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Corticosteroids for Post–COVID-19 Condition

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Summary of Abstracts

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Questions or requests for information about this report can be directed to **requests@cadth.ca**

Key Messages

- We found 1 non-randomized study about the clinical effectiveness of corticosteroids for the treatment and management of patients with post–COVID-19 condition.
- We did not find any studies about the safety of corticosteroids for the treatment and management of patients with post–COVID-19 condition.

Research Questions

1. What is the clinical effectiveness of corticosteroids for the treatment and management of patients with post–COVID-19 condition?
2. What is the safety of corticosteroids for the treatment and management of patients with post–COVID-19 condition?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were post–Covid-19 and corticosteroids. No filters were applied to limit the retrieval by study type. Conference abstracts were omitted from the search results. The search was completed on October 17, 2022, and limited to English-language documents published since January 1, 2020. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications.

Table 1: Selection Criteria

Criteria	Description
Population	Patients diagnosed with post–COVID-19 condition (also long COVID, post-acute sequelae SARS-CoV-2 infection, post–COVID-19 syndrome), defined as any symptoms experienced 12 weeks or more after initial infection, diagnosis, or symptom onset that cannot be explained by another cause
Intervention	Corticosteroids (e.g., cortisone, dexamethasone, prednisone or prednisolone) alone or in combination with other treatments
Comparator	Q1 and Q2: Other corticosteroids or alternate dosing regimens, alternate treatments, placebo, no comparator

Criteria	Description
Outcomes	Q1: Clinical effectiveness (e.g., reduction in mortality, lung function, lung abnormalities, symptoms reduction, quality of life or others) Q2: Safety (e.g., adverse events leading to discontinuation, severe adverse events)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Results

One non-randomized study[1] regarding the clinical effectiveness of corticosteroids for the treatment and management of post–COVID-19 condition was identified. No relevant health technology assessments, systematic reviews, or randomized controlled trials were identified.

Additional references of potential interest that did not meet the inclusion criteria (e.g., used a different definition for post–COVID-19 condition) but provide information regarding the clinical effectiveness and/or safety of corticosteroids for the treatment and management of post–COVID-19 condition are summarized in Appendix 1. Other articles of potential interest are provided in Appendix 2. Registered ongoing clinical trials are provided in Appendix 3.

Overall Summary of Findings

One non-randomized study[1] was identified regarding the clinical effectiveness of corticosteroids for the treatment and management of post–COVID-19 condition. Patients were selected based on having the post–COVID-19 condition as described by the WHO where patients exhibit symptoms more than 12 weeks since their COVID-19 infection.[1] The study found that in patients with severe isolated dysphonia during post–COVID-19, treated with systemic steroids, moisturizing inhalation with hyaluronic acid, and protective agents against laryngopharyngeal reflux showed improved structural and functional state of the larynx.[1] In addition voice function and quality improved in all patients, post treatment.[1]

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References

Health Technology Assessments

No literature identified.

Systematic Reviews

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

1. Jeleniewska J, Niebudek-Bogusz E, Malinowski J, Morawska J, Milkowska-Dymanowska J, Pietruszewska W. Isolated severe dysphonia as a presentation of post–COVID-19 syndrome. *Diagnostics (Basel)*. 2022;12(8):29. PubMed

Appendix 1: References of Potential Interest

Note that this appendix has not been copy-edited.

The following publications were not eligible for inclusion in the main body of the report as they did not meet the WHO definition of post–COVID-19 condition. WHO defines post–COVID-19 condition as individuals experiencing symptoms of COVID-19 for at least 3 months. One systematic review and 1 randomized controlled trial studied the use of corticosteroids for patients with persisting symptoms for 4 to 12 weeks from the onset of infection. The rest of the studies investigated the use of corticosteroids in patients who had persisting symptoms for a time not specified in the abstract. A detailed summary of the clinical effectiveness and safety studies is available in Table 2.

Table 2: Summary of Relevant Clinical Effectiveness and Safety Studies

Study citation	Study design; population; post–COVID-19 criteria	Intervention and comparator(s)	Main outcome(s)	Study findings
Systematic reviews				
Asvapoositkul et. al (2022)[a]	SR with 11 studies **Population**: Patients with persistent olfactory dysfunction related to COVID-19 infection. **N = 1414**	**Intervention**: Intranasal and oral corticosteroids with OT **Comparator**: OT alone	Subjective or objective olfactory assessment (Visual Analogue score, TDI score, Identification of Sniffin Sticks test) Major and minor adverse reactions	No significant differences in olfactory scores between the corticosteroid group +olfactory training compared to olfactory training alone. After olfactory training there was a significant improvement in olfactory scores such as TDI scores.
O'Bryne et al. (2022)	SR with 2 studies **Population**: Patients with COVID-19 related olfactory disturbance persisting for ≥ 4 weeks **N = 18**	**Intervention**: Systemic corticosteroids with intranasal corticosteroid/ mucolytic/decongestant **Comparator**: No intervention	Recovery of sense of smell Disease-related QoL Serious adverse effects Change in sense of smell General QoL Prevalence of parosmia Other adverse effects (nosebleeds/bloody discharge)	No meaningful conclusions can be made.
Randomized controlled trials				
Dhooria et al. (2022)[a]	**Study design:** open-label randomized trial **Population:** Patients with symptomatic post–COVID-19 diffuse parenchymal lung abnormalities **N =** NR	**Intervention:** High-dose prednisolone **Comparator:** Low-dose 6- week prednisolone	Clinical, physiological, and radiological outcomes Health-related QoL	High dose prednisolone is not superior to the low-dose prednisolone in improving outcomes in patients with symptomatic post–COVID-19 diffuse parenchymal lung abnormalities

Study citation	Study design; population; post–COVID-19 criteria	Intervention and comparator(s)	Main outcome(s)	Study findings
Vaira et al. (2021)	**Study design**: multicentre randomized case-control study **Population**: Patients with COVID-19 related anosmia or severe hyposmia ≥ 4 weeks **N = 18**	**Intervention:** Systemic prednisone and nasal irrigation with betamethasone, ambroxol, and rinazine **Comparator:** No treatment	Olfactory function using Chemosensory Clinical Research Center *CCCRC* test scores	Patients who were treated had significantly better olfactory scores and function than controls at follow-up compared to baseline
Non-randomized studies				
Sousa et al. (2022)[a]	**Study design**: Nonrandomized study **Population:** Patients with post–COVID-19 olfactory dysfunction **N = 47**	**Intervention:** OT + Topical corticosteroid; OT + Topical corticosteroid + Vitamin B complex **Comparator:** OT alone	Subjective and objective olfactory assessments	Patients in all groups showed a significant improvement in olfactory threshold at 3-month follow-up. OT alone showed lower mean threshold improvements compared to OT with additional therapies.
Goel et al. (2021)	**Study design**: retrospective cohort study **Population**: Patients with COVID-19 symptoms 4 weeks after initial infection **N = 49**	**Intervention:** Deflazacort (systemic steroid) **Comparator:** No comparator	Occurrence of breathlessness Cough Tachypnea Hypoxia MMRC breathlessness scale Occurrence of normal chest X-ray Occurrence of normal CT thorax	Occurrence of breathlessness and cough significantly decreased. The median MMRC breathlessness significantly decreased. Patients who were tachpnoeia and hypoxia showed improvement. Occurrence of chest X-ray significantly decreased. Occurrence of abnormal CT thorax decreased.

OT = olfactory training; QoL = quality of life

[a]Time COVID-19 Symptoms Persist After Initial Infection Not Specified

Systematic Reviews

Unclear Population — Time COVID-19 Symptoms Persist After Initial Infection Not Specified

Asvapoositkul V, Samuthpongtorn J, Aeumjaturapat S, et al. Therapeutic options of post–COVID-19 related olfactory dysfunction: a systematic review and meta-analysis. *Rhinology*. 2022. PubMed

Alternative Population- Patients With Persisting COVID-19 Symptoms For Less Than 12 Weeks

O'Byrne L, Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ. Interventions for the treatment of persistent post–COVID-19 olfactory dysfunction. *Cochrane Database Syst Rev*. 2022;9(9):CD013876. PubMed

Randomized Controlled Trials

Unclear Population — Time COVID-19 Symptoms Persist After Initial Infection Not Specified

Dhooria S, Chaudhary S, Sehgal IS, et al. High-dose versus low-dose prednisolone in symptomatic patients with post–COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial). *Eur Respir J.* 2022;59(2):02. PubMed

Alternative Population — Patients With Persisting COVID-19 Symptoms For Less Than 12 Weeks

Vaira LA, Hopkins C, Petrocelli M, et al. Efficacy of corticosteroid therapy in the treatment of long-lasting olfactory disorders in COVID-19 patients. *Rhinology*. 2021;59(1):21-25. PubMed

Non-Randomized Studies

Unclear Population — Time COVID-19 Symptoms Persist After Initial Infection Not Specified

Sousa FA, Machado AS, da Costa JC, et al. Tailored approach for persistent olfactory dysfunction after SARS-CoV-2 infection: a pilot study. *Ann Otol Rhinol Laryngol*. 2022:34894221111093. PubMed

Goel N, Goyal N, Nagaraja R, Kumar R. Systemic corticosteroids for management of 'long-COVID': an evaluation after 3 months of treatment. *Monaldi Archives for Chest Disease*. 2021;92(2):03. PubMed

Zubairi ABS, Shaikh A, Zubair SM, Ali AS, Awan S, Irfan M. Persistence of post–COVID lung parenchymal abnormalities during the three-month follow-up. *Adv Respir Med*. 2021;89(5):477-483. PubMed

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Appendix 2: Additional References

Previous CADTH Reports

Post–COVID-19 condition: a summary of existing guidelines. Ottawa (ON): CADTH; 2022: https://www.cadth.ca/post–COVID-19-condition-summary-existing-guidelines. Accessed 2022 Oct 24.

Post–COVID-19 condition treatment and management: rapid living scoping review. Ottawa (ON): CADTH; 2022: https://www.cadth.ca/post–COVID-19-condition-treatment-and-management-rapid-living-scoping-review. Accessed 2022 Oct 24.

An overview of post‑COVID-19 condition (long COVID). Ottawa (ON): CADTH; 2021https://www.cadth.ca/overview-post–COVID-19-condition-long-covid. Accessed 2022 Oct 24.

Case Series

Cooper S, Tobar A, Konen O, et al. Long COVID-19 liver manifestation in children. *J Pediatr Gastroenterol Nutr*. 2022;75(3):244-251. PubMed

Metyas S, Chen C, Aung T, Ballester A, Cheav S. Rheumatologic manifestations of post SARS-CoV-2 infection: a case series. *Curr Rheumatol Rev*. 2022;18(4):346-351. PubMed

Carubbi F, Alunno A, Leone S, et al. Pericarditis after SARS-CoV-2 infection: another pebble in the mosaic of long COVID? *Viruses*. 2021;13(10). PubMed

Review Articles

Carson E, Hemenway AN. A scoping review of pharmacological management of postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection in 2021. *Am J Ther*. 2022;29(3):e305-e321. PubMed

Appendix 3: Ongoing Clinical Trials

Table 3: Registered Clinical Trials of Corticosteroids for People with Post–COVID-19

Trial name (registration number); link; country	Population; age	Intervention	Comparator	Study design	Trial phase	Number of expected participants	Expected trial primary completion cate
Randomized, Open, Parallel, Single-centre, Non-inferiority Clinical Trial, With an Active Control Group, Comparing Two Oral Prednisone Regimens With the Aim of Optimizing the Therapeutic Strategy in Patients With Organizing Pneumonia Post–COVID-19 Infection- NORCOVID (NCT04534478); Oral Prednisone Regimens to Optimize the Therapeutic Strategy in Patients With Organizing Pneumonia Post–COVID-19 - Full Text View - ClinicalTrials.gov; Spain	Patients with post COVID-19 Organized Pneumonia Diagnosis	Prednisone 0.75mg / Kg / d 4 weeks; 0.5mg / Kg / d 4 weeks; 20mg / d 4 weeks; 10mg / d 6 weeks; 5mg / d 6 weeks (6m)	Prednisone 0.5mg / Kg / d 3 weeks, 20mg / day 3 weeks; 15mg / day 2 weeks; 10mg / day 2 weeks, 5mg / day 2 weeks and discontinue	Open, parallel single-centre non-inferiority RCT	Phase IV	120	December 15, 2021[a]
Phase-II Randomized Clinical Trial to Evaluate the Effect of Pirfenidone Compared to Placebo in Post–COVID19 Pulmonary Fibrosis- FIBRO-COVID (NCT04607928); Pirfenidone Compared to Placebo in Post–COVID19 Pulmonary Fibrosis COVID-19 - Full Text View - ClinicalTrials.gov; Spain	Patients with fibrotic lung sequelae after recovery from acute phase severe COVID-19 pneumonia; 18 years or older	Pirfenidone	Placebo	Double-blind RCT	Phase II	148	June 30 2022

Trial name (registration number); link; country	Population; age	Intervention	Comparator	Study design	Trial phase	Number of expected participants	Expected trial primary completion cate
Short-term Low Dose Corticosteroids for Management of Post Covid-19 Pulmonary Fibrosis (NCT04551781); Short Term Low Dose Corticosteroids for Management of Post covid19 Pulmonary Fibrosis - Full Text View - ClinicalTrials.gov; Egypt	Patients with persistent radiological changes in chest CT; 18 years or older	Prednisone	Control	RCT	NR	450	July 30, 2022[a]
Comparative study of the efficacy of olfactory training and intranasal corticosteroids in post–COVID-19 olfactory dysfunction: A randomized controlled trial (TCTR20211005002); ::: TCTR : Thai Clinical Trials Registry :::; Thailand	Patients with persistent olfactory dysfunction; 18 years or older	Mometasone furoate intranasal corticosteroid	Olfactory training	RCT	Phase II/III	36	August 31, 2022
Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2 (NCT05350774); Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2 - Full Text View - ClinicalTrials.gov; US	Patients who had COVID-19 at least 6 weeks ago and have ongoing neurologic symptoms such as dizziness, trouble walking, or problems with strength; 18 years or older	IV methylprednisolone	IV immunoglobulin and IV normal saline	RCT	Phase II	60	December 30, 2022

Trial name (registration number); link; country	Population; age	Intervention	Comparator	Study design	Trial phase	Number of expected participants	Expected trial primary completion cate
The Potential Therapeutic Effect of Vitamin D Nasal Drops in the Treatment of Post COVID-19 Parosmia (NCT05269017); Vitamin D Nasal Drops in Post COVID-19 Parosmia - Full Text View- ClinicalTrials.gov; Egypt	Patients with post COVID parosmia; 18 years or older	Budesonide nasal spray	Vitamin D3 nasal drops	RCT	Phase II	60	March 2023
COCOS trial **COrticosteroids for COVID-19-induced loss of Smell–protocol for a single-centred, double-blind, randomized, placebo-controlled trial (N L9635.);** e060416.full.pdf (bmj.com); Netherlands	Patients with persistent smell loss within 12 weeks of COVID-19 diagnosis; 18 years or older	Prednisolone	Placebo	Single-centre placebo-controlled trial	NR	116	NR
Post COVID-19 Anosmia treatments (UMIN000043537); UMIN Clinical Trials Registry; Egypt	Patients with post–COVID-19 smell dysfunction; 45 to 60 years old	Local corticosteroids nasal spray	Antihistamines nasal spray, normal saline, combination of local corticosteroids and antihistamines nasal spray	Double-blind parallel RCT	NR	200	NR

COVID-19 = Coronavirus disease 2019; NR = Not reported; RCT = randomized controlled trial.

[a]Final data collection date for primary outcome measure.

Note that this table has not been copy-edited.