SHORT COMMUNICATION

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Do Package Inserts Reflect Symptoms Experienced in Practice?

Assessment Using an Automated Phone Pharmacovigilance System with Varenicline and Zolpidem in a Primary Care Setting

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Abstract

Background: While the US FDA maintains a voluntary reporting system, postmarketing adverse drug events (ADEs) are underreported, and this case report-based system does not allow accurate determination of incidence.

Objective: The aim of the study was to assess the usefulness of an automated phone pharmacovigilance system for ambulatory patients by comparing systematically collected, patient-reported symptoms to reflect possible ADEs with those reported on the package inserts of two drugs with postmarketing safety concerns, varenicline and zolpidem.

Methods: English-speaking adults who received a prescription for zolpidem (n = 370) or varenicline (n = 107) from a primary care physician at one of 11 participating clinics, and who participated in the pharmacovigilance system during 2008–2010, were included in the study. Patients were called approximately 4 weeks following their visit and asked to complete a standard script that asked about adherence and pre-specified symptoms.

Main Outcome Measures: The main outcome measures were elicited rates of pre-specified symptoms or possible ADEs.

Results: Compared with the package insert, patients taking zolpidem were significantly ($p < 0.001$) more likely to report fatigue (9.0% vs 1.0%), itching (4.5% vs 1.0%) and muscle aches (5.6% vs 1.0%). Elicited rates of depression and hallucination were similar to those reported in the package insert. Patients taking varenicline were significantly more likely to report confusion (1.7% vs 0.1%), depression (3.4% vs 0.1%), fatigue (6.0% vs 1.0%), hallucinations (1.7% vs 0.1%), muscle aches (6.0% vs 1.0%) and sexual dysfunction (4.3% vs 0.1%).

Conclusions: Automated phone pharmacovigilance can provide estimates of possible ADEs in clinical practice. In the case of varenicline, these data support some of the safety concerns that have come to light postmarketing, while others such as depression and hallucination related to zolpidem were not detected. These data highlight the potential value of, and innovative ways of collecting, information about possible ADEs directly from patients.

Background

The safety of prescription drugs is an ongoing public health concern. A report by the US General Accounting Office found that 51% of all approved drugs have at least one type of serious adverse drug event (ADE) that was not recognized during the approval process.[1] During the pre-marketing phase drugs are typically evaluated in trials with rigorously selected patients to optimize compliance, and limit comorbidity and the use of other medications. These populations rarely represent the more 'typical' patient who ultimately takes a drug in clinical practice.[2,3]

While the US FDA maintains a voluntary ADE reporting system for postmarketing surveillance, it is estimated that 1–10% of ADEs are reported,[4] and these case reports lack accurate denominators to estimate incidence. Current ADE reporting has also been criticized because it substantially under-estimates the firsthand experience of patients.[4-6] While efforts are underway to considerably expand capacity for active surveillance using electronic health records (EHRs) and claims data,[7] these data will not fully capture the patient experience as clinicians often do not fully document a patient's symptoms.[4,5] The FDA requires that package inserts include estimates of ADE rates. In 2006, the format of the package insert was revised to provide clearer emphasis and summary of pertinent adverse reactions seen in clinical trials experience and postmarketing experience, typically based on spontaneous reports to the FDA.

Varenicline and zolpidem are two commonly used drugs for which safety concerns have been raised postmarketing. In 2009, total sales of zolpidem approached $US1 billion, and sales of varenicline approached $US500 million.[8] Varenicline was approved for use in the US in 2006 as an aid to smoking cessation treatment. Postmarketing reports of potential ADEs, including depression, agitation and suicidal thoughts, began in 2007 and prompted the FDA to require modification of the product labelling, with the addition of a 'black box' warning in 2009.[9] Zolpidem was approved in 1992 for the treatment of insomnia. In 1995, labelling was revised to include warnings about an increased risk of depression or suicidal thinking. Additional changes in 2008 included warnings about complex behaviours, including sleep driving and hallucinations.

To address some of the limitations of current ADE monitoring in primary care practice, we developed an automated monitoring system using an interactive voice response system (IVRS).[10] We describe our experience conducting standardized symptom monitoring, as a signal for possible ADEs, for zolpidem and varenicline in clinical practice.

Methods

Setting and Patient Eligibility

We conducted this study in 11 primary care clinics affiliated with the Brigham and Women's Primary Care-Based Research Network. Patients were eligible if they were between the ages of 18–84 years, English-speaking and were recently started on one of the target medications by a primary care provider. The study was reviewed and approved by the Partners Healthcare Institutional Review Board.

Protocol

Our protocol has been described previously.[10] In brief, potentially eligible patients prescribed

selected medications were identified bi-monthly from our EHR and were mailed an informational letter that included directions for 'opting-out' if desired. Patients who did not opt-out within a 2-week period (91.1%) were called up to 15 times over a 10-day period using IVRS (CallAssure™; Vocantas, Inc., Ottawa, ON, Canada). IVRS is a phone technology that allows a computer to detect voice using a normal phone call, including mobile phones.[11] The computerized system engages individuals in conversation through realistic recordings of an actual human voice, programmed to be responsive to the participant's speech, without the use of touchtone buttons or other data entry. A standard script with branching logic asked whether each individual had experienced any of 29 pre-specified symptoms based on our prior work (see the appendix for the list of symptoms [Supplemental Digital Content, http://links.adisonline.com/DSZ/A70]).[6] For each drug–symptom combination we were therefore able to calculate an ADE rate for patients prescribed the drug. Information about demographic (age, sex, race/ethnicity) and clinical characteristics (history of liver disease or chronic renal insufficiency noted on the patient's problem list) was obtained from the EHR. Overall, 21.7% of patients with a working phone number (30.6% of individuals in a household where a live individual answered the phone) completed the IVRS tool. Older patients were more likely to participate than younger patients, Hispanics were less likely to participate than Whites, and those who lived in a low-income community were less likely to participate than those who lived in a high-income community.[10]

Review of Package Inserts

The package inserts and Micromedex® (Thomson Reuters) were reviewed to obtain published rates for each symptom for varenicline and zolpidem.[12-14] If a symptom was not listed, the rate was assumed to be 0.1%. In several instances the symptom had been reported in postmarketing experience but a specific rate was not specified. In this situation the maximum rate was assumed to be 0.1%, due to the common use of these drugs.[9]

Data Analysis

A Chi-squared statistic was used to compare the observed patient-reported symptoms and expected rates of ADEs for each drug-symptom combination. A Bonferonni-adjusted p-value of <0.001 was used as the threshold of statistical significance because of the number of comparisons made. In a sensitivity analysis, we assumed that everyone who did not participate in our pharmacovigilance system did not experience a symptom, to provide the most conservative estimate of the occurrence of these possible ADEs.

Results

The average age was 55 years for patients taking zolpidem and 51 years for those taking varenicline. The majority of our sample was female (69.7% and 66.4%, respectively, for the two drugs), of White ethnicity (69.5% and 65.4%), and few had chronic liver (2.7% and 7.5%) or kidney disease (1.1% and 0.9%).

Symptoms Associated with Zolpidem

Of the 370 patients taking zolpidem, 163 (44.1%) reported at least one symptom. Of those with a symptom, 22 (13.5%) thought that the medication was related to the symptom, 99 (60.7%) thought that the symptom was not related to the medication and the remainder did not know or did not report an association. We did not observe a significant difference in the rates of confusion, depression or hallucination compared with what was reported on the package insert (figure 1). We did, however, observe increased rates of fatigue, itching and muscle aches. Of these, only the reported rate of fatigue was statistically significant even after assuming that patients who did not participate in the survey did not experience the symptom.

Symptoms Associated with Varenicline

Of the 107 patients taking varenicline, 48 (44.8%) reported at least one symptom. Of those with a symptom, 30 (62.5%) thought that the medication was related to the symptom, 9 (18.8%) thought

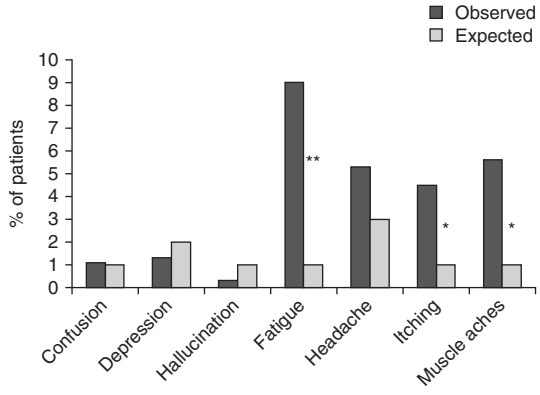

Fig. 1. Symptoms associated with zolpidem. * $p < 0.001$, ** $p < 0.001$ in the sensitivity analysis with the assumption that all non-respondents did not experience the symptom. Expected rate of adverse drug event specified as 'at least 1%' for confusion and muscle aches. Itching was not noted in the package insert and the rate of adverse drug event was assumed to be 0.1% for the purposes of calculating the Chi-squared statistic.

that the symptom was not related to the medication and the remainder did not know or did not report an association. For varenicline, we did observe significantly greater rates of confusion, depression, hallucination, muscle aches, sexual dysfunction and fatigue compared with what is described in the package insert (figure 2). The rates of abdominal pain and nausea (not shown) did not differ significantly from the rates reported in the package insert. Observed rates of depression, sexual dysfunction and fatigue remained significantly higher than the package insert rates even after assuming that all individuals who did not respond to the survey did not experience a symptom.

Discussion

Recognizing the occurrence and frequency of ADEs experienced by patients is central to ensuring the safety of drugs in clinical practice. However, it is challenging to establish standardized mechanisms for such monitoring. While infrastructure is under development to perform active surveillance through the mining of EHR and claims data,[7] these systems may not fully capture the experience of patients.[4,5] Our study demonstrates that automated, proactive monitoring of ambulatory patients recently prescribed a medication can capture important differences in their experience compared with what is described in the package insert. Both varenicline and zolpidem are commonly used drugs for which postmarketing safety concerns have been noted. In the case of zolpidem, rates of confusion, depression and hallucination were similar to those reported in the package insert. In contrast, our findings for varenicline did demonstrate an increased risk of symptoms consistent with the case reports.

The rates that we observed may differ from those reported in the pre-marketing trials for several reasons. Patients in trials are healthier and less diverse than the general population, with particular underrepresentation of the elderly, women and racial/ethnic minorities.[3,15] They are also more carefully monitored than patients in general practice, with formal symptom assessment. Once approved, many drugs are used for a variety of other indications, often with little to no evidence of efficacy, a practice known as 'off-label prescribing'.[2] It is possible that patients may be more willing to report 'sensitive' symptoms, such as depression and sexual dysfunction, to an automated machine than they would to

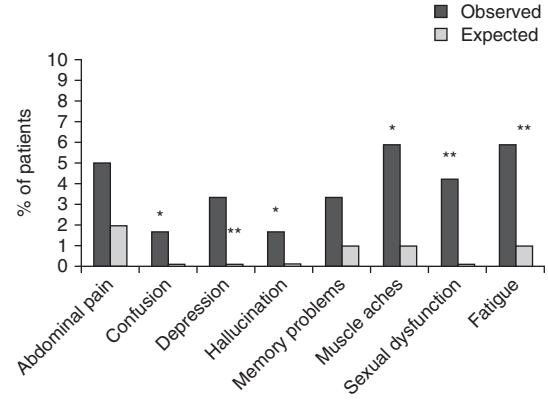

Fig. 2. Symptoms associated with varenicline. * $p < 0.001$, ** $p < 0.001$ in the sensitivity analysis with the assumption that all non-respondents did not experience the symptom. Postmarketing reports of depression and hallucination have been reported, although incidence is unknown. Muscle aches, sexual dysfunction, memory problems and confusion were not noted in the package insert. In both instances the rates of adverse drug events were assumed to be 0.1% for the purposes of calculating the Chi-squared statistic.

their physician or during participation in a clinical trial. This hypothesis should be investigated further.

In several instances we needed to assume a maximum estimated rate where either none was reported or the symptom was noted to have occurred only during the postmarketing experience. The lack of standard symptom reporting in package inserts is also problematic as we could not directly match some of our symptom categories to those reported on the package insert. 'Mood swings' are noted for varenicline for up to 1% of patients, but we did not believe that this was directly comparable to the information that we collected about 'depression or sadness'. We collected information about 'fatigue' but could not compare this to the combined rate of 'fatigue, malaise or asthenia' reported for varenicline. Current guidance for industry on ADE reporting suggests that seriousness, severity, frequency and strength of causal link be considered when reporting ADEs.[16] While the presentation of potential ADEs should be prioritized based on these criteria, our data speak of the need to create better registries so that population-based ADE rates can be determined more precisely.

Because our study has several limitations, this should be considered a pilot study of using this type of methodology to detect possible ADEs in clinical practice. Our sample size was relatively small and we have not verified these patient reports with detailed investigation. While pre-marketing trials of varenicline included over 4500 subjects, only approximately 450 were exposed to the drug for at least 24 weeks, the duration recommended by the manufacturer.[13] Zolpidem was studied in 1701 US patients, but only 685 received the drug for at least 10 nights, and 152 patients received the drug for up to 35 nights.[12] Our sample sizes are therefore not dissimilar to the pre-marketing data for longer-term use. Our findings cannot be considered causal, but rather a description of rates seen in clinical practice.

Conclusions

Automated pharmacovigilance systems can provide valuable estimates of possible ADEs experienced by patients in clinical practice. In the case of zolpidem, postmarketing concerns for depression and hallucination are not supported by our work. However, for varenicline, rates of most of the pre-specified symptoms were significantly higher than those mentioned in the package insert. These data underscore the importance of collecting systematic information about symptoms as a proxy for possible ADEs directly from patients to fully assess the safety of prescription drugs.

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