Trends in Boxed Warnings and Withdrawals for Novel Therapeutic Drugs, 1996 Through 2012

Boxed warnings describe potentially life-threatening risks associated with certain prescription drugs.1 The warnings are surrounded by a border or “box” in the drug label and may be present at the time of drug approval (ie, a premarket warning) or added during the postmarket period (ie, a postmarket warning). Despite the use of boxed warnings for the most serious adverse reactions, trends and associated predictors for such warnings have not been well characterized. The objective of this study was to determine the frequency of premarket and postmarket boxed warnings and safety-related withdrawals for novel therapeutics approved between 1996 and 2012.

Methods | Institutional review board approval was waived by the University of California, San Francisco, Committee on Human Research. All drug labeling histories, boxed-warning-related safety announcements, and safety-related withdrawals associated with novel therapeutics (ie, new pharmacological or biological molecular entities) approved between 1996 and 2012 were reviewed. Primary data sources were the Center for Drugs Evaluation and Research (CDER) and MedWatch websites2-5; the Physicians’ Desk Reference was used for historic labels unavailable online. Approval date, presence or absence of a premarket warning, and date of US Food and Drug Administration (FDA) communications issued between 1996 and 2013 for a safety-related withdrawal or addition of new safety risks to a boxed warning were recorded. Median times to first postmarket boxed warning or withdrawal based on presence or absence of a premarket boxed warning were calculated and compared using the Wilcoxon rank sum test. Descriptive statistics were used to examine patterns in drug type (pharmacological or biological) and approval year (before or after 2004, the study midpoint). Multiple logistic regression analyses were used to estimate the likelihood of a boxed warning based on drug type and approval year. We used SAS version 9.3 (SAS Institute Inc) for statistical analyses, and P < .05 was considered statistically significant.

Results | There were 522 novel therapeutics approved during our study, including 441 pharmacological and 81 biological products. One hundred eighty had ever received a boxed warning (136 pharmacological and 44 biological products); 105 had only received premarket warnings, 50 only acquired postmarket warnings, and 25 had both (eTable 1 in the Supplement). In total, there were 89 postmarket boxed warnings, and 11 withdrawals (eTable 2 in the Supplement), most of which (81%) occurred after 2004 (Figure, A).

Premarket warnings were more common among biological than pharmacological products (31% vs 22%, respectively; odds ratio, 2.0, 95% CI, 1.2-3.3) and among drugs...
approved after 2004 compared with drugs approved earlier (36% vs 18%, respectively; odds ratio, 2.4; 95% CI, 1.6-3.6) (Figure, B).

Median time from approval to first postmarket boxed warning or withdrawal was 4.2 years (range, 0.2-15.2 years) and was shorter for drugs with premarket warnings (2.3 years; range, 0.2-11.8 years) than drugs without premarket warnings (4.9 years; range, 0.2-15.2 years) (P < .001).

Discussion | Our study demonstrates that boxed warnings are common, affecting more than one-third of recent drug approvals. While nearly three-quarters of boxed warnings had been applied to novel therapeutics at the time of approval, more than 40% acquired the warning after a median market period of 4 years. Not surprisingly, the frequency of boxed warnings increased in the post-2004 period, which coincided with the aftermath of the rofecoxib (Vioxx, Merck) withdrawal and subsequent launch of FDA initiatives to strengthen drug safety surveillance, particularly postmarket reporting.4,5 Our finding that half of biological products had boxed warnings is consistent with literature suggesting that biological products pose greater risks of serious adverse events compared with other drug types.6 It should be noted, however, that our study was limited in sample size and excluded biological products under jurisdiction of the Center for Biologics Research and Evaluation. Furthermore, our study included only CDER-regulated drugs and therefore was not a comprehensive review of all drugs approved since 1996. Clinicians should be aware of the prevalence and growing numbers of boxed warnings and the importance of continued adverse event reporting for identifying new safety concerns.

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Study concept and design: All authors.

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Correction: This article was corrected on August 25, 2014, to revise a table entry in eTable 1 in the Supplement.


COMMENT & RESPONSE

Diagnostic Value of Adenosine Conversion of Wide Complex Tachycardia

To the Editor | In the excellent case presentation of a 46-year-old patient with stable, regular wide complex tachycardia (WCT) with a recent echocardiogram showing a structurally normal heart, Schuller et al1 describe the use of adenosine as a diagnostic tool for stable WCT. In their case, after adenosine administration the patient’s retrograde P waves disappeared and the WCT was not converted. This eliminated the possibility of supraventricular tachycardia (SVT) with aberrancy as a diagnostic possibility and confirmed the diagnosis of ventricular tachycardia (VT). According to the authors, “If the arrhythmia had terminated with adenosine use, or the atrial arrhythmia continued in the absence of ventricular conduction, the diagnosis of SVT with aberrancy would have been confirmed.”2

It is important to note that the clinicians did not use the presence of conversion or lack of conversion, alone, to make the diagnosis of VT. Adenosine-sensitive VT is well-reported in the literature.2-4 Some patients with VT will have their condition converted by adenosine.

Advanced cardiovascular life support guidelines recommend adenosine as a safe and potentially effective therapy in the initial management of stable, regular, monomorphic WCT.5 A generalist, unfamiliar with the nuance in differentiating VT from SVT with aberrancy, should know that his or her patient with WCT that converts with adenosine still needs appropriate cardiology consultation. It may be VT, much less benign than SVT with aberrancy.

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