EUROPEAN REFERENCE NETWORKS
Helping patients with rare or low-prevalence complex diseases

https://epi-care.eu
MANAGEMENT OF RARE EPILEPSIES & COVID-19

- General advice for persons with epilepsy
- Antiseizure drug interactions and COVID-19
- Rescue drugs for prolonged epileptic seizures and COVID-19
- Q & A

Panel and affiliations:
- Pr Alexis Arzimanoglou, Coordinator ERN EpiCARE, University Hospitals of Lyon, FRANCE & SJD Barcelona Children’s Hospital Research coordinator, Barcelona, SPAIN
- Pr Emilio Perucca, National Neurological Hospital, C. Mondino Foundation, and Department of Internal Medicine and Therapeutics, University of Pavia, ITALY
- Pr Cecilie Landmark, The National Center for Epilepsy and Dpt of Pharmacology, Oslo University Hospital, NORWAY
- Pr Eugen Trinka, Department of Neurology, Christian-Doppler-Klinik (CDK), University Hospital, Paracelsus Medical University, Salzburg, AUSTRIA

https://epi-care.eu
GENERAL ADVICE FOR PERSONS WITH EPILEPSY

• AVOID DISINFORMATION, CONSULT OFFICIAL SOURCES


COVID-19 and Epilepsy – ERN EpiCARE Recommendations

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With the current global pandemic of COVID-19, the experts of EpiCARE ERN Steering Committee have prepared the following consensus statement regarding COVID-19 and epilepsy care. The document will be updated as necessary.

- English – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Spanish – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Portuguese – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Greek – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Croatian – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Dutch – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Finnish – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- French – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Italian – COVID-19 and Epilepsy – ERN EpiCARE Recommendations
- Polish – COVID-19 and Epilepsy – ERN EpiCARE Recommendations

EpiCARE Epilepsy Nurse Coordinator:

Or

Use the Contact Form on our website

https://www.ilae.org/

COVID-19 and Epilepsy

For patients

For clinicians

For researchers

This presentation is owned by the ERN and may contain information that is confidential, proprietary or otherwise legally protected.
Neurological Manifestations of COVID-19

- Neurological signs / symptoms in 25 to 50% of patients
  - Dizziness, headache, impaired consciousness, ageusia, anosmia
  - Concerns for risk of stroke, especially for severe cases

- Reports of individual cases with ‘encephalitis-like’ presentation

- Seizures not commonly seen
  - Rarely as initial presentation
  - May occur in severely ill patients as part of hypoxic / encephalopathic complications or stroke
  - May occur as part of underlying co-morbidity (epilepsy)

GENERAL ADVICE FOR PERSONS WITH EPILEPSY

MANAGING PEOPLE WITH SEIZURES AND EPILEPSY IN THE CURRENT COVID-19 SCENARIO

• Clear communication, planning and reassurance

• Individuals with epilepsy are NOT more likely to be infected by the virus.
• People with epilepsy are NOT more severely affected by COVID-19.
• Give clear instructions on how to deal with specific situations
  (e.g. breakthrough seizures, fever, symptoms, what to do should a caregiver require quarantine, or hospitalization)

EpiCARE Steering Committee, 2020;  
French et al Neurology, published online April 23, 2020
**GENERAL ADVICE FOR PERSONS WITH EPILEPSY**

**MANAGING PEOPLE WITH SEIZURES AND EPILEPSY IN THE CURRENT COVID-19 SCENARIO**

- **SAFETY FIRST**
  - **Prevention of infection** (minimization of hospital visits, special protection for people at high risk)
  - **Prevention of epilepsy-related complications**
    (deferral of non-urgent treatment changes, lower threshold for using rescue medication, emphasize adherence, secure drug supply)
  - **Deferral of non-urgent investigations** (EEG, MRIs, as appropriate)
  - **Ensure easy access to phone/online consultations - including whenever feasible psychological support services**

EpiCARE Steering Committee, 2020; French et al Neurology, published online April 23, 2020
GENERAL ADVICE FOR PERSONS WITH EPILEPSY

MESSAGE FOR THE PATIENTS & CAREGIVERS

• Do not modify usual medications practices without medical advice;
• Do not discontinue your medication.
• Maintain a regular contact with your treating physician and/or epilepsy specialist;
• If seizure presentation changes think of asking a family member to make a home video and request a teleconsultation.
• If you are living alone make sure having a regular contact with a family member, a friend or even better with a neighbor several times a day.
• If you suffer from associated anxiety and/or depression, call if needed your epilepsy specialist and/or neuropsychologist or psychiatrist.
• Children receiving methylphenidate for an Attention Deficit – Hyperactivity Disorder (ADHD) should not interrupt treatment, particularly during confinement.

EpiCARE Steering Committee, 2020; French et al Neurology, published online April 23, 2020
European webinar, April 27, 2020

ANTISEIZURE MEDICATIONS AND CHALLENGES IN THE COVID-19 PANDEMIC

Focus on drug interactions

Cecilie Johannessen Landmark, PhD
The National Center for Epilepsy and Oslo University Hospital, Norway

Emilio Perucca, MD
C. Mondino National Neurological Hospital, Pavia and University of Pavia, Italy
Outline

- General introduction to Covid-19 and epilepsy
- Special treatment issues in PWE, interactions and risks
- Classification of drug interactions and predictions
- Interactions between covid-19 treatments and ASMs
- Special clinical management issues (separate slide file)
The Evolution of the Covid-19 Pandemic Across the World

Several countries have turned the corner, with numbers of new cases now in decline

Daily confirmed cases (7-day rolling avg.), by number of days since 30 daily cases first recorded
Stars represent national lockdowns ★

### Age Distribution of Covid-19 Casualties in Italy

<table>
<thead>
<tr>
<th>Age range</th>
<th># casualties</th>
<th>% casualties</th>
<th>death rate (% of infected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 9</td>
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<td>10 - 19</td>
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<td>20 - 29</td>
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<td>30-39</td>
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<td>40-49</td>
<td>213</td>
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<td>50-59</td>
<td>870</td>
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<td>60-69</td>
<td>2.612</td>
<td>11,1%</td>
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<td>70-79</td>
<td>6.951</td>
<td>29,5%</td>
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<td>80-89</td>
<td>9.544</td>
<td>40,5%</td>
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<td>&gt;90</td>
<td>3.328</td>
<td>14,1%</td>
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<td>Total</td>
<td>23.576</td>
<td>100,0%</td>
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Does COVID-19 Affect the CNS?
Tissues Expressing ACE2 Receptors - Possible Targets of Covid-19 Infection

Managing Covid-19 Infection in People with Seizures and Epilepsy: Special Concerns

- Influence of COVID-19 treatments on seizure susceptibility (e.g. seizure precipitation by drugs used to treat COVID and its symptoms)

- Influence of antiseizure medications (ASMs) on COVID-19 and its symptoms (e.g., immunosuppression by everolimus or steroids, respiratory depression by benzodiazepines)

- Interactions between COVID-19 treatments and ASMs
Mechanisms of Drug-Drug Interactions

• **Pharmacodynamic interactions**
  • Occur at the site of action
  • Do not involve changes in plasma drug levels
  • Example: additive QT prolongation by chloroquine and azithromycin

• **Pharmacokinetic interactions**
  • Absorption
  • Distribution
  • Metabolism (enzyme induction or inhibition)
  • Excretion

• **Clinical impact**
  • May have no, moderate or serious consequences
  • Individual variability is common
  • *Ask, measure, act*

Pharmacodynamic interactions: Risk of Serious Cardiac Dysrhythmias as an Example

- Caution when co-prescribing drugs that alter cardiac rhythm or conduction (ECG check advisable)

Examples: Lopinavir/ritonavir, lacosamide and eslicarbazepine all prolong PR interval

Atazanavir, chloroquine, hydroxychloroquine, azithromycin all prolong QT interval

Combining drugs that prolong PR and/or QT interval may increase risk of dysrhythmias

Propofol also has relatively high pro-arrhythmic potential

ECG check before /after treatment may be indicated
The enzymes responsible for the metabolism of individual drugs are mostly known.

Effect of individual drugs on those enzymes are also mostly known.

This set of information permits to predict with reasonable accuracy whether a drug affects the metabolism of another drug, or vice versa.
• Phenytoin is a potent inducer of cytochrome CYP3A4 - lopinavir and ritonavir are CYP3A4 substrates

• Predictably phenytoin increases lopinavir and ritonavir clearance

• Ritonavir inhibits CYP3A4, which metabolizes carbamazepine (CBZ), and induces UGT1A4, which metabolizes lamotrigine (LTG)

• Predictably, ritonavir may increase the serum levels of CBZ, and reduce those of LTG

• Consider medications being taken by the individual (whether Covid-19 related or not), and other medications likely to be started during the course of Covid-19

• Select an ASM unlikely to be involved in adverse interactions with those medications

• Other factors need to be considered, e.g. seizure type and context, comorbidities, any need for rapid titration, availability of monitoring services, etc.

• In the light of current uncertainty about the evolution of the pandemic, these considerations may apply to any patient started on ASMs in the coming months
### Potential Interactions between ASMs and Drugs Used in the Management of Covid-19

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATV</th>
<th>LPV/rit</th>
<th>RDV</th>
<th>FAVI</th>
<th>CLQ</th>
<th>HCLQ</th>
<th>NITAZ</th>
<th>RBV</th>
<th>TCZ</th>
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<tbody>
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<td>Carbamazepine</td>
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</table>

**Text Legend**
- **↑**: 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

**Key to abbreviations**
- **ATV**: Atazanavir
- **CLQ**: Chloroquine
- **HCLQ**: Hydroxychloroquine
- **RBV**: Ribavirin
- **TCZ**: Tocilizumab
- **IFN β**: Interferon beta

**Colour Legend**
- Red: These drugs should not be coadministered
- Orange: Potential interaction which may require a dose adjustment or close monitoring
- Yellow: Potential interaction likely to be of weak intensity. Additional action monitoring or dosage adjustment unlikely to be required.
- Green: No clinically significant interaction expected

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[https://www.covid19-druginteractions.org](https://www.covid19-druginteractions.org) (accessed April 8, 2020)

• In a real world setting, the most vulnerable patients will receive not only ASMs, but other medicines which may also interact with Covid-19 treatments – in critically ill patients, PK changes unrelated to drug interactions also occur

• Drug-drug interactions may not be easily avoided, particularly in patients taking enzyme inducing ASMs

• Reliable information on magnitude of expected interactions is often missing – even when available, individual variability can be substantial

• Risk to benefit ratio is difficult to assess – focus especially on risk, as benefit from Covid-19 treatments is unclear at present (this will change in the future, as Covid-19 trials are completed)

• Adverse consequences can be minimized by dose adjustments, aided by monitoring tools as appropriate (e.g., ECG for cardiac affects, plasma drug level monitoring, etc) - close clinical observation is essential
### Susceptibility to cause interactions

| Enzyme inducers (CYP3A, CYP2B, CYP2C, UGT, and possibly other enzymes) |
| Enzyme inhibitors (specific enzymes inhibited vary across ASMs) |
| Mixed inducer/inhibitor (enzymes affected vary across ASMs) |

#### Older
- Ethosuximide
- Phenobarbital
- Phenytoin
- Carbamazepine
- Clonazepam
- Clobazam
- Primidone
- Sulthiame
- Valproic acid
- Other BZ

#### Newer
- Felbamate
- Gabapentin
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Pregabalin
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

#### Newest
- Cannabidiol
- Brivaracetam
- Cenobamate
- Eslicarbazepine
- Everolimus
- Lacosamide
- Perampanel
- Rufinamide
- Stiripentol

### Most ASMs are affected by interactions

Exceptions are those ASMs that are excreted renally as their main pathway of elimination.

### Bold characters indicate stronger interaction potential

Some drugs shown in green might occasionally affect the metabolism of some substrates, usually at high doses (e.g., perampanel 12 mg/day increases the clearance of contraceptive steroids).

# Drugs Used in Covid-19 Treatment

**Antimalaria drugs:**
- Chloroquine*
- Hydroxychloroquine*

**Antiviral drugs:**
- Remdesivir (experimental, Ebola)*
- Lopinavir/Ritonavir *
- Darunavir/cobicistat
- Oseltamivir
- Favipiravir
- Atazanavir
- Ribavirin
- Nitazoxanide

**Immunomodulating drugs:**
- Interferon-beta*
- Tocilizumab
- Anakinra
- Emapamulab
- Sarilumab

**Antibacterial drugs:**
- Azithromycin
- Ceftriazone
- Piperacillin/tazobactam

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Based on recommendations and reports from:
- WHO, China, South-Korea, US, EMA
  
- Cao B et al., New Eng J Med, March 2020
  
  [Clinical management of severe acute respiratory infection when novel coronavirus (ncov)-infection is suspected](https://www.eahp.eu/sites/default/files/covid-19-clinical-information-and-treatment-guidelines_0.pdf), April 24th 2020
- EMA
  
- CDC
  
  [Therapeutic options](https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html), April 24th, 2020
Antimalaria drugs & ASMs

Enzyme inducing ASMs are expected to reduce serum levels of chloroquine and hydroxychloroquine – not necessarily a contraindication to combined use.

Chloroquine
Hydroxychloroquine

Evaluation:
- Widely used in malaria
- Immune modulating effects (RA)
- Available in many countries
- Some evidence of efficacy
- May prolong QT-interval
- Ongoing studies, Hydroxy- less toxic

No evidence of changes in levels of most commonly used ASMs. Chloroquine and hydroxychloroquine may lower seizure threshold, but risk is probably negligible.

https://www.covid19-druginteractions.org

Chen et al., MedRxiv, preprint, April 10, 2020
https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86Thswf3KmKUF2fP30LF_oe6aOMguYM1UzTt1C8
Antiviral Drugs & ASMs

Antiviral drugs
Ritonavir, lopinavir
(strong inhibitors of CYP3A4)
Cobicistat, Atazanavir
(CYP3A4 inducers)
Ritonavir
(UGT inducer)

Enzyme inducing ASMs
(elect especially carbamazepine, phenobarbital, phenytoin):
Increase clearance of antiviral drugs

Risk of altered ASM response, and risk of lack of efficacy of antiviral drugs
Dosage adjustments may be necessary

- Ritonavir/lopinavir antiretroviral drugs used in HIV
- Available in many countries
- Some evidence of interactions with ASMs
- Ongoing studies in Covid-19, negative study, Cao et al.

Asconape, Curr Neurol Neurosci rep, 2018, Burger et al., Clin Pharm Ther, 2008
https://www.covid19-druginteractions.org

https://www.ilaero.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_10.104.pdf?fbclid=IwAR37EDyf8Nr7Y86-Thswhf3KmkUFZIt3P30LFe6e6a0MguxKM1UzTiTc8
Examples: Antiviral Drugs & ASMs

ASMs affecting antiretroviral drugs

Phenytoin: Reduces serum concentration of lopinavir/ritonavir by 30-50%, requires up to 50% dosage increase of antiviral drugs to maintain a stable serum concentration. Use TDM if possible.

Antiretroviral drugs affecting ASMs

Ritonavir/lopinavir: May increase the serum concentrations of carbamazepine and other CYP3A substrates e.g. everolimus due to potent CYP3A4 inhibition and P-glycoprotein inhibition. Dosage adjustments may be required to maintain stable serum ASM concentrations. Use TDM if possible.

Ritonavir (combined with lopinavir or atazanavir): Reduces serum concentrations of lamotrigine (LTG) by 30-50%, requires up to 50% increase of LTG dosage to maintain a stable serum LTG concentration, due to induction of UGT1A4. Use TDM if possible.

Asconape, Curr Neurol Neurosci rep, 2018, Burger et al., Clin Pharm Ther, 2008
https://www.ilaee.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19_01.04.pdf?fbclid=IwAR37EDyf8Nr7Y86-Thswhf3KmkUfZlP30LF_oee6a0MguxKM1UzT4tC8
Corticosteroids & ASMs

Phenobarbital, phenytoin and carbamazepine induce CYP3A and decrease the serum concentrations of the steroids by 30-50%. Dosage increase of prednisone/prednisolone/methylprednisolone 1.5-2-fold suggested for patients taking phenobarbital, phenytoin and carbamazepine.

Corticosteroids cause enzyme induction in high doses, but clinical relevance in terms of potential interactions unclear. No effect on CYP3A metabolism (midazolam) at 10 mg prednisone for 28 days.

Evaluation:
- May be relevant as comedication in critically ill patients

Summary

• **Pharmacodynamic interactions**: consider pharmacological properties of drugs being combined!
• **Pharmacokinetic interactions**: mostly affecting drug metabolism
  - Can be bidirectional
  - May cause enhancement or loss of activity of the affected drug
  - Can be anticipated based on knowledge of affected enzymes affected
  - Magnitude of interaction in the individual poorly predictable
  - May be controlled by use of TDM and dose adjustment
• **Use or avoidance of potentially interacting drugs** rests on careful assessment of risk to benefit ratio in the individual patient
• **Always monitor clinical response** carefully, and adjust treatment as appropriate
THANK YOU
DO NOT HESITATE TO WRITE TO US
YOUR QUESTIONS WILL BE COMMUNICATED TO THE PANELLISTS OR TO MEMBERS OF EPICARE IN YOUR COUNTRY

CONTACTS

• EPICARE EPILEPSY NURSE COORDINATOR
  EMAIL: GHE.EPICARE.COORDINATION@CHU-LYON.FR

• EPICARE COORDINATION CONTACT: https://epi-care.eu/contact-us/