Schwartz
EXHIBIT NO. 49
AK 1/11/08

Unknown

From: Duff, David J
Sent: Tuesday, September 03, 2002 6:54 PM
To: Hokanson, Rosemary; Orio, Michael A; Foy, W Garren G; Massie, David A; Allsop, Jeffery; Fretwell, Parker; Bevis, Rachel A; Hauptman, Jon S; Soler, Joseph; Lyons, David R; Myers, Michael; Page, Mark
Cc: Paulson, Alfred N; Gough, Ed; Smith, Brian P (MC Sales); Lloyd (Washington) Lisa M; Harrington, Kurt M (Marketing); Lawrence, Terri; Leon, Ann L; Rubenstein, Vance; Hazen, Lisa
Subject: Action Requested: Please cascade to PSSs, MISs: Rosenheck VA article # 2 and objection handler

Attachments: Rosenheck VA utilization article 9-02.pdf; Rosenheck VA objection handler_revised.doc

Dear All,

Please cascade this message to all RSBDs, DSMs, PSSs and MISs. Attached is another article published by Dr. Rosenheck which paints Seroquel in a negative light. **An objection handler is also attached so that everyone is prepared to respond to questions from customers. Please note this information is being shared as an "FYI" only. Do not proactively raise this publication with customers.**

Dave


Rosenheck VA utilization artic...


Rosenheck VA objection handler...

25

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Publication Alert: Retrospective Claims Data Analysis of the Department of Veterans Affairs

From Conventional Antipsychotics to Atypicals and Back: Dynamic Processes in the Diffusion of New Medications

A retrospective analysis on the Department of Veterans Affairs (VA) pharmacy claims data by Douglas L. Leslie, Ph.D. and Robert A. Rosenheck, M.D. will be published, in the near future, in the following journal: *American Journal of Psychiatry* and a poster will be presented at the Seventh Annual Meeting of the International Society of Pharmacoeconomics and Outcomes Research on May 18-24 in Arlington, Virginia.

What were the objectives of the study?

The objective of the study was to examine antipsychotic prescription patterns to determine how new antipsychotics have diffused in a national healthcare system.

This training document has been developed to help you become familiar with the information in retrospective claims data analysis as well as prepare you for any inquiries from your physicians. Please take some time to review the following information.

This study should not be proactively discussed with physicians.

What was the design of the study?

This is an analysis of pharmacy claims data collected for all outpatients with a diagnosis of schizophrenia in the Department of Veteran Affairs (VA). Patients were identified using ICD-9-CM codes for schizophrenia during fiscal years (FY) 1999 to 2000. Patients who were stable on an antipsychotic regimen for 3 months, defined as being prescribed the same agent for 3 months, were identified and then tracked from September 1999 through September 2000 to see whether they switched antipsychotic medications. A patient will be considered to have switched drugs if they filled a prescription for a different antipsychotic during that time.

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What were the results of the study?

There were 28,408 patients with a diagnosis of schizophrenia who had a prescription for an antipsychotic in June 1999. Among these patients, 1,085 (3.8%) were prescribed clozapine, 6,613 (23.3%) were prescribed risperidone, 7,649 (26.9%) were prescribed olanzapine, 621 (2.2%) were prescribed quetiapine and 12,440 (43.8%) were prescribed conventional antipsychotics. A total of 21,873 patients were prescribed an antipsychotic and remained stable on the antipsychotic for three months. Among the patients who were stable for three months, 17.8% of clozapine patients (n=858), 24.2% of risperidone patients (n=4,801), 24.0% of olanzapine patients (n=5,614), 37.4% of quetiapine patients (n=278) and 25.8% of conventional antipsychotics patients (n=10,322) switched to another medication during FY 2000 ($p<0.0001$, Chi-square test). Among the patients who switched medications, the mean days to switch were 269 days for clozapine, 253 days for risperidone, 257 days for olanzapine, 246 days for quetiapine and 276 days for conventional antipsychotics ($p<0.0001$, ANOVA).

A total of 5,426 patients switched to a new medication during FY 2000. Among them, 35.1% (1,907 patients) switched to olanzapine, 29.1% (1,581 patients) switched to risperidone, 21.0% (1,140 patients) switched to conventional antipsychotics, 14.0% (758 patients) switched to quetiapine and 0.7% (40 patients) switched to clozapine. Half (49.9%) of these patients eventually switched back to their original medication by the end of the year. For patients who switched back to their original medication, 74.5% of patients originally on clozapine, 55.4% patients originally on olanzapine, 48.9% patients originally on risperidone, 46.4% originally on conventional antipsychotics and 45.2% patients originally on quetiapine switched back to their original medication ($p<0.0001$, Chi-Square). About 9.9% (1,140 patients) of the patients who switched their medication switched from an atypical antipsychotic to a conventional antipsychotic. Among these patients, 19.4% of patients who were originally stable on quetiapine were the most likely to switch to a conventional antipsychotic, followed by olanzapine (10.9%), risperidone (8.9%) and clozapine (5.6%) ($p=0.0064$, Chi-Square). There was no statistically significant difference in the length of time on original atypical medication before the switch among the patients who switched to a conventional antipsychotic ($p=0.4940$, ANOVA).

What were some of the flaws of this study?

1. The authors failed to control for severity of illness for the patients who were prescribed different atypical antipsychotics. In fact, in the table comparing characteristics of the study sample, they did not list any of the patient characteristics, including comorbid illness, by the type of medication prescribed to them so there was no way of knowing whether patients who switched medications were patients who had more severe illness or not. There is a strong possibility that Seroquel® patients may have been on other atypical medications

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and failed, given Seroquel® is the newest to the market, but this data was not available in the study and thus, was not controlled for.

2. The authors mentioned in the discussion section: "Studies of the effectiveness and risks associated with atypical antipsychotics have not shown conclusively that one atypical is more effective or has fewer side effects than other atypicals." But then they went on to talk about quetiapine and weight gain, which seems like they are trying to imply quetiapine causes weight gain: "Quetiapine has been linked with weight gain and new-onset diabetes, but so have other atypical antipsychotic medications." This statement is not supported by data. Brecher et al. (Brecher 2000) and a review by Sussman (Sussman 2001) suggested that Seroquel® is not associated with diabetes or its exacerbation with chronic use.
3. In the discussion section, the authors pointed out that the median dose of quetiapine is 200mg/day compared with 400mg/day for clozapine, 10mg/day for olanzapine and 4mg/day for risperidone. This shows that more than half of the quetiapine patients were not adequately dosed, since the current dosing recommendation is 300-400mg/day for the target dose range (SEROQUEL Prescribing Information, 2001). Given the low dose of quetiapine, possibly attributable to unfamiliarity with the drug among clinicians at the time the data was collected, NO conclusions can be drawn relative to the efficacy of quetiapine relative to other atypical antipsychotics.
4. In the discussion section, it was mentioned that "Although there is evidence that quetiapine is as effective as haloperidol, while risperidone and olanzapine are slightly more effective than haloperidol, one cannot conclude from this that quetiapine is less effective than risperidone or olanzapine." The reference that the authors cited for this statement was a meta-analysis by Leucht et al. Conclusions regarding comparative efficacy should not be drawn based on meta-analyses. In fact, Seroquel® has been compared to risperidone in a multicenter, 4 month, open-label, randomized clinical trial (Mullen 2001) and the results of the study suggested that quetiapine is as effective as risperidone for the treatment of psychotic symptoms, is more effective for depressive symptoms, may have a more favorable EPS profile and has comparable overall tolerability.

References

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3. Mullen J, Jibson MD, Sweitzer D, et al. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: The Quetiapine Experience with Safety and Tolerability (QUEST) Study. *Clin Therapeut.* 2001;23(11): 1839-1854.
4. Sussman N. Review of atypical antipsychotics and weight gain. *Journal of Clinical Psychiatry* 2001; 62(Suppl 23):5-12.
5. SEROQUEL Prescribing Information. AstraZeneca Pharmaceuticals, July 2001.