False-Positive Urine Screening for Benzodiazepines: An Association with Sertraline? A Two-year Retrospective Chart Analysis

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ABSTRACT

Objective: To determine the frequency of false-positive benzodiazepine screens associated with sertraline use at the authors' institution.

Method: Urine drug screen results spanning a two-year period were data mined to identify those positive for benzodiazepines. When confirmatory gas chromatography-mass spectrometry determined false positives, they were subsequently cross-referenced against pharmacy records to identify patients with active prescriptions for sertraline at the time of the initial urinary drug screen.

Results: Of the 522 records reviewed, 160 were later determined to be false positives by confirmatory gas chromatography-mass spectrometry. Sixty-two of those were associated with a concomitant benzodiazepine prescription. Of the 98 remaining, 26 were associated with a concomitant sertraline prescription.

Conclusion: Our findings suggest that sertraline may be an unreported cause of false-positive

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benzodiazepine results in a widely used screening assay.

INTRODUCTION

A crucial part of the examination of any psychiatric patient is an evaluation for the effects of toxic substances, including medications and drugs of abuse. Routine screening tests are helpful during the early stages of formulating a differential diagnosis, especially considering that many patients who use illicit substances may be untruthful about their substance histories. Positive results in these screening tests usually prompt automatic and expensive confirmatory testing by gas chromatography-mass spectrometry (GC-MS). The results of these confirmatory tests are often delayed for several days, a less-than-ideal situation in a difficult case.

False-positive screens for drugs of abuse can potentially hamper diagnosis and treatment. If a patient's clinical presentation is prematurely ascribed to a substance disorder, a medical workup may be less aggressively pursued, potentially forestalling the correct diagnosis and early treatment. Moreover, when patients are misdiagnosed with a substance-related disorder based on false test results—despite their truthful denial of substance use—the crucial therapeutic alliance may be damaged. Such potential consequences underscore the importance of knowing the validity of screening tests for drugs of abuse.

A series of three false-positive benzodiazepine urine drug screen (UDS) results associated with sertraline use at our institution compelled us to research this topic further. A review of secondary sources revealed sertraline to be a well-described cause of false-positive benzodiazepine screens. In 2006, Rapuri et al[1] list sertraline and oxaprozin as causing false-positive screening results for benzodiazepines. The table in the article contains four references,[2–5] but none of them implicates sertraline as a cause of false-positives. *The Merck Index*[2] purports that sertraline and oxaprozin both cause false positives in urine benzodiazepine screens; however, the text mistakenly cites a 1995 *Clinical Chemistry* article[7] that focuses solely on oxaprozin without mentioning sertraline. Further confusing any clinician seeking answers from the literature is a 2006 article by Vincent et al[8] that does not list sertraline as a potential agent that could cause a false-positive benzodiazepine screen.

The confusion surrounding this topic stems partially from a series of articles published in the late 1990s that compared various commercial screening assays. A 1995 study by Wu et al[9] acknowledged the cloned enzyme donor immunoassay (CEDIA) technique cross-reacted with sertraline. This issue made its first appearance in the clinical literature when Gear[10] described a series of urine toxicology screens that returned false-positive results for benzodiazepines in patients who were taking sertraline.

In 1997, the manufacturers of CEDIA, Boehringer Mannheim (now Roche), funded a paper proclaiming their improved CEDIA no longer cross-reacted with the inactive hydroxyl ketone metabolite of sertraline.[11] Notably, none of the other commercially available immunoassays (OnLine, Roche; TDx, Abbott; RIA, Roche; Emit II, Syva; TRIAGE, Biosite) were subject to false results secondary to interference of sertraline metabolites.[12] Boehringer soon after funded a comparison study between CEDIA and EMIT II that revealed two CEDIA false positives for benzodiazepines in patients who had received sertraline, but curiously offered no explanation regarding the false positives, an issue Beohringer had ostensibly resolved when they released their reformulated, "improved" CEDIA.[13] Since then, literature on this topic has essentially disappeared, but the confusion surrounding both formulations of CEDIA have permeated the literature and become lore among many psychiatrists. Without knowledge of the specific assay being used, any article proposing that sertraline is or is not an interferant of benzodiazepine screening assays is of little value.

We recently became aware of three false positives for benzodiazepine screens in patients taking sertraline while employing Abbott's AEROSET and ARCHITECT® c8000 System, of which the initial package insert (list number 01E16, published February 2004), neither listed sertraline as an agent causing false positive results nor as an interferant in general; however, the updated package insert (list number 03L39, published February 2008) lists sertraline and norsertraline as compounds producing false positives at concentrations above 500 and 1000µg/mL, respectively (levels at least 200 times higher than expected from normal therapeutic sertraline use in normal healthy patients). The only literature addressing this is by Lum et al[14] who focused on problems associated with Abbott's implementation of a new polyclonal antibody pool in the benzodiazepine reagent used on the Architect analyzer. According to the authors, this reformulation increased the test's sensitivity but appreciably lowered its specificity, stating that their positive screen rate nearly doubled after they began using Abbott's reformulated reagent. A review of records indicated that of the 50 false-positive results, 16 (32%) were found in patients taking sertraline.[14]

METHODS

To determine the accuracy of the urine benzodiazepine screening test employed at our institution, we performed a two-year (January 2007 to December 2008) retrospective analysis of UDS results (of both inpatient and outpatient records) to identify those which, upon confirmatory GC-MS, were determined to be false positives. The resulting list of false-positive benzodiazepine assays was then

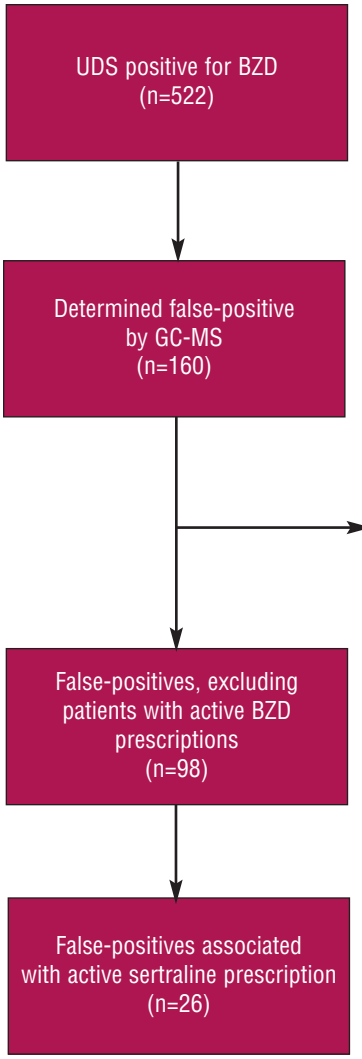

FIGURE 1. Summary of data

cross-referenced against our pharmacy's database to identify those patients who had active prescriptions for sertraline at the time of the initial UDS. False-positive results that were found to be associated with a concomitant benzodiazepine prescription were excluded. Though presence of a concomitant active benzodiazepine prescription does not necessarily indicate concomitant benzodiazepine use, the authors felt inclusion of those results would obfuscate our evaluation of the association between sertraline and test results.

All data were derived from the approved Naval Medical Center, Portsmouth, Virginia, institutional review board (IRB) protocol titled "Sertraline as a Cause of False-Positive Benzodiazepine Screen: A Retrospective Analysis" (CIP#2008.0080).

RESULTS

A two-year (January 2007 to December 2008) retrospective analysis of UDS results identified 522 results that were positive for benzodiazepines. Of those 522 positive urine screens, 160 were later determined to be false positive by GC-MS, yielding a positive predictive value of 69.3 percent. When cross-referenced against pharmacy records, 62 of those 160 results were associated with a concomitant, active prescription for a benzodiazepine. Of the 98 remaining records, 26 (26.5%) were associated with an active sertraline prescription (Figure 1).

CONCLUSION

After observing a series of false positive urine drug screens for benzodiazepines at our institution, we suspected that false-positive results might be more common than many clinicians realize. Our findings confirm that suspicion: A widely used benzodiazepine screening test commonly produces false-positive results, and a significant portion of those (26.5%) occurred in patients who had active prescriptions for sertraline at the time of screening. These results raise several questions. Though not the primary focus of our investigation, we calculated our institution's use of the AEROSET and ARCHITECT® c8000 System yields a 69.3-percent overall positive predictive value for detection of benzodiazepines, which may be lower than many who interpret these results might suspect. Our finding that 26.5 percent of those false-positive results were found in patients taking sertraline supports our suspicion that sertraline is a cause of false-positive results in this particular testing system and is accordant with similar findings by Lum et al[14] (32%).

Our study's limitations are those that are inherent to chart review studies in general, which include incomplete documentation (e.g., missing records, information that is unrecoverable or unrecorded) and difficulty verifying information (i.e., a person prescribed sertraline may not necessarily be taking sertraline; absence of prescription for a benzodiazepine does not eliminate benzodiazepine use; presence of a concomitant benzodiazepine prescription does not indicate concomitant use). In addition, our retrospective study only allowed for analysis of positive tests results, prohibiting calculation of sensitivity, specificity, and negative predictive value—values a prospective study could elucidate through confirmatory testing of all test results, both positive and negative. A prospective design may also permit some form of direct patient questioning regarding medication use, which would allow for some degree of verification of information derived from patient records. We hope these findings will prompt others to further examine this issue through prospective studies, as we intend to do. Perhaps more importantly, we hope these data not only caution against overreliance on this specific test's results, especially in the setting of concomitant sertraline use, but also remind us to maintain a healthy sense of skepticism when evaluating any initial screening labs for drugs of abuse before making crucial diagnostic and treatment decisions.

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