DrugWAS: Drug-wide association studies for COVID-19 drug repurposing

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Study highlights

- The study used electronic health records to search for drug candidates that could be repurposed to treat COVID-19
- The study found 17 drug ingredients that are significantly associated with a decreased • risk of death and other severe COVID-19 outcomes
- The list of drugs proposed by this study could provide additional insights into • developing new candidates for COVID-19 treatment

Patient selection



Significant drug associations grouped by outcome

Drug study (by outcome)	Drug class	Total exposed	Total unexposed	Severity rate (exposed)	Severity rate (unexposed)	Odds Ratio	OR	[95% CI]
Primary outcome: all-cause of death								
*PCV13a	vaccine	338	8868	2.2	5.4		0.31	[0.12; 0.81]
*PCV13b	vaccine	572	8634	2.0	4.9		0.33	[0.15: 0.73]
Diphtheria toxoid vaccine inactivated	vaccine	937	8269	0.9	22		0.38	$[0\ 15\ 0\ 93]$
Tetanus toxoid vaccine, inactivated	vaccine	938	8268	0.9	2.1		0.38	[0.15; 0.93]
O								
Secondary outcome: on ventilator, c	umulative severity							
*PCV13a	vaccine	338	8891	2.2	5.9		0.28	[0.11; 0.72]
*PCV13b	vaccine	572	8657	2.0	5.4		0.29	[0.13; 0.64]
Diphtheria toxoid vaccine, inactivated	vaccine	938	8291	1.0	2.5		0.37	[0.16; 0.85]
Tetanus toxoid vaccine, inactivated	vaccine	939	8290	1.0	2.5		0.37	[0.16; 0.85]
Acellular pertussis vaccine, inactivated	vaccine	902	8327	1.1	2.4		0.41	[0.18; 0.95]
*PPSV23	vaccine	478	8751	2.8	6.5		0.46	[0.22; 0.96]
Secondary outcome: in ICU, cumulat	ive severity							
*PCV13a	vaccine	339	8928	2.5	6.7		0.27	[0.11; 0.67]
*PCV13b	vaccine	574	8693	2.3	6.2		0.29	[0.14; 0.61]
Flaxseed extract	supplement	192	9075	4.0	11.6		0.37	[0.14; 0.97]
Diphtheria toxoid vaccine, inactivated	vaccine	941	8326	1.3	3.0		0.40	[0.19: 0.84]
Tetanus toxoid vaccine, inactivated	vaccine	942	8325	1.3	3.0	_ _	0.40	[0.19: 0.84]
Acellular pertussis vaccine, inactivated	vaccine	905	8362	1.4	2.9		0.44	[0.21: 0.93]
*PPSV23	vaccine	480	8787	3.2	7.4		0.44	[0.22; 0.89]
Secondary outcome: hospitalized_m	ild cumulative seve	ritv						
Ethinyl estradiol	astrogen	667	0081	1 1	3.0		034	[0 13 0 88]
	supplement	1/18	9001	6.1	1/ /		0.04	[0.13, 0.00]
	supplement	140	9000	0.1	14.4		0.41	[0.17, 1.00]
	supplement	142	9000	7.7 0.4	10.0		0.41	[0.19, 0.92]
FF3V23 *DCV12b	vaccine	510 617	9232	9.4	1/.2		0.40	[0.32, 0.73]
FCVIOD		017 507	9131	0.7	14.0		0.49	[0.33, 0.74]
Estracion	estrogen derivative	537 010	9211	3.2	0.4		0.49	[0.26, 0.94]
	supplement	213	9535	12.9	23.2		0.49	[0.27, 0.89]
	antinistamine	489	9259	5.6	10.6		0.51	[0.30; 0.86]
Pseudoepnedrine	decongestant	733	9015	3.0	6.3		0.51	[0.29; 0.90]
^PCV13a	vaccine	367	9381	9.7	15.5		0.51	[0.31; 0.85]
Dextromethorphan	antitussive	765	8983	4.0	6.7		0.60	[0.36; 1.00]
Omega-3 fatty acids	supplement	445	9303	11.7	17.0		0.63	[0.41; 0.98]
Fluticasone	corticosteroid	2134	7614	6.2	9.0		0.67	[0.51; 0.89]
Ibuprofen	NSAID	3086	6662	5.2	7.0	-=-	0.70	[0.54; 0.92]
Secondary outcome: in ICU, exclusiv	e severity							
*PCV13b	vaccine	566	8607	1.1	3.0		0.32	[0.12; 0.87]
Secondary outcome: hospitalized-m	ild, exclusive severi	ty						
Turmeric extract	supplement	144	9405	3.5	10.0		0.32	[0.10; 0.99]
Ethinyl estradiol	estrogen	666	8883	0.9	2.7		0.35	[0.13: 0.97]
Azelastine	antihistamine	477	9072	3.3	7.5	_	0.42	[0.22: 0.80]
Estradiol	estrogen derivative	532	9017	2.3	4.9		0.46	[0.22: 0.98]
*PPSV23	vaccine	499	9050	6.5	11.8		0.52	[0.31: 0.85]
Pseudoenhedrine	decongestant	728	8821	2.4	4.7		0.53	[0.28.0.99]
*PCV13b	vaccine	602	8947	67	10.2		0.60	[0 38 0 94]
Fluticasone	corticosteroid	2091	7458	4.5	64		0.00 0 68	[0 40· 0 0/1
Ibuprofen	NSAID	3044	6505	3.7	5.2		0.70	[0.51; 0.94]
					C	0.05 0.5 1 2 5		
						UUUS TAILU (30% UI)		

Patient characteristics

_	All patients		Hospitalized patients		
Characteristic	Ν	%	Ν	%	
Total	9,748	100	667	100	
Age, y*	42	20	60	19	
Sex					
Men	3,878	39.8	336	50.4	
Women	5,870	60.2	331	49.6	
Race					
White	8,212	84.2	495	74.2	
Black	1,276	13.1	155	23.2	
Asian	260	2.7	17	2.5	
Ethnicity					
Not Hispanic or Latino	9,411	96.5	646	96.9	
Hispanic or Latino	337	3.5	21	3.1	

Drug class associations

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Drug class	ТСе	TCu	SRe	SRu	OR	95% CI
Primary o	outcome: a	II-cause	of deat	th		
Antidepressants	2,227	6,979	1.5	2.6	0.61	(0.31 - 1.18)
Antihistamines	2,941	6,265	1.5	2.1	0.88	(0.50 - 1.58)
NSAIDs	4,495	4,711	1.1	1.6	0.53	(0.28 - 1.00)
Omega-3 supplements	687	8,519	2.9	5.1	0.59	(0.30 - 1.18)
Sigma-1 receptor agonists	1,448	7,758	1	2.4	0.44	(0.20 - 0.97)
SNRIs	512	8,694	2.4	3.8	0.75	(0.31 - 1.83)
SSRIs	1,381	7,825	1.9	2.4	0.73	(0.36 - 1.48)
Tricyclic antidepressants	316	8,890	1.5	3.4	0.41	(0.11 - 1.50)
Secondary outcom	e: on vent	ilator, cu	mulati	ve sev	erity	
Antidepressants	2,232	6,997	1.7	3.2	0.54	(0.29 - 0.98)
Antihistamines	2,945	6,284	1.6	2.6	0.72	(0.42 - 1.22)
NSAIDs	4,507	4,722	1.3	2	0.54	(0.31 - 0.96)
Omega-3 supplements	. 691	, 8,538	3.4	5.6	0.62	(0.33 - 1.19)
Sigma-1 receptor agonists	1.448	7.781	1	2.8	0.36	(0.17 - 0.76)
SNRIS	514	8 715	28	44	0.71	(0 31 - 1 64)
SSRIs	1 384	7 845	2.0		0.66	(0.34 - 1.27)
Tricyclic antidepressants	218	2 Q Q 1 1	2.1	30	0.00	(0.34 - 1.27)
		0,911		5.5	0.51	(0.10 - 1.37)
Secondary out			lative s	sevent	у о го	(0.24, 0.02)
Antidepressants	2,242	7,025	2.1	3.9	0.53	(0.31 - 0.92)
Antinistamines	2,960	6,307	2	3.1	0.74	(0.46 - 1.19)
NSAIDs	4,528	4,739	1.6	2.5	0.53	(0.31 - 0.88)
Omega-3 supplements	694	8,573	3.8	6.5	0.58	(0.31 - 1.06)
Sigma-1 receptor agonists	1,451	7,816	1.2	3.4	0.36	(0.18 - 0.72)
SNRIs	516	8,751	3.2	5.1	0.66	(0.30 - 1.42)
SSRIs	1,389	7,878	2.5	3.6	0.65	(0.35 - 1.18)
Tricyclic antidepressants	320	8,947	2.8	4.7	0.53	(0.19 - 1.47)
Secondary outcome:	hospitalize	e <mark>d-mild,</mark>	cumula	ative s	everity	1
Antidepressants	2,414	7,334	7.9	9.9	0.81	(0.60 - 1.10)
Antihistamines	3,147	6,601	7.1	8.7	0.86	(0.66 - 1.13)
NSAIDs	4,820	4,928	6	7.5	0.74	(0.56 - 0.98)
Omega-3 supplements	757	8,991	11.1	15.4	0.67	(0.46 - 0.97)
Sigma-1 receptor agonists	1,520	8,228	5.5	9.1	0.56	(0.39 - 0.80)
SNRIs	572	9,176	12.1	12.9	0.93	(0.60 - 1.43)
SSRIs	1.472	8.276	7.8	10.3	0.7	(0.49 - 0.99)
Tricyclic antidepressants	355	9.393	12.1	12	1.19	(0.70 - 2.03)
Secondary outcor	ne: on ven	tilator. e	xclusiv	e seve	ritv	(0.0.0
Antidepressants	2 203	6 949	09	18	0 46	(0 21 - 1 02)
Antihistamines	2 915	6 237	0.8	1 4	0.63	(0.31 - 1.28)
	1 / 57	1 695	0.0	1 1	0.05	$(0.31 \ 1.20)$
Omogo 2 cupploments	4,437	9 470	2.0	1.1 2.2	1.07	(0.20 - 1.17)
Sigma 1 recentor agonists	1 427	0,470 7 71 5	2.5	2.5	0.21	(0.40 - 2.48)
	1,437	7,715	0.5	1.0 C	0.21	(0.07 - 0.08)
SINRIS	507	8,645	1./	2	0.87	(0.29 - 2.60)
SSRIs	1,365	/,/8/	0.9	1./	0.48	(0.20 - 1.17)
Secondary ou	come: in l	CU, exclu	isive se	everity		
Antidepressants	2,208	6,965	1	2.3	0.41	(0.20 - 0.85)
Antihistamines	2,927	6,246	1.1	1.7	0.76	(0.41 - 1.40)
NSAIDs	4,470	4,703	0.8	1.4	0.47	(0.24 - 0.93)
Omega-3 supplements	679	8,494	1.9	3.2	0.6	(0.26 - 1.37)
Sigma-1 receptor agonists	1,442	7,731	0.6	1.9	0.35	(0.14 - 0.86)
SNRIs	508	8,665	1.8	2.6	0.68	(0.25 - 1.85)
SSRIs	1,367	7,806	1	2	0.43	(0.18 - 1.01)
Tricyclic antidepressants	316	8,857	1.5	2.5	0.52	(0.14 - 1.95)
Secondary outcome	: hospitaliz	zed-mild	, exclu	sive se	verity	
Antidepressants	2,350	7,199	6	6.5	0.96	(0.68 - 1.36)
Antihistamines	3,073	6,476	5.2	6	0.92	(0.68 - 1.24)
NSAIDs	4,698	4,851	4.5	5.3	0.8	(0.59 - 1.09)
Omega-3 supplements	727	8.822	7.8	10.5	0.71	(0.46 - 1.08)
Sigma-1 receptor agonists	1.501	8.048	<u> </u>	6.4	0.66	(0.44 - 0.98)
SNRIS	55/	8 995	9 /	8 7	1 00	(0.67 - 1.76)
	1 425	0 1 1 4	<u>, т</u>	7.2	0.72	(0.49 ± 1.07)



In ICU



In ICU

Included in the severe COVID-19 group Included in the non-severe COVID-19 group Excluded from the study

Statistical analysis

- The study applied the overlap weighing with a propensity score method to adjust for differences between the patients exposed to the drug prior to being diagnosed with SARS-CoV-2 (exposed group) and those not exposed (unexposed group)
- The propensity score for being exposed to a drug was estimated by a ٠ multivariable logistic regression model using age, sex, race, ethnicity, and weighted Elixhauser comorbidity score.
- The effect of drug exposure on COVID-19 outcomes was estimated using • weighted multivariable logistic regression
- All drugs with corresponding effect estimates indicating reduced severity • risk (OR < 1) were reported as potential candidates for COVID-19 treatment repurposing.

Associations conducted for primary and secondary outcomes

On ventilator	6	69	223	0	21	l 164
In ICU	Significant 7	Potential 81	Total 238	Significant	Potential	Total 178
Hospitalized-mild	14 +	89 Jo	304 213	9 4	72 Jo	2 289
On ventilator	6	69	223	0	21	164
In ICU	7	81	238	1	35	178
Hospitalized-mild	14	89	304	9	72	289

Patient counts for each severity group included in the study

Severity group	Cumulative severity	Exclusive severity
Dead	138	13
On ventilator	161	8
in ICU	199	10
Hospitalized mild	620	10

Weighted Elixhauser como	rbidity score	
-0	1 1 1 1	14 5

<0	1,414	14.5	71	10.6	
0	4,600	47.2	147	22	
1-4	1,363	14	69	10.3	
5+	2,371	24.3	380	57	
* Reported as age mean and standard deviation					

Reported as age mean and standard deviation

Effect tre	trends across COVID-19 outcomes		
	A. Cumulative severity	B. Exclusive severity	
	OR 08 08	OR 05 10 15	
	0.5 0.0 0.9	0.0 1.0 1.0	
*PCV13a *PCV13b			
*PPSV23			
Acellular pertussis vaccine, inactivated			
Adenosine monophosphate			
Alprazolam			
Amlodipine			
Ascorbic aciu Atorvastatin			
Azelastine			
Benzonatate			
Cefdinir			
Cephalexin			
Clavulanate			
Dextromethorphan			
Diethylstilbestrol			
Diphtheria toxoid vaccine, inactivated			
Doxycycline			
Eicosapentáenoate			
_Escitalopram			
Esomeprazole			
FISN OIIS			
FlaxSeeu exilaci			
Fluticasone propionate			
Folic acid			
Glucosamine			
Guaifenesin			
Hydrochlorothiazide			
IDUPROTEN			
Influenza A virus (H3N2) antigen			
Influenza B virus antigen			
Ketorolac			
Lisinopril			
Loratadine			
Losartan			
Metoprolol succipate			
Munirocin			
Naproxen			
Omega-3 fatty acids			
Oxymetazoline			
Propofol			
Rosuvastatin			
Simvastatin			
Tastastarana			
Tetanus toxoid vaccine inactivated			
Thioquanine			
Tropicamide			
Varicella zoster virus glycoprotein E			
Vitamin B12			

