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# Behavioral, Environmental and Pharmacotherapy Challenges in Dementia during COVID-19 Pandemic: Solutions and Management Issues

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**ABSTRACT**

With the increase in the world's elderly population, age-related disorders such as cognitive disorders and dementia have increased in this group, and with the onset of the COVID-19 pandemic in 2019, many of the world's rules and regulations have changed, and personal protection recommendations against infection have been recommended by various medical centers, which is very challenging for patients with dementia and can even lead to the development or exacerbation of behavioral symptoms in their everyday life.

On the other hand, caregivers of dementia patients are exposed to the burden of disease caused by the stress of transmitting infection along with the usual care needed for dementia patients, which has definitely increased this time during the pandemic. Therefore, caregivers of dementia patients, both at home and in care centers, need the advice to care for patients and prevent pandemic physical and psychological complications on themselves and their patients.

Regarding the administration of drugs effective on COVID-19 infection and the possibility of their interaction with drugs prescribed in patients with dementia or cognitive complications, delirium, and exacerbation of dementia, there is a need for solutions that are briefly reviewed in this report. It is hoped to provide assistance and support in providing services and care to dementia patients, health care providers, and physicians.

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## Introduction

The elderly are more prone to the complications of diseases and natural disasters, and the same is true of COVID-19. Due to the extensive spread of the virus in the community, the mortality rate in the elderly has also increased (1).

In total, more than 50 million people with dementia live in the world, and recently, dementia is recognized as a pandemic worldwide. The increased effects of two simultaneous pandemics of dementia and COVID-19 need special attention in patients with dementia (2).

Patients with dementia have limited access to accurate information about COVID-19 and have problems remembering and following self-care-related health guidelines, such as using a mask and personal hygiene, which increase their risk of infection (3-5).

As another view, in many countries, people with dementia are cared for in nursing homes, which reduce the possibility of social distancing, and in a way, they are excluded from society and communication because they cannot use virtual communication tools (6).

Also, there is some evidence that shows prescribing numerous drugs in dementia patients could influence their response to the treatment of COVID-19 infection. So that these complications and drug-drug interactions alternate prognosis of infection and ultimately mortality rate (7, 8).

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***Behavioral recommendations***

There are many challenges for patients with dementia during the COVID-19 pandemic: These patients lose many of their routines, and also cognitive stimuli are reduced in them (9). Likewise, increased feelings of anxiety and fear put them at risk for developing and exacerbating depression.

Many of these patients experience severe symptoms, sleep disorders, and behavioral changes that can lead to their transfer to a nursing home (10).

Self-help guides to reduce stress, including relaxation meditation exercises, should be provided using cyberspace. Psychological counseling and behavioral interventions should be provided to patients in nursing homes. It is also recommended that the children of patients with dementia spend more time and contact with their parents (11).

Caregivers of patients with dementia face many challenges in caring for these patients, which can increase the risk of transmitting the virus. They may decide to reduce their support and care to reduce the risk of transmission. Furthermore, staying in an isolated and confined environment can increase the risk of aggression and harm to the patients (12).

Some caregivers may be older people who do not have access to the internet for more information. In addition, some caregivers may have cultural, religious, and most importantly, financial constraints on caring for patients and obtaining reliable information, or they do not have enough education to acquire knowledge in this regard (13).

It is recommended to prepare clear information about the symptoms of COVID-19 infection, which be available to patients with dementia due to the fact that patients with dementia have different levels of education, training and verbal skills and virtual training and make sure dementia patients and their caregivers are aware of accessible health care services. Social communication is maintained through different remote methods, including telephone help and online support platforms (14).

It is suggested that a person with dementia should have a regular daily schedule, adequate exercise, a healthy diet, and be able to get fresh air when it is convenient and possible. Alternatively, medications and their changes are well managed and precisely monitored for side effects (15).

In addition, due to the stress caused by the infection and the tension triggered by the care conditions, many of these elderly people and caregivers might feel burned out. Many people with COVID-19 develop hypoxia and delirium following admission to the ICU, which can exacerbate the symptoms of dementia. In these patients, in addition to physical protection, social and psychiatric support should also be provided (16).

Challenges in Nursing home care

To reduce the risk of infection in care centers, special instructions should be developed for COVID-19 prevention. A study of nursing homes in China found that these elderlies lost face-to-face contact with family members, leading to social isolation (17).

Many health care providers in nursing homes have an increased workload due to the stress of reducing staff. In addition, fear of COVID-19 transmission can disrupt the services provided to the residents of these homes. Furthermore, in many countries, appropriate clothing and equipment are not provided to the personnel (18).

The possibility of isolating a person living in a nursing home who is suspected of COVID-19 is very challenging because it can disturb other residents. Ultimately it seems that people with dementia who live in nursing homes are becoming a more serious challenge in the COVID pandemic (19).

***Medications challenges***

The treatment options for COVID-19 have an ever-changing list, and while some of them are no longer recommended by the world health organization, they are still being used in some countries since some of the other recommended options are not available or as an investigational treatment approach (20). Although some of the drug choices for COVID-19 management, such as remdesivir, favipiravir, and tocilizumab, seem to not need any consideration, there are many challenges and probable interactions between medications prescribed in dementia and other prevalent choices of medications routinely given in COVID -19 infection(atazanavir, ritonavir, lopinavir, hydroxychloroquine, and ketoconazole) (21, 22) (Tabel 1).

**Table 1.** Summary of considerations of medications used in COVID-19 and Alzheimer's disease

| Medication | Interaction | Consideration |
|---|---|---|
| Donepezil | CYP 3A4 inhibitors (ketoconazole, atazanavir, ritonavir, and lopinavir) | possibility of increasing the dose of donepezil and its side effects, such as bradycardia |
| | Cardiotoxicity (Torsade's de Pointes, QTc prolongation) caused by chloroquine/hydroxychloroquine and donepezil in concomitant use | ECG monitoring, especially in patients at risk, including old age, female gender, congenital long QT syndrome, and electrolyte imbalances particularly hypokalemia, hypomagnesaemia |
| Galantamine | CYP3A4 and CYP2D6 inhibitors (atazanavir and ritonavir-boosted lopinavir) | No report on any clinical interaction.<br>Pharmacologically the interaction may lead to excessive cholinergic effects in the patients |
| Rivastigmine | No reported interaction | In theory, the risk of torsade de pointes may increase with concomitant use of rivastigmine and hydroxychloroquine or chloroquine |
| Memantine | No reported interaction | - |

Two classes of drugs are currently approved for Alzheimer's disease, cholinesterase inhibitors (ChEIs), and N-Methyl-D-aspartate (NMDA) receptor antagonists. These drugs represent advantages on cognition, behavior, and general function (23).

ChEIs increase acetylcholine in neurosynaptic cleft by inhibiting acetylcholinesterase (AChE), and to a smaller degree, butyrylcholinesterase (BuChE), resulting in enhancing the physiological function of acetylcholine and boosting nerve impulse passing. Eventually, ChEIs compensate for the decreased cholinergic function in Alzheimer's disease (24, 25).

***Donepezil***

Donepezil hydrochloride is a reversible cholinesterase inhibitor and is used in mild, moderate, and severe Alzheimer's disease. (26). Donepezil is metabolized mainly by CYP 3A4 (high affinity) and CYP 2D6 (low affinity). The excretion of the parent drug and its metabolites is mainly through urine (57%) and feces (17%) (27).

Regarding drug interactions, Cytochrome P450 3A is inhibited by atazanavir and ritonavir (28). In the study of Tiseo et al. in 18 healthy volunteers, the potent CYP450 3A4 inhibitor ketoconazole (200 mg/day) increased the mean peak plasma concentration and area under the curve of donepezil (5 mg/day) (29). Therefore, there is a possibility of increasing the dose of donepezil and its side effects, such as bradycardia, in concomitant use with CYP 3A4 inhibitors (e.g., atazanavir, ritonavir, and lopinavir).

Cardiotoxicity (Torsade's de Pointes, QTc prolongation) caused by chloroquine/hydroxychloroquine (30) and donepezil (31) in concomitant use can be serious and need more ECG monitoring, especially in patients at risk, including old age, female gender, congenital long QT syndrome, and electrolyte imbalances particularly hypokalemia, hypomagnesaemia (30).

***Galantamine***

Galantamine is a tertiary alkaloid that was approved for mild to moderate AD. It is a selective and reversible inhibitor of acetyl-cholinesterase (AChE) (32, 33). Galantamine has a hepatic metabolism through cytochrome P450 isoenzymes, chiefly CYP2D6 and CYP3A4. Thus potent CYP3A4 and CYP2D6 inhibitors may increase the serum level of galantamine and augment the cholinergic effects (32). Antiviral drugs such as atazanavir and ritonavir-boosted lopinavir are CYP3A4 inhibitors (34, 35). Clinically important interactions between galantamine and these antiviral drugs have not been reported. But hypothetically, co-administration of these agents, especially ritonavir-boosted lopinavir with galantamine, may lead to excessive cholinergic effects in the patients. So, it is recommended that susceptible patients be monitored for signs and symptoms of cholinergic side effects.

***Rivastigmine***

Rivastigmine was approved for the treatment of mild, moderate, and severe AD. It inhibits both BuChE and AChE with the same potency. Rivastigmine does not have hepatic metabolism (25, 33). No interaction has been reported between rivastigmine and the drugs used to treat COVID-19; however, theoretically, the risk of torsade de pointes may increase with concomitant use of rivastigmine and hydroxychloroquine or chloroquine. Because rivastigmine may have vagotonic effects on the sinoatrial and atrioventricular nodes and can cause bradycardia or heart block (36-38)and hydroxychloroquine or chloroquine may prolong the QT interval (39). Both bradycardia and QT interval prolongation are risk factors for torsade de pointes.

***Memantine***

Memantine is an antagonist of glutamate NMDA receptors and is approved for moderate and severe Alzheimer's disease (40). Memantine and its inactive metabolites are mainly excreted by the kidneys (41). Memantine has an inhibitory effect on the CYP2B6. This is clinically significant (42). No interaction has been reported between memantine and the drugs used to treat COVID-19.

***Renal impairment***

Acute kidney injury (AKI) may occur in patients with COVID-19 infection (43). Direct kidney involvement in COVID-19 may cause multiple organ dysfunction and a more severe form of the disease (44). This condition can potentially result in the accumulation of drugs with significant renal clearance. Drug dosing adjustments are necessary to prevent toxicity.

Renal clearance of galantamine is about 20% after oral administration (45). Therefore, galantamine is not recommended for severe renal impairment. There are no dosage adjustments in patients with a creatine clearance ≥9 ml/min (32). For patients with renal impairment and taking rivastigmine, the drug can be used at dosages the same as those administered to patients with good renal function (46). No dosage adjustment of donepezil is necessary for renal impairments (26).

With a normal dose of 10 mg/twice daily, memantine does not require dose adjustment in mild to moderate renal impairment. However, while in severe renal failure, memantine at a dose of 5 mg/twice daily is recommended (47).

***Hepatic impairment***

Liver damage has been reported in patients with COVID-19 infection. This might be caused by the direct infection of hepatic cells with SARS-CoV-2 and/or drug-induced hepatotoxicity. Furthermore, systemic inflammatory responses such as cytokine release and pneumonia-induced hypoxia might also cause liver failure in these patients (48). Galantamine is not recommended in patients with severe hepatic impairment, and in patients with moderate hepatic impairment, dose titration should be done with caution (49). Rivastigmine does not have hepatic metabolism, but dose titration should proceed cautiously in patients with mild to moderate hepatic impairment. There are no studies investigating rivastigmine in patients with severe hepatic

impairment (50). No dosage adjustment of donepezil is necessary for hepatic impairments (26).
In patients with liver problems, caution should be considered in memantine administration according to hepatic side effects (51, 52).

## Conclusion

On the whole, caregivers and physicians involved with dementia patients have more challenges and responsibilities with encountering the COVID-19 pandemic. They should apply special considerations to the training of social distancing and personal protection methods against COVID-19 infection. Particularly in patients living in nursing homes, more attention to these interventions is needed. On the other hand, due to possible drug interactions in the treatment of dementia and concomitant COVID-19 infection, a holistic and interdisciplinary approach and consultation between neurologists, psychiatrists, and clinical pharmacists should be considered.

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