ORIGINAL ARTICLE

Drug information centre queries and responses about drug interactions over 10 years—A descriptive analysis

Carina Tukukino[1,2] | Susanna M. Wallerstedt[2,3] (iD)

[1]Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden

[2]Department of Pharmacology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]HTA-centrum, Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence
Susanna M. Wallerstedt, Department of Pharmacology, Sahlgrenska Academy, University of Gothenburg, Box 430, 405 30 Gothenburg, Sweden.
Email: susanna.wallerstedt@pharm.gu.se

Abstract

Many people are treated with ≥1 drug, implying that risks of drug interactions need to be considered. The aim of this study was to describe drug interaction queries from healthcare professionals to a drug information centre in Sweden over 10 years focusing on drugs frequently asked about and the advice provided. Advice was recorded in mutually exclusive groups: *Avoid*, *Adjust dose, Separate intake*, *Vigilance* or *No problem*. For queries with *Avoid*, *Adjust dose* or *Separate intake* advice, alerts were extracted from an interaction database (*J*anusmed). Of 4335 queries to the centre in 2008-2017, 589 (14%) concerned interactions. Most were posed by physicians (91%) and concerned a specific patient (83%) before treatment initiation (76%). Sertraline, warfarin and methotrexate were the most frequently asked about, whereas queries about cyclophosphamide and rifampicine occurred most often in relation to the number of exposed patients. Advice provided in 557 (95%) replies comprised *Avoid*: n = 85 (15%), *Adjust dose*: n = 57 (10%), *Separate intake*: n = 17 (3%), *Vigilance*: n = 235 (42%) or *No problem*: n = 163 (29%). In all, 113 (71%) of 159 queries with *Avoid/Adjust dose/Separate intake* advice elicited an action alert on *J*anusmed, whereas 31 (20%) did not result in any alert at all. Summarized, seven in ten replies from the drug information centre recommended an explicit drug treatment action, regarding either specific prescribing aspects, for instance dose adjustments, or active follow-up including monitoring potential adverse reactions and/or laboratory results. Readily accessible decision support regarding drug interactions often provides relevant action alerts, but cannot be solely relied on.

KEYWORDS
clinical advice, drug information centre, drug interactions, healthcare professionals, interaction database

1 | INTRODUCTION

Drugs are an important treatment modality in health care, used to cure, prevent, relieve and diagnose diseases. Both the number of approved drugs and the number of people exposed to many drugs are increasing,[1,2] which implies an increased risk of drug interactions.

Depending on the type of interaction, desired effects may be reduced or unwanted effects may be increased. The underlying mechanism may be pharmacodynamic (PD) and/or pharmacokinetic (PK). In a PD interaction, a drug either potentiates or reduces the pharmacological effects of another drug; in a PK interaction, a drug affects the absorption, metabolism or excretion of another drug,[3] for example

by reducing the formation of pharmacologically active metabolites.[4]

In Europe, drug information centres have been available to respond to health professionals' drug-related queries for many decades.[5-8] The queries include concerns about adverse reactions, pregnancy issues and interactions.[7,9] From 1990 to 2012, the proportion of queries about interactions queries increased.[7] For these queries, several available sources of information can be used as a basis for the reply.[10]

To the best of our knowledge, interaction queries posed to a drug information centre have not previously been characterized. Such analyses could provide valuable insights as they illustrate the need for interaction information from a clinical perspective. Indeed, many scientific publications on interactions are based on data from registers[11,12] and therefore do not perfectly reflect the clinical context. Analysing interaction queries and replies can also contribute insights into the type of advice provided in specific cases versus that provided by general decision support systems.

The aim of this study was to describe healthcare professionals' queries about drug interactions to a drug information centre over 10 years, focusing on frequently queried drugs and the advice provided.

2 | METHODS

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[13] It was approved by the Regional Ethical Review Board in Gothenburg, Sweden (reference number: 524-18).

We extracted all queries on drug interactions posed in 2008-2017 to the drug information centre in Region Västra Götaland, in the south west of Sweden. This region has a population of 1.7 million (17% of the Swedish population), one university hospital, eight general hospitals and approximately 200 primary healthcare centres. The queries are received by a team of resident physicians, pharmacists and registered nurses, who search and compile the available evidence in a reply to the questioner, in close collaboration with a specialist in clinical pharmacology who countersigns the contents. When further clinical information is needed before a reply can be achieved, the questioner is contacted. All queries are handled according to a standard operating procedure, for example instructions on which sources to search for interaction queries.

From each interaction query, questioner characteristics were extracted, including profession, workplace and gender. We also recorded whether the query concerned a specific patient or patients in general and whether the query was posed prior to the initiation of treatment or during or after treatment. In addition, we recorded whether the reply was provided by phone or in writing.

We recorded the substances concerned in each query. If two specific substances in combination were queried, both were recorded. If the query concerned one substance in relation to a medication list, that substance and all on the specified list were recorded. The substances were categorized as (a) drugs licensed for use in Sweden, (b) drugs licensed for use in another country but not in Sweden, (c) herbal remedies, (d) dietary supplements, (e) food and (f) recreational drugs.

To relate drugs found most frequently in healthcare professionals' queries about drug interactions to the number of exposed patients, we extracted the number of patients in Region Västra Götaland who filled at least one prescription for substances appearing in 10 or more queries. For this purpose, we used publicly available data from the Swedish Prescribed Drug Register (SPDR).[14] This register covers all prescription drugs dispensed by any pharmacy in Sweden,[15] whereas over-the-counter drugs and drugs used in hospitals are not recorded. The public part of SPDR does not allow data to be aggregated over the years. Therefore, we used data from 2017 as an approximation of the extent of use.

To determine the value of the reply to the questioner, we assessed whether or not clinical advice was provided. For the purpose of this study, we also categorized all queries answered with advice in the following mutually exclusive groups: (a) *Avoid*—an increased risk of severe adverse events or reduced effects for ≥1 drug, (b) *Adjust dose*—the combination may require dose adjustments for ≥1 drug, (c) *Separate intake*—combined treatment is possible, but requires administration at separate times, via different administration routes, or a specific delay before changing to a new drug, (d) *Vigilance*—the combination requires active follow-up and monitoring of potential adverse reactions and/or laboratory samplings and (e) *No problem*—according to what is known, the combination is safe. These categories were chosen to reflect clinically relevant alternatives to handle drug interactions. Each query was categorized according to the most severe interaction identified as indicated by the order of the categories.

In queries with *Avoid*, *Adjust dose* or *Separate intake* advice, we also recorded whether the case had been subject to an action alert on the national open-access interaction database (*J*anusmed),[16] which is also integrated into electronic health record systems to support physicians' treatment decisions. *J*anusmed provides information about clinical consequences and general recommendations for identified interactions, including the underlying mechanism as well as the evidence.[17] The system allows many drugs to be entered in the same search, but the alerts concern only two drugs at a time and cover primarily PK interactions. In *J*anusmed, interactions are classified into one of four groups: *A* indicates a minor interaction without clinical relevance; *B*, an interaction where the clinical relevance is uncertain or varies; *C*, a clinically relevant interaction that can be handled by dose adjustments

or separated intake; and *D*, a clinically relevant interaction and a recommendation to avoid the drug combination.[18] In the electronic health record system, C and D interactions are alerted. To determine to what extent the decision support system elicits alerts in relevant cases, we recorded whether an action alert, defined as a C or a D interaction, was elicited when the drugs in queries with *Avoid/Adjust dose/Separate intake* advice were entered (October/November 2018). If no alert at all was elicited, including A-D interactions, we recorded whether substances other than licensed drugs were involved and whether the drug information centre reply referred to PD or patient-related factors.

To learn which important substance combinations were most often queried, we recorded all combinations for substances occurring in 10 or more queries with at least one *Avoid*, *Adjust dose* or *Separate intake* piece of advice. For these combinations, we also extracted the *J*anusmed alerts (October/November 2018). For drug combinations with *Avoid/Adjust dose/Separate intake* advice where no alert at all, including A-D interactions, was elicited on *J*anusmed, we recorded the type of substances queried about as well as whether the drug information centre reply referred to PD or patient-related factors.

To understand the extent of the efforts required to achieve a reply, we recorded the sources cited, including (a) the Swedish National Formula, which is based on the text in the Summary of Product Characteristics,[19] (b) *J*anusmed,[17] (c) Stockley's Drug Interactions,[20] (d) Micromedex[21] and (e) scientific publications. We also recorded whether PK and/or PD considerations were discussed in the reply, based either on (a) general theoretical reasoning about aspects such as affiliated metabolism within the cytochrome P450 system or to QT prolongation or (b) publications where the specific interaction had been investigated in clinical studies or was reported in case reports.

2.1 | Statistics

We performed descriptive analyses using SPSS (IBM SPSS Statistics for Windows, version 24.0). To relate the number of queries to the extent of use of specific substances, we calculated a ratio between the number of queries in 2008-2017 and the number of individuals treated in 2017. Values are presented as counts (percentages), if not stated otherwise.

3 | RESULTS

During 2008 to 2017, a total of 4335 queries were posed to the regional drug information centre, 589 (14%) of which were categorized as interaction queries. Characteristics of the questioners, queries and replies are presented in Table 1. Most queries originated from hospital care (n = 362, 61%) were posed by a physician (n = 534, 91%) and concerned a

specific patient (n = 486, 83%) before the initiation of treatment (n = 446, 76%).

In the queries, 573 unique substances appeared, most frequently within the drug groups antidepressants (n = 201), antiepileptics (n = 121), antithrombotic agents (n = 110), antipsychotics (n = 96), lipid-modifying agents (n = 72) and antimetabolites (n = 65). A total of 326 (55%) queries concerned two substances, and 115 (20%) queries concerned five or more. The maximum number of substances in a single query was 25 (n = 1, 0.2%). All queries concerned at least one licensed drug, and 95 (16%) also concerned an unlicensed drug, a dietary supplement, a food, a herbal remedy or a recreational drug (Table 1). Sertraline, warfarin, methotrexate, omeprazole and mirtazapine were the drugs most frequently asked about; however, queries about cyclophosphamide and rifampicine occurred most often in relation to the number of exposed patients (Table 2).

3.1 | Advice at the query level

In all, 557 (95%) of 589 replies provided clinical advice. An explicit drug treatment action was suggested in 395 (71%) cases, concerning either specific prescribing matters (n = 159, 29%) or conducting active follow-up (n = 235, 42%). Of the 159 replies with *Avoid/Adjust dose/Separate intake* advice, 113 (71%) elicited an action alert when entered in *J*anusmed (Table 3). In contrast, 34 (21%) replies did not result in any alert at all, whereas an A or B alert was obtained in 12 (8%) cases. Some of the non-alerted queries included unlicensed drugs (n = 4) or dietary supplements (n = 3). Pharmacodynamic and patient-related aspects contributed to the advice in 23 and 32 non-alerted queries, respectively. The latter included aspects such as the presence of a disease requiring extra caution or the use of multiple drugs with potential additive interacting effects. Eight non-alerted replies did not include any PD or patient-related aspects.

The 32 (5%) replies lacking advice either merely forwarded information from another source, without any input from the drug information centre (n = 25), or did not provide advice with referral to the lack of scientific literature (n = 7).

3.2 | Advice at the drug combination level

The 27 substances asked about at least 10 times and the corresponding advice regarding specific combinations are presented in Table 4. In all, 355 (60%) queries concerned at least one of these substances. In the replies, advice was provided for 996 substance combinations: *Avoid* (n = 107, 11%), *Adjust dose* (n = 79, 8%), *Separate intake* (n = 2, 0.2%), *Vigilance* (n = 288, 29%) and *No problem* (n = 520, 52%). Within the *Avoid, Adjust dose* and *Separate intake* pieces of advice, 20 (11%) substance combinations occurred more than once. Tamoxifen/fluoxetine and tamoxifen/paroxetine were the most common drug-drug

T A B L E 1 Characteristics of interaction queries posed to a drug information centre in 2008-2017 (n = 589)

	n (%)
Questioner	
Profession	
Physician	534 (91)
Nurse	29 (5)
Dentist	13 (2)
Pharmacist	5 (1)
Other	8 (1)
Workplace	
Hospital	372 (63)
Primary health care	148 (25)
Specialist clinic	66 (11)
Regional drug committee	3 (1)
Female	383 (65)
Query	
Question formulation	
General	103 (17)
Patient-specific	486 (83)
Timing	
Before initiation of treatment	446 (76)
Drug treatment in progress	118 (20)
Drug treatment discontinued	25 (4)
Drugs	
Licensed drugs	589 (100)
Unlicensed drugs	43 (7)
Food	20 (3)
Herbal remedy	16 (3)
Dietary supplement	9 (2)
Recreational drug	7 (1)
Reply	
Handover	
By phone	217 (37)
In writing	372 (63)
Pharmacokinetics	
General	280 (48)
Specific	97 (16)
Pharmacodynamics	
General	197 (33)
Specific	47 (8)
Resources	
Swedish National Formula [19]	479 (81)
National drug interaction database (*J*anusmed) [16]	456 (77)
Stockley's drug interactions [20]	370 (63)
Micromedex [21]	310 (53)
Scientific publications	213 (36)
	(Continues)

T A B L E 1 (Continued)

	n (%)
Clinical advice provided	557 (95)
Type of advice	
Avoid	85 (15)
Adjust dose	57 (10)
Separate intake	17 (3)
Vigilance	235 (42)
No problem	163 (29)

interactions with *Avoid* recommendations, represented by responses to 5 and 4 queries, respectively.

When the 168 unique substance combinations resulting in *Avoid/Adjust dose/Separate intake* advice were entered in *J*anusmed, 123 (73%) elicited an action alert, 30 (18%) did not result in any alert at all, and an A or B alert was obtained in 15 (9%) cases. Some of the non-alerted combinations included an unlicensed drug (n = 1) or a dietary supplement (n = 3), and PD and patient-related aspects contributed to the advice in 9 and 16 cases, respectively.

The median number of sources cited in a reply was 4 (range 0-10). In 26 (4%) replies, the Swedish National Formula and/or *J*anusmed were the only sources cited. A total of 213 (36%) replies cited one or more scientific publications. Scientific publications on the PK or PD aspects of a specific substance combination were cited in 97 (16%) and 47 (8%) queries, respectively.

4 | DISCUSSION

Over 10 years, 589 queries on interactions, representing 14% of all queries, were posed to a drug information centre serving healthcare providers for a population of 1.7 million. The typical query concerned a specific patient in the hospital setting before the physician was about to initiate treatment. It is reassuring that almost all interaction queries resulted in clinical advice, as this is considered an important aspect of the perceived quality of written responses.[22] Seven in ten replies suggested an explicit action, regarding either specific prescribing matters, such as reducing/increasing doses and recommending alternative drugs, or conducting active follow-up, including monitoring potential adverse reactions and/or laboratory results. The remaining three in ten replies stated that the combination was safe from adverse interactions.

One in seven of the drug information centre replies suggested that a combination should be avoided because of either increased risk of adverse reactions or reduced beneficial effects. When entered in *J*anusmed, three in four of these cases resulted in an action alert. Correspondingly, one in eight of the drug information centre's replies recommended dose

TABLE 2 Drugs evaluated in ≥10 interaction queries to the drug information centre in 2008-2017 and query rate in relation to the number of patients treated in 2017

Substance	Queries n (%)	Treated individuals n	Queries/1000 treated individuals
Sertraline	37 (6)	53 717	0.6
Warfarin	31 (5)	23 543	1.3
Methotrexate	30 (5)	9559	3.1
Omeprazole	29 (5)	128 062	0.2
Mirtazapine	26 (4)	4091	0.6
Carbamazepine	23 (4)	5502	4.1
Simvastatin	23 (4)	61 796	0.3
Fluorouracil	22 (4)	N/A[a]	N/A[a]
Lamotrigine	21 (4)	9282	2.3
Tamoxifen	21 (4)	2824	7.4
Terbinafine	20 (3)	5762	3.5
Rivaroxaban	20 (3)	7503	2.7
Lithium	20 (3)	3799	5
Isotretinoin	19 (3)	1897	10
Fluconazole	19 (3)	14 048	1
Rifampicine	18 (3)	304	56
Bupropion	16 (3)	5906	3
Methylphenidate	16 (3)	10 806	1
Quetiapine	15 (2)	6959	2
Aripiprazole	14 (2)	4312	3
Cyclophosphamide	14 (2)	206	68
Valproic acid	13 (2)	4360	3
Cyclosporine	12 (2)	825	15
Tacrolimus	12 (2)	5552	9
Clonazepam	11 (2)	1694	7
Lymecycline	11 (2)	8217	1
Colchicine	10 (2)	734	14

[a]Used in hospital care; information on the number of treated individuals not available.

adjustment or separated intake. When entered in *J*anusmed, two in three of these cases resulted in an action alert. The discrepancies between replies from the drug information

TABLE 3 The most severe piece of advice in the 557 replies providing such guidance, and the corresponding recommendation in *J*anusmed. Values are presented as n (per cent)

		*J*anusmed	
	Total	Action alert[a]	No action alert[b]
Avoid	85 (15)	64 (75)	21 (25)
Adjust dose	57 (10)	40 (70)	17 (30)
Separate intake	17 (3)	9 (53)	8 (47)

[a]*J*anusmed categories C (=clinically relevant interaction that can be handled by dose adjustments or separated intake) or D (=clinically relevant interaction where the recommendation is to avoid the drug combination).
[b]No interaction alert or *J*anusmed categories A (=minor interaction without clinical relevance) or B (=clinical interaction where the clinical relevance is uncertain or varies).

centre and results obtained for the same substances entered in *J*anusmed suggest that such a system cannot be solely relied on. Indeed, this decision support focuses on PK interactions, and a substantial number of these replies concerned PD aspects. Further, as stated in *J*anusmed, the information provided is general and needs to be interpreted in the context of the specific patient, considering, for instance, medical history, age and renal function. Our finding that patient-related factors contributed in advice provided from the drug information centre support such an approach in prescribing. These findings accord with those found for the applicability of general indicators of prescribing quality.[23] They may also illustrate that pharmacotherapy is a complex art, where benefits must be weighed against risks according to the condition and preferences of the specific patient. An overemphasis on algorithms may make health care less patient-centred, and evidence-based guidelines often map poorly to complex multimorbidity.[24] Nevertheless, interaction alerts integrated into

TABLE 4 Drugs evaluated in ≥10 interaction queries to the drug information centre in 2008-2017, the clinical advice provided[a], and specific combinations where *Avoid*, *Adjust drug* or *Separate intake* was recommended, as well as the corresponding level of alert in *J*anusmed[b] (in parentheses)

Substance	Advice for specific combinations[a]	Avoid	Adjust dose	Separate intake
Sertraline	3/1/0/9/35	[1]Desmopressin (-) [1]Linezolid (D) [1]Varenicline (-)	[1]Rifampicin[c] (C)	(-)
Warfarin	9/0/0/16/19	[1]Cox-inhibitors (D) [2]Nabumeton (D) [1]Omega-3 (B) [1]Oxandrolone (-) [1]Primidone (C) [1]Propafenone (C) [2]Rifampicin[c] (C)	(-)	(-)
Methotrexate	7/0/0/17/9	[1]Acitretin (D) [1]Ciprofloxacin (C) [2]Isotretinoin[c] (-) [2]Lymecycline[c] (C) [1]Meropenem (-)	(-)	(-)
Omeprazole	0/1/0/3/43	(-)	[1]Mycophenolate (C)	(-)
Mirtazapine	0/2/0/10/31	(-)	[1]Carbamazepine[c] (C) [1]Rifampicine[c] (C)	(-)
Carbamazepine	6/10/0/19/24	[1]Abiraterone (C) [1]Docetaxel (C) [1]Enzalutamide (C) [1]Felodipine (D) [1]Rivaroxaban[c] (C) [1]Tamoxifen[c] (D)	[1]Aripiprazole[c] (C) [1]Colchicine[c] (D) [1]Cyclophosphamide[c] (C) [1]Desloratadine (-) [1]Fentanyl (C) [1]Ibuprofen (-) [1]Mirtazapine[c] (C) [1]Quetiapine[c] (D) [1]Tramadol (C) [1]Zonisamide (C)	(-)
Simvastatin	12/1/1/8/35	[1]Azithromycin (B) [1]Clarithromycin (D) [3]Fluconazole[c] (B) [1]Garcinia-Mangostana (-) [2]Grapefruit juice (D) [1]Imatinib (C) [1]Mikonazol (-) [1]Podophyllotoxin (C) [1]Supergreen (-)	[1]Imatinib (C)	[1]Cholestyramine (-)
Tamoxifen	21/0/0/14/29	[3]Bupropion[c] (D) [1]Carbamazepine[c] (D) [1]Cinacalcet (D) [3]Duloxetine (D) [5]Fluoxetine (D) [1]Levomepromazine (-) [4]Paroxetine (D) [1]Quinidine (D) [1]Ritonavir (B) [1]Terbinafine[c] (C)	(-)	(-)
Fluorouracil	1/2/0/19/25	[1]Flecainide (-)	[1]Phenytoin (C) [1]Tocopherol (-)	(-)

(Continues)

TABLE 4 (Continued)

Substance	Advice for specific combinations[a]	Avoid	Adjust dose	Separate intake
Lamotrigine	0/6/0/9/28	(-)	$_1$Clonazepam[c] (B) $_1$Drospirenone/ ethinyl estradiol (C) $_1$Escitalopram (-) $_1$Quetiapine[c] (C) $_1$Ritonavir (C) $_1$Valproic acid[c] (C)	(-)
Terbinafine	4/4/0/10/24	$_3$Metoprolol (C) $_1$Tamoxifen[c] (C)	$_1$Aripiprazole[c] (-) $_1$Paroxetine (C) $_1$Venlafaxine (B) $_1$Zuclopenthixol (C)	(-)
Lithium	0/1/0/22/22	(-)	$_1$Metronidazole (B)	(-)
Isotretinoin	2/0/0/15/13	$_2$Methotrexate[c] (-)	(-)	(-)
Fluconazole	12/7/0/5/33	$_2$Atorvastatin (C) $_1$Budesonide (C) $_1$Clopidogrel (C) $_2$Fentanyl (D) $_1$Fluvastatin (C) $_1$Mefloquine (-) $_1$Phenobarbital (-) $_1$Prednisolone (B) $_2$Simvastatin[c] (B)	$_1$Amitriptyline (C) $_1$Atorvastatin (C) $_1$Felodipine (C) $_1$Prednisolone (B) $_1$Phenytoin (C) $_1$Quetiapine[c] (C) $_1$Budesonide (C)	(-)
Rivaroxaban	6/1/0/7/7	$_1$Carbamazepine[c] (C) $_1$Efavirenz (C) $_1$Enzalutamide (C) $_1$Glucosamine (-) $_2$Rifampicin[c] (C)	$_1$Abiraterone (-)	(-)
Rifampicine	7/17/0/3/8	$_2$Apixaban (C) $_1$Bedaquiline (D) $_1$Mefloquine (D) $_1$Quetiapine[c] (D) $_1$Rivaroxaban[c] (C) $_1$Warfarin[c] (C)	$_1$Amitriptyline (C) $_1$Aripiprazole[c] (C) $_1$Celecoxib (C) $_1$Clindamycin (B) $_1$Cyclosporine[c] (C) $_1$Delamanid (D) $_1$Donepezil (C) $_1$Escitalopram (C) $_1$Linezolid (C) $_1$Mirtazapine[c] (C) $_1$Nitrazepam (C) $_1$Ondansetron (C) $_1$Paroxetine (-) $_1$Prednisolone (C) $_1$Reboxetine (C) $_1$Sertraline[c] (C) $_1$Valproic acid[c] (C)	(-)
Bupropion	5/5/0/6/8	$_3$Tamoxifen[c] (D) $_2$Tramadol (D)	$_1$Citalopram (B) $_1$Clopidogrel (C) $_1$Dabrafenib (-) $_1$Dapoxetine (-) $_1$Vortioxetine (C)	(-)
Methylphenidate	1/3/0/7/13	$_1$Clomipramine (C)	$_1$Energy drinks (-) $_1$Fluoxetine (-) $_1$Oxicodone (-)	(-)

(Continues)

BCPT
Basic & Clinical Pharmacology & Toxicology

TABLE 4 (Continued)

Substance	Advice for specific combinations[a]	Avoid	Adjust dose	Separate intake
Quetiapine	1/2/0/11/21	$_1$Rifampicin[c] (D)	$_1$Carbamazepine[c] (D) $_1$Fluconazole[c] (C) $_1$Lamotrigine[c] (C)	(-)
Cyclophosphamide	1/2/0/9/14	$_1$Flecainide (-)	$_1$Carbamazepine[c] (C) $_1$Phenytoin (C)	(-)
Aripiprazole	0/4/0/10/13	(-)	$_1$Carbamazepine[c] (C) $_1$Levomepromazine (B) $_1$Rifampicine[c] (C) $_1$Terbinafine[c] (-)	(-)
Valproic acid	4/3/0/12/12	$_1$Ertapenem (D) $_1$Imipenem (D) $_1$Meropenem (D) $_1$Topiramate (C)	$_1$Cisplatin (C) $_1$Lamotrigine[c] (C) $_1$Rifampicine[c] (C)	(-)
Cyclosporine	1/2/0/12/10	$_1$Grapefruit juice (D)	$_1$Colchicine[c] (D) $_1$Rifampicin[c] (C)	(-)
Tacrolimus	2/1/0/9/5	$_1$Cranberry (C) $_1$Pomegranate (C)	$_1$Ibrutinib (-)	(-)
Clonazepam	0/1/0/12/19	(-)	$_1$Lamotrigine[c] (B)	(-)
Colchicine	0/2/1/8/17	(-)	$_1$Carbamazepine[c] (D) $_1$Cyclosporine[c] (D)	B$_{12}$ (-)
Lymecycline	2/0/0/6/3	$_2$Methotrexate[c] (C)	(-)	(-)

Note: Subscript number denotes the number of queries in which the specific combination appeared.

[a]Avoid/Adjust dose/Separate intake/Vigilance/No problem (in order of severity).

[b]*J*anusmed: (A) = minor interaction without clinical relevance, (B) = clinical interaction where the clinical relevance is uncertain or varies, (C) = clinically relevant interaction that can be handled by dose adjustments or separated intake, (D) = clinically relevant interaction where the recommendation is to avoid the drug combination, (-) = no interaction alert.

[c]Includes more than one of the most frequent substances (ie the combination is presented for both substances).

medical records may be valuable: the prescriber can directly assess whether an interaction alert is clinically relevant and needs to be acted upon for specific patients given their clinical condition and overall drug treatment.[17,25]

In 2018, *J*anusmed had information on 23 102 substance combinations.[16] Although the coverage of this database is impressive, our results illustrate that reliance solely on an alert tool may entail risks; one in five cases with *Avoid/Adjust dose/Separate intake* recommendations were not alerted at all. Indeed, studies on the clinical benefits of drug interaction alerts report various results.[9,18,26,27] Therefore, although electronic decision support systems may facilitate clinical decision-making, it is essential that physicians also have adequate pharmacologic skills. Key learning outcome during medical school, including drug interactions in clinical pharmacology and therapeutics, has been proposed.[28] Increased pharmacological training may be necessary for physicians to acquire sufficient prescribing skills, and performing medication reviews during medical school may increase the reflection on drug interactions.[29]

The educational value of responses from a drug information centre is illustrated by the included discussions on general PK and PD aspects. Continuing education after medical school is important, in particular as medical school may not provide all students with sufficient knowledge within pharmacotherapy.[30,31] As the standard operating procedure of our drug information centre entails a literature search, our finding that PK/PD publications for specific combinations were seldom cited may illustrate the scarcity of such evidence. Therefore, appropriate theoretical reasoning, based on a comprehensive understanding of the complexity of PK/PD, is essential among prescribers. In recent years, replies of general interest from our centre have been entered in an established open database[32,33] in order to disseminate drug information.

We were not surprised that sertraline, omeprazole and simvastatin were among the substances appearing most often in the drug interaction queries. These drugs are among the most frequently used in our region, as shown by the number of treated individuals. For the drugs most often queried about, combination use was usually considered safe or active follow-up was encouraged, illustrating that interactions may not be a major problem in most cases. Nevertheless, assurance about the absence of expected interactions has been shown to be valuable to prescribers.[34]

Drugs well known to affect metabolizing enzymes within the cytochrome P450 family, including the inducers

rifampicine and carbamazepine as well as the inhibitors fluconazole, terbinafine and bupropion, were among those often asked about. Other drugs frequently asked about were those with a narrow therapeutic window, for example warfarin, methotrexate, lithium, colchicine, tacrolimus, cyclosporine, cyclophosphamide and fluorouracil.[19,35,36] It has previously been shown that relatively few drugs account for the great majority of the drug-drug interactions,[37] and our results suggest that questioners are well informed about risk drugs, posing queries upon uncertainties.

Tertiary sources are common in drug information centre replies regarding interaction queries.[38] In the present study, almost all replies cited sources other than the Swedish National Formula and *J*anusmed. Indeed, more than half of the replies cited Stockley's drug interactions and Micromedex, respectively, databases that include both PK and PD interactions but occasionally lack data on drugs which are relevant in the Swedish setting. These results suggest that queries are posed when physicians are making complex clinical decisions and readily accessible sources do not suffice; this supports previous arguments in favour of the role of a drug information centre.[9] Compared with standard drug interaction databases, more than half of clinically relevant drug interactions have been reported to be missing or insufficiently characterized in the Summary of Product Characteristics.[39] Our results suggest that interaction databases also have limitations regarding their applicability at the individual level. The challenges for drug information centres to provide decision support for individual patients have been discussed before.[9] Interestingly, non-licensed substances were included in one in six queries, illustrating the lack of easily accessible information in such cases. For example, eight in ten queries about colchicine were posed prior to its market authorization.

An important strength of this study is that it provides compiled information on interaction queries received by a drug information centre. Covering a 10-year period and almost 600 replies, the study contributes important insights on drug interaction issues in health care. A limitation of the study is that it includes queries posed to one drug information centre only. However, replies from such centres have been shown to be concordant, and the quality assessed as satisfactory to good, provided that they were countersigned,[40] which is standard procedure in our centre. Nevertheless, although our aim was to reflect clinical practice, it may be regarded as a limitation that the replies and advice were not validated. No interaction queries with an available reply were excluded, and the external validity of the results should therefore be acceptable. Another strength of the study is that it highlights the necessity of pharmacological understanding in the clinical context, given that relevant information was sometimes not obtained in an interaction database with general recommendations. Nevertheless, the number of *Avoid/Adjust dose/Separate intake* recommendations was quite low considering the years and therapeutic areas covered. Regarding the discrepancies found between the drug information centre advice and the *J*anusmed alerts, it must be acknowledged that the latter are revised over time, in response to emerging evidence. Therefore, the *J*anusmed alerts in 2018 may not be consistent with those provided in earlier years. Further, like other interaction databases,[20,21] the *J*anusmed alerts concern only two drugs at a time, but in our study almost half of the queries involved interactions between more than two drugs.

5 | CONCLUSION

This study shows that drug interaction queries from healthcare professionals often concern specific patients. In most cases, the drug information centre recommends an explicit action in drug treatment, regarding either the prescribing per se or an active follow-up. Readily accessible decision support regarding drug interactions often provides action alerts when relevant, but cannot be solely relied on.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. During the study period, they regularly (CT) and occasionally (SMW) worked in the drug information centre.

ORCID

Susanna M. Wallerstedt https://orcid.org/0000-0001-7238-1680

REFERENCES

1. Hovstadius B, Hovstadius K, Åstrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005–2008. *BMC Clin Pharmacol*. 2010;10:16.
2. Zeukeng M, Seoane-Vazquez E, Bonnabry P. A comparison of new drugs approved by the FDA, the EMA, and Swissmedic: an assessment of the international harmonization of drugs. *Eur J Clin Pharmacol*. 2018;74:811-818.
3. Cascorbi I. Drug interactions - principles, examples and clinical consequences. *Dtsch Arztebl Int*. 2012;109:546-556.
4. Mannheimer B, Eliasson E. Drug-drug interactions that reduce the formation of pharmacologically active metabolites: a poorly understood problem in clinical practice. *J Intern Med*. 2010;268:540-548.
5. Schjøtt J, Pomp E, Gedde-Dahl A. Quality and impact of problem-oriented drug information: a method to change clinical practice among physicians? *Eur J Clin Pharmacol*. 2002;57:897-902.
6. Hedegaard U, Damkier P. Problem-oriented drug information: physicians' expectations and impact on clinical practice. *Eur J Clin Pharmacol*. 2009;65:515-522.

7. Alván G, Andersson ML, Asplund AB, et al. The continuing challenge of providing drug information services to diminish the knowledge-practice gap in medical practice. *Eur J Clin Pharmacol.* 2013;69(Suppl 1):65-72.

8. Troger U, Meyer FP. The regional drug-therapy consultation service centre-a conception that has been serving patients and physicians alike for 30 years in Magdeburg (Germany). *Eur J Clin Pharmacol.* 2000;55:707-711.

9. Schjøtt J. Challenges in psychopharmacology: a drug information centre perspective. *J Clin Pharm Ther.* 2016;41:4-6.

10. Patel R, Beckett R. Evaluation of resources for analyzing drug interactions. *J Med Libr Assoc.* 2016;104:290-295.

11. Zheng W, Richardson L, Li L, Day R, Westbrook J, Baysari M. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2018;74:15-27.

12. Thai M, Reeve E, Hilmer SN, Qi K, Pearson SA, Gnjidic D. Prevalence of statin-drug interactions in older people: a systematic review. *Eur J Clin Pharmacol.* 2016;72:513-521.

13. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & Clinical Pharmacology & Toxicology Policy for Experimental and Clinical studies. *Basic Clin Pharmacol Toxicol.* 2018;123:233-235.

14. National Board of Health and Welfare. Public version of the Swedish Prescribed Drug Register. https://sdb.socialstyrelsen.se/if_lak/val.aspx. Assessed June 26, 2019.

15. Wettermark B, Hammar N, MichaelFored C, et al. The new Swedish Prescribed Drug Register - opportunities for pharmaco-epidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf.* 2007;16:726-735.

16. Stockholm County Council, the Health and Medical Care Administration. Janusmed interactions [Web page]. http://www.janusinfo.se. Assessed March 27, 2019.

17. Böttiger Y, Laine K, Andersson ML, et al. SFINX - a drug-drug interaction database designed for clinical decision support systems. *Eur J Clin Pharmacol.* 2009;65:627-633.

18. Andersson ML, Böttiger Y, Lindh JD, Wettermark B, Eiermann B. Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care. *Eur J Clin Pharmacol.* 2013;69:565-571.

19. FASS. Läkemedelsindustriföreningens Service AB (LIF) [Pharmaceutical Industry Association]. https://www.fass.se/LIF/startpage. Assessed June 26, 2019.

20. Stockley's Drug Interactions. London: Pharmaceutical Press. https://about.medicinescomplete.com/publication/stockleys-drug-interactions/. Assessed June 26, 2019.

21. IBM Micromedex. Greenwood Village, CO: IBM Watson Health. http://www.micromedexsolutions.com. Accessed June 26, 2019.

22. Reppe LA, Spigset O, Kampmann JP, et al. Quality assessment of structure and language elements of written responses given by seven Scandinavian drug information centres. *Eur J Clin Pharmacol.* 2017;73:623-631.

23. Lönnbro J, Wallerstedt SM. Clinical relevance of the STOPP/START criteria in hip fracture patients. *Eur J Clin Pharmacol.* 2017;73:499-505.

24. Greenhalgh T, Howick J, Maskrey N. Evidence based medicine: a movement in crisis? *BMJ Evid Based Med.* 2014;348:g3725.

25. Böttiger Y, Laine K, Korhonen T, et al. Development and pilot testing of PHARAO - a decision support system for pharmacological risk assessment in the elderly. *Eur J Clin Pharmacol.* 2018;74:365-371.

26. Bryant A, Fletcher G, Payne T. Drug interaction alert override rates in meaningful use era. *Appl Clin Inform.* 2014;5:802-812.

27. Olvey EL, Clauschee S, Malone DC. Comparison of critical drug-drug interaction listings: the Department of Veterans Affairs medical system and standard reference compendia. *Clin Pharmacol Ther.* 2010;87:48-51.

28. Brinkman DJ, Tichelaar J, Mokkink LB, et al. Learning outcomes for clinical pharmacology and therapeutics education in Europe: a modified Delphi study. *Clin Pharmacol Ther.* 2018;104:317-325.

29. Eriksson AL, Wallerstedt SM. Developing confidence in basic prescribing skills during medical school: a longitudinal questionnaire study investigating the effects of a modified clinical pharmacology course. *Eur J Clin Pharmacol.* 2018;74:1343-1349.

30. Lönnbro J, Nylen K, Wallerstedt SM. Developing professional confidence in the art of prescribing - a randomized controlled study on structured collegial discussions during internship. *Eur J Clin Pharmacol.* 2019;75:687-696.

31. Aronsson P, Booth S, Hägg S, et al. The understanding of core pharmacological concepts among health care students in their final semester. *BMC Med Educ.* 2015;15:235.

32. Regional Medicines Information and Pharmacovigilance Centres in Norway and Sweden. RELIS database -a question–answer pair database. https://www.relis.no/. Accessed March 6, 2019.

33. Schjøtt J, Reppe LA, Roland PD, Westergren T. A question-answer pair (QAP) database integrated with websites to answer complex questions submitted to the Regional Medicines Information and Pharmacovigilance Centres in Norway (RELIS): a descriptive study. *BMJ Open.* 2012;2:e000642.

34. Andersson ML, Böttiger Y, Bastholm-Rahmner P, Ovesjo M, Veg A, Eiermann B. Evaluation usage patterns and user perception of the drug-drug interaction database SFINX. *Int J Med Inform.* 2015;84:327-333.

35. Sjöqvist F. Interaction between drugs. Läkemedelsindustriföreningens Service AB (LIF). Updated 2018-06-18. http://www.fass.se. Assessed June 26, 2019.

36. Fang L, Jiang YI, Yang Y, et al. Determining the optimal 5-FU therapeutic dosage in the treatment of colorectal cancer patients. *Oncotarget.* 2016;7:81880-81887.

37. Holm J, Eiermann B, Eliasson E, Mannheimer B. A limited number of prescribed drugs account for a great majority of drug-drug interactions. *Eur J Clin Pharmacol.* 2014;70:1375-1383.

38. Schjøtt J, Böttiger Y, Damkier P, et al. Use of references in responses from scandinavian drug information centres. *Medicines (Basel).* 2018;5:1-12.

39. Bergk V, Haefeli W, Gasse C, Brenner H, Martin-Facklam M. Information deficits in the summary of product characteristics preclude an optimal management of drug interactions: a comparison with evidence from the literature. *Eur J Clin Pharmacol.* 2005;61:327-335.

40. Amundstuen Reppe L, Lydersen S, Schjøtt J, et al. Relationship between time consumption and quality of responses to drug-related queries: a study from seven drug information centers in Scandinavia. *Clin Ther.* 2016;38:1738-1749.