Detecting drug–drug interactions that increase the incidence of long QT syndrome using a spontaneous reporting system

Short title: Drug interactions that increase incidence of LQTS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Japanese Adverse

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CONFLICT OF INTEREST

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Abstract

What is known and objective: Drug-induced long QT syndrome (diLQTS) is a rare but serious adverse drug reaction. Drug–drug interaction (DDI) is one of the risk factors for the development of diLQTS. However, the combinations of drugs that increase the risk of diLQTS have not been extensively investigated. This study was performed to analyze the potential DDIs that elevate the incidence of diLQTS using a spontaneous reporting system.

Methods: The Japanese Adverse Drug Event Report database from April 2004 to January 2020 was used to assess adverse event reports. We calculated the reporting odds ratio and 95% confidence interval for signal detection.

Results and discussion: Signals for concomitant use risk were detected in 31 drug combinations. Combinations of antipsychotics and antidepressants were the most common (olanzapine & fluvoxamine, olanzapine & trazodone, quetiapine & paroxetine, sulpiride & fluvoxamine, sulpiride & trazodone). Sixteen, 17, and 21 combinations were designated as requiring precaution for concomitant use in at least one of the package inserts in Japan, the United States, and the United Kingdom, respectively, although no such precautions were described for the remaining combinations. On the other hand, a combination of bepridil & clarithromycin was categorized as "X (avoid combination)" and two combinations (chlorpromazine & haloperidol, amiodarone & metildigoxin) were classified as "D (modify regimen)" in the Lexicomp® risk rating.

What is new and conclusion: This study identified 31 combinations of drugs that may elevate the risk of diLQTS. The use of these drug combinations should be monitored more carefully in future.

1 WHAT IS KNOWN AND OBJECTIVE

Drug-induced long QT syndrome (diLQTS) is a rare but serious adverse drug reaction that causes a ventricular tachycardia referred to as torsade de pointes (TdP), syncope, and sudden cardiac death. Not only antiarrhythmics but also non-cardiovascular drugs, such as antibiotics, antipsychotics, and antihistamines, are known to cause diLQTS.[1] The CredibleMeds® website classifies drugs based on their risk of diLQTS or TdP.[1] The main mechanism of diLQTS involves inhibition of the rapid component of the delayed rectifier potassium current encoded by the human ether-a-go-go-related gene (hERG).[2] A previous retrospective study showed that 51% of patients took at least one QT-prolonging drug during hospitalization,[3] suggesting that patients may be exposed to a variety of drugs with the potential to cause diLQTS.

Risk factors for the development of prolonged QT interval include drug–drug interactions (DDIs).[4] The diLQTS induced by DDIs can be divided into two classes according to their mechanisms, i.e., pharmacokinetic (PK) interactions defined as increased blood concentrations of QT-prolonging drugs by modification of their absorption, distribution, metabolism, or excretion and pharmacodynamic (PD) interactions defined as additive effects of drugs that inhibit the hERG channel.[5]

Spontaneous reporting systems provide information about adverse events in clinical settings and are utilized to assess postmarketing drug safety. In addition, these systems have also been applied to detect adverse events associated with DDIs, because two or more suspected drugs for each event can be given.[6–8] In Japan, the Pharmaceuticals and Medical Devices

Agency (PMDA) maintains a spontaneous reporting system database called the Japanese Adverse Drug Event Report (JADER) database. Whereas data mining approaches have been used for the detection of adverse events by disproportionality analysis, possible DDIs are detected based on the concept that when a suspected adverse event is reported more frequently with the combination of two drugs compared to the situation where they are used alone, this association may indicate the existence of a DDI.[8]

Our previous study using the JADER database focused on diLQTS associated with fluoroquinolone antibiotics and detected a signal indicating that coadministration of garenoxacin and disopyramide may increase the risk of diLQTS compared to the use of either drug alone.[9] In contrast to moxifloxacin, which is contraindicated for concomitant use with disopyramide, garenoxacin in combination with disopyramide is not contraindicated in Japan. Our results suggested that attention may also be required to combinations of drugs that do not have alerts regarding DDI risk on their package inserts. These findings prompted us to investigate which combinations of drugs other than fluoroquinolone antibiotics increase the risk of diLQTS.

This study was conducted to elucidate the potential DDIs that would increase the incidence of diLQTS using the JADER database.

2 METHODS

2.1 Data sources

We collected adverse event reports in the JADER database from April 2004 to January 2020 and evaluated signal detection using DRiFOs® (Luminary Medical K.K., Japan), an online system for licensed users to search the most updated adverse drug events reported to the PMDA using the JADER. The adverse events reported in the JADER database followed the definitions provided by the Medical Dictionary for Regulatory Activities (MedDRA) ver. 22.1. For the detection of diLQTS, preferred terms (PTs) were extracted from Standardized MedDRA Queries (SMQs), which have been released by the MedDRA Maintenance and Support Services Organization. Among the PTs that matched the SMQ for *torsade de pointes*/*QT prolongation* (SMQ code: 20000001), we used 6 PTs categorized in a narrow scope as follows: electrocardiogram QT interval abnormal (PT code: 10063748), electrocardiogram QT prolonged (PT code: 10014387), long QT syndrome (PT code: 10024803), long QT syndrome congenital (PT code: 10057926), torsade de pointes (PT code: 10044066), and ventricular tachycardia (PT code: 10047302). In the JADER database, each drug was assigned a code according to its association with adverse events; suspected drug, concomitant drug, or interacting drug. In this study, all drugs assigned as suspected or interacting drugs were included in the analysis. For signal detection of concomitant drug use, we focused on combinations of two drugs that have 20 or more diLQTS cases alone. Among these combinations, three or more reports were utilized for signal detection.

2.2 Signal detection

We calculated the reporting odds ratio (ROR) using two-by-two contingency tables of the presence or absence of a particular drug and a particular adverse event in the case reports (Table 1).[10] Safety signals were considered significant when the lower limit of the 95% confidence interval (CI) of the ROR value exceeded 1.[10] For detection of concomitant use risk, the combination of two suspected or interacting drugs was regarded as a drug of interest. We calculated the RORs and 95% CIs of the concomitant use group and single drug use groups separately as described above. The possibility of an adverse event caused by a suspected DDI was expected to be increased if the ROR of the coadministration group was higher than those of single use groups and these 95% CIs were mutually exclusive.[6,7]

CredibleMeds® places drugs into one of three categories of TdP risk: known risk, possible risk, and conditional risk.[1] We classified drugs according to their TdP risk (accessed July 2020) and therapeutic area according to the previous report.[1]

We categorized possible mechanisms of diLQTS caused by signal-positive drug combinations into PK interaction if one drug had the potential to alter the pharmacokinetics of another drug known to prolong the QT interval and/or PD interaction if both of the concomitant drugs had been reported to block the hERG channel based on a search in the PubMed database. We also confirmed whether the package inserts specify caution for drug combination in Japan (as of March 2021), the United States (USA, as of July 2021), the United Kingdom (UK, as of July 2021), and Lexicomp® (accessed September 2020).

3 RESULTS

3.1 Number of diLQTS cases and RORs for each drug

A total of 611336 reports were included in the present study and the number of diLQTS reports was 3958. Fifty-eight drugs for a broad spectrum of therapeutic areas had 20 or more case reports of diLQTS: 17 drugs for cardiovascular disease, eight for psychosis, six for cancer, five for bacterial infection, five for depression, four for central nervous system, two for gastrointestinal disease, two for fungal infection, one for urology, one for attention deficit hyperactivity disorder, and seven for miscellaneous diseases (Table 2). The number of reports and RORs of diLQTS for these drugs are also shown in Table 2. The lower limits of 95% CIs of RORs exceeded 1 for 55 drugs other than imatinib, levetiracetam, and lansoprazole.

3.2 Number of diLQTS cases and RORs for concomitant drugs

We evaluated the reports of diLQTS for concomitant use of two of the 58 drugs shown in Table 2. Table S1 shows the number of diLQTS reports for each combination. Of the total of 1653 combinations, 108 had three or more diLQTS cases (Tables 3 and S2). Thirty-one combinations showed concomitant use risk, suggesting a possible association with the elevated incidence of diLQTS (Table 3). On the other hand, we could not calculate the RORs for 13 combinations (bepridil & sevoflurane, bepridil & propofol, bepridil & remifentanil, bepridil & rocuronium, amiodarone & sulpiride, clarithromycin & propofol, clarithromycin & bisoprolol, clarithromycin & remifentanil, clarithromycin & rocuronium, donepezil & cibenzoline,

donepezil & disopyramide, levofloxacin & flecainide, aprindine & fluvoxamine), because there were no non-case reports in these combinations (Table S2).

3.3 Characteristics of drug combinations with concomitant use risk

Table 4 shows characteristics of the 31 signal-positive combinations of 33 drugs. "Antipsychotic and antidepressant" was the most common combination: olanzapine & fluvoxamine, olanzapine & trazodone, quetiapine & paroxetine, sulpiride & fluvoxamine, and sulpiride & trazodone. According to the CredibleMeds® risk categories, 13 and 12 drugs were classified as "known risk" and "conditional risk", respectively, whereas eight drugs were not included in any category. There were six combinations in which both coadministered drugs were categorized as "known risk", 10 combinations of drugs that were classified as "known risk" + "conditional risk", and five combinations in which both of the drugs were categorized as "conditional risk". As possible mechanisms of diLQTS occurring due to DDIs, eight and 14 combinations were estimated to be due to PK/PD and PD interactions, respectively. The mechanisms of the remaining combinations could not be determined.

Sixteen, 17, and 21 combinations were described as precautions for coadministration in at least one of the package inserts in Japan, the USA, and the UK, respectively (Table 4). In the package insert of haloperidol in the UK, haloperidol was contraindicated for concomitant use with chlorpromazine. However, there was no information about caution for concomitant use related to diLQTS in the remaining combinations. According to the Lexicomp® risk rating,

the combination of bepridil & clarithromycin was classified as “X (avoid combination)”. Furthermore, two combinations (chlorpromazine & haloperidol, amiodarone & metildigoxin) were categorized as “D (modify regimen)”, three (olanzapine & fluvoxamine, metildigoxin & clarithromycin, clarithromycin & voriconazole) as “C (monitor therapy)”, and four (sulpiride & azithromycin, sulpiride & levofloxacin, donepezil & azithromycin, clarithromycin & sevoflurane) as “B (no action needed)”. The remaining combinations were classified as “A (no interaction)” or “no information”.

4 DISCUSSION

Signal detection using spontaneous reporting systems is helpful to survey the incidence of rare but serious adverse events occurring due to DDI.[6–9] In the present study, a signal for concomitant use risk was detected in 31 combinations.

Cardiovascular drugs were the most common drugs included in the signal-positive combinations. In contrast, the most common combination with concomitant use risk was the coadministration of an antipsychotic and an antidepressant, i.e., non-cardiovascular drugs. This implies that, in addition to cardiovascular drugs, the risk of diLQTS caused by concomitant use of non-cardiovascular drugs may require attention. A previous study on the prevalence of diLQTS related to DDIs in psychiatry wards indicated that 51.7% of patients received QT-prolonging drugs concomitantly and that the coadministration of antipsychotic and antidepressant as well as coadministration of two antipsychotics were common combinations.[11]

Both antipsychotics and antidepressants have the potential to inhibit the hERG channel.[12–18] In addition, certain antidepressants have the ability to inhibit the metabolism of antipsychotics.[19] For the signal-positive combinations of antipsychotic and antidepressant in this study, diLQTS caused by coadministration of olanzapine & trazodone, quetiapine & paroxetine, sulpiride & fluvoxamine, and sulpiride & trazodone was estimated to be due to PD interaction. On the other hand, diLQTS occurring due to the concomitant use of olanzapine & fluvoxamine was estimated to be due to both PK and PD interactions.[12,14,20] However, it should be noted that there was only one combination (olanzapine & fluvoxamine) categorized as risk rating C (monitor therapy) in Lexicomp® and described in the cautions for coadministration associated with diLQTS in the package inserts of both drugs (Table 4). Therefore, careful monitoring of the other combinations will be necessary in future.

The antipsychotic, sulpiride, was included in the greatest number of combinations with concomitant use risk. The degree of hERG inhibition by sulpiride is considered to be small at clinically relevant concentrations.[13] On the other hand, sulpiride has broad indications for schizophrenia, depression, and peptic ulcer. Therefore, this drug is predicted to be used frequently in combination with other QT-prolonging drugs. Coadministered drugs may affect the incidence of sulpiride-related diLQTS.

Among the antidepressants, paroxetine, fluvoxamine, and trazodone were each included in three signal-positive combinations. Trazodone has the ability to block the hERG channel at clinically relevant concentrations.[15] In addition, trazodone is predicted to be

coadministered with psychoactive drugs, because it is commonly prescribed as a hypnotic for sleep disturbance caused by comorbid psychiatric disorders.[21] Therefore, attention is required for the risk of serious arrhythmia caused not only by single use of trazodone but also by its concomitant use along with other QT-prolonging drugs.

Donepezil was included in four signal-positive combinations. Donepezil is thought to induce diLQTS by hERG inhibition.[22] As donepezil is usually prescribed to elderly patients due to its indications, the risk of fatal ventricular arrhythmia may be relatively high in this population. Although diLQTS and TdP are described as serious potential side effects in the package insert of donepezil in Japan, there are no cautions regarding concomitant use with drugs that may cause diLQTS. Our results suggest that the coadministration of donepezil and other QT-prolonging drugs should be monitored carefully in future.

Similar to donepezil, the macrolide antibiotic, clarithromycin, was included in four combinations with concomitant use risk. As clarithromycin exerts inhibitory effects on the hERG channel and cytochrome P450 3A4 (CYP3A4)/P-glycoprotein (P-gp),[23,24] PK and/or PD interactions with clarithromycin are likely involved. The three signal-positive combinations detected in this study (clarithromycin & bepridil, metildigoxin, or voriconazole) were thought to cause diLQTS due to both PK and PD interactions. Although the combination of clarithromycin & bepridil was classified as risk rating X, which corresponded to contraindication in Lexicomp®, the package inserts only described this combination as "precaution for coadministration" in Japan (Table 4). Thus, the degree of caution for this

combination is dependent on the drug information source. As the combination of clarithromycin & bepridil was associated with 17 cases of diLQTS, the highest number of such cases among the 31 signal-positive combinations detected in this study, more care is required regarding the coadministration of these drugs in Japan. In this study, azithromycin was also included in two signal-positive combinations, although this drug itself has only modest or no inhibitory effect on the hERG channel and CYP3A4/P-gp.[23,25] According to a report by the USA Food and Drug Administration, half of the reports of diLQTS associated with macrolide antibiotics, including azithromycin, mentioned concomitant use of QT-prolonging drugs.[4] These findings suggest that azithromycin-related diLQTS may be caused by PD interaction. The combinations of azithromycin with donepezil or sulpiride were categorized as risk rating B (no action needed) in Lexicomp®. However, these combinations were described as precautions for coadministration related to diLQTS in at least one of the package inserts in Japan, the USA, and the UK, except that there was no such information regarding concomitant use of azithromycin with donepezil in Japan (Table 4). Furthermore, the administration of azithromycin to patients having a risk of QT prolongation, such as those receiving other QT-prolonging drugs, was alerted in "warnings and precautions" section of its package inserts in the USA and the UK. Therefore, the coadministration of azithromycin with other QT-prolonging drugs should be monitored carefully in future.

Cardiac glycosides, digoxin or metildigoxin, were included in three combinations with concomitant use risk. Digoxin has been reported to reduce the hERG current via inhibition of

hERG trafficking at concentrations higher than clinical blood levels.[26] As these drugs are excreted mainly by the kidneys through glomerular filtration and P-gp-mediated tubular secretion, their coadministration with P-gp inhibitors would result in elevation of blood concentrations of digoxin and metildigoxin, leading to increased risk of diLQTS. Of the concomitant drugs included in the signal-positive combinations containing digoxin and metildigoxin, in this study, amiodarone and clarithromycin were P-gp inhibitors.[24,27] These findings suggest that the concomitant use of metildigoxin (and digoxin) with amiodarone or clarithromycin may increase the risk of diLQTS caused by both PK and PD interactions. The combination of digoxin & amiodarone was classified as risk rating D (modify regimen) in Lexicomp®. Moreover, digoxin was designated as "precaution for concomitant use" in the package inserts of amiodarone and clarithromycin in Japan, the USA, and the UK, but no such precautions were noted for metildigoxin. However, metildigoxin exerts the same pharmacological effects on the heart as digoxin. Therefore, the concomitant use of metildigoxin with amiodarone and clarithromycin may require as much care as that of digoxin.

Among the gastric acid secretion inhibitors, famotidine (H_2 blocker) and lansoprazole (proton pump inhibitor) were included in the signal-positive combinations. To our knowledge, there have been no reports of hERG inhibition by H_2 blockers, although lansoprazole has been reported to block the hERG channel at concentrations higher than clinical blood levels.[28] On the other hand, some previous studies showed that these drugs could cause diLQTS in the presence of other risk factors, such as electrolyte imbalance and DDIs.[28,29] In this study, the

combination of lansoprazole & escitalopram showed a positive signal for concomitant use risk. It has been reported that lansoprazole increases blood concentrations of escitalopram through the inhibition of escitalopram metabolism catalyzed by CYP2C19.[30] Therefore, the PK interaction may contribute partly to the increased risk of diLQTS associated with their coadministration.

This study had several limitations. First, we could not exclude duplicates, as events in the same patient could be reported two or more times as different cases from different manufacturers or healthcare professionals in the JADER database. Therefore, the concomitant use risk of diLQTS may have been overestimated in this study. Second, signal detection analysis was performed by focusing on the combinations of two suspected drugs in this study. However, there have been reports of concomitant use of three or more suspect drugs. We cannot exclude the possibility that a third drug may be a confounding factor on the relationship between coadministration and risk of diLQTS. Finally, the risk of diLQTS using the ROR adjusted for age, sex, etc., was not evaluated due to the small number of case reports. The signal detection approach using spontaneous reporting systems is utilized to obtain information about the potential associations between drugs and adverse events. Further studies using other approaches are required to demonstrate the consequences of coadministered drugs on risk of diLQTS.

5 WHAT IS NEW AND CONCLUSION

We detected 31 signal-positive combinations of drugs that may increase the risk of diLQTS

using the JADER database. diLQTS was estimated to be due to PK/PD interactions for eight combinations and PD interactions for 14 combinations. Furthermore, our results showed that the degree of caution for coadministration of drugs with concomitant use risk is dependent on drug information source. Therefore, the concomitant use of these drugs should require careful monitoring in future.

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TABLE 1 Two-by-two contingency table used for the calculation of RORs

	Suspected adverse drug events (Cases)	All other adverse drug events (Non-cases)
Suspected drug	A	b
All other drugs	C	d

TABLE 2 Number of reports and RORs of diLQTS associated with drugs that have ≥ 20 diLQTS cases

Drug	Therapeutic area	Case (*n*)	Non-case (*n*)	Total (*n*)	ROR	(95% CI)
Bepridil	Cardiovascular	387	413	800	159.27	(138.12 – 183.67)
Amiodarone	Cardiovascular	208	2037	2245	16.48	(14.24 – 19.08)
Pilsicainide	Cardiovascular	198	647	845	49.38	(41.98 – 58.09)
Nilotinib	Cancer	155	1882	2037	13.11	(11.1 – 15.49)
Disopyramide	Cardiovascular	146	381	527	61.02	(50.29 – 74.04)
Clarithromycin	Bacterial infection	134	3647	3781	5.80	(4.87 – 6.91)
Donepezil	CNS	120	1847	1967	10.25	(8.5 – 12.36)
Cibenzoline	Cardiovascular	115	824	939	22.03	(18.08 – 26.84)
Sevoflurane	Miscellaneous	113	986	1099	18.07	(14.84 – 22.01)
Arsenic trioxide	Cancer	112	321	433	55.07	(44.31 – 68.45)
Famotidine	Gastro-intestinal	90	3505	3595	4.01	(3.24 – 4.95)
Sulpiride	Psychosis	77	1627	1704	7.39	(5.86 – 9.3)
Nifekalant	Cardiovascular	66	37	103	278.36	(185.89 – 416.83)
Cilostazol	Cardiovascular	63	2357	2420	4.15	(3.23 – 5.34)
Levofloxacin	Bacterial infection	62	4657	4719	2.06	(1.6 – 2.65)
Osimertinib	Cancer	55	1307	1362	6.53	(4.98 – 8.57)
Flecainide	Cardiovascular	55	116	171	73.77	(53.44 – 101.84)
Crizotinib	Cancer	52	1115	1167	7.24	(5.47 – 9.58)
Furosemide	Cardiovascular	52	2945	2997	2.73	(2.07 – 3.6)
Digoxin	Cardiovascular	51	569	620	13.92	(10.44 – 18.57)
Risperidone	Psychosis	49	3534	3583	2.14	(1.61 – 2.84)
Paroxetine	Depression	47	3019	3066	2.41	(1.8 – 3.21)
Olanzapine	Psychosis	45	2348	2393	2.96	(2.2 – 3.99)
Propofol	Miscellaneous	45	2098	2143	3.32	(2.47 – 4.47)

Aprindine	Cardiovascular	45	282	327	24.76	(18.05 – 33.97)
Escitalopram	Depression	44	538	582	12.68	(9.31 – 17.27)
Haloperidol	Psychosis	44	1551	1595	4.39	(3.25 – 5.93)
Garenoxacin	Bacterial infection	39	1957	1996	3.08	(2.24 – 4.23)
Voriconazole	Fungal infection	38	1672	1710	3.51	(2.54 – 4.85)
Guanfacine	ADHD	38	197	235	29.88	(21.08 – 42.34)
Fluvoxamine	Depression	37	1115	1152	5.13	(3.69 – 7.13)
Azithromycin	Bacterial infection	37	1530	1567	3.74	(2.69 – 5.19)
Sertraline	Depression	36	1267	1303	4.39	(3.15 – 6.12)
Imatinib	Cancer	36	4716	4752	1.17	(0.84 – 1.63)
Quetiapine	Psychosis	35	2659	2694	2.03	(1.45 – 2.84)
Carvedilol	Cardiovascular	34	1332	1366	3.94	(2.8 – 5.55)
Verapamil	Cardiovascular	33	473	506	10.79	(7.57 – 15.37)
Moxifloxacin	Bacterial infection	32	671	703	7.37	(5.16 – 10.52)
Dasatinib	Cancer	32	1484	1516	3.33	(2.34 – 4.73)
Sotalol	Cardiovascular	31	99	130	48.42	(32.31 – 72.57)
Pirmenol	Cardiovascular	30	27	57	171.80	(102.05 – 289.23)
Trazodone	Depression	29	503	532	8.91	(6.12 – 12.97)
Aripiprazole	Psychosis	29	2741	2770	1.63	(1.13 – 2.35)
Bisoprolol	Cardiovascular	27	801	828	5.20	(3.54 – 7.64)
Clozapine	Psychosis	26	1904	1930	2.10	(1.43 – 3.1)
Chlorpromazine	Psychosis	24	677	701	5.47	(3.63 – 8.22)
Remifentanil	Miscellaneous	24	1168	1192	3.17	(2.11 – 4.75)
Etizolam	CNS	23	1884	1907	1.88	(1.24 – 2.84)
Evocalcet	Miscellaneous	23	45	68	78.89	(47.69 – 130.5)
Galantamine	CNS	22	865	887	3.92	(2.56 – 5.99)

Levetiracetam	CNS	22	2268	2290	1.49	(0.98 – 2.27)
Fluconazole	Fungal infection	21	523	544	6.19	(4 – 9.58)
Solifenacin	Urology	21	800	821	4.04	(2.62 – 6.24)
Cinacalcet	Miscellaneous	21	614	635	5.27	(3.41 – 8.15)
Metildigoxin	Cardiovascular	20	208	228	14.83	(9.36 – 23.48)
Ropivacaine	Miscellaneous	20	578	598	5.33	(3.41 – 8.34)
Rocuronium	Miscellaneous	20	1362	1382	2.26	(1.45 – 3.52)
Lansoprazole	Gastrointestinal	20	4164	4184	0.74	(0.47 – 1.14)

Abbreviations: ADHD, attention deficit hyperactivity disorder; CNS, central nervous system.

TABLE 3 Number of reports and RORs of diLQTS associated with signal-positive drug combinations

Drugs			Case (*n*)	Non-case (*n*)	Total (*n*)	ROR	(95% CI)
Bepridil	without	Clarithromycin	370	412	782	151.92	(131.52 – 175.48)
Clarithromycin	without	Bepridil	117	3646	3763	5.04	(4.18 – 6.08)
Bepridil	and	Clarithromycin	17	1	18	2620.00	(348.58 – 19692.54)
Amiodarone	without	Famotidine	201	2028	2229	15.97	(13.77 – 18.53)
Famotidine	without	Amiodarone	83	3496	3579	3.70	(2.97 – 4.61)
Amiodarone	and	Famotidine	7	9	16	119.56	(44.51 – 321.21)
Amiodarone	without	Metildigoxin	205	2035	2240	16.25	(14.02 – 18.82)
Metildigoxin	without	Amiodarone	17	206	223	12.71	(7.75 – 20.87)
Amiodarone	and	Metildigoxin	3	2	5	230.36	(38.48 – 1379.03)
Clarithromycin	without	Sevoflurane	129	3646	3775	5.58	(4.67 – 6.67)
Sevoflurane	without	Clarithromycin	108	985	1093	17.27	(14.12 – 21.12)
Clarithromycin	and	Sevoflurane	5	1	6	768.25	(89.73 – 6577.52)
Clarithromycin	without	Voriconazole	129	3620	3749	5.62	(4.7 – 6.72)
Voriconazole	without	Clarithromycin	33	1645	1678	3.10	(2.19 – 4.38)
Clarithromycin	and	Voriconazole	5	27	32	28.45	(10.95 – 73.92)
Clarithromycin	without	Metildigoxin	128	3642	3770	5.54	(4.63 – 6.63)
Metildigoxin	without	Clarithromycin	14	203	217	10.62	(6.17 – 18.26)
Clarithromycin	and	Metildigoxin	6	5	11	184.43	(56.26 – 604.56)
Donepezil	without	Famotidine	116	1831	1947	9.99	(8.25 – 12.08)
Famotidine	without	Donepezil	86	3489	3575	3.84	(3.1 – 4.77)
Donepezil	and	Famotidine	4	16	20	38.40	(12.83 – 114.92)
Donepezil	without	Azithromycin	117	1845	1962	10.00	(8.27 – 12.08)
Azithromycin	without	Donepezil	34	1528	1562	3.44	(2.44 – 4.83)
Donepezil	and	Azithromycin	3	2	5	230.36	(38.48 – 1379.03)

Donepezil	without	Sertraline	114	1827	1941	9.83	(8.11 – 11.91)
Sertraline	without	Donepezil	30	1247	1277	3.71	(2.58 – 5.34)
Donepezil	and	Sertraline	6	20	26	46.11	(18.51 – 114.87)
Donepezil	without	Solifenacin	117	1837	1954	10.04	(8.31 – 12.14)
Solifenacin	without	Donepezil	18	790	808	3.51	(2.2 – 5.6)
Donepezil	and	Solifenacin	3	10	13	46.07	(12.67 – 167.47)
Cibenzoline	without	Aprindine	110	822	932	21.09	(17.24 – 25.8)
Aprindine	without	Cibenzoline	40	280	320	22.14	(15.87 – 30.88)
Cibenzoline	and	Aprindine	5	2	7	384.12	(74.5 – 1980.52)
Sevoflurane	without	Bisoprolol	108	984	1092	17.29	(14.14 – 21.14)
Bisoprolol	without	Sevoflurane	22	799	821	4.24	(2.77 – 6.49)
Sevoflurane	and	Bisoprolol	5	2	7	384.12	(74.5 – 1980.52)
Famotidine	without	Digoxin	86	3494	3580	3.84	(3.09 – 4.77)
Digoxin	without	Famotidine	47	558	605	13.07	(9.69 – 17.63)
Famotidine	and	Digoxin	4	11	15	55.86	(17.78 – 175.5)
Sulpiride	without	Levofloxacin	73	1619	1692	7.03	(5.55 – 8.91)
Levofloxacin	without	Sulpiride	58	4649	4707	1.93	(1.49 – 2.5)
Sulpiride	and	Levofloxacin	4	8	12	76.80	(23.12 – 255.17)
Sulpiride	without	Olanzapine	65	1570	1635	6.44	(5.02 – 8.27)
Olanzapine	without	Sulpiride	33	2291	2324	2.22	(1.57 – 3.14)
Sulpiride	and	Olanzapine	12	57	69	32.40	(17.37 – 60.43)
Sulpiride	without	Azithromycin	74	1626	1700	7.10	(5.61 – 8.98)
Azithromycin	without	Sulpiride	34	1529	1563	3.43	(2.44 – 4.83)
Sulpiride	and	Azithromycin	3	1	4	460.72	(47.91 – 4430.25)
Sulpiride	without	Fluvoxamine	63	1541	1604	6.36	(4.93 – 8.2)
Fluvoxamine	without	Sulpiride	23	1029	1052	3.44	(2.28 – 5.21)

Sulpiride	and	Fluvoxamine	14	86	100	25.07	(14.24 – 44.14)
Sulpiride	without	Trazodone	65	1590	1655	6.36	(4.95 – 8.17)
Trazodone	without	Sulpiride	17	466	483	5.62	(3.46 – 9.12)
Sulpiride	and	Trazodone	12	37	49	49.92	(26.01 – 95.8)
Furosemide	without	Paroxetine	49	2940	2989	2.58	(1.94 – 3.42)
Paroxetine	without	Furosemide	44	3014	3058	2.25	(1.67 – 3.04)
Furosemide	and	Paroxetine	3	5	8	92.14	(22.01 – 385.7)
Paroxetine	without	Quetiapine	40	2966	3006	2.08	(1.52 – 2.85)
Quetiapine	without	Paroxetine	28	2606	2634	1.65	(1.14 – 2.4)
Paroxetine	and	Quetiapine	7	53	60	20.30	(9.22 – 44.68)
Paroxetine	without	Etizolam	39	2854	2893	2.11	(1.53 – 2.9)
Etizolam	without	Paroxetine	15	1719	1734	1.34	(0.81 – 2.23)
Paroxetine	and	Etizolam	8	165	173	7.45	(3.66 – 15.16)
Olanzapine	without	Fluvoxamine	33	2314	2347	2.20	(1.56 – 3.1)
Fluvoxamine	without	Olanzapine	25	1081	1106	3.57	(2.4 – 5.31)
Olanzapine	and	Fluvoxamine	12	34	46	54.32	(28.11 – 104.98)
Olanzapine	without	Trazodone	35	2328	2363	2.32	(1.66 – 3.24)
Trazodone	without	Olanzapine	19	483	502	6.06	(3.83 – 9.6)
Olanzapine	and	Trazodone	10	20	30	76.92	(35.98 – 164.43)
Propofol	without	Bisoprolol	39	2094	2133	2.88	(2.09 – 3.95)
Bisoprolol	without	Propofol	21	797	818	4.06	(2.63 – 6.27)
Propofol	and	Bisoprolol	6	4	10	230.53	(65.03 – 817.25)
Escitalopram	without	Lansoprazole	40	536	576	11.56	(8.37 – 15.96)
Lansoprazole	without	Escitalopram	16	4162	4178	0.59	(0.36 – 0.96)
Escitalopram	and	Lansoprazole	4	2	6	307.22	(56.25 – 1677.84)
Haloperidol	without	Chlorpromazine	27	1401	1428	2.97	(2.03 – 4.35)

Chlorpromazine	without	Haloperidol	7	527	534	2.04	(0.97 – 4.3)
Haloperidol	and	Chlorpromazine	17	150	167	17.46	(10.56 – 28.86)
Fluvoxamine	without	Trazodone	23	1071	1094	3.31	(2.19 – 5.01)
Trazodone	without	Fluvoxamine	15	459	474	5.03	(3 – 8.42)
Fluvoxamine	and	Trazodone	14	44	58	49.00	(26.83 – 89.48)
Quetiapine	without	Etizolam	29	2592	2621	1.72	(1.19 – 2.49)
Etizolam	without	Quetiapine	17	1817	1834	1.44	(0.89 – 2.32)
Quetiapine	and	Etizolam	6	67	73	13.76	(5.97 – 31.74)
Bisoprolol	without	Remifentanil	22	799	821	4.24	(2.77 – 6.49)
Remifentanil	without	Bisoprolol	19	1166	1185	2.51	(1.59 – 3.95)
Bisoprolol	and	Remifentanil	5	2	7	384.12	(74.5 – 1980.52)
Bisoprolol	without	Rocuronium	21	795	816	4.07	(2.64 – 6.28)
Rocuronium	without	Bisoprolol	14	1356	1370	1.59	(0.94 – 2.69)
Bisoprolol	and	Rocuronium	6	6	12	153.69	(49.54 – 476.73)
Garenoxacin	without	Disopyramide	33	1956	1989	2.60	(1.84 – 3.68)
Disopyramide	without	Garenoxacin	146	381	527	61.02	(50.29 – 74.04)
Garenoxacin	and	Disopyramide	6	1	7	922.13	(110.99 – 7661.48)

TABLE 4 Characteristics of signal-positive drug combinations

Therapeutic area		Combination		CredibleMeds® risk category		Mechanism of DDIs	Description of precautions in the package inserts			Lexicomp® risk rating
Drug 1	Drug 2	Drug 1	Drug 2	Drug 1	Drug 2		Japan	USA	UK	
Psychosis	Bacterial infection	Sulpiride [a)]	Azithromycin	Known	Known	PD	Sulpiride alone	Azithromycin alone	Both	B
Psychosis	Bacterial infection	Sulpiride [a)]	Levofloxacin	Known	Known	PD	Both	None	Both	B
Psychosis	CNS	Quetiapine	Etizolam [a,b)]	Conditional	No information	No information	Quetiapine alone	Quetiapine alone	Quetiapine alone	A
Psychosis	Depression	Olanzapine	Fluvoxamine	Conditional	Conditional	PK, PD	Both	Both	Both	C
Psychosis	Depression	Olanzapine	Trazodone	Conditional	Conditional	PD	None	Trazodone alone	Both	A
Psychosis	Depression	Quetiapine	Paroxetine	Conditional	Conditional	PD	Quetiapine alone	Quetiapine alone	Quetiapine alone	A
Psychosis	Depression	Sulpiride [a)]	Fluvoxamine	Known	Conditional	PD	Sulpiride alone	None	Sulpiride alone	A

Psychosis	Depression	Sulpiride [a)]	Trazodone	Known	Conditional	PD	Sulpiride alone	Trazodone alone	Both	A
Psychosis	Psychosis	Chlorpromazine	Haloperidol	Known	Known	PK, PD	Haloperidol alone	Haloperidol alone	Both	D
Psychosis	Psychosis	Olanzapine	Sulpiride [a)]	Conditional	Known	PD	Sulpiride alone	None	Both	A
Depression	Cardiovascular	Paroxetine	Furosemide	Conditional	Conditional	PD	None	None	None	A
Depression	CNS	Paroxetine	Etizolam [a,b)]	Conditional	No information	No information	None	None	None	A
Depression	CNS	Sertraline	Donepezil	Conditional	Known	PD	Sertraline alone	Sertraline alone	Sertraline alone	A
Depression	Depression	Fluvoxamine	Trazodone	Conditional	Conditional	PK, PD	None	Both	Trazodone alone	A
Depression	Gastro-intestinal	Escitalopram	Lansoprazole	Known	Conditional	PK	Escitalopram alone	None	Escitalopram alone	A
CNS	Bacterial infection	Donepezil	Azithromycin	Known	Known	PD	None	Azithromycin alone	Azithromycin alone	B
CNS	Gastro-intestinal	Donepezil	Famotidine	Known	Conditional	No information	None	None	None	A

CNS	Urology	Donepezil	Solifenacin	Known	Conditional	PD	Solifenacin alone	Solifenacin alone	None	A
Cardiovascular	Bacterial infection	Bepridil [a,b)]	Clarithromycin	Known	Known	PK, PD	Both	Clarithromycin alone	Clarithromycin alone	X
Cardiovascular	Bacterial Infection	Disopyramide	Garenoxacin [a,b)]	Known	Conditional	PD	Garenoxacin alone	None	Disopyramide alone	No information
Cardiovascular	Bacterial Infection	Metildigoxin [a,b)]	Clarithromycin	No information	Known	PK, PD	Metildigoxin alone	None	Clarithromycin alone	C [c)]
Cardiovascular	Cardiovascular	Amiodarone	Metildigoxin [a,b)]	Known	No information	PK, PD	Metildigoxin alone	Amiodarone alone	Amiodarone alone	D [c)]
Cardiovascular	Cardiovascular	Aprindine [a,b)]	Cibenzoline [a,b)]	No information	No information	PD	None	None	None	No information
Cardiovascular	Gastro-intestinal	Amiodarone	Famotidine	Known	Conditional	No information	None	Amiodarone alone	Amiodarone alone	A
Cardiovascular	Gastro-Intestinal	Digoxin	Famotidine	Not classified	Conditional	No information	None	None	None	A

Cardiovascular	Miscellaneous	Bisoprolol	Propofol	Not classified	Known	No information	None	None	None	A
Cardiovascular	Miscellaneous	Bisoprolol	Remifentanil	Not classified	Not classified	No information	None	None	None	A
Cardiovascular	Miscellaneous	Bisoprolol	Rocuronium	Not classified	Not classified	No information	None	None	None	A
Cardiovascular	Miscellaneous	Bisoprolol	Sevoflurane	Not classified	Known	No information	None	Sevoflurane alone	None	A
Bacterial Infection	Fungal infection	Clarithromycin	Voriconazole	Known	Conditional	PK, PD	None	Both	Both	C
Bacterial Infection	Miscellaneous	Clarithromycin	Sevoflurane	Known	Known	PD	None	Both	Clarithromycin alone	B

Abbreviation: CNS, central nervous system.

[a] Unapproved drugs in the USA.

[b] Unapproved drugs in the UK.

[c] Risk rating based on digoxin.