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Analysis of the toxic and lethal doses of one over-the-counter drug product in humans and the ingredients that may be abused: Building a drug database to prevent drug overdoses

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Abstract: Pharmacists who provide medication to patients immediately before they overdose should intervene appropriately; however, little information exists on the types and amounts of over-the-counter (OTC) drugs that are dangerous. This study investigated the toxicity and characteristics of overdosing on a single package of commercially available OTC drugs in humans. We researched 14,107 OTC drugs. The number of products that could contain a lethal dose if taken as a single package was 1,223 (8.7%) and a toxic dose was 2,982 (21.1%). A single product containing a lethal dose to humans by therapeutic category included skin drugs (n = 672, 25.0%), psychotropic drugs (n = 288, 17.9%), and public health drugs (n = 92, 26.1%) in descending order. Comparing before and after April 2023, the number of OTC pharmaceuticals that contained ingredients that may be abused, significantly increased: psychotropic drugs (44.9% increase), respiratory drugs (8.2% increase), and urogenital and anal organs drugs (3.5% increase) ($p <$ 0.05). These products had not been previously designated as hazardous despite their potential for abuse. The registrants in the "Drug Database for Overdose Prevention" that made these public included 199 pharmacists, registered sellers, and doctors as of July 31, 2024. The city with the most users was Osaka (377 users) and an average engagement time of 41.8 seconds, followed by Sapporo, Fukuoka, and Nagoya. These areas were consistent with urban centers and high numbers of emergency transports due to overdose. Our findings provide important pharmaceutical information that pharmacists can use for their gatekeeper activities.

***Keywords*:** database, overdose, over-the-counter drug, lethal dose, toxic dose, pharmacist

Introduction

Overdoses have increased in recent years, particularly for the use of over-the-counter (OTC) drugs (*1,2*). There have been reports in Japan and other countries of OTC drugs being used for self-harm and suicide (*3*). Japanese OTC drugs contain multiple ingredients and have some characteristics that are not present in overseas OTC drugs; however, there is little information on what types and amount of OTC drugs are dangerous. This valuable information can be used as a gatekeeper to prevent overdose.

Individuals who play a role in preventing overdose and suicide by "noticing" and "listening" are considered "gatekeepers." The Japanese Ministry of Health, Labor, and Welfare stated that "pharmacists who have many opportunities to come into contact with information about residents' health conditions through dispensing medicines and selling pharmaceuticals" as examples of gatekeepers (*4*). In contrast, according to a survey of pharmacists and registered sellers, when acting as a gatekeeper, the percentage of individuals who answered "There is no information or measures to prevent overdosing" and "There is no specific information on dosage regarding overdosing" was 52% and 53.4%, respectively (*5*). Furthermore, in response to the question of what type of information would be useful for taking measures against overdoses, the percentage of individuals who wanted "information on the names of dangerous drugs in the event of an overdose" and "information on drugs used in current overdoses" was 72.8% and 76.2%, respectively (*5*). Thus, it is evident that there is a lack of information available that would enable measures to be taken to prevent overdose in clinical settings, such as pharmacies and drugstores. Furthermore, in a previous report by the author, "workplace measures" were identified as a factor in the ability to intervene as a gatekeeper with subjects by both pharmacists and registered sellers. Thus, it is important to introduce tools to combat overdose (*5*).

In a recent report, 65.9% of drugs used in overdoses

were obtained from brick-and-mortar stores, whereas only 9.3% were purchased online (*6*). Therefore, pharmacists and registered distributors who may hand over medication to a patient just before they overdose should be aware of the toxicity of the product itself and intervene where appropriate. However, there have been no reports examining the toxicity to humans caused by overdosing on a single package of OTC drug products currently on the market. In this study, we characterized the toxicity to humans of overdosing on a single package of OTC drugs that are currently in circulation. In addition, we examined the characteristics of products that contain ingredients that may be abused. The scope of these ingredients has been expanded as of April 2023, as specified by the Minister of Health, Labor, and Welfare.

Materials and Methods

Survey of OTC drugs and their toxicity to human

This study covered the ingredients of OTC drugs listed in the Japan Pharmaceutical Information Center (JAPIC) over-the-counter drug collection (July 2021 edition). The amount of each ingredient contained in the entire product was calculated. We also surveyed the dosage that is considered dangerous in the event of an overdose using the Japanese Society for Clinical Toxicology's Guide to Standard Clinical Practice for Acute Poisoning (*7*), Clinical Toxicology (*8*), the pharmaceutical package insert, and the literature (*9-15*). Next, we built a centralized database that could be used to gather all of the information. In addition, we focused on ingredients that the Minister of Health, Labor, and Welfare has warned of potential abuse. Thus, a database was established that provides an assessment of toxicity for a particular dose. For risk classification, we examined Class 1 drugs, Class 2 drugs, Designated class 2 drugs, Class 3 drugs, and Quasi drugs. We also evaluated drugs by 18 therapeutic categories, which included psychotropic drugs, digestive tract drugs, cardiovascular and hematological drugs, respiratory drugs, urogenital and anal organ drugs, tonic health drugs, women's drugs, allergy drugs, skin drugs, ophthalmic drugs, otorhinolaryngological drugs, dental and oral cavity drugs, smoking cessation agents, Kampo preparations, herbal preparations (preparations not belonging to other therapeutic classes), public health drugs, general test kits, and others (preparations not belonging to any therapeutic category). These classifications were registered in the JAPIC over-the-counter drug collection.

OTC drugs that contain ingredients that may be abused as designated by the Minister of Health, Labor, and Welfare

We examined the number of products that contain ingredients for which the Minister of Health, Labor, and Welfare has warned about the risk of misuse. The specific ingredients included ephedrine, codeine, dihydrocodeine, bromovalerylurea, pseudoephedrine, and methylephedrine. We compared the products containing these designated ingredients up until March 2023 with those containing the designated ingredients after the April 2023 additions, based on the therapeutic category (*16*). We also determined the toxic and lethal doses of these substances in humans based on the literature (*7-15*).

Building a drug database to prevent drug overdoses

For the server, XServer was used (PHP 7.4, MySQL 5.7, Apache version 2.4). WordPress 6.3 was used as the Contents Management System (CMS). Data on the drugs was gathered as described in the previous section, and the basic data was constructed. The drug data was exported in Comma Separated Values (CSV) format and imported in bulk using the WordPress plugin WP All Import. A drug search function was created using WordPress.

Number of people registered with and access to the "Drug Database for Overdose Prevention"

The database was made public on the Internet and linked to Google Analytics. We examined changes in access to the homepage and the characteristics of the search results. The survey period was from April 1, 2023, to June 25, 2024, and the number of registered users were as of July 31, 2024.

Statistical analysis

Chi-square test was conducted using JMP Pro 18 software (SAS Institute Inc., NC, USA). The significance level was set to 0.05.

Ethical statement

This study was reviewed and approved by the Institutional Review Board of the Graduate School of Pharmaceutical Sciences, Chiba University (No. R054).

Results

OTC drugs surveyed and their toxicity to humans per product

We determined whether each OTC drug product constituted a toxic or lethal dose in humans. The survey covered 10,773 different products, and 14,107 products when multiple contents were considered. The number of products that could contain a lethal dose if one package were to be taken as an overdose was 1,223 (8.7%), whereas the number of products that could contain a toxic dose was 2,982 (21.1%) (Table 1). With respect to a therapeutic category, the most common products with

lethal doses to humans were dermatological drugs (672, 25.0%), followed by psychoneurological drugs (288, 17.9%), and public health drugs (92, 26.1%).

Relationship between risk categories of surveyed OTC drugs and toxic or lethal doses in humans

We determined the relationship between the risk classification of OTC drugs and the toxic or lethal dose in humans. The number of products that fell into this risk category by therapeutic category is listed in Table 2. A comparison of risk categories (Class 1 drugs, *etc.*) and drugs whose total content in one package corresponds to a lethal or toxic dose for humans (Table 1) indicated that they do not necessarily match.

Ingredients that are toxic or lethal to humans in one product

To determine which ingredients per product could pose toxic or lethal doses to humans, the data were examined by therapeutic category. Specific ingredients included caffeine, acetaminophen, diphenhydramine, ethanol, menthol, salicylic acid, and aspirin. There were also cases in which the entire content of one package contained a lethal dose to humans (Table 3). For public health drugs, there were examples in which the entire amount of a single package of characteristic ingredients, such as N, N-Diethyl-meta-toluamide (DEET), dichlorvos, fenitrothion, sodium hypochlorite, trichlorfon, and cresol, was sufficient to be lethal to humans.

Changes in regulations regarding OTC drugs containing ingredients that may be abused as designated by the Minister of Health, Labor, and Welfare

To determine the regulatory status of each ingredient, we evaluated products that contain ingredients designated by the Minister of Health, Labor, and Welfare as likely to be abused. Until March 31, 2023, the Minister of Health, Labour, and Welfare determined that the products containing ingredients that may be the subject of abuse were respiratory organ drugs (188, 35.9%), followed by psychotropic drugs (131, 8.2%) and otorhinolaryngological drugs (92, 27.2%), in order of efficacy. Next, we examined the increase in the number of products resulting from the addition of new designations after April 1, 2023, according to the therapeutic category. A significant increase was observed ($p < 0.05$) for psychotropic drugs (44.9% increase), respiratory drugs (8.2% increase), and urogenital and anal organ drugs (3.5% increase), with additional products in other therapeutic categories (Table 4). These products had not previously been designated as hazardous despite their potential for abuse.

Table 1. The number of OTC drugs surveyed and risk of being abused or have lethal and toxic doses

Therapeutic Category[a]	Number of target products (JAPIC OTC drugs, July 2021 edition) *n*	Number of products surveyed: multiple contents *n*	When taking 1 product (1 box/1 bottle)	
			Number of products with toxic doses for human[b] *n* (%)	Number of products with lethal doses for human[c] *n* (%)
Psychotropic drugs	1,188	1,607	255 (15.9)	288 (17.9)
Digestive tract drugs	1,094	1,730	136 (7.9)	0 (0)
Cardiovascular and Hematological Drugs	246	407	12 (2.9)	0 (0)
Respiratory drugs	407	524	45 (8.6)	65 (12.4)
Urogenital and anal organs drugs	167	230	153 (66.5)	0 (0)
Tonic health drugs	1,609	2,236	80 (3.6)	3 (0.1)
Women's drugs	101	151	61 (40.4)	0 (0)
Allergy drugs	26	34	4 (11.8)	2 (5.9)
Skin drugs	2,305	2,684	253 (9.4)	672 (25.0)
Ophthalmic drugs	478	482	33 (6.8)	2 (0.4)
Otorhinolaryngological drugs	272	338	116 (34.3)	79 (23.4)
Dental and oral cavity drugs	258	305	0 (0)	0 (0)
smoking cessation agents	11	27	0 (0)	20 (74.1)
Kampo preparation	2,120	2,697	1,726 (64.0)	0 (0)
Herbal preparation (Preparations not belonging to other therapeutic classes)	226	280	108 (38.6)	0 (0)
Public health drugs	244	352	0 (0)	92 (26.1)
General test kits	17	17	0 (0)	0 (0)
Others (preparations not belonging to any therapeutic category)	4	6	0 (0)	0 (0)
Total	10,773	14,107	2,982 (21.1)	1,223 (8.7)

[a]Classifications registered with JAPIC. [b,c]Total number. The denominator of the percentage was the number of products in the multiple contents survey.

Table 2. Risk classification of surveyed OTC drugs

Therapeutic Category[a]	Number of products surveyed: multiple contents *n*	Risk classification				
		Class 1 drugs, *n* (%)	Class 2 drugs, *n* (%)	Designated class 2 drugs, *n* (%)	Class 3 drugs, *n* (%)	Quasi drugs, *n* (%)
Psychotropic drugs	1,607	18 (1.1)	236 (14.7)	1,323 (82.3)	25 (1.6)	5 (0.3)
Digestive tract drugs	1,730	19 (1.1)	789 (45.6)	308 (17.8)	536 (31.0)	78 (4.5)
Cardiovascular and Hematological Drugs	407	3 (0.7)	287 (70.5)	8 (2.0)	109 (26.8)	0 (0)
Respiratory drugs	524	2 (0.4)	82 (15.6)	268 (51.1)	135 (25.8)	37 (7.1)
Urogenital and anal organs drugs	230	18 (7.8)	62 (27.0)	146 (63.5)	0 (0)	4 (1.7)
Tonic health drugs	2,236	2 (0.1)	645 (28.8)	38 (1.7)	1,258 (56.3)	293 (13.1)
Women's drugs	151	9 (6.0)	63 (41.7)	11 (7.3)	64 (42.4)	4 (2.6)
Allergy drugs	34	0 (0)	31 (91.2)	3 (8.8)	0 (0)	0 (0)
Skin drugs	2,684	43 (1.6)	996 (37.1)	465 (17.3)	1,041 (38.8)	139 (5.2)
Ophthalmic drugs	482	0 (0)	239 (49.6)	0 (0)	238 (49.4)	5 (1.0)
Otorhinolaryngological drugs	338	1 (0.3)	214 (63.3)	120 (35.5)	0 (0)	3 (0.9)
Dental and oral cavity drugs	305	0 (0)	25 (8.2)	19 (6.2)	164 (53.8)	97 (31.8)
Smoking cessation agents	27	6 (22.2)	0 (0)	21 (77.8)	0 (0)	0 (0)
Kampo preparation	2,697	0 (0)	2,675 (99.2)	18 (0.7)	4 (0.1)	0 (0)
Herbal preparation (Preparations not belonging to other therapeutic classes)	280	0 (0)	194 (69.3)	36 (12.9)	49 (17.5)	1 (0.4)
Public health drugs	352	16 (4.5)	324 (92.0)	0 (0)	10 (2.8)	2 (0.6)
General test kits	17	7 (41.2)	10 (58.8)	0 (0)	0 (0)	0 (0)
Others (preparations not belonging to any therapeutic category)	6	1 (16.7)	0 (0)	0 (0)	5 (83.3)	0 (0)

[a]Classifications registered with JAPIC. The denominator of the percentage was the number of products in the multiple contents survey.

Table 3. Ingredients in surveyed OTC drugs that are at lethal or toxic doses to humans

Therapeutic Category[a]	1 product (1 box/1 bottle): Human toxic dose ingredient name (example)	1 product (1 box/1 bottle): Human lethal dose ingredient name (example)
Psychotropic drugs	bromovalerylurea, caffeine, ibuprofen, liquorice, Cyperus rhizome, acetaminophen, diphenhydramine	bromovalerylurea, caffeine, methylephedrine, acetaminophen, aspirin, dihydrocodeine
Digestive tract drugs	liquorice, Cyperus rhizome	not applicable
Cardiovascular and Hematological Drugs	liquorice, caffeine	not applicable
Respiratory drugs	liquorice, theophylline, caffeine, diphenhydramine	methylephedrine, dihydrocodeine, caffeine, menthol
Urogenital and anal organs drugs	lidocaine, liquorice	not applicable
Tonic health drugs	caffeine, liquorice, Cyperus rhizome	caffeine
Women's drugs	caffeine, liquorice, Cyperus rhizome	not applicable
Allergy drugs	liquorice, diphenhydramine	diphenhydramine, methylephedrine
Skin drugs	liquorice, diphenhydramine, menthol, naphazoline, isopropanol, lidocaine	diphenhydramine, menthol, ethanol, isopropanol, benzalkonium chloride, salicylic acid, ammonia solution
Ophthalmic drugs	naphazoline, boric acid	boric acid
Otorhinolaryngological drugs	naphazoline, fexofenadine, caffeine, loratadine	ephedrine
Dental and oral cavity drugs	not applicable	not applicable
smoking cessation agents	not applicable	nicotine
Kampo preparation	liquorice, Cyperus rhizome, Scutellaria root, rhubarb	not applicable
Herbal preparation (Preparations not belonging to other therapeutic classes)	liquorice, Cyperus rhizome, Scutellaria root	not applicable
Public health drugs	not applicable	DEET, dichlorvos, fenitrothion, sodium hypochlorite, trichlorfon, saponated cresol solution, ethanol, diazinon
General test kits	not applicable	not applicable
Others (preparations not belonging to any therapeutic category)	not applicable	not applicable

[a]Classifications registered with JAPIC.

Publication and access status of the "Drug Database for Overdose Prevention"

For safety reasons, the constructed database was made available on the Internet with registration and permission (*https://overdose-med.com*). The database also makes public the specific product names of the OTC drugs as well as the literature and package insert information.

To determine how the published website was being used, Figure 1A shows the change in user engagement over time since publication on the Internet. We also determined the regions and countries from which the homepages were accessed (Figure 1B). In terms of access, Japan had the highest interaction at 5,290, followed by the United States of America with 125, and Taiwan R.O.C. with 99 (Figure 1B). Access was detected not only from Japan and Asia, but also from North America and Europe. A total of 199 people were registered with the website, including 187 pharmacists (94.0%), 7 registered sellers (3.5%), and 5 others (2.5%), including doctors (Figure 1C). We also identified the top 15 regions by city/town/village based on the number of users in Japan, excluding the not set, which did not register a region (1,620 users, average engagement time 29.6 s) (Figure 1D). The city with the most users was Osaka at 377 users and an average engagement time of 41.8 s, followed by Sapporo, Fukuoka, Nagoya, Chiyoda city, and Yokohama (Figure 1D). These areas are urban and corresponded to a high number of people being taken to emergency facilities for drug overdoses.

Discussion

Of the OTC drugs included in this study, 1,223 products contained a lethal dose if taken in one package, whereas 2,982 contained a toxic dose. Overall, the fatal and toxic dose rates were 8.7% and 21.1%, respectively. The specific ingredients found in lethal doses from a single package included methylephedrine, caffeine, diphenhydramine, and ethanol, which are present in OTC drugs across multiple therapeutic categories. In addition, characteristic public health drugs were listed, including DEET, dichlorvos, and fenitrothion. Furthermore, the risk classification of OTC drugs (Class 1 drugs, *etc*.) did not always match the number of drugs that were considered lethal or toxic to humans in one full package. Therefore, pharmacists and other individuals with specialized knowledge should provide appropriate warnings, manage the distribution of OTC medicines, and provide guidance on how to properly use them. The risk classification is currently under review by the Drug Sales System Review Committee of the Ministry of Health, Labor, and Welfare. As of February 2024, two categories of medicines remain under discussion: medicines sold by pharmacists and medicines sold by pharmacists or registered sellers. It will be necessary to monitor these for future regulatory changes.

Table 4. Number of OTC drugs surveyed that are at risk of being abused or lethal or toxic

Therapeutic Category[a]	Number of products surveyed: multiple contents *n*	Number of over-the-counter drugs containing ingredients designated by the Minister of Health, Labour and Welfare as "drugs that may be abused, *etc*."			*p*
		Total, *n* (%)	Number of products till March 31, 2023 *n* (%)	Number of additional products from April 1, 2023 *n* (%)	
Psychotropic drugs	1607	852 (53.0)	131 (8.2)	721 (44.9)	< 0.01*
Digestive tract drugs	1730	0 (0)	0 (0)	0 (0)	-
Cardiovascular and Hematological Drugs	407	0 (0)	0 (0)	0 (0)	-
Respiratory drugs	524	231 (44.1)	188 (35.9)	43 (8.2)	< 0.01*
Urogenital and anal organs drugs	230	11 (4.8)	3 (1.3)	8 (3.5)	0.03*
Tonic health drugs	2236	0 (0)	0 (0)	0 (0)	-
Women's drugs	151	0 (0)	0 (0)	0 (0)	-
Allergy drugs	34	2 (5.9)	0 (0)	2 (5.9)	-
Skin drugs	2684	2 (0.1)	0 (0)	2 (0.1)	-
Ophthalmic drugs	482	1 (0.2)	1 (0.2)	0 (0)	-
Otorhinolaryngological drugs	338	108 (32.0)	92 (27.2)	16 (4.7)	0.18
Dental and oral cavity drugs	305	0 (0)	0 (0)	0 (0)	-
smoking cessation agents	27	0 (0)	0 (0)	0 (0)	-
Kampo preparation	2697	0 (0)	0 (0)	0 (0)	-
Herbal preparation (Preparations not belonging to other therapeutic classes)	280	0 (0)	0 (0)	0 (0)	-
Public health drugs	352	0 (0)	0 (0)	0 (0)	-
General test kits	17	0 (0)	0 (0)	0 (0)	-
Others (preparations not belonging to any therapeutic category)	6	0 (0)	0 (0)	0 (0)	-

[a]Classifications registered with JAPIC. *p*-value indicate number of products till March 31, 2023 *vs.* Total Chi-square test; *$p < 0.05$.

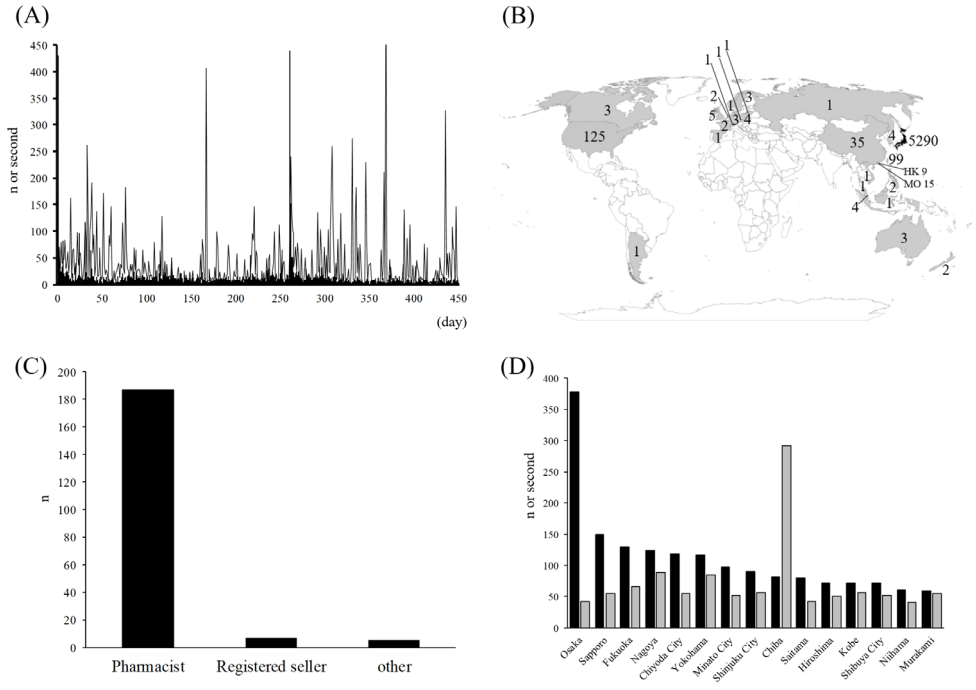

Figure 1. Data on the "Drug Database for Overdose Prevention" website. (A) Users and average engagement time over time since publication on the Internet. Black bar graph: Users (*n*), Solid black line: average engagement time (seconds). **(B)** Number of website accesses from each region and country. April 1, 2023, to June 25, 2024. **(C)** Database registrants; as of July 31, 2024 (*n*). **(D)** Top 15 users by region in Japan and the average engagement time (seconds). Black bar graph: Users by region (*n*), grey bars: Average engagement time (seconds). Users of "not set" were not included.

Although there are no legal restrictions, such as the designation of ingredients as potentially misused, there have been reports of ingredients being abused. As an example, surveys of young people and medical professionals have shown an increase in caffeine abuse (*17,18*). Similarly, studies among USA adolescents indicate the increased abuse of diphenhydramine (*19*). These ingredients are toxic and dangerous. A retrospective study of emergency care facilities in Japan reported that caffeine overdose can cause symptoms such as tachypnea, tachycardia, hypokalemia, and hyperlactatemia, and can even result in death (*20*). Diphenhydramine also has no antidote and because it acts directly on the vascular system as well as the autonomic and somatic central nervous systems, it may cause multiple serious side effects, including death (*21,22*). Pesticides and insecticides, such as DEET and organophosphates, which are classified as public health drugs, are also likely to be used for suicide (*13,23*). Thus, for these ingredients, measures must be taken by pharmacists with specialized pharmaceutical knowledge when the product is sold. Moreover, children and individuals with cognitive impairment may unintentionally misuse OTC drugs, leading to poisoning and death (*23*). According to the data on lethal doses of OTC drugs in humans surveyed in the present study, it was considered necessary to actively listen to the circumstances of the purchasers and to alert parents and caregivers to the importance of managing medications at home.

Similar poisoning information databases, such as POISINDEX® (TECHNOMICS, INC.), are available under contract, however, these do not cover Japanese OTC drug products; therefore, the database that we established is novel in this respect. In contrast, because many OTC drugs in Japan contain multiple ingredients, toxicity resulting from drug-drug interactions is an issue to be considered. Thus, it is necessary to clarify toxicity due to drug-drug interactions. Analysis of the logs revealed that most users were from urban areas of Japan, where there are many incidents of drug overdose. This suggests that the database is being used effectively in these areas, although a more detailed analysis is needed. In addition, access to the published website from other countries was detected; thus, it is necessary to make the database available in English in the future.

The newly published Comprehensive Suicide Prevention Principles (Ministry of Health, Labor, and Welfare), which was approved by the Cabinet in October 2022 (*4*), continues to place expectations on pharmacists to act as gatekeepers. The database established in this study is expected to be used as one of the tools for gatekeepers to prevent overdose and suicide. Currently, 94% of the registered users are pharmacists. In a recent report, 65.9% of drugs used in overdoses were obtained from brick-and-mortar stores, whereas only 9.3% were purchased online (*6*). This suggests that local pharmacists are likely to play an active role as gatekeepers in the prevention of

medication overdose. In contrast, overdoses can occur repeatedly (*24,25*). Therefore, pharmacists at hospitals where the patients are transported or examined should provide information to local pharmacies and other professionals, including doctors. Thus, there is a need to strengthen cooperation between hospitals and pharmacies.

One limitation of this study is that there is limited information on the toxic or fatal doses of certain drugs in humans. Based on the literature (*7-15*), we evaluated the toxic and lethal doses for humans. The usual amount of drug used is the amount in which safety has been confirmed, which is listed on the package insert; however, the effects on humans in the event of an overdose must be based on post-marketing reports. Therefore, it is important to note that there are compounds whose effects in some cases of overdose are unknown. In conclusion, the database established in this study is expected to be useful as a tool for gatekeepers to prevent overdose and suicide associated with OTC drugs.

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