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Correlation between Drug Market Withdrawals and Socioeconomic, Health, and Welfare Indicators Worldwide

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The relationship between the number of withdrawn/restricted drugs and socioeconomic, health, and welfare indicators were investigated in a comprehensive review of drug regulation information in the United Nations (UN) countries. A total of of 362 drugs were withdrawn and 248 were restricted during 1950-2010, corresponding to rates of 12.02 ± 13.07 and 5.77 ± 8.69 (mean ± SD), respectively, among 94 UN countries. A socioeconomic, health, and welfare analysis was performed for 33 OECD countries for which data were available regarding withdrawn/restricted drugs. The gross domestic product (GDP) per capita, GDP per hour worked, health expenditure per GDP, and elderly population rate were positively correlated with the numbers of withdrawn and restricted drugs ($P < 0.05$), while the out-of-pocket health expenditure payment rate was negatively correlated. The number of restricted drugs was also correlated with the rate of drug-related deaths ($P < 0.05$). The World Bank data cross-validated the findings of 33 OECD countries. The lists of withdrawn/restricted drugs showed markedly poor international agreement between them (Fleiss's kappa = -0.114). Twenty-seven drugs that had been withdrawn internationally by manufacturers are still available in some countries. The wide variation in the numbers of drug withdrawals and restrictions among countries indicates the need to improve drug surveillance systems and regulatory communication networks.

Keywords: Product Recalls and Withdrawals; Product Surveillance; Postmarketing; Organization for Economic Cooperation and Development; Health Expenditures; Socioeconomic Factors

INTRODUCTION

Drug market withdrawals (DMWs) may serve as an indicator for an efficient drug-surveillance and better healthcare systems of a country. Despite the length and cost of drug development, potentially damaging drugs might still be approved (1). In the 1950s, soon after thalidomide was introduced for reducing morning sickness, its terrible side effect causing limb malformations in the fetus resulted in its immediate withdrawal from the market (2). As other examples, rofecoxib and celecoxib were promoted as blockbuster drugs showing similar efficacy but fewer gastrointestinal side effects compared to traditional non-steroidal anti-inflammatory drugs, but they were recently voluntarily withdrawn by the pharmaceutical companies from the market because of increasing death rates (3). The frequency of drug withdrawals for newly approved and marketed drugs is reportedly as high as 4%-10% (4,5).

Drug withdrawals are classified into two categories: 1) the voluntary withdrawal of a drug occurs when a pharmaceutical company decides that the drug is to be withdrawn from the market and it is withdrawn worldwide immediately, and 2) the mandatory withdrawal of a drug by regional regulatory bodies or withdraw of its approval. The type of regulatory decision can differ markedly between countries because it depends on each country's health care and drug approval system, the status of the adverse drug reaction (ADR) surveillance system, socioeconomic factors, and cultural attitudes toward using and prescribing drugs. In an effort to overcome these drug regulatory variations among countries, the World Health Organization (WHO) has committed to working with more than 100 member countries of the United Nations (UN) in designing a worldwide drug surveillance system since 1997 (6). However, some drugs that are withdrawn in one country due to safety concerns are still prescribed in other countries, and there is a wide variability in the lists of withdrawn drugs in different countries. Fung reported that of 121 drugs withdrawn from the market between 1960 and 1999 due to safety reasons, 42.1%, 5.0%, and 3.3% were withdrawn from the European, North American, and Asia Pacific markets alone, while 49.6% were withdrawn from multiple continents (7). Moreover, only 19% of drugs were reportedly banned worldwide among the 151 drugs that are withdrawn by at least 1 country (8).

These discrepancies in DMWs occur even among well-developed countries (8,9). However, only a few studies have investi-

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gated the causes of and factors associated with DMWs. Moreover, evaluation studies have been conducted for the developed world only. Twice as many drugs were withdrawn from the United Kingdom (UK) market than from the United States (US) market from 1971 to 1992, with the main explanation being that the US regulatory agency applied more stringent premarket reviews and/or standards, which also took longer than the regulatory checks performed in the UK and so prevented unsafe drugs marketed in the UK from entering the US market (10). However, that study compared only the US and UK, whose drug regulations are strict and include active ADR surveillance systems, and so its results cannot be easily generalized to other countries. Countries with more elaborate premarket evaluation systems do not necessarily have fewer withdrawn drugs, since there a fewer withdrawn drugs in African countries and more withdrawn drugs in North American and European countries (7). Countries with better health care systems probably have more efficient drug surveillance systems, which would make it more likely to filter out drugs with severe ADRs at an early stage (11, 12). In contrast, countries with poor health care systems and/or poor ADR surveillance systems probably have difficulties in detecting harmful drugs and making timely decisions to withdraw them. The difference in DMWs among countries could be a useful measure for comparing health care systems across countries. Moreover, determining whether a drug that has been withdrawn internationally continues to be prescribed in a particular country could be useful for evaluating the drug administration system of that country. Previous studies on DMWs have only focused on a few well-developed countries, such as the US, UK, France, and Germany (5,9).

The present study investigated the distributions of withdrawn and/or restricted drugs in 94 UN countries and three organizations in Europe including European Commission, European Medicines Agency, and Council of Europe based on reports issued by the UN General Assembly since 1979. We also analyzed the association between the number of withdrawn/restricted drugs for each country and socioeconomic, health, and welfare factors reported by the OECD and the World Bank. More specifically, we focused on three questions: 1) Is the number of withdrawn drugs in each country correlated with major health indicators such as mortality/morbidity rate and life expectancy? 2) Can the number of withdrawn drugs of a country be used as a national health and welfare index? 3) How many drugs that are withdrawn internationally are currently prescribed in any country?

MATERIALS AND METHODS

Data source

Information about DMWs was collected by reviewing official lists of withdrawn drugs issued by the UN (UN Consolidated Lists) (6,13-15), which are the most comprehensive lists of drugs that have been withdrawn or severely restricted by at least one government. The 8th UN Consolidated List was published in 2003, which collected information about previously withdrawn/restricted drugs, and the 10th, 12th, and 14th lists provide updated information only. Drugs that were withdrawn or restricted in use internationally by the manufacturer were annotated in the lists as 'World,' and we defined these drugs as being internationally withdrawn. The WHO collected information about drug withdrawal and restriction in the UN Consolidated Lists from national authorities based on new regulatory decisions and from manufacturers on voluntary withdrawals on the grounds of safety concerns. This includes other drug-related information issued by the WHO through WHO Rapid Alerts, the WHO Pharmaceuticals Newsletter, and the journal WHO Drug Information. A drug was considered to be withdrawn if it has been withdrawn, removed, banned, or disapproved by at least one country for any reason. Drugs that have not been withdrawn but have severe restrictions for their use were counted as restricted drugs and used in further analysis in the present study.

We collected data from the OECD (16) and World Bank (17) to allow the comprehensive evaluation of the factors associated with drug withdrawals and/or severe restrictions. We focused on OECD countries since these countries exhibit comparable levels of economic development. Among the numerous statistics offered by OECD, we selected 21 health-and-welfare-related factors based on a Korean report (18) that categorized 21 indicators of health and welfare into the following 5 sectors to make composite indexes of health and welfare:

1) Economic dynamism: employment rate, real gross domestic product (GDP) growth, GDP per hour worked, consumer price index, and GDP per capita.
2) Financial sustainability: general government gross financial liabilities, general government net borrowing or net lending, and total tax revenue.
3) Welfare demand: elderly population rate (percentage of population aged at least 65 yr), Gini coefficient, relative poverty rate (50% median income), and unemployment rate.
4) Welfare fulfilment: out-of-pocket payment rate (percentage of total expenditure on health), social expenditure on childcare and preprimary education, social expenditure related to incapacity, corruption perception index, and public social expenditure.
5) National happiness: suicide mortality rate, total fertility rate, life expectancy at birth, and life satisfaction.

We added 14 health-related factors (19) to these 21 indicators, including mortality rate, life expectancy, and mortality due to major diseases. Since the last UN Consolidate List was published in 2009, providing drug regulation information from 2005 to 2008, the factors for OECD were collected from 2009 to 2010

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as well. For the purpose of validating the positive findings from the OECD data analysis, comparison data were downloaded from the World Bank website in 2010 (at http://data.worldbank.org). We analyzed these indexes of 34 member countries as well as 5 partners (Brazil, China, India, Indonesia, and South Africa) of the OECD.

Lastly, we extracted data on prescription drugs for Korea from the Health Insurance Review & Assessment Service—National Patients Sample (HIRA-NPS) of year 2011. HIRA-NPS of 2011 (serial number: HIRA-NPS-2011-0133) was a sex and 5-yr age interval-stratified random sample from the total HIRA claims data of 2011 (20). HIRA claims data covers about 90% of the total Korean population (20). The HIRA-NPS data of 2011 was comprised of 24,379,430 claims, 16,754,916 prescriptions, 1,539 prescribed drugs, and 1,375,842 patients (2.72% of the total Korean population in 2011). The listed prescription drugs were compared with the listed withdrawn drugs to identify any internationally withdrawn drugs that were prescribed in Korea. In addition, we reviewed drug regulation information obtained from the Ministry of the Korean Food and Drug Safety (KMFDS) to evaluate whether there were discrepancies between the list of withdrawn drugs for Korea reported in the UN Consolidated Lists and the actual list of drugs withdrawn in Korea. The online medicine library of KMFDS, which has collected safety letters since 2001, was reviewed at http://drug.mfds.go.kr/html/index.jsp.

Data analysis

The correlation between the numbers of withdrawn and restricted drugs was quantified using Pearson's correlation coefficient. Spearman's nonparametric correlation method was applied to evaluate the association between the number of withdrawn and restricted drugs reported to the UN and the 35 health and financial factors from the OECD and the World Bank. The intercountry agreement for the lists of withdrawn drugs was assessed using Fleiss's kappa. All quoted probability values are two-tailed. Statistical analysis was performed by the R Statistical Package, version 3.1.2 (21).

RESULTS

Number of withdrawn and/or restricted drugs

There were 362 drugs that were withdrawn and 248 drugs that were restricted (but not withdrawn) in at least 1 country in the UN Consolidated Lists. The overall numbers of withdrawn and restricted drugs on a per-country basis in the 94 countries were 12.02 ± 13.07 and 5.77 ± 8.69, respectively (Fig. 1A). The lists also reported the drugs withdrawn and restricted by the European Commission, European Medicines Agency, and Council of Europe; there were 3, 7, and 1 withdrawn drugs and 6, 4, and 0 restricted drugs, respectively, for these organizations. There were also 27 and 2 internationally withdrawn and restricted drugs, respectively. There was a significant correlation between the numbers of withdrawn and restricted drugs for the 94 countries ($P < 0.001$, $r = 0.81$) (Fig. 1B).

The five countries with the largest numbers of withdrawn drugs were Germany, USA, Oman, France, and UK, showing 68, 59, 43, 42, and 41 withdrawn drugs, respectively. The five countries with the largest numbers of restricted drug were Germany, UK, US, France, and Italy, showing 52, 42, 31, 26, and 20 restricted drugs, respectively (Supplementary Fig. 1).

Among the 39 OECD members and partners, after excluding 6 countries lacking drug regulation-related information in the UN Consolidated Lists (i.e., Czech Republic, Estonia, Luxembourg, Poland, Slovak Republic, and Slovenia), 33 countries were included for further analysis. The overall numbers of withdrawn and restricted drugs on a per-country basis in these 33 countries were 18.95 ± 15.77 and 11 ± 12.06, respectively (Fig. 2).

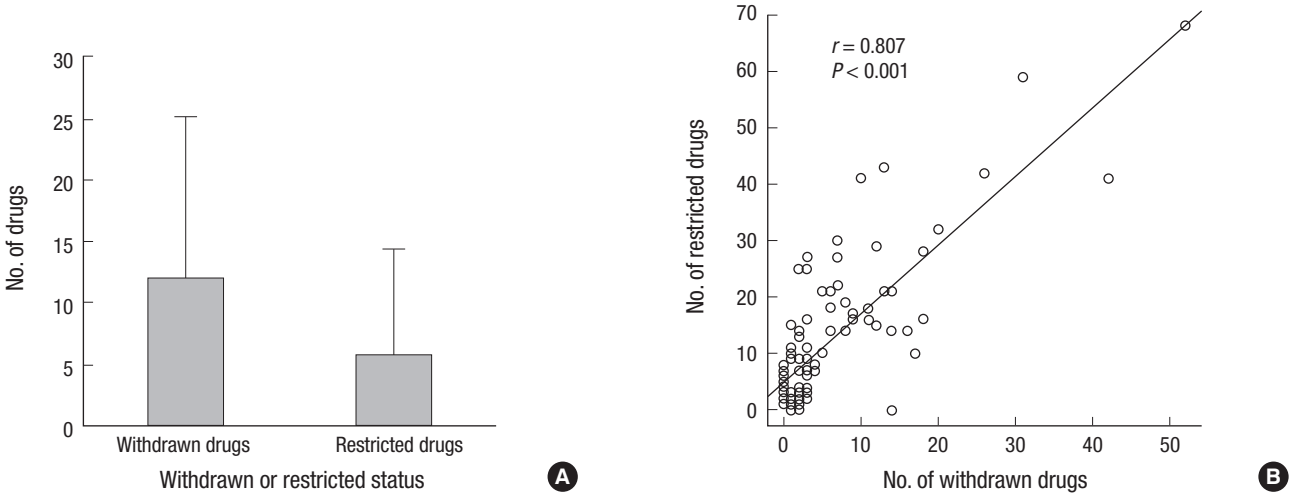

Fig. 1. Withdrawn and restricted drugs worldwide. (**A**) Distribution on a per-country basis (mean and SD data) and (**B**) correlation across 94 countries.

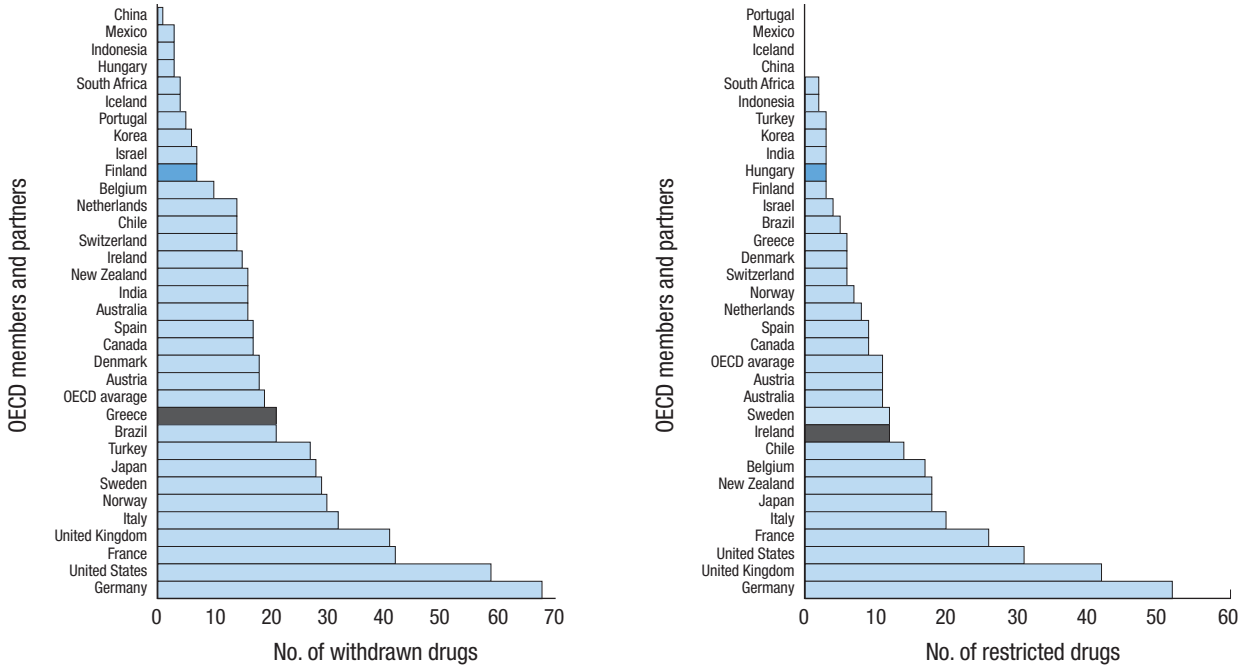

Fig. 2. Distributions of the numbers of withdrawn and restricted drugs in 33 OECD members and partners.

DMWs and OECD health and economic data

Five OECD health-and-welfare indicators—GDP per capita, GDP per hour worked, health expenditure per GDP, out-of-pocket payment rate, and elderly population rate—were significantly correlated with the numbers of withdrawn and restricted drugs ($P < 0.05$, Fig. 3 and 4). The number of restricted drugs was also significantly correlated with the number of drug-related deaths per 100,000 persons ($P < 0.05$, Fig. 4F). Out-of-pocket payment rate showed a negative correlation with the numbers of withdrawn and restricted drugs, while the other indicators showed positive correlations.

Validation of health and economic factors from the World Bank data

Six factors showed significant correlations with the numbers of drugs withdrawn and/or restricted for each of the 33 OECD countries: GDP per capita, GDP per hour worked, health expenditure per GDP, out-of-pocket payment rate, elderly population rate, and rate of drug-related deaths. These correlations were cross-validated by downloading and analyzing the matched data from the World Bank for 2010. Since the GDP per hour worked and the rate of drug-related deaths were absent from the World Bank data, we compared only the GDP per capita, health expenditure per GDP, out-of-pocket payment rate, and elderly population rate from the World Bank data with the number of withdrawn/restricted drugs for each country. As for the OECD indexes, the GDP per capita, health expenditure per GDP, and elderly population rate showed significant positive correlations with the number of withdrawn drugs in the 94 UN countries ($r = 0.496$, $P < 0.001$; $r = 0.313$, $P = 0.002$; and $r = 0.338$, $P = 0.001$; respectively) and the number of restricted drugs ($r = 0.471$, $P < 0.001$; $r = 0.442$, $P < 0.001$; and $r = 0.487$, $P < 0.001$). The out-of-pocket payment rate was negatively correlated with the number of withdrawn ($r = -0.277$, $P = 0.008$) and restricted ($r = -0.349$, $P = 0.001$) drugs in the 94 UN countries.

Poor agreement between the lists of withdrawn drugs across countries

Drugs withdrawn in one country may be prescribed in others. To evaluate the degree of agreement between the lists of drugs withdrawn from different countries, Fleiss's kappa values were measured for the five countries with the largest numbers of withdrawn drugs according to the UN Consolidated Lists (Fig. 5A) (kappa = -0.114, $P < 0.001$) and OECD data (Fig. 5B) (kappa = -0.116, $P < 0.001$) and they showed low agreements. Table 1 lists the withdrawn drugs internationally and the five countries with the largest numbers of DMWs in the OECD.

Case study: Korea

We performed a case study of withdrawn and restricted drugs for one country, Korea. Korea was ranked 26th (n = 6) in drug withdrawals and 23th (n = 2) in drug restrictions among the 33 OECD countries (Fig. 2). Two of the 27 internationally withdrawn drugs were being prescribed in Korea as of 2011. One the two, loperamide, was withdrawn internationally only in the form designed for use by children, and this form was also restricted in Korea. The other drug, aprotinin, is an antifibrinolytic molecule used to prevent major bleeding during major surgery, and

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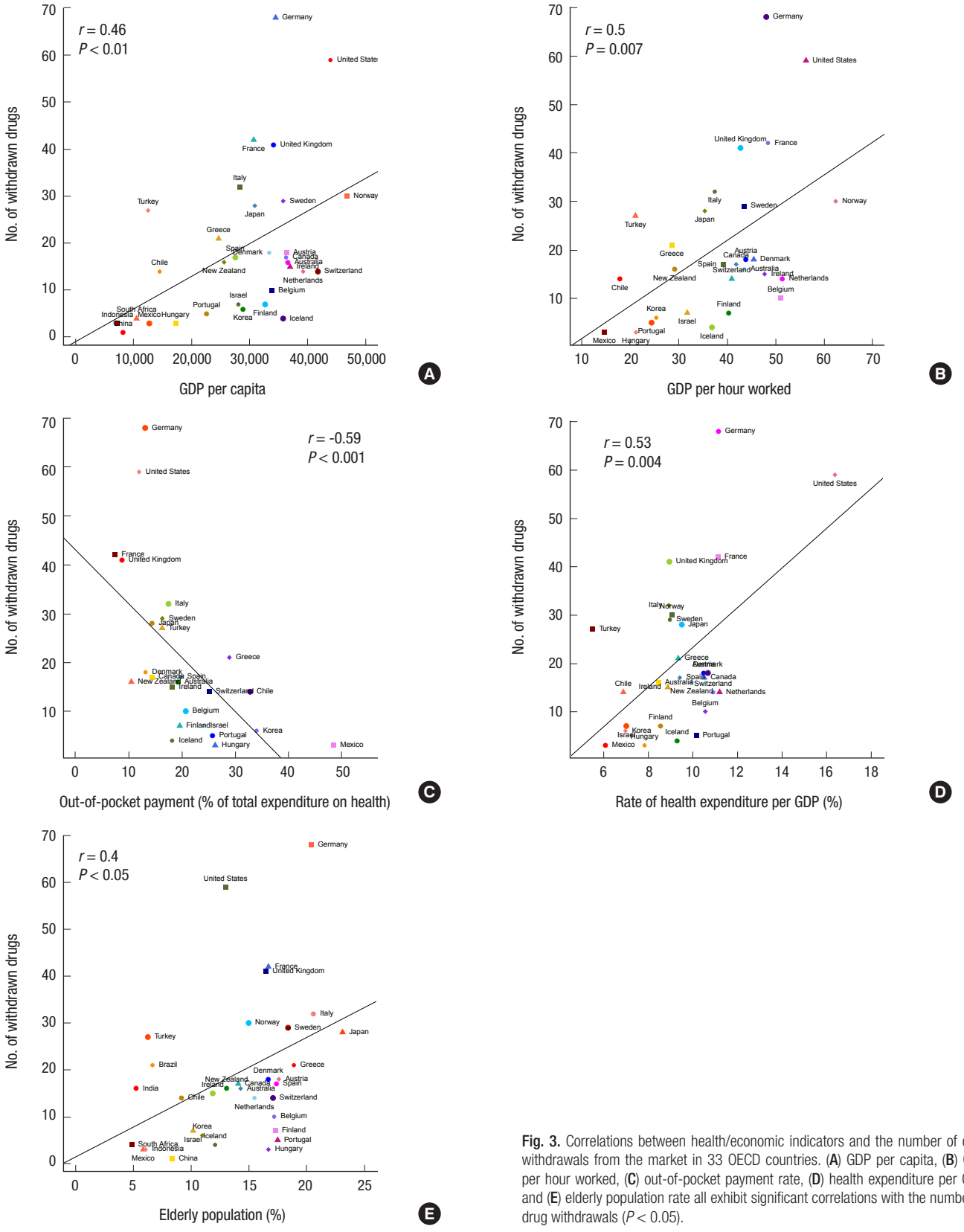

Fig. 3. Correlations between health/economic indicators and the number of drug withdrawals from the market in 33 OECD countries. (**A**) GDP per capita, (**B**) GDP per hour worked, (**C**) out-of-pocket payment rate, (**D**) health expenditure per GDP, and (**E**) elderly population rate all exhibit significant correlations with the number of drug withdrawals ($P < 0.05$).

was withdrawn worldwide in 2008, and cited as 'The manufacturer (Bayer Inc.) has been advised to suspend the marketing of this product' in the UN Consolidated Lists. The UN Consolidated Lists report that six drugs have been withdrawn (aminophen-

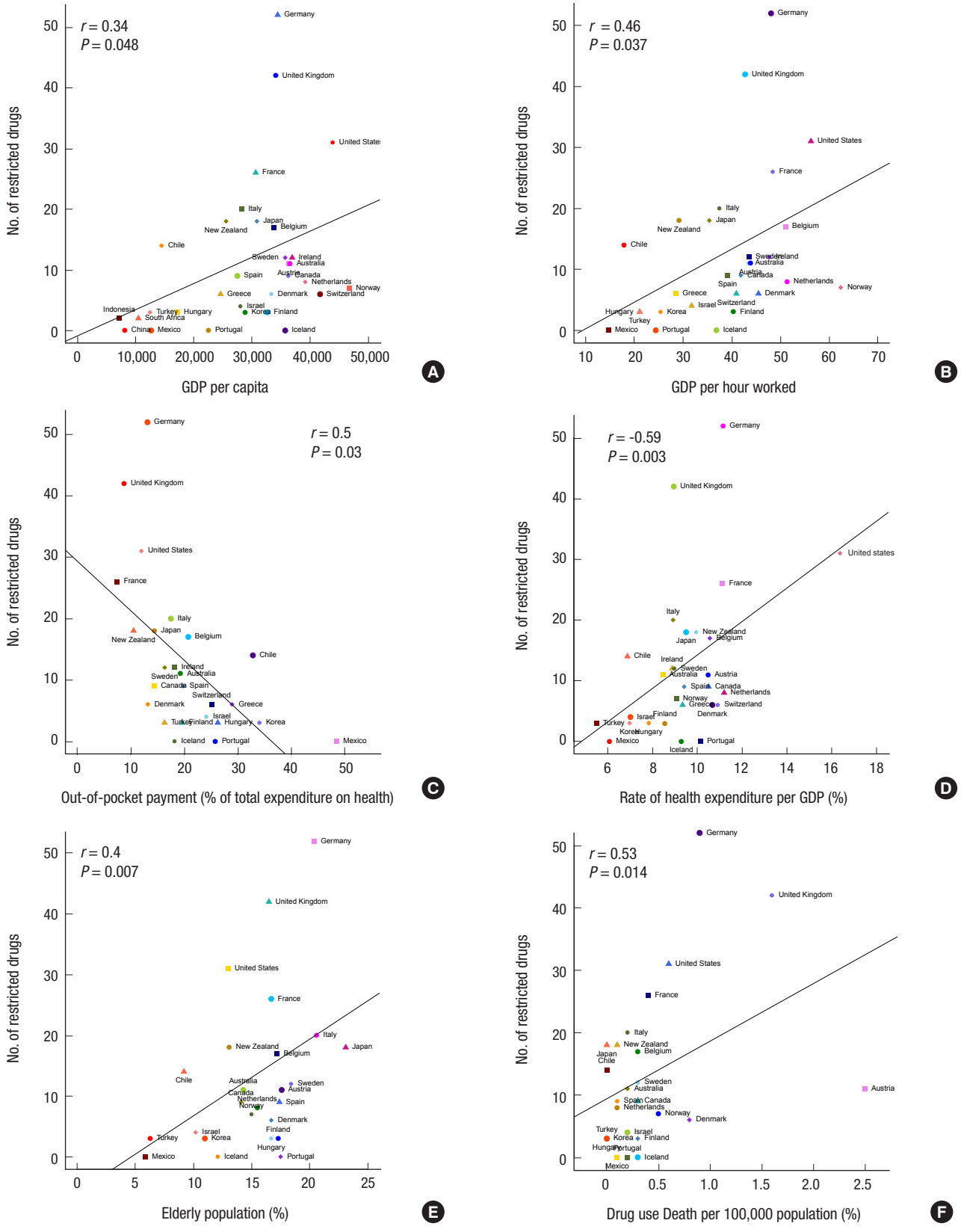

Fig. 4. Correlations between health and economic indicators and the number of drug market restrictions in the market in 33 OECD countries. (**A**) GDP per capita, (**B**) GDP per hour worked, (**C**) out-of-pocket payment rate, (**D**) health expenditure per GDP, (**E**) elderly population rate, and (**F**) drug-use deaths per 100,000 persons all exhibit significant correlations with the number of drugs restricted ($P < 0.05$).

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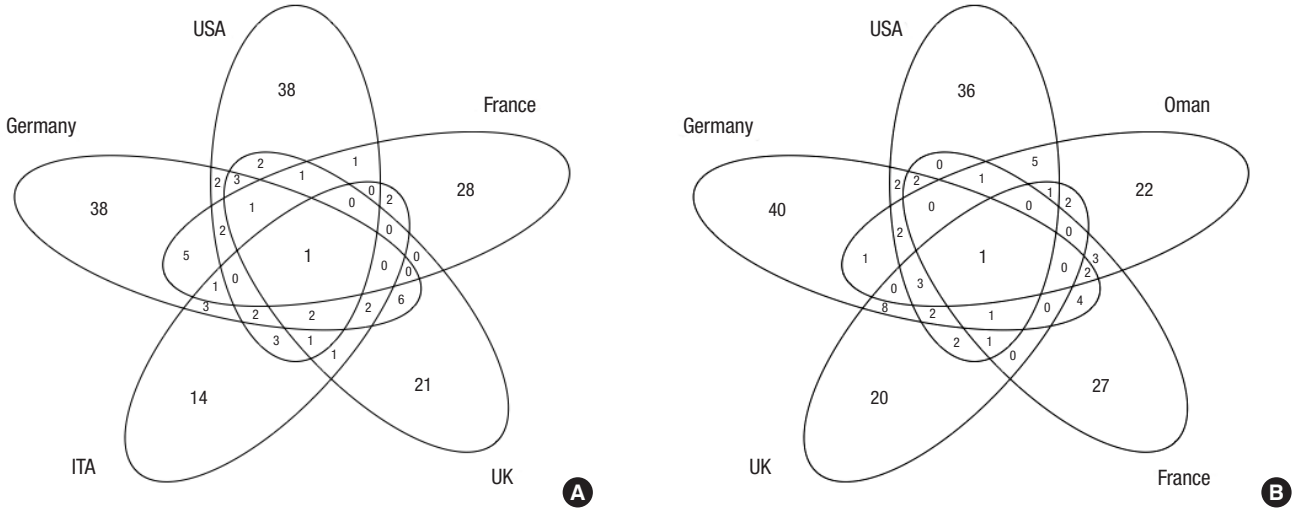

Fig. 5. Agreement of the list of withdrawn drugs in the five countries with the largest numbers of (**A**) withdrawn and (**B**) restricted drugs.

azone, boric acid and borates, difenoxin, diphenoxylate, furazolidone, and thioridazine) and three drugs have been restricted (atropine in combination, loperamide, and streptomycin) in Korea. All of these drugs are in the 8th UN Consolidated List published in 2003 (except for thioridazine, which was reported in 2005). To evaluate the possibility of underrepresentation of the UN Consolidated Lists for decisions of drug withdrawn by the KMFDS, we compared the list of withdrawn drugs collected from the online library of KMFDS with the UN Consolidated Lists. In total, 183 safety letters written from August 2001 to March 2015 were reviewed. The safety letters listed 14 ingredient drugs that were banned/withdrawn in Korea. Before October 2008, which covers the same period as the UN Consolidated Lists, three drugs were reported as being withdrawn: nefazodone hydrochloride (in 2003), thioridazine (in 2005), and aprotinin (in 2007). Aprotinin re-entered the market in the same year, and so there were actually two drugs withdrawn from August 2001 to October 2008. In the UN Consolidated Lists, six drugs were reported to be withdrawn in Korea: aminophenazone (in 1978), boric acid and borates (in 1973), difenoxin (in 1991), diphenoxylate (in 1991), furazolidone (in 1988), and thioridazine (in 2005). As a result, the nefazodone withdrawal decision in 2003 was not reported to the UN.

DISCUSSION

To our best knowledge, the present study is the first to comprehensively evaluate global drug withdrawals and restrictions in comparison with official health and economic indicators. The results demonstrate that countries with higher GDP and/or higher health expenditure per GDP withdraw more drugs. The number of withdrawn drugs was strongly and positively correlation with GDP per capita, GDP per hour worked, and health expenditure per GDP, and strongly and negatively correlated with the out-of-pocket payment rate. It is suggested that the number of drug withdrawal/restriction is relatively low in countries with high resident self-payments for health care and low government-covered payments. Pharmaceutical spending is a major component of health care expenditure among more developed countries (22), and the number of withdrawn drugs may be used as an indicator of how much a country invests in its health care system.

It is widely known that GDP per capita is correlated with major health care indicators such as life expectancy and infant mortality rate (22). We expected that drug regulation, in the form of drug withdrawals and restrictions, would also be influenced by each country's economic index and this was confirmed according to our study. But disease mortality and life expectancy were not significantly correlated with the number of drug withdrawals. It is convincing enough, because of the major health indicator, such as life expectancy or major disease mortality, were influenced mainly by infantile mortality rate, infection control, and major risk factor control (23). The impact of appropriate drug regulation on the population health could be measured by other specific indexes such as number of adverse drug reactions or drug-related mortality.

Unexpectedly, the number of drug-use deaths per 100,000 persons was positively correlated with the number of restricted drugs (Fig. 4F). This was unexpected because one would expect to see smaller drug-use death rates in a country with a higher number of restricted drugs. It could be possible that there was a detection/reporting bias in that the countries that survey and report drug-related death more accurately could regulate the dangerous drugs more strictly. Because the illicit drug use and

Table 1. The list of withdrawn drugs in the top 5 OECD countries having highest number of withdrawn drugs and the list of internationally withdrawn drugs

Country (No. of withdrawn drugs)	Drugs
Germany (n = 68)	Albumin, alclofenac, aminophenazone, aminorex, anagestone acetate, aristolochic acid, benzarone, betaethoxylacetanilide, boric acid and borates, bucetin, buformin, canrenone, canthaxanthin, cartilage extract, cell preparations, chloroform, chlorphentermine, cianidanol, cinchophen, cisapride, clofibrate, cloforex, dantron, difemerine, dionaeamuscipula extract, ethylene dichloride, feprazone, gangliosides, germander, ginkgo biloba, glafenine, glucosamine sulfate, herpes simplex vaccines, indoprofen, isoxicam, ketoconazole, L-tryptophan, megestrol acetate, mesna, methapyrilene, mibefradil, muzolimine, nitrefazole, nomifensine, omeprazole, orgotein, oxeladin, oxyphenisatine acetate, phenacetin, phenformin, phenylpropanolamine, polyvidone, potassium canrenoate, practolol, pyrrolizidine, rubiaetinctorumradix, sulfacarbamide, sulfadicramide, sulfadimidine, sulfaguanidine, sulfamerazine sodium, sulfanilamide, sulfisomidine, suloctidil, tienilic acid, triacetyl diphenolisatin, urethane, vincamine
United States (n = 59)	Androgens, amaranth, amfetamine, aminoglutethimide, aminophenazone, amiprilose, aphrodisiac drugs, benzyl penicilin sodium topical preparations, bithionol, bromfenac, bunamiodyl, calamus, chlormadinoneacetate, chloroform, cisapride, cobalt non radioactive forms, cyclandelate, dalkonshield, dantron, depot medroxyprogesterone acetate (dmpa), dexamfetamine, dihydrostreptomycin, dimazole, ephedra, ethylnitrite spirit, halogenated salicylanilides, hydromorphone hydrochloride, interferon gamma 0b, iodinated caseinstrophanthin neo barine, l-tryptophan, laetrile, levacetyl methadol, levamfetamine, metamizole sodium, methapyrilene, metofoline, mibefradil, oxyphenisatineacetate, pemoline, pergolide, pexiganan, phenacetin, phenformin, phenylpropanolamine, pipamazine, pituitary chorionicgonadotropin injectable, prasterone, quininesulfate, sargramostim, somatropin pituitary derived, sulfathiazole, technetium-99 mtc fanolesomab, terfenadine, tetracycline paediatric, thenalidine, tienilicacid, urethane, valdecoxib, vinarol and viga
France (n = 42)	Acetyl salicylic acid (paediatric), alpidem, amineptine, aminophenazone, aristolochic acid, benzbromarone, bismuth salts, bovine tissue derived medicines, camellia sinensis, chloramphenicol, clometacin, coumarine synthetic, dithiazanineiodide, germander, glafenine, indalpine, isaxoninephosphate, isoxicam, ketoconazole, lead oxide and lead salts, medifoxamine, metamizole sodium, moxisylyte, mucopolysaccharide polysulfuric acidester, muzolimine, naftidrofuryl parenteral formulations, nandrolonedecanoate injectable, oxeladin, oxyphenisatine acetate, phenformin, phenobarbital, phenolphthalein, placental tissue derived medicine, podophyllumresin, potassium chloride, potassium nitrate, proxibarbal, terfenadine, thenalidine, tienilicacid, tilbroquinol, xenazoic acid
United Kingdom (n = 41)	Albumin, alclofenac, amfepramone hydrochloride, aminophenazone, aristolochia, bicalutamide, boric acid and borates, chlormadinone acetate, chloroform, cisapride, dalkonshield, dinoprostone, droperidol, factorvIII, fenclofenac, feprazone, flosequinan, gamelonic acid, grepafloxacin hydrochloride, indoprofen, l-tryptophan, meprobamate, methapyrilene, metrodin-hp, mibefradil, nomifensine, noscapine, oxyphenbutazone, phenformin, phentermine, phenylephrine, practolol, pumactant, pyrrolizidine, sertindole, somatropin (pituitary-derived), thenalidine, tolcapone, triazolam, troglitazone, ximelagatran
Italia (n = 32)	Alclofenac, aminophenazone, arsenic based compounds, barbital, benzyl penicillin sodium topical preparations, chlormadinone acetate, chloroform, cianidanol, cinchophen, clioquinol (see also halogenated hydroxyquinoline derivatives), dienestrol, diethylstilbestrol, dihydro streptomycin, dithiazanine iodide, halogenated hydroxyquinoline derivatives, hexestrol, indoprofen, iproniazid, isoxicam, lobelia, methapyrilene, opiumin antitussive preparations, phenacetin, piperazine, podophyllum resin, polyoxyethylated castor oil, suxibuzone, tetracycline (paediatric), tranylcypromine, triacetyldiphenolisatin, triazolam, urethane
Internationally withdrawn drugs (n = 27)	Benoxaprofen, chlormezanone, cianidanol, dilevalol, domperidone (injectable), fenfluramine, glafenine, indoprofen, isoxicam, loperamide, nebacumab, nomifensine, phenolphthalein, pirprofen, polyoxyethylatedcastoroil, prenylamine, remoxipride, suloctidil, suprofen, temafloxacin, terodiline, tolrestat, vaccines (for mumps, measles, and rubella), zimeldine, zomepirac, cerivastatin, aprotinin

drug-related mortality are difficult to survey even in developed countries (24), the countries with more well-organized drug surveillance and regulation system would not only have more restricted drugs but also higher drug-related death rates. However, it is hard to conclude that there would be such biases in reported drug-related death only from this study so further evaluation is needed.

The drugs listed as being withdrawn were highly variable even among the top five countries. This finding is consistent with previous reports of many single market withdrawals, where most of these withdrawals were in European countries (7). The difference may be due to differences in the drugs used by different countries, the control that major pharmaceutical companies have over the prescription drug market, the drugs newly entering the market, and cultural and institutional standards related to the prescribing of drugs.

Two drugs that were withdrawn prior to 2008 worldwide were still prescribed in 2011 in Korea. In case of loperamide, the withdrawal applied only to the syrup form for use by children, and its use by children was also restricted in Korea. Aprotinin was withdrawn in 2008 due to the increasing death rate among patients, but 4 yr later the European Union reapproved it due to its effectiveness being considered to override its harmful effects. The Korea Food and Drug Administration allowed this drug for use only in limited cases according to a safety letter published in 2008 (25). Drugs that were withdrawn from the US market did not appear either in the withdrawn or the prescription drug list in Korea. Some drugs withdrawn in Europe were found to be not withdrawn from the prescription drug list in Korea. It seems that the drugs withdrawn in the US may have failed to enter the Korean pharmaceutical market and that there may be some authority-level interactions in drug regulation processes. As indicated in Table 1, the 27 internationally withdrawn drugs represent 46% of the 59 drugs withdrawn by the US Food and Drug Administration according to the UN Consolidated Lists. Therefore, it is important for regulatory authorities to globally monitor ADRs and regulatory decisions for drugs and to establish their own drug surveillance systems and regulatory guidelines.

It may not be necessary for any particular country to withdraw all drugs that are withdrawn by other countries. The decision for a drug withdrawal is influenced by various factors, in-

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cluding social, cultural, economic, and ethical issues. A DMW is a result of complex political, social, ethical, and economic issues as well as ADRs and drug effectiveness. Therefore, we must ascertain the regulatory decisions in other countries sensitively and at the same time identify the local occurrence of severe ADRs in a timely manner. The regulatory decision-making in Korea has largely reflected decisions made in large countries such as the US, Japan, and European countries (26). Because ADRs depend on patterns of drug use that differ between countries, it is necessary to establish a domestic surveillance system and appropriate regulatory guidelines.

An important limitation of the present study is that the observed correlations do not necessarily indicate causality. Regulation of a drug involves a variety of functions; licensing, inspection of manufacturing facilities and distribution channels, product assessment and registration, ADR monitoring, quality control, control of drug promotion and advertising, and control of clinical drug trials (27). In this study, countries with many withdrawn/restricted drugs tend to be well developed and hence also have large pharmaceutical industries. The number of withdrawn drugs is clearly correlated with the number of drugs marketed or the overall market size of the country. Thus, the results of the present study on health and economic factors could have been affected by many confounders. However, it is highly likely that the number of drugs withdrawn/restricted by a regulatory authority can be a useful indicator for a country's optimum level of economic investments in the health care system affecting drug regulation processes.

Another limitation is that the number of imported drugs was not counted due to a lack of information. If a country operates a slow and conservative drug approval system, the rate of post-market drug withdrawals may be lower. Evaluation of the different drug approval systems was beyond the scope of the present study. Because drug approval systems have evolved over time, time-series analyses of approved and banned drugs for different countries should be performed in future comparative studies.

The UN Consolidated Lists of Products are not perfect. Some important data are clearly missing, as exemplified in the case study of Korea where one of the two withdrawn drugs has not been reported to the UN for 8 yr. Nevertheless, the lists are known to be the most comprehensive and authorized available information sources. Finally, the claims data for the whole Korean population from the Health Insurance Review Agency are related to prescription drugs only, and not over-the-counter drugs.

In conclusion, the number of drug withdrawals and restrictions can be used as an indicator of a country's level of investment in its health care system. The lists of withdrawn and restricted drugs vary markedly between countries, such that a drug withdrawn in one country may be prescribed in another. Even drugs withdrawn internationally by drug manufacturers are still being prescribed in some countries. While authorities closely collaborate with each other, it seems that there remains room for improvements in the current drug regulatory systems worldwide. New drugs will continuously appear both with improved health care benefits and potentially harmful ADRs. Moreover, new indications for drugs will emerge and the usage patterns will change constantly. Further improvements at both the global and national levels are required in drug surveillance systems and regulatory communication networks.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceived and designed the study: Lee KH, Kim JH. Data collection and analysis: Lee KH, Kim GJ. Writing the first draft: Lee KH. Review and revision: Lee KH, Kim GJ, Kim JH. Agreeing with manuscript results and conclusions, approval of final manuscript: Lee KH, Kim GJ, Kim JH.

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