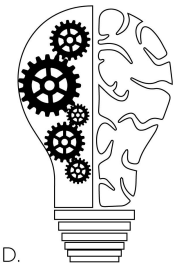
Episode 078:COVID-19 and the Brain: Delirium & Viral Encephalitis

Joseph Wong B.S., B.A., Alexis Carnduff, B.S., David Puder, M.D.



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There are no conflicts of interest for this episode.

In a previous episode, we covered COVID-19 and its effect on mental health. In today's episode of the podcast, we will be covering COVID-19 from the medical perspective with regards to its effect on the brain as well as treatment options, their side effects and special considerations.

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Abstract:

The non-specific symptoms (e.g. fever, cough) and respiratory complications (e.g. ARDS) of COVID-19 have been well-described in literature, but new research has shown that there are increasing cases of neurologic complications (e.g. delirium, acute cerebrovascular events) associated with COVID-19. New cases of COVID-19 have also shown that the changes in smell (hyposmia or anosmia) and taste (hypogeusia) are early signs that may precede fever or cough. Commonly used treatments for delirium may exacerbate complications and interact with current treatments for COVID-19 (e.g. antipsychotics and prolonged QTc interval in acute cardiac injury secondary to COVID-19 as well as prolonged QTc due to azithromycin), which may change inpatient management of delirium patients positive for COVID-19.

What we know about COVID-19

In December 2019, a virus coined 2019 novel coronavirus (2019-nCoV), was isolated from patients with pneumonia of unknown etiology in Wuhan, China (Lu, Stratton, & Tang, 2020). 2019-nCoV was soon renamed coronavirus disease (COVID-19) by the World Health Organization (WHO) on February 11, 2020 and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020; WHO, 2020). Further investigation found that within the last month, **most infected patients had visited the Huanan Seafood market**, a large live animal and seafood market that sold live exotic animals including bats. (Lu, Stratton, & Tang, 2020; WHO,

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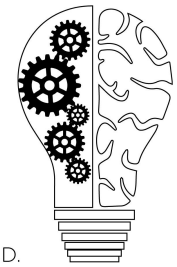

2020). Through genomic investigations, SARS-CoV-2 was shown to be a **positive-strand single-stranded RNA virus closely related to bat-derived SARS-like coronaviruses** (Chan et al., 2020; Jiang, Du & Shi, 2020; Lu et al., 2020; Ren et al., 2020; Zhu et al., 2020). Based on the genomic evidence and the fact most of the infected patients had recently visited the Huanan Seafood market, SARS-CoV-2 most likely **mutated from a bat virus** and was introduced through live bats or animal products contaminated with bat droppings.(Chen et al., 2020; Jiang, Du & Shi, 2020; Zhou et al., 2020). **On January 30, 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC)**, earning a place alongside Kivu Ebola in the Democratic Republic of Congo (2019), Zika (2016), Ebola in West Africa (2014), Polio (2014) and H1N1 (2009) (Heymann et al., 2016; Soghaier, Saeed, & Zaman, 2015; WHO, 2019; WHO, 2020).

Epidemiology of COVID-19

As of **April 3, 2020**, WHO reports that there are **972,640 confirmed cases of COVID-19 globally** with 76,190 new cases in the past 24 hours and **50,325 deaths** thus far with 4,826 deaths in the past 24 hours (WHO, 2020). **In the US, there are 247,473 confirmed cases** thus far with 30,561 new cases in the past 24 hours and **5,600 deaths thus far** with 1,061 deaths in the past 24 hours (WHO, 2020). Contributing factors to the rapid spread of COVID-19 worldwide include mode of transmission, transmission through asymptomatic carriers and the ease and convenience of global travel.

Multiple studies have now shown that **transmission of SARS-CoV-2 is person to person** (ie droplets from coughing or sneezing or direct contact) **as well as through fomites** (Carlos, Dela Cruz, Cao, Pasnick & Jamil, 2020; Chan et al., 2020; Huang et al., 2020; Li et al., 2020; Phan et al., 2020). A recent study by van Doremalen et al. (2020) tested stability and viability of SARS-CoV-2 on 5 environmental conditions: aerosols, cardboard, copper, plastic and stainless steel. The authors found that **SARS-CoV-2 remained viable in the air for up to three hours** as droplets and could survive for up to four hours on copper, up to 24 hours on cardboard and up to two to three days on stainless steel and plastic (van Doremalen et al., 2020).

Our current understanding of the **mean incubation period for SARS-CoV-2 is about 5-6 days**. Backer, Klinkenberg & Wallinga (2020) looked at 88 travellers from Wuhan from January 20, 2020 to January 28, 2020 and estimated the mean incubation period for SARS-CoV-2 to be 6.4 days (95% credible interval (CI): 5.6–7.7), and the incubation period ranging from 2.1 days to

11.1 days (2.5th to 97.5th percentile). Li et al. (2020) looked at all reported cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) up until January 22, 2020 and estimated the mean incubation period to be 5.2 days (95% confidence interval [CI], 4.1 to 7.0); the 95th percentile of the distribution was **12.5 days** (95% CI, 9.2 to 18). These studies among others have led to the estimated range of incubation period of **1 to 14 days** by WHO, the CDC, and the European Centre for Disease Prevention and Control (ECDC) (CDC, 2020; ECDC, 2020; WHO, 2020).

All of these factors in conjunction with a high possibility of transmission through asymptomatic carriers and global travel have resulted in an explosive rise in SARS-CoV-2 cases, which has resulted in the current COVID-19 pandemic (Bai et al., 2020; Biscayart et al., 2020).

Clinical Manifestations of COVID-19

In terms of clinical signs and symptoms of COVID-19, the most common symptom was fever, followed by **cough, upper respiratory congestion, dyspnea, myalgia, fatigue, and headache** (Chang et al., 2020; Huang et al., 2020; Lai, Shih, Ko, Tang & Hsueh, 2020; Zhou et al., 2020). Less common symptoms include sputum production, **hemoptysis, and diarrhea** (Huang et al., 2020). Among patients with **dyspnea**, many need intensive care with ventilation as they could not breathe spontaneously (Li, Bai & Hashikawa, 2020). **Complications** due to COVID-19 include **ARDS with ground glass opacities** noted on chest imaging, **acute cardiac injury** (e.g. elevated troponins) and **secondary infection** (Chang et al., 2020; Huang et al., 2020; Li, Bai & Hashikawa, 2020). **Risk factors** for increased morbidity and mortality associated with COVID-19 include **older age and comorbid health conditions** such as diabetes, hypertension, cardiovascular disease, and cerebro-vascular disease (Chen et al. (2020; Liu et al., 2020; McMichael et al., 2020; Zhou et al., 2020).

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Table 1
compares the general situation and clinical manifestations of the two groups.

Variable	Elderly ($n = 18$)	Young and middle-aged ($n = 38$)	P
Age (years)	68.00 (65.25–69.75)	47.00 (35.75–51.25)	<0.001
Male (n,%)	12(66.67%)	19(50.00%)	0.198
Smoking history (n,%)	8(44.44%)	14(36.84%)	0.667
Past medical history (n,%)			
Liver disease	1(5.56%)	0(0)	–
Chronic kidney disease	0(0)	1(2.63%)	–
Hypertension	5(27.78%)	5(13.16%)	0.782
Dabetes	3(16.67%)	1(2.63%)	0.246
Coronary heart disease	2(11.11%)	0(0)	–
Persistent atrial fibrillation	1(5.56%)	0(0)	–
Clinical symptoms			
Cough and sputum	6(33.33%)	15(39.47%)	0.284
Chest tightness, Difficulty breathing	2(11.11%)	2(5.26%)	0.351
Fever	14(77.78%)	30(78.95%)	0.008
Fatigue	2(11.11%)	3(7.89%)	0.385
Nasal congestion, runny nose	1(5.56%)	2(5.26%)	0.786
Sick and vomit	3(16.67%)	7(18.42%)	0.558
Pneumonia severity index			
PSI score	121 (95–148)	79 (55–107)	<0.001
PSI grades IV and V	4(22.22)	2(5.26)	<0.001

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., ... & Yu, T. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, *395*(10223), 507-513.

Recently, there has been new evidence that anosmia (loss of smell) may be a symptom of COVID-19 (Giacomelli et al., 2020). A statement written by ENT UK, a professional ENT membership body in the United Kingdoms, **reported that in Germany, two out of three confirmed COVID-19 cases had anosmia while in South Korea, 30% of people with mild symptoms who tested positive for COVID-19 reported anosmia as their main symptom** (ENT UK, 2020). A cross sectional study carried out in Iran showed significant correlation between anosmia and COVID-19 patients (Spearman correlation coefficient; 0.87, P-value <0.001) (Bagheri, et al., 2020). The onset of anosmia **was sudden in 76.24%** at the time of filling the questionnaire, and 60.90% patients stated decreased sense of smell was constant (Bagheri, et al., 2020). On March 22nd, the American Academy of Otolaryngology–Head and Neck Surgery also recommended that anosmia be added to the list of COVID-19 symptoms used for screening potential COVID-19 cases.

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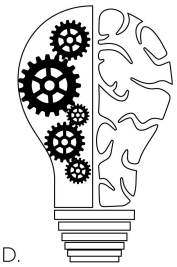
Delirium, Strokes and COVID-19

Although the pulmonary (e.g. ARDS) and cardiac complications (e.g. acute cardiac injury) of COVID-19 have been the focus of medical complications of COVID-19 in recent literature, **neurologic (e.g. delirium) and cerebrovascular (e.g. stroke) events** associated with COVID-19 have recently gained traction. Previous studies of other coronaviruses such as SARS-CoV 1 and MERS-CoV have neuroinvasive potential and seem to favor the **brainstem** (Glass, Subbarao, Murphy & Murphy, 2004; Li et al., 2016; McCray Jr. et al., 2007; Netland, Meyerholz, Moore, Cassell & Perlman, 2008). Additionally, these same studies have shown that coronaviruses may initially **invade peripheral nerve terminals**, and through trans-synaptic transfer, gain access to the CNS.

But why does this new finding, loss of smell, tie in so intricately with the profound dyspnea seen in severe cases? A study by the Journal of Medical Virology (Li, et al., 2020) **described how the nose is directly linked with the brain**. Increasing evidence shows that CoVs may first invade peripheral nerve terminals, particularly via **olfactory nerves**, and proceed to gain access to the **CNS via a synapse-connected route**. The sister SARS-CoV virus has been studied much more in depth, yielding virus in the brains from both patients and experimental animals, **where the brainstem was heavily infected**. For instance, experimental studies using transgenic mice reveal that SARS-CoV, when given intranasally, could enter the brain, possibly via olfactory nerves, and thereafter rapidly spread to some specific brain areas, including the **thalamus and brainstem** (Baig et al., 2020). It is quite likely that the potential neuroinvasion of SARS-CoV2 is **at least partially responsible** for the acute respiratory failure of COVID-19 patients. If the neuroinvasion of SARS-CoV-2 does take a part in the development of respiratory failure, the **precaution with masks will absolutely be the most effective measure to protect against the possible entry of the virus into the CNS**.

In addition to anosmia, numerous other neurological symptoms have been reported worldwide. A retrospective case series in three designated COVID-19 care hospitals of the Union Hospital of Huazhong, University of Science and Technology in Wuhan, China reported 3 main areas of concern: **CNS, PNS, and muscular symptoms** (Mao et al., 2020). In patients with CNS



symptoms, the most common complaints were **dizziness** (16.8%) and **headache** (13.1%). Moreover, **impaired consciousness** and **acute cerebrovascular disease** were significantly associated with **severe cases** as compared with non-severe cases. These included acute **cerebrovascular disease (ischemic stroke and cerebral hemorrhage; p <0.05), impaired consciousness (p < 0.001), and muscle injury (p < 0.01).** (Azhideh et al., 2020; Mao et al., 2020).

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Table 1 Clinical characteristics of patients with COVID-19

	Total (n=214)	Severe (n=88)	Non-severe (n=126)	*P*
Age (y), means ± standard deviations	52.7±15.5	58.2±15.0	48.9±14.7	
Age, n (%)				<0.001
<50 y	90 (42.1)	24 (27.3)	66 (52.4)	
≥50 y	124 (57.9)	64 (72.7)	60 (47.6)	
Sex, n (%)				<0.05
Female	127 (59.3)	44 (50.0)	83 (65.9)	
Nervous system symptoms, n (%)				
Any	78 (36.4)	40 (45.5)	38 (30.2)	<0.05
CNS	53 (24.8)	27 (30.7)	26 (20.6)	0.094
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	0.415
Headache	28 (13.1)	15 (17.0)	13 (10.3)	0.151
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<0.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	<0.05
Ataxia	1 (0.5)	1 (1.1)	0 (0.0)	NA
Epilepsy	1 (0.5)	1 (1.1)	0 (0.0)	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	0.691
Hypogeusia	12 (5.6)	3 (3.4)	9 (7.1)	0.243
Hyposmia	11 (5.1)	3 (3.4)	8 (6.3)	0.338
Hypopsia	3 (1.4)	2 (2.3)	1 (0.8)	0.365
Neuralgia	5 (2.3)	4 (4.5)	1 (0.8)	0.074
Muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<0.001

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Mao, L., Wang, M., Chen, S., He, Q., Chang, J., Hong, C., ... & Li, Y. (2020). Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study.

As of April 3, 2020 novel findings have been distributed concerning an especially complicating diagnosis: **acute necrotizing encephalopathy (ANE)**. Characterized by respiratory or gastrointestinal infection and high fever, rapid alteration of consciousness and seizures, ANE accompanies a poor prognosis with high morbidity and mortality rates (Salehiomran et al., 2013). According to the Henry Ford Health System in Detroit, Michigan, a middle aged patient initially presented with generalized symptoms (cough and fever). However, the patient was additionally found to be altered. A full workup ruled out herpes simplex virus 1 and 2, varicella zoster virus, and West Nile virus. PCR confirmed the diagnosis of COVID-19. After extensive imaging, notable findings included **symmetric hypoattenuation within bilateral medial thalami and hemorrhagic rim enhancing lesions within bilateral thalami, medial temporal lobes, and subinsular regions** (Poyiadji et al., 2020).

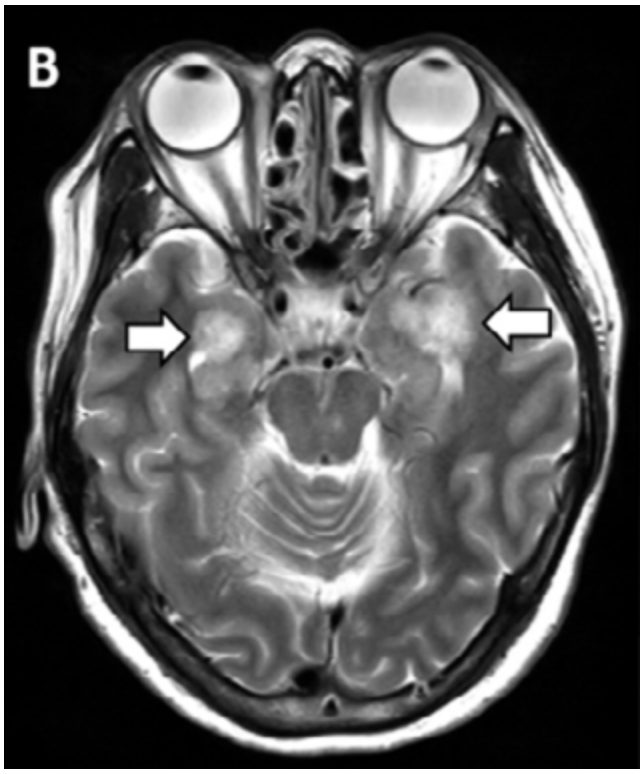

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Figure 2b: MRI images demonstrate T2 FLAIR hyperintensity within the bilateral medial temporal lobes and thalami (*A, B, E, F*) with evidence of hemorrhage indicated by hypointense signal intensity on susceptibility-weighted images (*C, G*) and rim enhancement on postcontrast images (*D, H*).

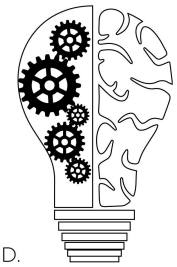
Although rarely seen, acute necrotizing encephalopathy is a **serious complication of influenza and other invasive viral conditions**. The proposed mechanism for the rapid decline in neurocognition is up for debate, but a recent article by the Lancet suggests a cytokine storm as an important implication. Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, included **elevated ferritin (mean 1297·6 ng/ml in non-survivors *vs* 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001)**, suggesting that mortality might be due to virally driven **hyperinflammation** (Mehta et al., 2020). **Still others continue to argue the spread of coronaviruses through synapse-connected routes of the olfactory and lower respiratory airways to the medullary cardiorespiratory centers of the brainstem** (Mao et al., 2020). Perhaps the most important takeaway from a surplus of new reported neurological findings is the broad spectrum of potential syndromes associated with COVID-19 and the need for detailed triage and intentional patient management, especially when faced with comorbidities such as stroke, delirium and now reported acute necrotizing encephalopathy.

Treatment of Delirium

Although no medication is currently approved by the FDA for treatment of delirium, some of the following medications (especially antipsychotics) have seen off-label use in delirium treatment:

Typical Antipsychotics:

- **Haloperidol (Haldol)**
    - Haloperidol has been used as the **gold-standard antipsychotic in treating delirium in the critical care setting** for many years (Breitbart et al., 2005; Devlin & Skrobik, 2011; Girard et al., 2018; Grover, Kumar & Chakrabarti, 2011; Han & Kim, 2004; Skrobik, Bergeron, Dumont & Gottfried, 2004).
    - However, recent studies have shown that **haloperidol may not have any effect on decreasing the duration of delirium** as compared to placebo. In a study of 105 mechanically ventilated patients, the number of days spent alive without delirium or coma was similar between haloperidol (median, 14.0 days;



interquartile range [IQR], 6.0–18.0 days) or ziprasidone (median, 15.0 days; IQR, 9.1–18.0 days) prophylaxis, and placebo (median, 12.5 days; IQR, 1.2–17.2 days) groups (p = 0.66) (Devlin & Skrobik, 2011).

- In a more recent randomized, double-blind, placebo-controlled trial consisting of 1183 ICU patients with acute respiratory failure or shock and hypoactive or hyperactive delirium, **IV haloperidol (maximum dose, 20 mg daily) and IV ziprasidone (maximum dose, 40 mg daily) were not found to significantly decrease the duration of delirium as compared to placebo** (Girard et al., 2018).
- Despite conflicting data on the efficacy of haloperidol on treating delirium, it is well-studied that haloperidol decreases aggression and agitation in delirious, ICU patients, which is important in reducing the spread of COVID-19 to health care professionals taking care of the patient (Riker, Fraser & Cox, 1994).
- The **addition of Lorazepam (Ativan) to haloperidol** compared to just haloperidol alone has also been found to **significant reduce persistent agitation** in cancer patients with delirium for more palliative end of life treatment (Hui et al., 2017). However Ativan might be pushing someone into more of a hypoactive delirium and might cause respiratory depression.
- In terms of side effects, **IV Haloperidol has long been known to cause QT prolongation, which increases the risk for arrhythmia and sudden cardiac death** (Hatta et al., 2001; Metzger & Friedman, 1993), which needs to be taken into consideration in a patient with pre-existing cardiac history or with acute cardiac injury brought about by COVID-19 (Huang et al., 2020).

- **Chlorpromazine (Thorazine)**
  - In a randomized double-blind, comparison trial of AIDS patients with delirium, **low dose neuroleptics haloperidol (n=11) and chlorpromazine (n=13) were found to be efficacious in treating symptoms of delirium** (e.g. improvement in cognitive function, as measured by the Mini-Mental State) with few side effects (Breitbart et al., 2005).
  - Chlorpromazine has long been used in treating agitation as it was the first of the first-generation antipsychotics (FGA) to be approved and marketed by the FDA; however as a lower potency typical antipsychotic, **chlorpromazine can** also **potentially exacerbate delirium due to its anticholinergic effects** and is **associated with more hypotension and lowered seizure threshold as compared to haloperidol, a higher potency FGA** (Schwartz & Masand, 2000;

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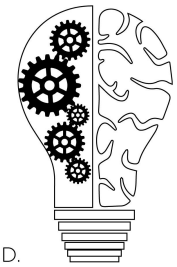
Straker, Shapiro, & Muskin, 2006; Wilson, Pepper, Currier, Holloman Jr & Feifel, 2012).

Atypical antipsychotics:

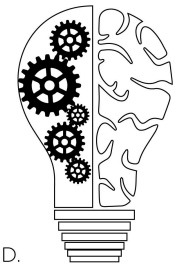
- **Olanzapine (Zyprexa)**
    - Olanzapine has been shown to be effective in treating delirium in the critical care setting (Grover, Kumar & Chakrabarti, 2011; Skrobik, Bergeron, Dumont & Gottfried, 2004)
    - In a study of 64 patients comparing **olanzapine, risperidone and haloperidol**, all three drugs were found to result in a **significant improvement in MMSE scores and significant reduction in DRS-R98 severity scores** over the period of 6 days with no difference in efficacy between the three drugs (Grover, Kumar & Chakrabarti, 2011).
    - In a quantitative review of nine double-blind, randomized, controlled clinical trials, the number needed to treat (NNT) for response to treatment for **agitation** versus placebo for **olanzapine 10 mg** was 3 (95% CI = 2 to 3), showing a **strong therapeutic effect** (Citrome, 2007). Among these studies, **olanzapine** was associated with a **high risk of orthostatic hypotension**, which is dangeorus in patients already volume depleted (number needed to harm (NNH = 50, 95% CI = 30 to 154) versus placebo) (Citrome, 2007).
    - In terms of side effects, **olanzapine was found to prolong the QTc interval to a pathological extent only when given in excessive doses** (Haddad & Anderson, 2002). **Sedation** was also found to occur **most frequently** with **olanzapine** as compared to other antipsychotics (Boettger, Jenewein & Breitbart, 2015; Grover, Kumar & Chakrabarti, 2011).

- **Risperidone (Risperdal)**
    - In a double-blind comparative study of 28 patients with delirium that either received a flexible-dose regimen of haloperidol or risperidone over 7 days, both **haloperidol and risperidone were found to be efficacious in treating delirium as shown by a decrease in Memorial Delirium Assessment Scale scores used to assess severity of delirium** (Han & Kim, 2004).
    - **Risperidone** has also been shown to be as **effective as haloperidol, aripiprazole, and olanzapine in treating delirium** without as high of a risk for EPS as haloperidol or sedation associated with olanzapine (Boettger, Friedlander, Breitbart & Passik, 2011; Boettger, Jenewein & Breitbart, 2015).



- **Oral risperidone** has also been found to be **well-tolerated** and **efficacious** in **treating hyperactive symptoms of delirium** in the **elderly** as well as **advanced cancer patients** (Ikezawa, Canuet, Ishii, Iwase, Teshima & Takeda, 2008; Kishi, Kato, Okuyama & Thurber, 2012).
- As compared to haloperidol, **risperidone has a decreased risk for EPS and QT prolongation** (Gupta, Sharma & Mattoo, 2005).

- **Ziprasidone (Geodon)**
  - In a case study of delirium in the ICU that was not responsive to haloperidol therapy, **IV Ziprasidone 20 mg was shown to be effective in reducing restlessness and agitation** (Young & Lujan, 2004).
  - However, in another study of 105 mechanically ventilated patients, the number of days spent alive without delirium or coma was similar between haloperidol (median, 14.0 days; interquartile range [IQR], 6.0–18.0 days) or ziprasidone (median, 15.0 days; IQR, 9.1–18.0 days) prophylaxis, and placebo (median, 12.5 days; IQR, 1.2–17.2 days) groups (p = 0.66) (Devlin & Skrobik, 2011).
  - In a more recent randomized, double-blind, placebo-controlled trial consisting of 1183 ICU patients with acute respiratory failure or shock and hypoactive or hyperactive delirium, IV haloperidol (maximum dose, 20 mg daily) and IV ziprasidone (maximum dose, 40 mg daily) were not found to significantly decrease the duration of delirium as compared to placebo (Girard et al., 2018).
  - In a quantitative review of nine double-blind, randomized, controlled clinical trials, the number needed to treat (NNT) for response to treatment for **agitation** versus placebo for **ziprasidone 10-20 mg** was **3** (95% CI = 2 to 4), showing a **strong therapeutic effect** (Citrome, 2007).
  - **Among the atypical antipsychotics, ziprasidone has the greatest association with QTc prolongation and torsade de pointe** (Wenzel-Seifert, Wittmann & Haen, 2011). An analysis of 1665 spontaneous reports of TdP cases to the FDA's Adverse Event Reporting System (AERS) (2004–2007) revealed that **ziprasidone was associated with most cases of torsade de pointes among the antipsychotic drugs**, which is significant in that is less commonly prescribed as compared to other antipsychotics (Wenzel-Seifert, Wittmann & Haen, 2011).
  - Therefore, risk factors for QTc prolongation and torsade de pointes such as preexisting cardiovascular disease, age >65, female sex, bradycardia, electrolyte



imbalances (e.g. hypokalemia, hypomagnesemia) should be taken into account with usage of ziprasidone (Wenzel-Seifert, Wittmann & Haen, 2011).

- **Quetiapine (Seroquel)**
  - In a 22 patient study, **quetiapine was shown to significantly decrease DRS-R-98 and CGI-s scores with >50% reduction in patients with delirium** (Pae, Lee, Lee, Lee & Paik, 2004).
  - In a retrospective review, a mean dose of 211.4 mg/day of quetiapine was shown to be as efficacious and even more well-tolerated as a mean dose of 3.4 mg/day haloperidol in showing a >50% improvement in DRS scores (Schwartz & Masand, 2000).
  - Another small clinical trial of 36 ICU patients with delirium compared escalating doses of quetiapine with placebo as add-on treatment to as-needed haloperidol (Devlin et al., 2010). **Quetiapine added to as-needed haloperidol was found to be associated with a shorter duration of delirium, reduced agitation, and higher rates of discharge** to home after hospitalization (Devlin et al., 2010).
  - In a double blind, randomized controlled trial consisting of 42 patients split between quetiapine and placebo groups, the **quetiapine** group **improved** 82.7% **faster** (S.E. 37.1%, *P*=.026) than the placebo group in terms of their **Delirium Rating Scale Revised 98** (**DRS-R-98**) **severity score** (Tahir et al., 2010). In addition, the **quetiapine** group **improved 57.7% faster** (S.E. 29.2%, *P*=.048) than the placebo group in terms of the **DRS-R-98 non-cognitive subscale**, which included non-cognitive items such as restlessness, **agitation**, thought disorder, etc (Tahir et al., 2010).
  - In terms of side effects, **quetiapine** was found to be associated with **only mild prolongation of the QTc interval** (Lieberman et al., 2005). However, there have been reported cases of torsade de pointes in association with the use of quetiapine (Wenzel-Seifert, Wittmann & Haen, 2011).

- **Aripiprazole (Abilify)**
  - In two case studies of delirium that were treated with 30 mg and 15 mg aripiprazole off market, both patients' confusion, disorientation, and agitation improved within 7 days of treatment (Alao & Moskowitz, 2006). The patient that received 30 mg had their Mini-mental status exam (MMSE) score improved from 5 to 28, while their Delirium rating scale (DRS) score decreased from 28 to 6.

The patient that received 15 mg had their MMSE score improved from 7 to 27, while their DRS score went down from 18 to 6 (Alao & Moskowitz, 2006).

- In another study with 14 patients, 12 patients had a **≥50% reduction in their DRS score** while 13 showed improvement on Clinical Global Impression scale (CGI) scores (Straker, Shapiro, & Muskin, 2006).
- **Aripiprazole has also been shown to be as effective as haloperidol, risperidone, and olanzapine** in treating delirium without as high of a risk for EPS as haloperidol or sedation associated with olanzapine (Boettger, Friedlander, Breitbart & Passik, 2011; Boettger, Jenewein & Breitbart, 2015).
- **Aripiprazole** is the **only partial D2 agonist approved for agitation**; however, in a quantitative review of nine double-blind, randomized, controlled clinical trials, the number needed to treat (NNT) for response to treatment for agitation versus placebo for aripiprazole 9.75 mg was 5 (95% CI = 4 to 8) as compared to NNT for ziprasidone 10-20 mg was 3 (95% CI = 2 to 4) and NNT for olanzapine 10 mg was 3 (95% CI = 2 to 3) (Citrome, 2007). This shows that **aripiprazole in comparison to other SGAs like ziprasidone and olanzapine is less efficacious in treating agitation** (Citrome, 2007).
- Unlike the aforementioned antipsychotics, **Aripiprazole has minimal effect on the QTc interval,** weight, lipids and glucose levels (low risk for metabolic syndrome) and thus should be a consideration for patients with these existing medical concerns (Reilly, Ayis, Ferrier, Jones & Thomas, 2000; Straker, Shapiro, & Muskin, 2006).
- Dosing: 5 mg/day to 30 mg/day depending on severity (Alao & Moskowitz, 2006; (Boettger, Friedlander, Breitbart & Passik, 2011).

Mood stabilizers:

- **Valproic Acid (Depakote, Depacon, Depakene)**
  - **Valproic acid** has been shown to be **efficacious in treating delirium** (Bourgeois, Koike, Simmons, Telles & Eggleston, 2005; Sher, Cramer, Ament, Lolak, & Maldonado, 2015).
  - In a consult-liaison service setting, **IV sodium valproate**, when used as **adjunctive treatment** to **conventional anti-delirium medications (e.g. Lorazepam, Haloperidol, Risperidone)**, resulted in **improved control of behavioral symptoms without significant side effects from valproic acid (see bullet point below)**. Consider adding valproic acid to control behavioral

symptoms of delirium when conventional anti-delirium therapies are ineffective, require large and/or frequent dosing, or when side-effects are concerning with regards to current medical conditions (Bourgeois, Koike, Simmons, Telles & Eggleston, 2005).

- In a randomized, double-blind, parallel-group trial consisting of 80 acutely agitated patients receiving either IV valproate sodium (20 mg/kg) or IV haloperidol (5 mg/1 ml), **IV valproate sodium** was found to be **as effective as haloperidol in reducing agitation with less risk of intense sedation** (2.5% vs 36.2%, *P*<0.001) (Asadollahi et al., 2015).
- **Consider IV Depacon (Valproate sodium) if patient does not have underlying liver compromise as Valproic acid is well-known to cause hepatic injury and even fatal hepatotoxicity** (Dols et al., 2013; Schmid et al., 2013)
    - Patients with **COVID-19** have been noted to have **higher rates of liver dysfunction with elevated liver transaminases** (Zhang, Shi & Wang, 2020)
    - Monitor BUN and LFTs, which can be elevated in COVID-19 and other inflammatory conditions (e.g. sepsis) (Szabo, Romics Jr & Frendl, 2002).
- Other side effects of valproic acid include vomiting, nausea, diarrhea, dizziness, sedation, hypotension, alopecia, tremors, thrombocytopenia, and pancreatitis (Naritoku & Mueed, 1999; Norton & Quarles, 2000; Porsteinsson et al., 2001).
- IV valproate sodium may be associated with less nausea than PO forms of valproic acid (Bourgeois, Koike, Simmons, Telles & Eggleston, 2005).
- Dosing:
    - Recommended initial dosing is 10–15 mg/kg/day BID or TID and can be given as IV valproate sodium for rapid onset of effect or through NGT as liquid valproic acid in a patient with a functioning gut and if the rapid onset of effect of IV valproate sodium is not needed (Bourgeois, Koike, Simmons, Telles & Eggleston, 2005).
    - The recommended serum trough level is 50–100 mg/liter (Bourgeois, Koike, Simmons, Telles & Eggleston, 2005).

Alpha agonists:

- **Dexmedetomidine (Precedex)**

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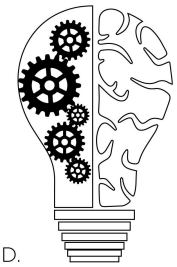
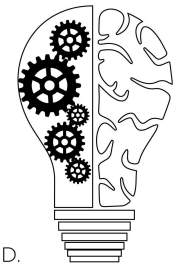


- Dexmedetomidine is an alpha-2 agonist with **useful sedative and analgesic effects** that has been well-studied in reducing post-operative delirium in the ICU (Arain & Ebert, 2002; Chrysostomou & Schmitt, 2008; Djaiani et al., 2016; Kaur & Singh, 2011; Maldonado, Wysong, Van Der Starre, Block, Miller & Reitz, 2009; Su et al., 2016).
- Dexmedetomidine is also **useful in treating ICU-associated delirious agitation**, which is important for reducing the rate of COVID-19 transmission to healthcare professionals (Reade et al., 2009).
- Dexmedetomidine has minimal respiratory depression which is useful considering the respiratory complications of COVID-19, but also **causes bradycardia and hypotension due to sympatholytic and vagal mimetic effects**, which needs to be balanced against the cardiac complications of COVID-19 (Arain & Ebert, 2002; Chrysostomou & Schmitt, 2008; Kaur & Singh, 2011).
- Starting dose could be as low as 0.2 mcg/kg/hr, especially in the elderly, with maintenance dose up to 0.7 mcg/kg/hr. Typical dose would be around 0.5 mcg/kg/hr, but can go up to 1.5 mcg/kg/hr (Pandharipande et al., 2007; Riker et al., 2009). Dosages above 1.5 mcg/kg/hr have not been shown to increase clinical efficacy (Venn, Newman & Grounds, 2003).

Other:

- **Melatonin**
  - There is currently **inconsistent data** concerning the **efficacy** of **melatonin in treating delirium**.
    - Melatonin has been shown to **decrease the incidence of delirium in elderly patients, prevent delirium in postoperative elderly patients, and be effective in treating delirium unresponsive to antipsychotics** in certain patients (Chen et al., 2016; Hanania & Kitain, 2002). In a study by Al-Aama et al. (2011), melatonin was associated with a lower risk of delirium (12.0% *vs*. 31.0%, $p = 0.014$) in a sample size of 145 patients with half being randomly assigned to the melatonin group vs placebo group, with an odds ratio (OR), adjusted for dementia and co-morbidities of 0.19 (95% confidence intervals (CI): 0.06–0.62).
    - However, in a study with 452 patients with acute hip fractures, melatonin was not shown to be beneficial in reducing delirium incidence with 55/186 (29.6%) in the melatonin group developing delirium v. 49/192 (25.5%) in



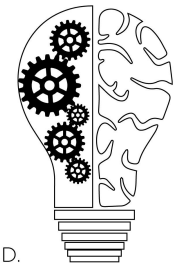
the placebo group; difference 4.1 (95% confidence interval -0.05 to 13.1) percentage points (de Jonghe et al., 2014).

- In addition to its role in treating delirium, **melatonin is also currently being investigated as an adjunctive treatment for COVID-19 due to its anti-inflammatory and anti-oxidative effects** that have been well-studied to be effective in acute lung injury (ALI) and ARDS, which COVID-19 is commonly associated with (Hu et al., 2016; Kücükakin, Gögenur, Reiter & Rosenberg, 2009; Tan & Hardeland, 2020; Zhang et al., 2016; Zhang et al., 2020). In mice studies, melatonin was given at 1mg/kg subcutaneously 3 days before and 10 consecutive days after inoculation (Tan & Hardeland, 2020). The mortality of the infected mice were reduced from 100% in untreated animals to 16%. Moreover, very high titers of IgM antibodies were found from three to seven weeks after virus inoculation (Tan & Hardeland, 2020).
- **Melatonin is also effective in improving morbidity rates in ICU patients by reducing anxiety, sedation use, and improving sleeping quality** (Zhang et al., 2020).
- In terms of safety, a high dose of 1 gram/day of melatonin over the span of a month has not been associated with any significant adverse effects (Zhang et al., 2020).

Treatment of COVID-19

- **Chloroquine/Hydroxychloroquine** has been shown to be effective in inhibiting COVID-19 replication and eliminating the COVID-19 virus from the body; however, studies have shown that **they prolongs QTc**, which in conjunction with the aforementioned antipsychotics used for agitation that also prolong QTc, **can increase the risk for arrhythmia and sudden cardiac death** (El Harchi, McPate, hong Zhang, Zhang & Hancox, 2009; Fossa, Wisialowski, Duncan, Deng & Dunne, 2007; Gao, Tian & Yang, 2020; Gautret et al., 2020; Touret & de Lamballerie, 2020).

- **Azithromycin** has also been shown to be an effective adjunct to hydroxychloroquine in reducing viral load of COVID-19 (Gautret et al., 2020). Azithromycin as well as other macrolides have been known to **induce QTc prolongation, which increases the risks for cardiac arrhythmias such as torsade de pointes** (Hancox, Hasnain, Vieweg,

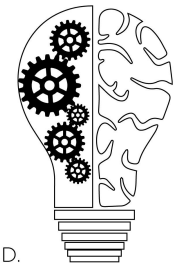


Crouse & Baranchuk, 2013). This risk is increased in elderly women with co-existing heart disease that were also taking other QTc prolonging drugs, so extra care needs to be taken with this population as they are also at higher risk for delirium and poorer outcomes associated with COVID-19 (Hancox, Hasnain, Vieweg, Crouse & Baranchuk, 2013; Ray, Murray, Hall, Arbogast & Stein, 2012).

- **Remdesivir** is a broad-spectrum antiviral that has been found to block viral replication in SARS and MERS and has now also been found to block viral SARS-CoV-2 infection in vitro (Wang et al., 2020).
    - **There is currently no research done that has looked at the drug-drug interactions of remdesivir and the aforementioned treatments for delirium.**

- High doses of **IV Vitamin C** is currently being investigated as an adjuvant treatment for hastening recovery in patients with COVID-19 (Vetter Eckerle & Kaiser, 2020). Vitamin C has been found to reduce mortality rates in patients with sepsis and ARDS, both of which are commonly associated with patients in the ICU, on ventilator support and now severe COVID-19 infection (Marik, Khangoora, Rivera, Hooper & Catravas, 2017; Truwit et al., 2019).
    - **There is currently no research done that has looked at the drug-drug interactions of Vitamin C and the aforementioned treatments for delirium.**

- **NSAIDs** have been used to treat certain symptoms of COVID-19 (e.g. fever, sore throat), but recent studies have shown that **ibuprofen has been found to prolong illness by depressing the immune response** and **results in more severe illness or complications** (e.g. respiratory, sepsis, cardiovascular) (Day, 2020). This correlates with previous research that has shown that NSAID use in community acquired pneumonia (CAP) was associated with more pleuropulmonary complications and a more complicated recovery course (Voiriot, Dury, Parrot, Mayaud & Fartoukh, 2011). **If NSAIDs have to be used, acetaminophen is recommended rather than ibuprofen** (Day, 2020).
    - **The most common drug class that results in drug-drug interactions are NSAIDs** (Hanlon et al., 2017). Although no well-known drug-drug interactions have been studied in NSAIDs and the aforementioned treatments for delirium besides an in vitro study that showed that doses of ibuprofen greater than 400 mg/day may displace valproic acid from albumin binding sites and increase



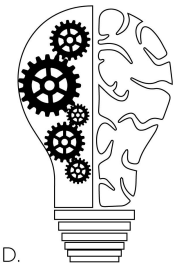
valproic acid levels, acetaminophen and the aforementioned antipsychotics are processed by CYP3A4 and so care needs to be taken if other co-administered drugs inhibit or induce CYP enzymes (Dasgupta & Volk, 1996; Urichuk, Prior, Dursun & Baker, 2008)

- **Corticosteroids** have previously been used in patients with SARS and MERS; however, **corticosteroid use in treating SARS-CoV-2 is not currently recommended** as there is no recorded benefit and more harm may be done than good due to increased risks of corticosteroid use including increased mortality, increased secondary infection rates of influenza, impaired clearance of SARS-CoV-2, prolonged viral shedding, and other side-effects of corticosteroid therapy such as psychosis and delirium (ENT UK, 2020; Russell, Millar, & Baillie, 2020; Vetter Eckerle & Kaiser, 2020; Wang et al., 2020).

- "**Convalescent plasma**" or **immunoglobulins** is an antibody-based COVID-19 treatment that has been shown to be effective for viral illnesses such as H1N1, SARS, MERS and Ebola and is **currently undergoing research as a treatment for COVID-19** (Casadevall & Pirofski, 2020; Chen, Xiong, Bao & Shi, 2020). Convalescent plasma is taken from patients who have recovered from COVID-19; the antibodies are currently thought to suppress viremia by viral neutralization and accelerating infected cell clearance (Casadevall & Pirofski, 2020; Chen, Xiong, Bao & Shi, 2020). Viremia typically peaks in the first week of infection for most viral illnesses (Cheng et al., 2005). The patient will develop a primary immune response by days 10–14, which is then followed by virus clearance (Cheng et al., 2005). Therefore, convalescent plasma is currently being investigated as a prophylactic measure since it should theoretically be more effective if it is administered at the early stage of COVID-19 (Cheng et al., 2005).

Other Considerations

Managing patients with delirium, especially hyperactive, already poses challenges, but managing patients with hyperactive delirium that have also tested positive for COVID-19 makes management that much more complicated as extra care needs to be taken to reduce the risk of cross-infection. According to Wang et al. (2020), 41% of patients were suspected to have contracted SARS-CoV-2 from presumed hospital-associated human-to-human interaction transmission. To mitigate this risk, implement the following considerations:



- **Screen and regularly assess** patients at risk for delirium through clinical tools such as 4AT.
- Reduce the risk of delirium by **addressing known precipitating factors**: medical illnesses, dehydration and malnutrition, cognitive impairment, vision and hearing impairment, use of physical restraints, urinary retention, constipation, pain and polypharmacy (Elie, Cole, Primeau & Bellavance, 1998; Fong, Tulebaev & Inouye, 2009; Inouye, 2000; LaHue & Liu, 2016; Rosen et al., 2015; Thorne & Geraci, 2009;).
- If pharmacologic intervention is needed for acute agitation, **be mindful of medication side-effects with regards to coinciding symptoms of COVID-19** or other existing medical conditions:
    - Benzodiazepines (e.g. Ativan) potentiating respiratory depression when the patient is already on ventilation support (Ekström, Bornefalk-Hermansson, Abernethy & Currow, 2014).
    - Antipsychotic medication (e.g. Risperdal, Haldol) in patients with pre-existing Parkinson's disease or dementia with Lewy bodies (Ma et al., 2014).
    - Anticholinergics in patients with delirium (Tune, 2001).
- Clarify code status and end of life goals with the patient or with surrogate decision makers if the patient's mental capacity is lacking.
- Mechanical restraints may be indicated in an agitated patient with multiple lines/monitors in place, but **consider that physical restraints precipitate and exacerbate delirium** as discussed previously (Inouye, 2000).
- It may be prudent to **avoid entering rooms with COVID-19 positive patients if there is significant risk of exposure, especially due to lack of personal protective equipment (PPE)**. Although tele-medecine is not optimal compared to assessing a patient in person, it may be necessary for your health as well as those around you.

Conclusion

These are unsettling times for mental health and medical professionals as each passing week brings a rise in positive COVID-19 cases and deaths, news breaks on novel presentations and associated symptoms, and even more media coverage sabotages the public. It is safe to say generalized anxiety and uncertainty has affected everyone. For patients in the hospital with COVID-19, they not only have to deal with their medical condition, but also internal crisis due to the uncertainty of their condition, of being isolated from family and friends, and even the possibility of death. Now is the time when being a stable source of comfort and compassion can mean the world to the patient and their family and is something that I have been thinking about

Episode 078:COVID-19 and the Brain: Delirium & Viral Encephalitis

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more frequently as I see my patients on a daily basis. For more information on COVID-19 and dealing with stress, anxiety and panic, refer to episode 76 of the podcast.