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

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 comedication classes. This table is adapted from their valuable work and includes other drugs. **In light of pharmacological interaction, single cases management is mandatory.**

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

	ATV	*DRV/c[1]	*LPV/r	RDV[2]	FAVI	CLQ	HCLQ	NITA	RBV	TCZ[3]	IFN-β-1a[4]	OSV
Brivaracetam	↔	↔	↓	↔	↔	↑	↑	↔	↑	↔	↔	↔
Carbamazepine	⇓↑	⇓↑	⇓↑	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Cannabidiol	↔	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔
Cenobamate	⇓	⇓	⇓	↔	↔	⇓	⇓	↔	↔	↔	↔	↔
Clonazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clobazam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	⇓♥	⇓	⇓♥	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Ethosuximide	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Felbamate	↓	⇓	↓	↔	↔	♥↓	♥↓	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	♥↔	⇑	♥↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	⇓	⇓↓	⇓	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Perampanel	↑	⇓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenytoin	⇓	⇓	⇓	⇓	↔	⇓	⇓	↑	↔	↓	↔	↔
Phenobarbital	⇓	⇓↓	⇓	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	⇓	⇓	⇓↓	⇓	↔	⇓	⇓	↔	↔	↓	↔	↔
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	⇓	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Sulthiame	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	⇓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproic acid	↔	⇓	⇑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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

↑ *Potential increased exposure of the co-medication;*
↓ *Potential decreased exposure of the co-medication;*
⇑ *Potential increased exposure of COVID drug;*
⇓ *Potential decreased exposure of COVID drug;*
↔ *No significant effect;*
♥ *One or both drugs may cause QT and/or PR prolongation.*

	Drugs should not be co-administered.
	Potential interaction which may require a dose adjustment or close 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] 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).

[2] Some data on drug interactions of **Remdesivir** are not available yet.

[3] An increase in IL-6, as well as other cytokines, can improve plasmatic concentration of administered drugs reducing hepatic metabolism (CYP-mediated), a treatment with **Tocilizumab** (anti-IL6R) could reduce plasmatic concentrations of other previous co-treatments due to hepatic metabolism normalization[2].

[4] No studies have been performed yet in humans to assess drugs-interactions.

Notes:

- Ritonavir is a strong inhibitor of CYP 3A and 2D6 *per se*, independently to co-administered antiviral.
- Atazanavir can increase **midazolam** plasmatic concentration until 4-fold.
- Also refer to **SmPC** for further information.

1. 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).
2. Kim, S., Östör, A. J. K. & Nisar, M. K. Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatology International* **32**, 2601–2604 (2012).

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