ISSN: 2577-8005

Review Article

Medical & Clinical Research

# EXTENDED Palliative (compassionate) medicines for COVID-19

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**Submitted:** 25 Aug 2020; **Accepted:** 29 Aug 2020; **Published:** 05 Sept 2020

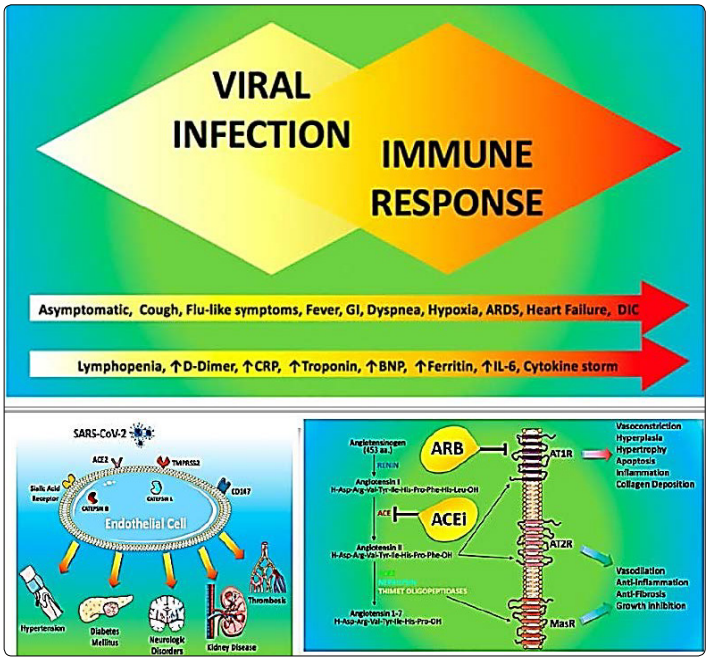
## Abstract

***Background:*** *Neuromodulation techniques are an important part of the chronic refractory neuropathic pain treatment. Their effectiveness is insufficiently documented in patients with tethered cord syndrome.*

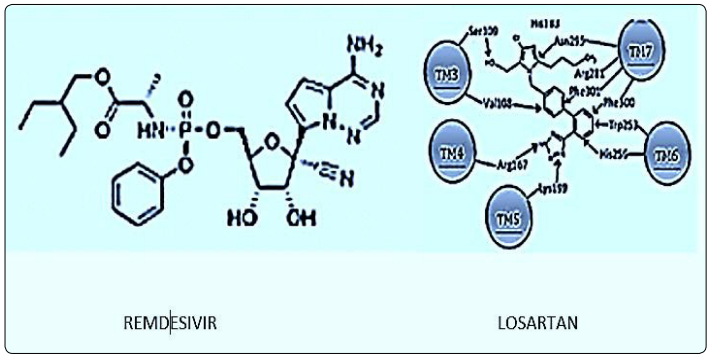
***Case Description:*** *We present the case of a 32-year-old woman with a history of myelomeningocele repair, followed by a detethering surgery complicated with cerebral fluid leakage. Her intractable pain in her left leg and low back was successfully treated with spinal cord stimulation. Pain intensity decreased from 8/10 to 1-2/10 on her visual analogue scale without regular analgesic intake and her quality of life improved significantly.*

***Conclusions:*** *A review of the literature documents only three case reports of similar efficacy of spinal cord stimulation in the treatment of pain in adult patients with tethered cord syndrome.*

Hypertension, Kidney Failure, Thrombosis, and Diabetes: Is COVID- 19 an Endothelial Disease? A -Diabetes: Is COVID Comprehensive Evaluation of Clinical and Basic Finding [1].




How 2-COV-SARS affects the body (credit ref.[1])



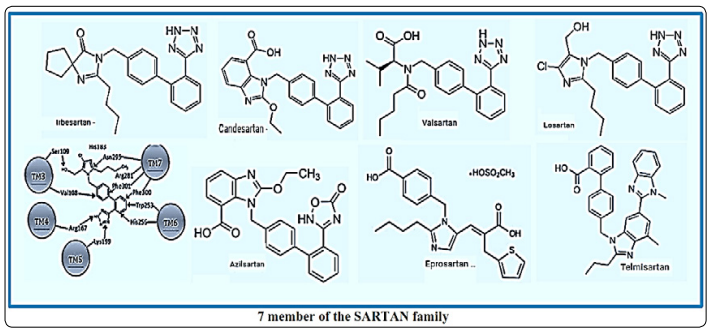

The CDC has identified adults and older people suffering from severe chronic medical conditions such as heart, lung or kidney disease at higher risk for COVID-19 [2]. According to the CDC, early data suggest that older people are twice as likely to have COVID-19. This is because as people advancing in age, their immune system changes, making it harder for their bodies to fight disease and infection, and because many older adults are more likely to suffer from underlying health conditions that make it difficult for them to cope and recover. Age increases the risk that the respiratory system or lungs will be shut down when an adult suffers from COVID-19. The CDC stressed that the best way to prevent disease is to avoid exposure [3].

The penetration of the virus into the human cell is a crucial step in its proliferation. This is through ACE2 receptors scattered; present and abundant everywhere in our tissues of many organs, including the brain, of the virus have aroused interest in other antihypertensive drugs from the "SARTAN" family.

ACE receptor blockers, ARBs, for example, Losartan, valsartan has similar effects to ACE inhibitors and may be beneficial in COVID-19 treatment) [4, 5]. The binding of SARS-CoV-2 spike protein to ACE2 has been suggested to cause Down-regulation of ACE2 from the cell membrane [6]. As a result, the down-regulation of ACE2 May lead to loss of protective electrons activated by ACEi / ARB in humans [7]. Such downregulation Of ACE2 is an attractive research area [8, 9]. Indeed, it could be a valid therapeutic target for him Improved response and clinical prognosis in patients with hypertension, caused by COVID-19. Moreover, several researchers have suggested restoring ACE2 by giving recombinant ACE2 to Reverse the process of lung injury during viral infections [4]. In fact, the same reporters are being investigated. In ongoing clinical trials. A relative study compared to ACE [10]. Finally, we must take into account the higher rate of heart damage and the negative results in hypertension. Patients during the COVID-19 epidemic [11]. Therefore, chronic ACEi / ARB treatment should not apply.

Discontinue in patients with hypertension with COVID-19. Indeed, the loss of their pneumonia and cardiovascular disease Aspects can be harmful [88]. Besides, in the absence of appropriate follow-up visits, Switching from ACEi / ARB to another treatment for hypertension may result in suboptimal control of Coronavirus disease (COVID-19).

The "SARTAN" family consists of a fairly new group of drugs (Losartan, valsartan, candsartan, irbsartan, telemisartan, eprosartan, azilsartan), all of which act as antagonists in the Angiotensin 1 Receptor (AT1). The AT1 receptor antagonists are Renin-Angiotensin-Aldosterone-System (RAAS)-specific. AT1 receptor-selective, and work independently on the ANG II synthesis pathway, allowing for a more selective blockade of the AT1-mediated effects of ANG-II compared to ACE inhibitors. However, by inhibiting the negative feedback that mediates ANG II's AT1 receptor on renal renin release, these drugs may induce AT2 receptor over-stimulation by improving plasma ANG II levels. An increase in the mediation of AT2 receptors in the production of blood relays (nitric oxide, cGMP, prostaglandins) as well as the anti-growth properties of this receptor may contribute to a further decrease in blood pressure and the prevention of hypertension and remodeling. AT1 receptor antagonists do not inhibit quinine degradation and cough is not a common side effect.



7 member of the SARTAN family

AT1 receptor antagonists widely applied as antihypertensive agents, especially in patients with type 2 diabetes or intolerance to ACE inhibitors. Researchers at the University Of Minnesota School Of Medicine have begun enrolling patients in recently launched clinical trials with blood pressure medication, Losartan, as a potential treatment for those recently diagnosed with COVID-19 [12]. Both studies are multi-site trials, one for patients in need of hospitalization and the other for diagnosed patients who do not need hospitalization [13].

The coronavirus virus interferes with the mechanism that regulates the level of the hormone (Angiotensin II); this leads to high blood pressure and damage to the lungs. Losartan, on the other hand, blocks the action of the hormone. The researchers hope that this will work against the effects of excess angiotensin II and prevent lung damage in COVID-19 patients [14].

## Heart Drugs Show Promise with Covid-19 Complications

The researchers are examining the early findings and ensuring that drugs currently approved for the treatment of heart disease can also prevent or reduce complications from Covid-19 and help hospitalized patients recover earlier.

Treatments tested include blood pressure medications, blood thinners, statins, antiplatelet drugs, and triglyceride-lowering drugs. The results of the studies, some of which could come as early as this summer, may offer doctors a new set of drugs to treat patients infected with the coronavirus.

Losartan is different from the other therapies currently under consideration - it is not an antiviral drug. Researchers are trying to turn COVID-19 into a common coronary virus disease-a cold.

## Does Losartan block the receptor used by the Coronavirus?

Losartan is not a receptor, but it blocks a chemical (angiotensin II), which binds to the receptor, type 1 angiotensin 2 (AT1), which lowers blood pressure.

Losartan does not block the virus that causes COVID-19, known as SARS-CoV-2, but it may reduce the activity of the renin-angiotensin system, which is overactive in people with high blood pressure, which may increase their risk of developing lung complications. From COVID-19.

Several animal studies have found that Losartan is beneficial in reducing severe lung simulation damage in mice contracted to other viruses, such as SARS. Few studies with humans have been conducted. For now, any beneficial effect of Lucarten is just a hypothesis (suggestion). It may be not a good idea to start any medical treatment based on an untested hypothesis as unexpected injuries may outweigh all the benefits.

For people who are already taking Losartan or any other ARB, advice from the medical community is to continue taking it unless your doctor tells you otherwise.

Cozaar belongs to a group of drugs called angiotensin receptor blockers, also known as angiotensin II receptor antagonists. Losartan works by blocking the receptor and thereby the action of a natural chemical called angiotensin II. ARBs prevent angiotensin II from binding to angiotensin 2 type 1 (AT1) receptors located in the heart, blood vessels, kidneys, adrenal cortex, lungs, and brain. Losartan, therefore, works on the renin-angiotensin (RAS) system, which is a A hormonal system that regulates blood pressure.

Losartan is not a receptor, but it blocks chemicals (angiotensin II) that bind to the receptor (AT1), which lowers the blood pressure. Losartan has attracted interest from the medical community since Losartan has been used in several preclinical studies to determine its efficacy against the SARS virus that first appeared in 2002. SARS was also a coronavirus and is similar to SARS-CoV-2, the virus that causes COVID-19.

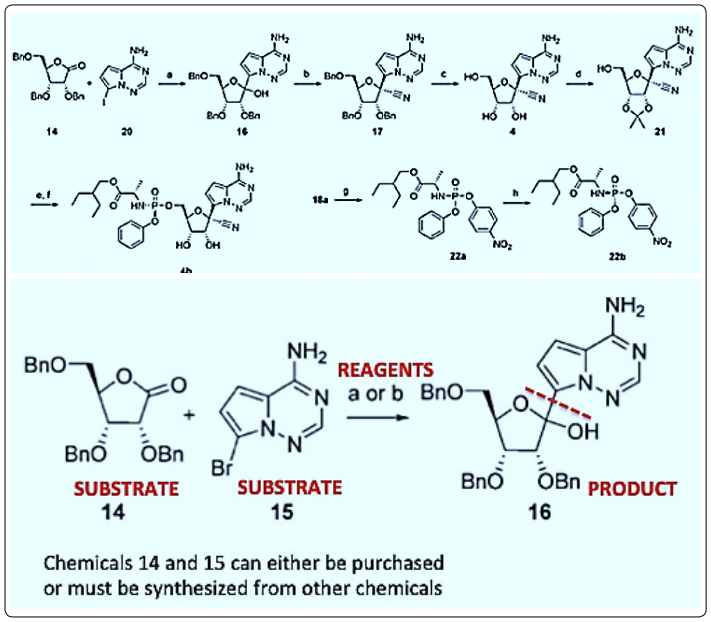
The study was based on the theory that inhibition of overactive RAS may increase the risk of pulmonary complications as a result of viral infections. The studies conducted include:

Mice treated with Losartan after acid-induced lung injury and exposed to the SARS virus had fewer lesions and healthy fluids around their lungs than placebo-treated mice. Losartan, in addition to the infusions of angiotensin-2, prevented severe damage to health and edema in mice that underwent all of their ACE-2 ACE2 infusions have improved lung injury in patientse with SARS Acute respiratory distress syndromes secondary to reduced ACE2 activity has been observed in other viral pneumonia, such as H5N1 and H7N influenza.

Mice given Losartan after H5N1 influenza infection reduced pulmonary edema and increased survival rate. We do not know if the estimated benefits of ARB diseases in the SARS infection episode.

Losartan has a confirmed safety profile and is readily available; Researchers wanted to test a readily available, cheap, FDA-approved the generic drug with potential efficacy against COVIID-19.

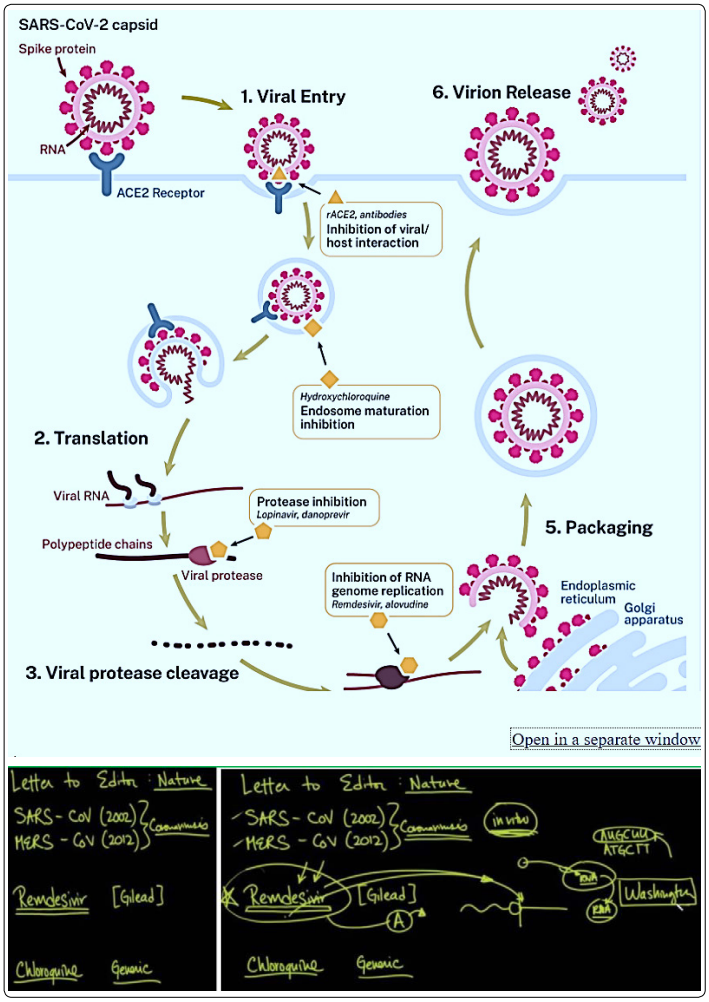
## Palliative (compassionate) Use of Remdesivir for Patients with Severe Covid-19[15].



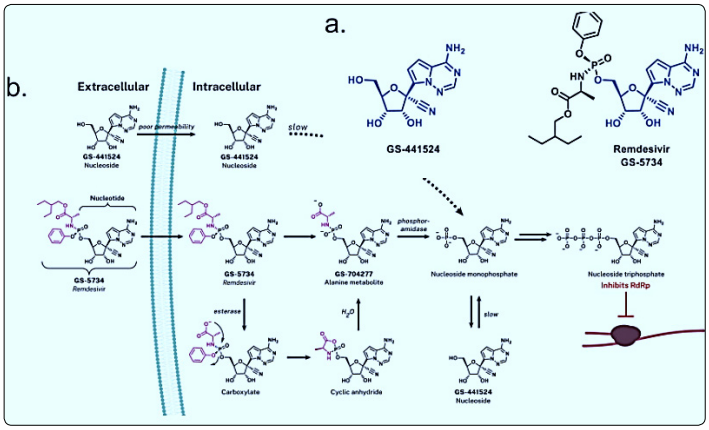

Remdesivir, first generation synthesis (credit ref. [16][17])

Since the first cases reported in December 2019, acute acute respiratory tract infection (SARS-CoV-2) has become a global epidemic. Covid-19 - the disease caused by SARS-CoV-2 - is a crucial health care system all over the world, elderly patients and those with pre-existing respiratory or cardiovascular conditions appear to be at greatest risk for severe complications [18]. In the absence of proven effective treatment, current treatment consists of supportive care, including support for invasive and non-invasive oxygen and antibiotic treatment. 9 In addition, many patients received treatment that was not labeled or used compassionately, including antiviral drugs, antiparasitic drugs, anti-inflammatory compounds, and plasma recovery [19].

Remdesivir is a protein drug of nucleotide analogues that is metabolically intercellular to an adenosine triphosphate analogue that inhibits viral RNA polymers. Remedivator has broad-spectrum activity against members of several viral families, including phyloviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle Eastern respiratory syndrome coronavirus [MERS-CoV]) and has demonstrated prophylactic and therapeutic efficacy in non-clinical models. Of these coronaviruses. In vitro tests have shown that remdesivir also has activity against SARS-CoV-2. Remedivator appears to have a positive clinical safety profile, as reported on the basis of experience in about 500 people, including healthy volunteers and patients treated for acute Ebola virus infection, and supported by our data (in a file and shared with the World Health Organization [WHO]) [20]. In this report we describe the results in a group of patients hospitalized for severe Covid-19 treated with drugs using compassionate treatment.




Remdesivir stopas Viral RNA synthesis (credit ref.[21])




Remdesivir and its intracellular conversion. (A) Chemical structures of GS-441524 that make up the nucleoside analog core (blue) of remdesivir (GS-5734). (B) Intracellular processing of the drug-drug (GS-5734), the aryloxy phosphorimidate (purple) -the drug-drug of GS-441524 monophosphate. After diffusion of remdesivir into a cell, it is metabolized to the nucleoside monophosphate form through a sequence of steps apparently initiated by the ester-mediated hydrolysis of the amino acid ester which releases the carboxylate cycle into the phosphorus that transfers the phenoxide. The unstable cyclic anhydride is liquefied by water into the alenine metabolite GS-704277 whose P-N bond is hydrolyzed by phosphoderma-type enzymes to release the monophosphate nucleoside or nucleotide analogues. An artificial nucleoside nucleoside is transferred to other phosphorus events (abduction of the endogenous phosphorus pathway) and yields the analogous nucleoside triphosphate form used by the RNA-dependent RNA polymerase virus (RdRp). The use of the GS-441524 nucleoside triphosphate analog by RdRp inhibits viral replication by causing late chain termination.

Global clinical trials of Remdesivir. Presented are the locations of clinical research sites for ongoing clinical studies of remdesivir for SARS-CoV-2 / COVID-19. The number of sites participating in each study respectively, if no specific information is provided, are shown in the participating countries. List the number of sites participating in each study respectively, if no detailed information is provided; The number of participating countries is displayed. The number is an extended access experience without specific sites listed in the registry. Illustration created with R, 91 using the natural packages.

## After recovery from COVID 19 side effects persist

### Introduction and Background

*Common comorbidities were. 19-Consecutive cases over 60 years old with COVID hypertension (40.8%), diabetes (16.0%) and cardiovascular disease (15.7%).* "If someone has weakness in their left arm, and they don't use their left arm as much, it's not going to get stronger if they don't receive physical therapy. The same happens in the brain. People need to receive brain rehabilitation in order to recover from COVID-19 symptoms." – Majid Fotuhi, Johns Hopkins University

## COVID-19 is tied to deadly brain inflammation in some patients

A new study published in COVID-19 can cause dangerous neurological problems, including brain inflammation delirium, encephalitis, nerve damage or stroke [23]. Furthermore, the study authors reported that a tumor-affecting patient in their hospital with a rare and sometimes fatal neurological syndrome called ADEM is acutely activated. All patients with ADEM have approved or suspected COVID-19, suggesting that the epidemic may lead to an increase in this condition [22-24].

The findings add to the growing body of evidence linking COVID-19 to brain effects, suggesting that physicians should be "vigilant and watch for these complications" among COVID-19 patients, co-authored by Dr. Michael Zandy, a neurologist at the National Hospital for Neurology and Neurosurgery in London Corona disease, COVID 19 is a severely damaging illness. It affects all parts of the body from the foot to the head, the brain. But even after medical recovery, the post-disease symptoms many cases do not leave patients and is not known today how long it will last [25]. Many politicians tend to take the disease lightly. Some deny the weight of its burden. The cure has not yet been discovered,

and there is no way other than quarantine, to prevent its spread. This is probably an epidemic that will reside here for a long time to come. This plague, like the plague of Justinian, the black plague, and this will change humanity. But one can only hope that the efforts of the scientists will bring the balm, to hope.

In Italy, a large number of patients with Coronavirus 2019 disease (COVID-19) showed symptoms (71.4% out of 31845 cases approved as of June 3, 2020) Common symptoms include cough, fever, respiratory inflammation, musculoskeletal symptoms (myalgia). Joint pain, fatigue), gastrointestinal symptoms, anosmia/dysgeusia. However, there is a lack of information on the symptoms that persist after recovery. We assessed persistent symptoms in patients discharged from the hospital after recovery from COVID-19 [26].

Often, the occurrence of the underlying complex, including hypertension, diabetes, and obesity, patients in the hospital, especially those treated with intensive care. Patients admitted to the hospital were adults, and most men and had an extended length of stay (median, 23 days); 78.0 percent developed acute kidney injury, and 35.2 percent required dialysis. Six of the patients who required mechanical ventilation (4.4 percent) were first discharged more than 14 days after the onset of the symptom. From the available data, the mortality rate of new coronavirus pneumonia is lower than COVID 19. And pneumonia caused by COVID 19. New populations of the coronavirus are generally susceptible, but older people with underlying diseases are more vulnerable. The basic conditions are diabetes, hypertension, cardiovascular disease and kidney disease. Older people are more susceptible to severe illness, and hospitalized in the intensive care unit, and the mortality of elderly patients is higher [27].

The researchers write that "Our study found that patients in hospitals with COVID-19 in New York City had high rates of basic comorbidity, and a significant proportion developed complications compared to U.S. and international partnerships. "Characterizing our patients can provide predictable guidance as the pandemic continues around the world [28].

## COVID 19 in elderly Patients is a very risky matter:

Men in these groups appear to be at a higher risk than females. Chronic obstructive pulmonary disease (COPD). Cardiovascular diseases, obesity, diabetes and hypertension identified as strong predictors for intensive care units (ICU) admission. Diabetes is already known [developing] to be a key risk factor for developing severe COVID- 19 and people with the condition are more likely to die [29-31].

## When is a Negative Covid-19 Test Truly Negative?

Between worrying about the availability of tests for Coronavirus 2019 (COVID-19), and focusing on the long delays sometimes in achieving results, clinicians and patients should be aware that a subset of tests - no matter how many tests are in each area and how quickly the results returned - would yield incorrect results.

While both false negatives and false positives are undesirable, false negatives run the risk of increasing community transmission if people mistakenly think they are non-infectious and fail to take the necessary precautions. This can occur whether people are not suffering from symptoms or whether they are suffering from symptoms but assume they are due to something other than COVID-19 [32].

## The new challenge of geriatrics: rescuing the elderly from SARS-COV-2 epidemic infection

The mortality of elderly patients with COVID-19 is higher than that of middle-aged patients, and the proportion of grade IV and V patients with PSI is significantly higher than the rate of middle-aged patients. Elderly people with COVID-19 may progress to a serious illness [33, 34].

Older adults with underlying diseases are more susceptible. The underlying conditions are diabetes, hypertension, cardiovascular disease, and cerebrovascular disease. 1 The elderly are more vulnerable to severe illness and admitted to the intensive care unit (ICU), and the death of elderly patients is higher [35].

## Duration of Isolation and Precautions for Adults with COVID-19

We do not know if anyone could be re-infected with COVID-19. Data to date show that a person who has recovered and recovered from COVID-19 may suffer from low levels of the virus in their body up to 3 months after diagnosis. This means that if the person who has recovered from COVID-19 is re-tested within 3 months of initial infection, he may continue to receive a positive test result, even though he does not distribute COVID-19.

To date there are no approved updates on a person re-infected with COVID-19 within 3 months of initial infection. However, further research is ongoing. Therefore, if a person recovering from COVID-19 suffers from new COVID-19 symptoms, the person may need to be evaluated for re-infection, especially if the person has been in close contact with someone infected with COVID-19. The person should isolate and contact a health care provider to assess the other causes of their symptoms, and possibly re-examine.

Until we know more, the CDC advises all people, whether or not they have undergone COVID-19, to continue to take safety precautions to avoid contracting COVID-19 [36].

*Cumulative evidence supports the termination of isolation and precautions for people with COVID-19 who use a symptom-based strategy. This update incorporates up-to-date evidence of the duration of isolation and the recommended precautions to prevent transmission of SARS-CoV-2 to others, while limiting unnecessary prolonged isolation and unnecessary use of laboratory test resources.*

The likelihood of recovery of a virus capable of replication decreases even after the onset of symptoms. For patients with mild to moderate COVID-19, a replicable virus did not recover 10 days after the onset of symptoms [37]. Recovery of the virus qualified for replication between 10-20 days after the onset of the symptom has been documented in people with severe COVID-19, which in some cases has been complicated by an immune condition [38]. However, in series of patients, it was estimated that 88% and 95% of their samples no longer produced a competent virus replicating after 10 and 15 days, respectively, after the onset of symptoms.

Recovery with SARS-CoV-2 has not yet been finally confirmed in any person who has been replaced so far. If, and if so when, people can be re-affected with SARS-CoV-2 remains unknown and is the subject of investigation. People infected with the human betacoronavirm virus appear to be associated with susceptibility again about 90 days after the onset of the infection. Thus, for people who have recovered from a SARS-CoV-2 infection, PCR is positive during the 90 days after the onset of the disease, probably representing a continued shedding of viral RNA rather than re-infection.

## Older people & COVID-19

COVID-19 changes the daily routine of older people, the care and support they receive, their ability to stay socially connected and how they are perceived. Older people are challenged by the demands of spending more time at home, lack of physical contact with other family members, friends and co-workers, temporary cessation of employment and other activities; And anxiety and fear of disease and death - theirs and that of others. It is therefore important that you create opportunities for fostering healthy aging during the epidemic. Older people who are infected with the coronavirus have a high risk of developing severe illness. How can they be protected? How hard is it for the elderly to adapt to restrictions in the pandemic?

The situation around the new virus (COVID-19) is changing rapidly, and the NCOA is taking proactive steps to share the best information we have to protect public health, especially among adults. It's time to stay up to date and follow basic tips for protecting yourself and those around you.

## Older at higher risk

The CDC has identified adults and older people suffering from severe chronic medical conditions such as heart, lung or kidney disease at higher risk for COVID-19. According to the CDC, early data suggest that older people are twice as likely to have COVID-19. This is probably because as people get older, their immune system changes, making it harder for their bodies to fight disease and infection, and because many older adults are more likely to suffer from underlying health conditions that make it difficult for them to cope and recover. Age increases the risk that the respiratory system or lungs will be shut down when an adult suffers from COVID-19. The CDC stressed that the best way to prevent disease is to avoid exposure [39, 40].

## What are the risk groups for the novel coronavirus?

1. People suffering from chronic respiratory or lung problems treated by a lung specialist
2. Chronic heart patients who are therefore eligible for the flu shot.
3. People with diabetes that is not completely controlled and / or involves complications.
4. People with kidney disease who need dialysis or are waiting for a kidney transplant.
5. People who are less resistant to infection because they are taking medications for autoimmune disease, and people who have undergone organ transplants or stem cell transplants. This includes: people suffering from blood disease; People who are less resistant to infection because they are taking drugs that weaken the immune system;
6. Cancer patients during chemotherapy and / or radiation, or within 3 months after receiving such treatment;
7. People with severe immune disorders for whom they need treatment from a doctor.
8. People who do not have a spleen, or who have a dysfunctional spleen, are not at additional risk due to severe COVID-19, but have an additional risk of possible (secondary) infection with pneumococcal disease
9. People with untreated (or untreated) HIV infection are treated by a doctor, or with HIV infection with a differentiation group 4 (CD4) below 200 / mm2
10. People with severe liver disease. People who are very overweight (morbid obesity).

**Concluding Remark**

Researchers found that among patients recovering from COVID-19 87.4% reported persistence of at least one symptom, particularly fatigue and dyspnea. Limitations of the study include lack of information on the history of symptoms before acute COVID-19 disease and lack of details on the severity of symptoms. Moreover, this is a single-center study with a relatively small number of patients and without a control group of patients discharged for other reasons. Patients with community-acquired pneumonia may also have persistent symptoms, suggesting that these findings may not be exclusive to COVID-19.6

Clinicians and researchers have focused on the acute phase of COVID- 19, but follow-up is needed after the release of long-term effects.

"Covid-19" is a young disease; it will soon celebrate the 1 years of roaring on the plannet. Killing one million and infecting more than 10 million humans, causing huge economic, Social, educational and behavioural changes. It certainly alters the way we used to live to an unknown mode of existence. It brings with it the anxiety, which is not yet in our comprehension [41, 42]. The 1 year is too

short a period to estimate the following effect of the disease, However, It seems that we will have to live with Covid-19, similar to the AIDS situation, assisted with medication, vaccinations and more as in any other chronic disease.

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