rate of new prescriptions for on-patent SGAs. Reasons for prescribing SGAs were not consistent with recent research findings regarding efficacy and side effects.

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### Take-Away Points

Second-generation antipsychotics (SGAs) may be used more often than clinically necessary. A nonrestrictive intervention of academic detailing coupled with a provider survey did not decrease the rate of new prescriptions for SGAs. Investigation of provider decision making found:

- A high rate of off-label SGA use in posttraumatic stress disorder where there is little evidence of efficacy, as well as for sleep problems where there are many less costly and better tolerated options.
- SGAs were commonly prescribed in patients with comorbid metabolic and cardiac disease where their use may exacerbate these conditions.

prescribing. Several meta-analyses of academic detailing have shown moderate effects.<sup>24</sup>

This study presents data on the impact of an intervention combining both academic detailing and completion of a required prescriber survey on SGA prescribing at a single Veterans Health Administration (VHA) hospital. The administrative assumptions were that academic detailing in combination with a survey prior to completing the prescription would stimulate a more thorough reflection on prescribing decisions and would create a mild disincentive for prescribing SGAs. In addition, survey results would provide insight into the reasoning behind provider decisions regarding SGA prescriptions.

## METHODS

### Intervention

The study began as a quality improvement project which evolved into a quasi-experimental study to test the effect of a novel intervention on the rate of SGA prescriptions over a 20-month period, from October 2007 until May 2009. The intervention consisted of 2 components: an academic detailing effort and an electronic survey completed at the time of every new prescription for an on-patent SGA.

Academic detailing consisted of 4 formal detailing sessions with the entire mental health service delivery section of the medical center, psychiatry residents, nurse practitioners, and the division of the outpatient clinic responsible for treating patients with schizophrenia, respectively. Each session included a 45-minute didactic presentation followed by a discussion. The sessions highlighted background on the high level of expenditures on SGAs nationally and in the VHA, as well as a number of specific trials including the VHA Cooperative study, CUtLASS, CATIE, and others.<sup>2-5</sup> The public policy issues regarding the cost-effectiveness of SGAs were also discussed.<sup>25</sup> Finally, various strategies for cost containment were reviewed in addition to the objectives, hypotheses, and procedures of the current cost-containment study. Sessions were given by professors of psychiatry from the Yale University School of Medicine who had joint appointments at the VHA.

The required survey was completed at the time any on-patent SGA on formulary (olanzapine, long-acting injectable [LAI] risperidone, aripiprazole, ziprasidone, or quetiapine) was ordered as a new, nonrefill prescription for an outpatient who had not previously been receiving the SGA prescribed. This study was approved by the institutional review boards of the Yale University School of Medicine and the VA Connecticut Healthcare System.

### Setting and Participants

The intervention was implemented throughout the VA Connecticut Healthcare System, which provides out-patient and inpatient treatment to approximately 10,000 veterans with mental illness annually,<sup>26</sup> and targeted at prescribers of SGAs who are limited at this institution as a utilization management strategy to psychiatry residents, fellows, attendings, advance practice registered nurses, and physician assistants. Primary care providers and other specialists did not have privileges for SGA prescribing but could place prescriptions for SGAs after pharmacy review.

### Survey

The survey was electronically delivered as part of the medication ordering system at the time of any new on-patent SGA prescription (risperidone was the only generic SGA at the time of the intervention). Survey completion was required before an SGA prescription could be electronically sent to the pharmacy. Thus, the survey completion rate was presumed to be 100%.

The survey consisted of 20 questions which documented the proposed medication, the primary psychiatric diagnosis under treatment, important comorbid psychiatric and medical diagnoses, the clinician's reasons for using the selected medication, prior medications attempted, and the professional background of the provider. A list of forced choice selections and write-in answers was given for each question.

### Analysis

*Exclusion Criteria.* Surveys in which information on the SGA prescribed was missing were excluded. Some surveys documented oral risperidone use even though it was off patent at the time and these were excluded.

*Outcome.* The outcome for this study was the number of new SGA prescriptions measured monthly as the number of surveys completed between November 1, 2007, and April 30, 2009. Results from the first and last month of the survey peri-

od were truncated, as the project started and finished mid month.

*Statistical Analysis.* Time trends in the prescription of atypical antipsychotics were evaluated by calculating the Spearman correlation between the study month (range 1-18) and total number of prescriptions per month. Analysis of differences in the number of SGA prescriptions over time for selected subgroups derived from survey questions was calculated using  $\chi^2$ . Data management and statistics were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

## RESULTS

### Sample Characteristics

The original data set contained 2648 observations of which 30 were excluded for missing data on the medication prescribed, while 442 were excluded for documenting oral risperidone prescriptions. The final sample consisted of 2176 surveys.

The average age of individuals receiving an SGA prescription was 54.5 years (standard deviation [SD] = 14.9) while the mean body mass index (BMI) was 29.2. (SD = 6.0) (Table 1). The most common medication prescribed was quetiapine (55.8% of prescriptions) while olanzapine and aripiprazole were less common (18.8% and 17.9%, respectively) and ziprasidone and LAI risperidone were least common (5.9% and 1.6%, respectively). Of the new prescriptions, 54.8% represented a new prescription of an SGA in the absence of prior antipsychotic therapy, 25.0% represented a change in antipsychotic to an SGA, and for 20.2% the prescription represented an addition to an FGA.

The distribution of diagnoses for which a prescription was made was fairly even among schizophrenia, bipolar disorder, other affective disorders, and PTSD (17.0%, 28.2%, 25.8%, and 20.4%, respectively). The most com-

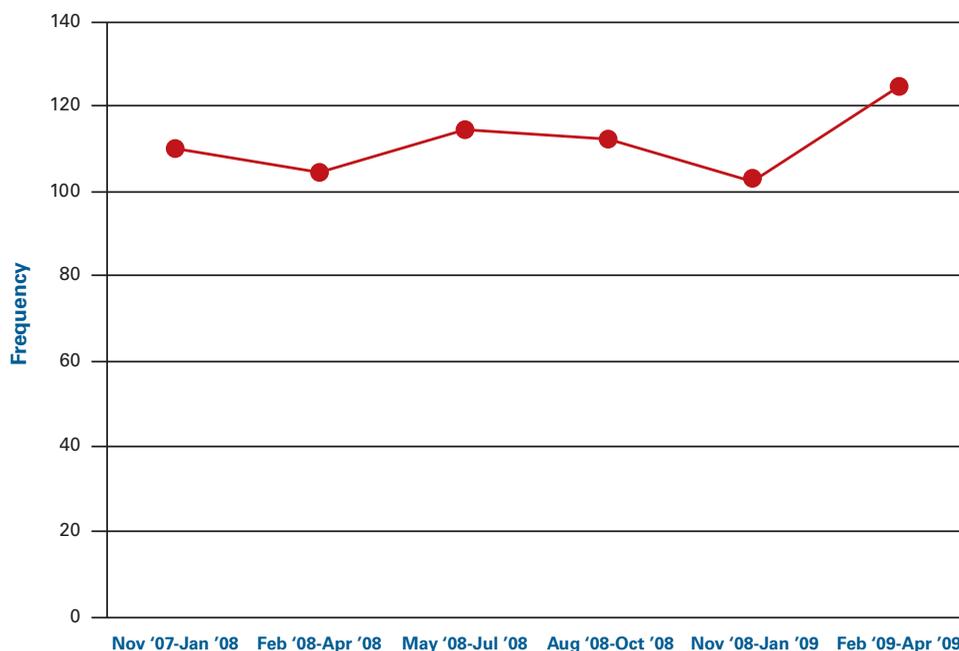
**Table 1.** Profile of Univariate Results for a Provider Survey Completed at the Time of Atypical Antipsychotic Prescription, N = 2178

Variable	N	(%)	Mean	SD
<b>Patient demographics and general health characteristics</b>				
Age			54.5	(14.9)
Race/ethnicity				
White	1650	(81.5)		
Black	360	(17.8)		
Hispanic	10	(0.5)		
Other	5	(0.3)		
BMI			29.2	(6.0)
AIMS score			0.7	(4.2)
GAF			44.7	(13.4)
<b>Medication prescribed</b>				
Aripiprazole	390	(17.9)		
Olanzapine	409	(18.8)		
Quetiapine	1216	(55.8)		
Ziprasidone	129	(5.9)		
LAI risperidone	34	(1.6)		
<b>Type of prescription</b>				
Change in prescription	534	(25.0)		
Additional prescription	430	(20.2)		
New initiation of a prescription	1170	(54.8)		
<b>Diagnosis treated<sup>a</sup></b>				
Schizophrenia	589	(27.0)		
Bipolar disorder	614	(28.2)		
Other affective disorder	561	(25.8)		
PTSD	444	(20.4)		
Other	240	(11.0)		
<b>Current comorbid disorder<sup>a</sup></b>				
Any movement disorder	241	(9.4)		
Tardive dyskinesia	102	(4.9)		
Extrapyramidal symptoms	108	(5.5)		
Akathisia	69	(3.4)		
Any metabolic/cardiac disease	1502	(58.5)		
Diabetes	316	(15.8)		
Hyperlipidemia	631	(34.5)		
Obesity (BMI >30)	480	(24.4)		
Hypertension	757	(38.5)		
Coronary artery disease	246	(15.1)		
<b>Reason for the new prescription<sup>a</sup></b>				
Side effect	633	(29.1)		
Intolerance to current drug	243	(13.2)		
Less extrapyramidal symptoms	296	(16.1)		
Less tardive dyskinesia risk	209	(11.4)		
Less akathisia	115	(6.3)		
Less sedation	128	(7.0)		
Efficacy	1297	(59.6)		
Efficacy	915	(49.8)		
Increased sleep/sedation	634	(34.5)		
Treatment of tardive dyskinesia	13	(0.7)		
Patient preference	608	(27.9)		
<b>Type of provider</b>				
Psychiatry APRN or PA	609	(28.0)		
Psychiatry resident or fellow	615	(28.3)		
Psychiatry attending	657	(30.2)		
Other specialty provider	295	(13.6)		

APRN indicates advanced practice registered nurse; AIMS, abnormal involuntary movement scale; BMI, body mass index; GAF, global assessment of functioning; LAI, long-acting injectable; PA, physician assistant; PTSD, posttraumatic stress disorder; SD, standard deviation.

<sup>a</sup>Providers could select more than 1 category.

■ **Figure.** The Mean 3-Month Frequency of New On-Patent SGA Prescriptions per Month Over the Study Period



mon reasons given for prescribing a particular SGA were improved efficacy (48.9%), improved sleep or sedation (34.5%), minimizing side effects as a group (29.1%), and patient preference (27.9%). Prescriptions were made relatively evenly among psychiatric provider types with 28.0% coming from advance practice nurses or physician assistants, 28.3% from psychiatric residents or fellows, and 30.2% from attending psychiatrists.

### Intervention Outcome

The number of new prescriptions did not decline or change significantly over the course of the study. The number of prescriptions averaged over 3 month periods are presented in the **Figure**. On average, there were 110 new prescriptions over the first 3 months of the study while there was an average of 124 over the last 3 months (a 12.7% increase). The Spearman correlation coefficient between the number of new prescriptions per month and the month of study was 0.254 ( $P = .31$ ), failing to indicate any decline or other significant relationship between the number of new prescriptions and month of study.

### Subgroup Analysis of Prescriptions Over Time

**Table 2** describes the results of a subgroup analysis of the change in the number of new SGA prescriptions over the course of the study among selected subgroups. Using a Bonferroni correction for 34 independent variables ( $P$  value for statistical significance of  $<.0014$ ), only hyperlipidemia displayed

a significant difference by month and graphical inspection did not show a consistent linear trend over time.

## DISCUSSION

The prescription of antipsychotics is a complex clinical decision potentially influenced by the clinical presentation of each patient, provider beliefs and experiences of relative effectiveness, tolerability, cost, expressed patient preferences, and provider exposure to marketing. Administrators and payers must balance a desire to contain costs, maximize effectiveness, and minimize risks while respecting patient preferences and supporting provider autonomy in the selection of treatments. We report on an intervention intended to encourage a decrease in the number of new starts of high-risk and expensive on-patent SGAs at a VHA medical center while respecting patient choice and maintaining provider autonomy. Together with an academic detailing effort, a provider decision-making survey at the time of prescription was employed to “nudge”<sup>27</sup> providers into decreasing the number of new on-patent SGA prescriptions. Instead of a decrease, we found a 12.7% increase in such prescriptions and no statistically significant association between the month of the study and the frequency of new on-patent SGA prescriptions. Available data show a 2.4% to 3.2% increase in mental health patients treated by the facility during the study period, which is not large enough to explain these findings.<sup>26,28</sup>

## Increasing the Use of Generic Antipsychotics

Of cost containment strategies available to payers and administrators, academic detailing is among the least restrictive, seeking to engage the provider in voluntary behavior change. There have been several systematic reviews of such interventions which show them to be effective and consistent in creating changes in physician practices compared with no intervention, audits with feedback, and continuing medical education.<sup>24,29</sup> In addition, there is some evidence that educational packages combined with other interventions have a greater impact than academic detailing alone.<sup>24</sup> One recent study by Benjamin et al (2011) found an 8.2% increase in the use of generic antipsychotics after an academic detailing campaign coupled with the provision of generic samples.<sup>30</sup>

The current study did not find similar results, but it differs substantially from Benjamin et al (2011) and other academic detailing initiatives in several respects.<sup>31-33</sup> First, our intervention relied heavily on the completion of a provider survey prior to each SGA prescription as a disincentive to prescribing. To our knowledge, this is the first study which has empirically examined this type of intervention. Because it is much less limiting than formulary restriction or prior authorization, the intervention may not have been a powerful or intrusive enough disincentive to alter provider behavior. In addition, only 28.3% of the providers in the current study were residents and fellows who are earlier in their careers, prescribers who could be considered more receptive to behavior change. In contrast, all the participants in the initiative described by Benjamin et al were trainees.

Soumerai and Avorn (1990) have laid out 8 principles of educational outreach,<sup>22</sup> not all of which were employed in this intervention. For instance, they call for investigating the motivation of providers prior to developing the scheme and providing reinforcement or follow-up as part of the intervention. These factors may be critical to the success of academic detailing exercises. A recent meta-analysis<sup>24</sup> found a wide variation in the structure of academic detailing efforts and the authors postulate that this accounts for the variation in effectiveness. In addition, most academic detailing efforts are aimed at provider behaviors that may be judged by prescribers as more clearly outside the bounds of safe practice, such as the prescription of highly anticholin-

**Table 2.** Subgroup Analysis of Survey Variables by Month of Prescription for Provider Survey Completed at the Time of Atypical Antipsychotic Prescription

Variable	$\chi^2$	P
<b>Age category<sup>a</sup></b>	28.8	.859
<b>Race/ethnicity<sup>b</sup></b>	80.1	.024
<b>BMI category<sup>c</sup></b>	34.7	.625
<b>Medication prescribed<sup>d</sup></b>	103.9	.019
<b>Type of prescription<sup>e</sup></b>	61.2	.010
<b>Diagnosis treated</b>		
Schizophrenia	23.9	.200
Bipolar disorder	11.5	.905
Other affective disorder	31.5	.035
PTSD	27.5	.094
Other	31.1	.040
<b>Reason for the new prescription</b>		
Side effect	23.6	.212
Intolerance to current drug	35.7	.012
Less extrapyramidal symptoms	18.5	.488
Less tardive dyskinesia risk	17.6	.091
Less akathisia	20.3	.377
Less sedation	22.6	.254
Efficacy	23.1	.232
Efficacy	36.1	.010
Increased sleep/sedation	18.7	.475
Treatment of tardive dyskinesia	19.4	.430
Patient preference	24.8	.166
<b>Comorbid medical disorder</b>		
Movement disorders	26.6	.115
Tardive dyskinesia	25.0	.159
Extrapyramidal symptoms	37.6	.007
Akathisia	25.1	.157
Metabolic/cardiac disease	33.7	.020
Diabetes	23.8	.206
Hyperlipidemia	45.7	.001
Obesity (BMI >30)	18.4	.496
Hypertension	25.0	.161
Cardiovascular disease	28.2	.080
<b>Provider type</b>	69.3	.128

BMI indicates body mass index; PTSD, posttraumatic stress disorder.

<sup>a</sup>Age categories = age  $\leq$ 30 y; age >30 y and age  $\leq$ 75 y; age >75 y.

<sup>b</sup>Race/ethnicity categories = white, black, Hispanic, other.

<sup>c</sup>BMI categories = normal  $25 \geq$ BMI; overweight  $25 <$ BMI  $\leq$ 30; obese  $30 <$ BMI.

<sup>d</sup>Medication includes aripiprazole, olanzapine, quetiapine, ziprasidone, and LAI risperidone.

<sup>e</sup>Types of prescriptions include change in prescription, additional prescription, and new initiation of a prescription.

ergic medications to the elderly.<sup>31</sup> Our intervention was targeted at an area of practice where there is still disagreement among experts, and where in many cases the drugs had been actively marketed for over a decade. It may be more difficult to change provider behavior in this context.

In spite of the failure to effect behavior change, notable information was obtained on the decision-making process of providers regarding SGAs. One prominent finding is that quetiapine was the most common SGA prescribed. The increase in quetiapine use among other SGAs has been documented in a 2008 study of national VHA data.<sup>1</sup> Reasons for the high rate of quetiapine use remain unclear given the drug's metabolic liability<sup>34</sup> and cost. However, its sedative and hypnotic properties<sup>35</sup> are likely the most important contributors, in addition to recent reports of its abuse potential<sup>36</sup> and use as a treatment for alcohol use disorders.<sup>37</sup>

Additionally, we found a high rate of SGA use in patients with affective disorders other than bipolar disorder and PTSD. At the time of this study, no SGA had received FDA approval for adjunctive use in nonresponsive depression, and there are no general indications for SGA use in PTSD. The off-label use of SGAs is very common, accounting for greater than 60% of SGA prescriptions in several studies.<sup>14,38,39</sup> A recent VHA study revealed that 40% of off-label SGA use was associated with PTSD and approximately 30% of those with PTSD received an SGA prescription, very similar to the current study.<sup>14</sup> These rates are especially notable in view of recent research showing that adjunctive risperidone use in SSRI-resistant PTSD showed no greater efficacy in decreasing PTSD symptoms<sup>40</sup> but increased adverse effects such as weight gain, fatigue, and somnolence. However, we must note that this evidence was not available at the time of the survey and there was some evidence<sup>41</sup> and a feeling among many prescribers in the VA Connecticut Healthcare System that atypical antipsychotics were helpful in PTSD. More research is needed into the reasons for off-label SGA use given the risks associated with these medications.

This study also found a high rate of metabolic and cardiac disorders in patients given SGAs. Although these diseases are common in individuals with psychiatric disorders<sup>42</sup> and in those who seek care in the VHA system,<sup>43</sup> SGAs have been associated with weight gain, impairment of glucose metabolism, and lipid abnormalities.<sup>10</sup> Current guideline recommendations call for the routine monitoring of weight and blood pressure, as well as screening of serum glucose and lipids in patients treated with SGAs.<sup>44</sup> The large proportion of cardio-metabolic diagnoses found in this study in addition to evidence of limited adherence to guidelines for the routine monitoring for these diseases<sup>45</sup> suggests an apparent failure of recent research on these risks to influence practice. There is a need for more research into ways such guideline recommendations can better influence practice.

There are also interesting patterns to be noted in the reasons chosen for the prescription of particular SGAs. The most common was "efficacy," which, while consistent with previous

efficacy research,<sup>8</sup> has been put into serious doubt by effectiveness research in more real-world practice settings.<sup>2,5</sup> The second most common reason was "sleep/sedation," which is likely related to quetiapine use and is puzzling given the host of other less costly and less metabolically active medications to improve sleep. The third most common reason was "patient choice," which may indicate that providers are implementing a shared decision-making process or which may reflect the influence of direct-to-consumer advertising. More investigation is needed into the specific rationale for the use of SGAs in these clinical circumstances.

There are several limitations to this study that deserve discussion. This intervention was aimed solely at psychiatric providers in a single VHA hospital who work in a vertically integrated organization with onsite pharmaceutical services where the costs of medications for patients are rarely an issue. These factors limit the generalizability of results, but given the integrated nature of this health system compared with private providers, one would expect a higher probability of success for an academic detailing intervention. In addition, the VHA electronic medical record and ordering system allowed implementation of the survey to be relatively easy. This intervention would be difficult in other health systems or private practice. Moreover, this was not a controlled trial where groups were randomly assigned to different interventions. We have no information of the rate of first-generation antipsychotics over the course of the study, although data on the total number of psychiatric patients at the facility suggests little change in the potential target population. In addition, a limitation of using VHA pharmacy prescription files is that they do not include prescriptions filled in non-VHA pharmacies. No data are available on the frequency of this practice, but our personal experience and discussions with VHA staff suggest that this practice is rare because it entails substantially increased costs to patients. Finally, the use of the survey to decrease on-patent SGA use may have biased survey results in an unknown manner. Given these circumstances, one would expect more conservative provider responses. Therefore, it is notable that we still found a stable and relatively high rate of pharmacologic practices that do not appear to be consistent with current evidence.

There are multiple strategies for influencing provider prescribing behavior. We describe a combination strategy of academic detailing and a point of care survey which preserves patient and provider autonomy. This cautious intervention did not influence the prescription rate of on-patent SGAs. In addition, somewhat disconcerting insight was gained into the frequent use of SGAs for questionable off-label practices. Further investigation is needed into the rationale for SGA use in disorders such as PTSD where there is little evidence of efficacy, in patients with comorbid metabolic and cardiac

disease where the use of these medications may exacerbate existing medical conditions, and in sleep disorders where there are a host of other less costly and better-tolerated options. In addition, the failure of this academic detailing intervention to produce behavior change underscores the need to determine which specific characteristics of these interventions are capable of producing practice change.

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