



Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19

The Liverpool Drug Interaction Group (based at the University of Liverpool, UK), in collaboration with the University Hospital of Basel (Switzerland) and Radboud UMC (Netherlands) (<http://www.covid19-druginteractions.org/>) is constantly updating a list of interactions for many co-medication classes. This table is adapted from their valuable work, summarize treatments in epilepsy and includes other drugs.

In light of pharmacological interactions, single cases management is mandatory.

Drugs reported (constantly updated): ANK, anakinra; ATV, atazanavir; AZT, azithromycin; CLQ, chloroquine; DRV/c, darunavir/cobicistat; EMP, emapalumab FAVI, favipiravir; HCLQ, hydroxychloroquine; IFN-β-1a, interferon β-1a; LPV/r, lopinavir/ritonavir; NITA, nitazoxanide; RBV, ribavirin; RDV, remdesivir/GS-5734; OSV, oseltamivir; SAR, sarilumab; TCZ, tocilizumab.

	ANK ¹	*ATV/r	AZT ^{2,3}	CLQ ⁴	*DRV/c ⁵	EMP ^{1,3}	FAVI	HCLQ ⁴	IFN-β-1a ³	*LPV/r ⁶	NITA	RBV	RDV ⁷	OSV	SAR ¹	TCZ ¹
Brivaracetam	↔	↔	↔	↑	↔	↔	↔	↑	↔	↓	↔	↑	↔	↔	↔	↔
Carbamazepine	↓	↔	↔	↓	↔	↓	↔	↓	↔	↔	↔	↔	↓	↔	↓	↓
Cannabidiol	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔
Cenobamate	↔	↓	↔	↓	↓	↔	↔	↓	↔	↓	↔	↔	↔	↔	↔	↔
Clonazepam	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↓	↓
Clobazam	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↓	↓
Diazepam	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↓	↓
Eslicarbazepine	↔	♥↓	↔	↓	↓	↔	↔	↓	↔	♥↓	↔	↔	↓	↔	↔	↔
Ethosuximide	↓	↑	↔	↔	↑	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Felbamate	↔	↓	↔	♥↓	↓	↔	↔	♥↓	↔	↓	↔	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ketamine	↔	↑	↔	↔	↔	↔	↑	↔	↔	↑	↔	↔	↔	↔	↔	↓
Lacosamide	↔	♥↔	↔	↔	↑	↔	↔	↔	↔	♥↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↔	↔	↔	↑	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↓	↓
Midazolam	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↓	↓
Oxcarbazepine	↔	↓	↔	↓	↓	↔	↔	↓	↔	↓	↔	↔	↓	↔	↔	↔
Perampanel	↔	↑	↔	↔	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Phenytoin	↓	↓	↔	↓	↓	↓	↔	↓	↔	↓	↑	↔	↓	↔	↓	↓
Phenobarbital	↓	↓	↔	↓	↓	↓	↔	↓	↔	↓	↔	↔	↓	↔	↓	↓
Pregabalin	↔	↔	♥↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	↓	↓	↔	↓	↓	↓	↔	↓	↔	↓	↔	↔	↓	↔	↓	↓
Propofol	↔	♥↔	↔	♥↔	↔	↔	↔	♥↔	↔	♥↔	↔	↔	↔	↔	↔	↔
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	↔	↓	↔	↓	↓	↔	↔	↓	↔	↓	↔	↔	↓	↔	↔	↔
Sulthiame	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Tiagabine	↔	↑	↔	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Thiopental	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproic acid	↓	↔	↔	↔	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↓	↓
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

*Should not be administered without booster drug (ritonavir or cobicistat). AED, antiepileptic drug.

- ↑ Potential increased exposure of the AED;
- ↓ Potential decreased exposure of the AED;
- ↗ Potential increased exposure of COVID drug;
- ↘ Potential decreased exposure of COVID drug;
- ↔ No significant effect;
- ♥ One or both drugs may cause dysrhythmia.

	Drugs should not be co-administered.
	Potential interactions which may require a dose adjustment or monitoring.
	Potential interaction likely to be of weak intensity. Additional acts/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected.

¹ An increase in IL-6, as well as other cytokines (e.g., IL-1), can improve plasmatic concentration of administered drugs reducing hepatic metabolism (CYP-mediated), a treatment with **Tocilizumab**, **Sarilumab** (both IL6Ra), **Anakinra** (IL1Ra) or **Emapalumab** (IFN γ -a) could reduce plasmatic concentrations of other previous co-treatments due to hepatic metabolism normalization^b.

² QT prolongations can occur with **Azithromycin**, **Chloroquine** and **Hydroxychloroquine**. Pay particular attention in case of co-administration of these drugs.

³ No specific studies have been performed in humans to assess drug-drug interactions.

⁴ **Chloroquine** should not be administered in patients with epilepsy. **Hydroxychloroquine** can lower the seizure threshold.

⁵ Currently, the *Johnson & Johnson*, holder of *Janssen Pharmaceutica* owner of the drug **Darunavir**, highlighted the lack of evidence to support use of Darunavir-based treatments for SARS-CoV-2 (<https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus>). See below for specific *cobicistat* interactions.

⁶ Recently, a randomized clinical trial has observed no benefits of the **lopinavir/ritonavir** treatment compared to standard care (<https://www.nejm.org/doi/full/10.1056/NEJMoa2001282>)

⁷ Some data on drug interactions of **Remdesivir** are not yet available.

Notes:

- **Ritonavir** is a strong inhibitor of CYP3A and 2D6 *per se*, independently to co-administered antiviral. **Carbamazepine**, **phenobarbital** and **phenytoin** are not recommended in co-treatment.
- **Cobicistat** is a strong inhibitor of CYP3A4 *per se*; **carbamazepine**, **phenobarbital** and **phenytoin** should not be used in co-treatment.
- **Atazanavir** can increase **midazolam** plasmatic concentration until 4-fold.
- Also refer to **SmPC** for further information.

a. Aitken, A. E., Richardson, T. A. & Morgan, E. T. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* **46**, 123–149 (2006).

b. Kim, S., Östör, A. J. K. & Nisar, M. K. Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatology International* **32**, 2601–2604 (2012).