

ELECTRONIC SUPPLEMENTAL MATERIALS

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Article: Feasibility of prioritizing Drug-Drug-Event Associations Found in Electronic Health Records

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Patient Timeline	Cell in 2x2 Table	Comment
	d	No Drug1 or Drug 2 and no Event
	d	Drug 1 or Drug 2 and no Event
	c	Event but no Drug 1 or Drug2
	c	Drug 1 or Drug 2 and Event After
	b	Drug 1 and Drug 2 but no Event
	a	Drug 1, Drug 2 and Event After

	Event	No Event
D1 & D2	a	b
At most D1 or D2	c	d

Figure A. Assignment of patient counts to the exposure-event contingency table for the method developed by Iyer *et al.* (19) to signal drug-drug-event associations from EHR data. This adapted figure shows in the patient timeline column how temporal information for drug exposure is used for cell assignment.

Table I. Drug-drug-event associations with a prioritization score ≥ 4 with no grouping of sources. The top-ranked associations based on scores from our original source grouping are highlighted in grey.

Rank	Drug 1	Drug 2	Event	Reporting	Literature	Prediction (DDI + AE)	Prediction (DDI)			Score	Odds Ratio
						TWOSIDES	INDI	Similarity-based Modeling	Pharmaco Interaction Networks		
1	cyclophosphamide	carboplatin	Neutropenia	1	1	1	0	0	1	5	10.3021
2	mercaptopurine	vincristine	Neutropenia	1	0	0	1	0	1	4	53.662
3	cyclophosphamide	cisplatin	Neutropenia	1	1	0	0	0	1	4	14.3057
4	tramadol	topiramate	Serotonin syndrome	0	0	1	1	0	1	4	13.6809
5	lamotrigine	mirtazapine	Serotonin syndrome	0	0	1	1	0	1	4	11.9991
6	fludarabine	methotrexate	Pancytopenia	0	0	1	1	0	1	4	7.48325
7	thalidomide	warfarin	Neutropenia	1	0	1	0	0	1	4	6.80803
8	vincristine	mercaptopurine	Pancytopenia	0	0	1	1	0	1	4	6.75531
9	lorazepam	aprepitant	Neutropenia	0	0	1	1	0	1	4	5.76483
10	tramadol	amitriptyline	Serotonin syndrome	0	1	0	1	1	0	4	4.11386
11	gemfibrozil	simvastatin	Rhabdomyolysis	1	1	1	0	0	0	4	3.69682
12	sumatriptan	quetiapine	Serotonin syndrome	0	0	1	1	0	1	4	3.38322
13	lorazepam	buspirone	Serotonin syndrome	0	0	1	1	0	1	4	3.33973
14	digoxin	carvedilol	Hyperkalaemia	1	0	1	1	0	0	4	2.65814
15	spironolactone	atenolol	Hyperkalaemia	1	0	1	1	0	0	4	2.60692
16	spironolactone	glimepiride	Hyperkalaemia	1	0	1	0	0	1	4	2.27854
17	furosemide	bumetanide	Hyperkalaemia	0	0	1	1	0	1	4	1.96399
18	atenolol	glipizide	Hyperkalaemia	0	0	1	1	1	0	4	1.78201
19	atenolol	hydralazine	Hyperkalaemia	0	0	1	1	0	1	4	1.63373
20	furosemide	nifedipine	Hyperkalaemia	0	0	1	1	0	1	4	1.29945
21	furosemide	losartan	Hyperkalaemia	0	0	1	1	0	1	4	1.25689
22	furosemide	eplerenone	Hyperkalaemia	1	0	0	1	0	1	4	1.15144

Table II. Drug-drug-event associations with a prioritization score ≥ 2 with an alternative grouping of reporting sources, prediction methods and literature. The top-ranked associations based on scores from our original source grouping are highlighted in grey.

Rank	Drug 1	Drug 2	Event	+ Reporting TWO SIDES	Prediction Methods (DDI)	Literature	Score	Odds Ratio
1	cyclophosphamide	cisplatin	Neutropenia	1	1	1	3	14.3057
2	cyclophosphamide	carboplatin	Neutropenia	1	1	1	3	10.3021
3	daunorubicin	etoposide	Neutropenia	1	1	0	2	55.4931
4	vincristine	mercaptopurine	Neutropenia	1	1	0	2	53.662
5	daunorubicin	ondansetron	Neutropenia	1	1	0	2	45.7784
6	cyclophosphamide	etoposide	Neutropenia	0	1	1	2	33.6945
7	vincristine	doxorubicin	Neutropenia	1	1	0	2	31.0798
8	fludarabine	allopurinol	Neutropenia	1	1	0	2	25.8783
9	vincristine	dexamethasone	Neutropenia	1	1	0	2	25.2882
10	doxorubicin	allopurinol	Neutropenia	1	1	0	2	24.3974
11	olanzapine	fluvoxamine	Rhabdomyolysis	1	1	0	2	20.3734
12	methotrexate	allopurinol	Neutropenia	1	1	0	2	20.1525
13	methotrexate	mercaptopurine	Neutropenia	1	1	0	2	19.973
14	doxorubicin	methotrexate	Neutropenia	1	1	0	2	17.8509
15	ciprofloxacin	bortezomib	Neutropenia	1	1	0	2	16.4949
16	duloxetine	eletriptan	Serotonin syndrome	1	1	0	2	14.9939
17	ifosfamide	lorazepam	Neutropenia	1	1	0	2	14.7006
18	tramadol	topiramate	Serotonin syndrome	1	1	0	2	13.6809
19	ifosfamide	carboplatin	Neutropenia	0	1	1	2	12.846
20	ifosfamide	methotrexate	Neutropenia	1	1	0	2	12.7