Different Black Box Warning Labeling for Same-Class Drugs

Orestis A. Panagiotou, MD[1], Despina G. Contopoulos-Ioannidis, MD[2,3], Panagiotis N. Papanikolaou, MD[1], Evangelia E. Ntzani, MD[1], and John P. A. Ioannidis, MD, DSc[1,4,5,6,7]

[1]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; [2]Department of Pediatrics, University of Ioannina School of Medicine, Ioannina, Greece; [3]Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; [4]Foundation for Research and Technology- Hellas, Biomedical Research Institute, Ioannina, Greece; [5]Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA; [6]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA; [7]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

INTRODUCTION: Black box warnings (BBWs) are the strongest medication-related safety warnings in a drug's labeling information and highlight major risks. Absence of a BBW or asynchronous addition of a BBW among same-class drugs could have major implications.

METHODS: We identified the 20 top-selling drugs in 2008 (10 with BBWs and 10 without BBWs on their label) that belonged to different drug classes. We collected labeling information on all drugs belonging in these 20 classes, and recorded differences in the presence and timing of acquisition of BBWs for same-class drugs.

RESULTS: Across the 20 evaluated drug classes, we identified 176 different agents, of which 7 had been withdrawn for safety reasons. The reasons for the withdrawals became BBWs in other same-class agents only in two of the seven cases. Differences were identified in 9 of the 20 classes corresponding to 15 BBWs that were not present in all drugs of the same class. The information for 10 of the 15 different BBWs were included in the labels of same-class drugs as simple warnings or text, while it was absent entirely in 5 BBWs. The median interval from the time the BBW had appeared in another drug of the same class was 66 months.

DISCUSSION: Differences in BBW labeling in same-class drugs are common and shape impressions about the safety of similar agents. BBW labeling needs to become more systematic.

KEY WORDS: black-box warning; FDA; adverse events; harms.
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INTRODUCTION

Adverse drug events may carry major morbidity.[1–4] Black box warnings (BBWs) are the strongest medication-related safety warnings that can be placed in a drug's labeling information according to the Food and Drug Administration (FDA)[5] and highlight major drug-related risks.[6] Based on evidence from animal, clinical, or post-marketing surveillance studies and reports, the FDA decides whether acquisition and/or updating of a BBW is required.[7–11] Between 2005–2008, approximately 14% of safety labeling changes were BBW additions or revisions.[12] About 20% of approved chemical entities acquire a BBW label or are withdrawn from the market because of causing serious harms within 25 years from their approval.[13] Currently, over 400 drugs have BBWs,[10,14] an almost two-fold increase within the past 15 years.[15]

Because serious drug-related adverse events (e.g., teratogenicity during pregnancy due to angiotensin-receptor blockers) are more often a function of the pharmacologic class of a drug rather than specific medication features, most BBWs are typically applied to all members of a given class ("class-wise fashion"),[13,14,16] which is defined on the basis of the mechanism of action, e.g., fluoroquinolone antibiotics.[17] Nevertheless, differences in the BBW acquisition have been reported,[13] where addition of a BBW is not universal for all drugs in the category.[17] Such differences in the acquisition of a BBW or timing thereof may sometimes be justified and may reflect differences in the available accumulated evidence for different agents. Drugs within the same class may have similar pharmacodynamic properties and chemical structures, but different pharmacokinetic properties, and these may justify discrepant BBW labeling. Additionally, indications and therapeutic classes may also be important for the issuance of a BBW. However, judging whether the drug class alone or the indication also is important is very difficult most of the time, and indications for each drug may change over time. It would be useful to make the evidence transparently available whenever a decision is made to place a BBW based on an indication rather than class. Such an example of indication-based BBW labeling is suicidality in major depressive disorder patients for Seroquel (quetiapine), which is approved as adjunctive treatment for this condition, but not for the same-class drug Risperdal (risperidone), which is not approved for this disorder.

On the other hand, the unjustified absence of a BBW or even the asynchronous acquisition of a BBW among same-class drugs can differentially favor drugs in the same category or create confusion in prescription patterns.[18] BBWs can have an impact on drug sales because of marketing prohibitions, increased litigation and negative media attention,[19–22] and claims have arisen about the resistance of pharmaceutical companies to accept new BBWs, especially for blockbuster drugs.[22]

Here, we aimed to evaluate systematically the concordance in the BBW labeling between same-class drugs. We

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wanted to assess whether some drugs do not get a BBW label when a BBW exists for other same-class drugs and whether differences occur in the time to acquisition of a BBW between same-class drugs.

METHODS

Selection of Drugs and Definitions

We used the list of the 200 top-selling drugs in the USA as published in the "Top 200 Drugs for 2008 by Sales."[23] Top-selling drugs are not necessarily the ones with the greatest number of prescriptions, but their impact on health care cost is the highest, and BBWs for these drugs may be expected to make a major difference in health care cost. Drugs were categorized initially according to *Physician's Desk Reference* (PDR)[24] categorization (e.g., antidiabetic agents, respiratory agents, antihypertensives, antilipidemic agents, etc). We further categorized drugs belonging to the same category in different drug classes according to their mechanism of action after we had thoroughly studied the respective drug labels. The mechanistic classification that we used brings together drugs with similar chemical structures. All drug-related information on active ingredients, category, mechanism of action, BBW status and time of acquisition thereof was retrieved from the electronic edition of the PDR (e-PDR) 2009 [24] and the Drugs@FDA database,[25] a publicly available FDA database for approved prescribed and over-the-counter drugs (last update February 16, 2010). When the precise mechanism of action of a drug was described as "not well understood" or "unknown" and a possible mechanism of action was proposed based on animal or in vitro studies, we assigned the drug class according to the proposed mechanism of action.

We aimed to study a total of 20 drug classes that included agents that were among the top in terms of total sales in 2008. These 20 drugs classes consisted of 10 classes where the respective top-selling drug has at least one BBW and another 10 classes where the top-selling drug has no BBW. Therefore, we went down the top-selling drug list and selected as index agents the first ten top-selling drugs with BBWs and the first ten top–selling drugs without BBWs, provided that each belonged to a different class and that each had at least one other same-class drug. We then searched and identified all respective same-class drugs for the 20 index agents based on e-PDR 2009 and Drugs@FDA. Same-class drugs also included combinations of the index drug with other agents. When an index drug with a BBW was a combination of drugs, we considered as same-class drug the constituent of the combination to which the BBW pertained. We considered separately formulations of the same drug with different pharmacokinetics (e.g., extended-release formulations, powder inhalations or aerosol inhalations) and drugs with the same active ingredient but different brand names. When more than one New Drug Application (NDA) number was identified in the Drugs@FDA database for the same brand name drug, we included only the marketed drug with the most recent available label. We excluded drugs whose labels could not be retrieved on Drugs@FDA or e-PDR 2009. Additionally, we excluded generics, because upon checking a random sample of 50 generics on Drugs@FDA, we observed that labels were unavailable in the vast majority.

Withdrawn Same-Class Drugs

We also searched for same-class drugs that might have been withdrawn from the US market for safety reasons either by the FDA or voluntarily by the manufacturer itself following identification of serious and/or life-threatening adverse reactions. Withdrawal information for the US market was retrieved from the "MedWatch"-based *Safety Alerts for Human Medical Products* database,[26] the Reports to the Nation from the Center for Drug Evaluation and Research,[27–34] and a published list of withdrawn drugs for pre-2000 withdrawals.[13] For each of these drugs, we confirmed its current marketing status in the US using information available on Drugs@FDA. We recorded whether a withdrawn drug had a BBW at the time of its withdrawal and, if so, whether that BBW was the same as the BBW of the index top-selling drug or the other same-class drugs that were still marketed. We also recorded whether the reason for withdrawal of a drug was issued to other same-class drugs as a BBW after its withdrawal.

BBW Differences

The labels of all evaluated drugs in each class were searched for in e-PDR and Drugs@FDA, and BBWs were noted. We identified differences in the presence of specific BBWs between non-withdrawn same-class agents. When drugs had more than one distinct BBW, each BBW was considered separately. When a BBW was absent from some agents in a given class, we examined if the issue raised by the BBW could be identified somewhere else in these labels, listed as a simple warning without a black box, or in the text of the label, e.g., in the sections of adverse reactions, precautions, warnings, contra-indications, or overdosage.

BBW Time Lag

We searched for any differences in the time of acquisition of BBWs between same-class agents. We excluded drugs discontinued before the issuance of the first BBW to the class; however, when a drug had a BBW by the time of its withdrawal, we evaluated the time lag for the other same-class drugs. The date of BBW acquisition was identified through Drugs@FDA or the *Safety Information* section [35] of "MedWatch", when labels for specific date of revisions were not available at Drugs@FDA. We defined as time lag a period ≥2 months between the first acquisition of a BBW by a drug and the appearance of the BBW in other drugs of the same class. In cases where a drug was approved after the first issuance of the BBW to the respective drug class, time lag was defined as an interval ≥2 months between its approval and the acquisition of the BBW. We did not assess secondary changes, such as addition of information on at-risk populations or explanatory notes. Time was censored on February 2010.

Data extraction was performed independently by two investigators (OAP, PNP), and inconsistencies were resolved in a consensus meeting of all investigators.

RESULTS

Database

For the 20 selected drug classes, a total of 243 same-class drugs were identified (see Online Appendix Table 1). Of those, 67 drugs were excluded because of lack of available label information (Online Appendix Table 1). Thus, 176 additional same-class drugs (range 2–23) belonging to the 20 drug classes were further analyzed (Table 1). A total of 25 BBWs were recorded across the 176 drugs, of which 15 were in the 10 top-selling drugs with a BBW.

Withdrawn Same-Class Drugs

In the eligible drug classes, we identified seven drugs withdrawn for safety reasons. Three of these drugs already had a BBW relevant to the reason for withdrawal [Rezulin (troglitazone), Prelay (troglitazone), and Bextra (valdecoxib)], whereas the remaining four drugs were withdrawn with no prior BBW [Vioxx (rofecoxib), Raxar (grepafloxacin), Trovan (trovafloxacin), and Baycol (cerivastatin)]. Even when the withdrawn drugs had a pre-existing BBW, this was different from the BBW of the respective index top-selling drug: Rezulin (troglitazone) and Prelay (troglitazone) had a BBW for hepatotoxicity, while the index top-selling Actos (pioglitazone) has one for congestive heart failure; Bextra's (valdecoxib) is marked for potentially fatal skin reactions, whereas the index Celebrex (celecoxib) is marked for cardiovascular and gastrointestinal risk.

COX-2 inhibitors Vioxx (rofecoxib) and Bextra (valdecoxib) were withdrawn because of cardiovascular risk, which subsequently became a BBW also for Celebrex (celecoxib). Conversely, the reasons for withdrawal for Rezulin/Prelay/troglitazone (hepatotoxicity), Trovan/trovafloxacin (hepatotoxicity), Raxar/grepafloxacin (severe cardiovascular events), and Baycol/cerivastatin (rhabdomyolysis) have not become BBWs of the respective same-class drugs.

BBW Differences

Of the 25 distinct BBW labels, 4 pertained to agents that were included in combination regimens and were not related to the respective drug class under study, e.g., lactic acidosis because of the presence of metformin in the combinations of thiazolidinediones with metformin was not considered a problem for thiazolidinediones. Of the remaining 21 BBWs, 6 appeared with the same language in all pertinent same-class drugs. Thus, 15 BBW labeling differences were identified, pertaining to 9 drug classes (Table 2).

Six BBWs assigned to four index top-selling drugs [suicidality in children, adolescents, and young adults for the 5-hydroxytryptamine 2-dopamine 2 (5HT2-D2) antagonists; suicidality in children, adolescents, and young adults for the serotonin norepinephrine reuptake inhibitors/serotonin norepinephrine dopamine reuptake inhibitors (SNRIs/SNDRIs); serious rashes and rash-related deaths for the voltage-sensitive sodium channel blockers; and drug-dependence, sudden death, and serious cardiovascular adverse events for the norepinephrine and dopamine reuptake inhibitors (NDRIs)] were not given for some of the respective same-class drugs, and another two index BBWs [drug dependence and fatal respiratory depression for Oxycontin (oxycodone)] were spared for all other same-class drugs. Additionally, the BBW of the index top-selling selective serotonin reuptake inhibitor (SSRI) Lexapro (escitalopram) precludes its use in pediatric patients because of suicidality, whereas some other SSRIs are approved for children with obsessive compulsive disorder (Table 2).

Increased risks of myocardial ischemia and hepatotoxicity in thiazolidinediones and serious skin rashes in cyclooxygenase (COX)-2 inhibitors were not BBWs for the index top-selling drug, but appeared in one or more other same-class drugs. Moreover, Risperdal Consta (risperidone) and Invega Sustenna (paliperidone), which are administered intra-muscularly for long-term action, do not have the BBW for post-injection delirium and/or sedation syndrome of Zyprexa Relprevv (olanzapine), which has the same pharmacokinetic properties. Finally, the index top-selling adenosine diphosphate (ADP) receptor inhibitor Plavix (clopidogrel) had no BBW, whereas the recently approved Effient (prasugrel) had a BBW for bleeding risk upon its approval, and Ticlid (ticlopidine) had a BBW for life-threatening hematologic reactions (Table 2).

Different BBWs Present in Other Levels of Warnings

In 10 of the 15 differences when a BBW was missing, the issue was raised in the label at some other level of warning (Table 3), while in 5 cases the BBW content was not listed anywhere in the drug label. The BBW for suicidality in children, adolescents, and young adults of the top-selling Seroquel (quetiapine) was not reported at all for other 5HT2-D2 antagonists [Zyprexa and Zyprexa Zydis (olanzapine) have this BBW only when combined with fluoxetine]. In the same class, Risperdal Consta (risperidone) and Invega Sustenna (paliperidone) do not report the possibility of post-injection delirium/sedation syndrome, which constitutes a BBW for Zyprexa Relprevv (olanzapine). The BBW for sudden death in NDRIs does not appear at all for Metadate XR (methylphenidate) and Didrex (benzphetamine), and Metadate XR (methylphenidate) also lacks the BBW for serious cardiovascular events. Finally, Actos/ActoPlus Met (pioglitazone) and Avandia/Avandaryl/Avandamet/Duetact (rosiglitazone) do not list hepatotoxicity.

Time Lag

Of the 11 drug classes with at least one BBW, we observed no time lag in three BBWs corresponding to three drug classes. These pertained to systemically administered quinolones for tendinitis and tendon rupture; thiazolidinediones for congestive heart failure; and SSRIs for suicidality. All drugs in these classes acquired the respective BBWs simultaneously. In all other cases, there were considerable time lags (see Online Appendix Table 2).

Table 1. The 20 Evaluated Drug Classes

Drug class	Index top-selling drug, active ingredient (2008 rank)	Indication(s)	Black box warning(s) of index top-selling drug	Same-class drugs (N)
Bronchodilators/LABAs, and steroidal anti-inflammatory agents	Advair Diskus, fluticasone and salmeterol (4th)	Asthma, COPD	Increased risk of asthma-related deaths	6
Miscellaneous antipsychotic agents/5HT2-D2 antagonists	Seroquel, quetiapine (6th)	Schizophrenia, bipolar I disorder	Increased mortality in elderly patients with dementia-related psychosis. Suicidality in children, adolescents, and young adults	11
Antidepressants-antianxiety agents/SNRIs-SNDRIs	Effexor XR, venlafaxine (8th)	Major depressive disorder, anxiety and panic disorders	Suicidality in children, adolescents, and young adults	5
Analgesics/narcotics/ opioid agonists	OxyContin, oxycodone (9th)	Continuous around-the-clock analgesia	Drug dependence. Fatal respiratory depression	22
Thiazolidinediones/PPAR-γ agonists	Actos, pioglitazone (10th)	Type 2 diabetes mellitus	Congestive heart failure	8
Antidepressants-antianxiety agents/SSRIs	Lexapro, escitalopram (11th)	Major depressive disorder, generalized anxiety disorder	Suicidality in children, adolescents, and young adults	10
Antiepileptics/voltage-sensitive sodium channel blockers	Lamictal, lamotrigine (19th)	Seizures, bipolar I disorder	Serious rashes (Stevens-Johnson syndrome, TEN, and rash-related deaths)	6
Analgesics/NSAIDs/COX-2 inhibitors	Celebrex, celecoxib (20th)	Inflammatory disorders of bones and joints	Cardiovascular risk. Gastrointestinal risk	2
Antibiotics, systemic/ quinolones	Levaquin, levofloxacin (22nd)	Bacterial infections	Increased risk of tendinitis and tendon rupture in all ages	12
CNS stimulants/NDRIs	Adderall XR, amphetamine/ d-amphetamine (23rd)	Attention deficit hyperactivity disorder	Drug dependence. Sudden death. Serious cardiovascular adverse events	17
Antilipidemic agents/HMG-CoA reductase inhibitors	Lipitor, atorvastatin (1st)	Cardiovascular disease-hyperlipidemia	None	10
Gastrointestinal agents/ proton pump inhibitors	Nexium, esomeprazole (2nd)	GERD, risk reduction of NSAID-associated gastric ulcer, *Helicobacter pylori* eradication, Zollinger-Ellison syndrome	None	9
Blood modifiers/antiplatelet agents/ADP receptor inhibitors	Plavix, clopidogrel (3rd)	Cardiovascular disease	None	2
Respiratory agents/leukotriene antagonists	Singulair, montelukast (7th)	Asthma, allergic rhinitis	None	1
Antivirals, systemic/nucleoside analogue DNA polymerase inhibitors against HSV	Valtrex, valacyclovir (16th)	Cold sores, genital herpes, chickenpox	None	2
Antidiabetic agents/insulin-insulin analogs	Lantus, insulin glargine (21st)	Type 1 and 2 diabetes mellitus	None	16
Antiepileptics/GABA analogs	Lyrica, pregabalin (24th)	Neuropathic pain, seizures, fibromyalgia	None	1
Antilipidemic agents/PPAR-α activators	Tricor, fenofibrate (26th)	Hypercholesterolemia, hypertriglyceridemia	None	6
Benign prostatic hyperplasia agents/alpha-1A adrenergic blockers	Flomax, tamsulosin (27th)	Benign prostatic hyperplasia	None	5
Alzheimer's disease management/ acetylcholinesterase inhibitors	Aricept, donepezil (31st)	Dementia of the Alzheimer's type	None	5

5HT, 5-hydroxytryptamine (serotonin); ADP, adenosine diphosphate; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; D, dopamine; GABA, γ-aminobutyric acid; GERD, gastroesophageal reflux disease; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HSV, herpes simplex virus; LABAs, long-acting beta-2 agonists; NDRIs, norepinephrine and dopamine reuptake inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; PPAR, peroxisome proliferator activated receptor; SNDRIs, serotonin norepinephrine dopamine reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TEN, toxic epidermal necrolysis

Overall, the time lag ranged from 2 months to 170 months (median 66; interquartile range 46–170).

DISCUSSION

We systematically assessed 176 drugs belonging to 20 drug classes and identified 15 differences in the BBW labeling among same class drugs. These differences affected 9 of the 20 drug classes, and often there was considerable time lag in the BBW acquisition. For five of these differences, the BBW context was not found anywhere in the drug labels of some same-class drugs, not even with a less intensive level of risk highlighting. Moreover, withdrawn drugs usually did not have a BBW labeling before their withdrawal, and the reason for their withdrawal rarely became a BBW in other same-class drugs.

Lasser et al. have previously reported inconsistencies among safety warnings and the time of BBW appearance among drugs

Table 2. Differences in Black Box Warnings

Drug class (top selling drug)	Black box warning	BBW present for the top-selling drug (yes/no)	Drugs without the BBW (% differences among other same-class drugs)
5HT2-D2 antagonists [Seroquel, quetiapine]	Suicidality in children, adolescents, and young adults	Yes	Risperdal, Geodon, Risperdal Consta, Invega, Fanapt, Invega Sustenna and Saphris, Zyprexa Relprevv (72%)
	Post-injection delirium/ sedation syndrome*	No	Risperdal Consta, Invega Sustenna (100%)
SNRIs/SNDRIs [Effexor XR, venlafaxine]	Suicidality in children, adolescents, and young adults	Yes	Meridia† (20%)
Opioid agonists [OxyContin, oxycodone]	Drug dependence	Yes	OxylR, Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Soma compound with codeine, Hycodan, Combunox (100%)
	Fatal respiratory depression	Yes	OxylR, Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Soma compound with codeine, Hycodan, Combunox (100%)
Thiazolidinediones [Actos, pioglitazone]	Myocardial ischemic events‡	No	Actos, Duetact, ActoPlus Met, ActoPlus Met XR, Rezulin§, Prelay§ (75%)
	Hepatotoxicity, sometimes fatal	No	Actos, Duetact, Avandia, Avandaryl, ActoPlus Met, ActoPlus Met XR, Avandamet (88%)
SSRIs [Lexapro, escitalopram]	Not approved in children (regardless of indications)	Yes	Luvox, Luvox CR, Paxil, Paxil CR, Pexeva, Zoloft, Prozac, Sarafem (80%)
Voltage-sensitive sodium channel blockers [Lamictal, lamotrigine]	Serious rashes and rash-related deaths	Yes	Trileptal, Banzel, Vimpat (50%)
COX-2 inhibitors [Celebrex, celecoxib	Serious skin reactions sometimes fatal	No	Celebrex, Vioxx§ (100%)
Norepinephrine and dopamine reuptake inhibitors [Adderall XR, amphetamine/ d-amphetamine]	Drug dependence	Yes	Didrex (6%)
	Sudden death	Yes	Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Metadate ER, Methylin, Ritalin, Ritalin LA, Ritalin, Didrex (65%)
	Serious cardiovascular adverse events	Yes	Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Metadate ER, Methylin, Ritalin, Ritalin LA, Ritalin, Didrex (65%)
ADP receptor inhibitors [Plavix, clopidogrel]	Significant, sometimes fatal, bleeding	No	Plavix, Ticlid|| (100%)
	Life-threatening hematological adverse reactions	No	Plavix, Effient (100%)

5HT, 5-hydroxytryptamine (serotonin); ADP, adenosine diphosphate; COX-2, cyclooxygenase-2 enzyme; D, dopamine; SNDRIs, serotonin norepinephrine dopamine reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

**The BBW is considered pertinent only for those 5HT2-D2 antagonists that are administered intra-muscularly and have a prolonged effective half-life (Zyprexa Relprevv, Risperdal Consta, Invega Sustenna)*

†Meridia is indicated only for weight loss and has been recently withdrawn from the EU and US markets because of increased cardiovascular risk

‡The BBW for myocardial ischemia with some thiazolodinediones was not considered pertinent for those drugs withdrawn before its issuance [Rezulin, Prelay (both troglitzone)]

§Drugs withdrawn in the US market for safety reasons

||Drugs discontinued from the US market for reasons other than safety

of the same class.[13] They observed different BBW labeling and a 2-year time lag in the acquisition of a BBW among beta-blockers. Beta-blockers are relatively inexpensive and thus were not included in our analysis, but we identified similar differences across classes of medications that lead the lists of drug expenditures.

BBWs may influence if and how a drug is prescribed, particularly when alternatives without BBWs exist.[5] The process by which a BBW is added to a drug is not systematic and may be affected by evidence, subjective choices, and conflicts of interest.[15,22] Evidence about safety is often fragmented or incomplete, and companies may justifiably pose resistance towards adopting a BBW based on evidence about another same-class drug. BBW labeling can sharply decrease sales,[19] as illustrated by the case of atypical antipsychotics.[21] Drug use dropped more than 50% after the BBW for increased mortality in dementia-affected elderly was released. This decline started within 1 month after the BBW issuance and persisted afterwards.[21] Similar sales declines were observed for droperidol [20,36] and antidepressants in children.[37,38] Consequently, drug companies resist altering the package labeling of their drugs.[22]

Table 3. Presence of the Different BBWs in Other Levels of Warnings

Drug class	Black box warnings	Drugs with differences on the BBW	BBW context in other levels of warning (drug name)
5HT2-D2 antagonists	Suicidality in children, adolescents, and young adults	Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, Risperdal, Geodon, Risperdal Consta, Invega, Fanapt, Invega Sustenna, Saphris	Adverse reactions (Invega Sustenna)
	Post-injection delirium/ sedation syndrome	Risperdal Consta, Invega Sustenna	No
SNRIs/SNDRIs	Suicidality in children, adolescents, and young adults	Meridia	Precaution (Meridia)
Opioid agonists	Drug dependence	Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Soma compound with codeine, Hycodan	Separate Section (Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Soma compound with codeine, Hycodan)
	Fatal respiratory depression	Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Soma compound with codeine, Hycodan	Warning (Roxicodone, Percocet, Percodan, Lortab, Norco, Vicodin, Vicodin ES, Vicodin HP, Zydone, Vicoprofen, Tussicaps, Tussionex Pennkinetic, Codeine Sulfate, Tylenol with codeine, Fioricet with codeine, Fiorinal with codeine, Hycodan) Overdosage (Soma compound with codeine)
Thiazolidinediones	Myocardial ischemic events	Actos, ActoPlus Met, Duetact	Warning (Actos, ActoPlus Met, Duetact)
	Hepatotoxicity	Actos, Avandia, ActoPlus Met, Avandamet, Avandaryl, Duetact	No (only abnormal liver function tests)
Voltage-sensitive sodium channel blockers	Serious rashes and rash-related deaths	Trileptal, Banzel, Vimpat	Warning/Precaution (Trileptal, Banzel, Vimpat)
COX-2 inhibitors	Serious skin reactions	Celebrex, Vioxx	Warning (Celebrex), Adverse Reaction (Vioxx)
Norepinephrine and dopamine reuptake inhibitors	Drug dependence	Didrex	Separate (Didrex)
	Sudden death	Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Metadate ER, Methylin, Ritalin, Ritalin LA, Didrex	Warnings (Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Methylin, Ritalin, Ritalin LA)
	Serious cardiovascular adverse events	Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Metadate ER, Methylin, Ritalin, Ritalin LA, Didrex	Warnings (Concerta, Focalin XR, Focalin, Daytrana, Metadate CD, Methylin, Ritalin, Ritalin LA); Contraindications (Didrex)
ADP receptor inhibitors	Bleeding risk	Plavix, Ticlid	Precaution (Plavix, Ticlid)
	Life-threatening hematological adverse reactions • TTP • aplastic anemia • neutropenia	Plavix, Effient	TTP: Warning (Plavix, Effient) aplastic anemia and neutropenia: adverse reaction (Plavix)

5HT, 5-hydroxytryptamine (serotonin); ADP, adenosine diphosphate; COX-2, cyclooxygenase-2; D, dopamine; SNDRIs, serotonin norepinephrine dopamine reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TTP, thrombotic thrombocytopenic purpura

Our study has certain limitations. We used 20 drug classes indexed by a top-selling drug. Although these drug classes do not represent all medical disciplines, a variety of common chronic diseases are included in our list, and it is unlikely that other drug classes would have more or fewer differences. We also focused on drugs marketed in the US. It would be useful for future research to examine the consistency of risk labeling in other countries, e.g., by the European Medicines' Agency (EMEA). There are numerous occasions where the FDA, EMEA, and other regulatory bodies have made different decisions on safety and efficacy issues.[39,40] Moreover, we could not find labels for all agents on Drugs@FDA, but missing information was limited and unlikely to have influenced the results much. Furthermore, we excluded generics, because we observed that the labels of these drugs were not available on Drugs@FDA. This lack of information may have important implications, since both physicians and recipients cannot draw safe conclusions on the BBW status of generic drugs.

We did not arbitrate here whether BBWs were justified based on the available evidence. Collecting, appraising and arbitrating evidence on 176 different drugs would require recapitulating decades of work by the FDA. Thus, we cannot exclude that some BBW differences are justified, e.g., very large studies may have shown that in contrast to other same-class agents, a particular drug carries no major risk. Regardless, we argue that the label should mention and justify why a major recognized risk is not an issue for a particular agent in the same class where other

members have demonstrated major toxicity. Unjustified omission of a BBW may leave patients largely unaware of potential risks, while unwarranted synchronicity of warnings within a drug class against reassuring existing evidence can adversely affect health by reducing adherence. When sufficient data from observational and clinical studies are simply not available on some drugs, while another agent in the same class has already acquired a BBW, this lack of evidence should be transparently mentioned.

Aiming to evaluate possible medical product safety issues quickly and securely, the FDA has recently initiated the Sentinel Network [41] and the Safe Use Initiative.[47] Additionally, large and well-designed randomized control trials can contribute information about medication-related harms,[42] but reporting and availability of harms information needs to be improved.[43] Systematic reviews[44] and multiple-treatments meta-analyses [45] of randomized trials may also help evaluate the efficacy and safety of drugs belonging to the same class. Such approaches may also be adopted by the FDA in order to evaluate same-class drugs. The crucial next step is improving access to the FDA reviews and disseminating consistent information to clinicians.[46,47]

Until large-scale robust evidence on adverse events becomes routinely available, the current creation and application of BBWs allows introduction of flaws.[22,48] Panels of advisors may consider only one or a few drugs, or may not discuss the labeling requirements, and there may be inconsistency about applying BBWs, as drugs may be evaluated separately. Overall, our findings imply that the process of BBW acquisition requires transparent and systematic rules and clear justification for the presence or lack of evidence for specific major risks for specific drugs.

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Corresponding Author: *John P. A. Ioannidis, MD, DSc; Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA 94305, USA (e-mail: jioannid@stanford.edu).*

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