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Medication use 3-6 months after acute covid-19 and fatigue

Results from the P4O2 COVID-19 study

Master thesis

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Samenvatting

Achtergrond

Na een doorgemaakte corona-besmetting kunnen sommige personen langdurige klachten aanhouden. Dat wordt long COVID genoemd. De klachten manifesteren zich als acute COVID-symptomen of ontwikkeling van nieuwe symptomen. Volgens onderzoek kan long COVID een negatieve invloed hebben op de kwaliteit van leven van patiënten, met fysieke beperkingen en verstoring van de geestelijke gezondheid tot gevolg. De pathofysiologie van long COVID is momenteel niet volledig begrepen; daarom is er een gebrek aan behandelingsopties voor deze patiënten. Tot op heden is onderzoek dat de relatie tussen medicatiegebruik en long COVID bestudeert schaars. Het doel van deze studie is het medicatiegebruik van long COVID-patiënten in kaart brengen en de impact van medicatiegebruik op vermoeidheid te evalueren.

Methode

De gegevens die in dit onderzoek zijn gebruikt, zijn afkomstig uit het onderzoek Precision Medicine for more Oxygen - COVID-19 (P4O2 COVID-19). Deze studie omvat 95 deelnemers in de leeftijd van 40-65 jaar, geworven vanuit COVID-19-poliklinieken in vijf verschillende ziekenhuizen in Nederland. Om deze studie uit te voeren verzamelden we sociodemografische gegevens, medicatiegegevens 3-6 maanden na corona-besmetting en vragenlijstgegevens over de ernst van de vermoeidheid. Het medicatiegebruik van deelnemers is middels het ATC (Anatomical Therapeutic Chemical) classificatiesysteem systematisch in kaart gebracht, waarna een beschrijvende statistische analyse is toegepast. De relatie tussen medicatiegebruik en de ernst van de vermoeidheid is statistisch door middel van logistische regressieanalyse onderzocht.

Resultaten

In totaal namen 95 deelnemers tussen de 40 en 65 jaar deel aan deze studie. De meeste deelnemers waren obees, ex-rokers en hadden een milde corona-besmetting. Door de data te analyseren met het programma R Studio is een overzicht van het medicatiegebruik verkregen. Medicijnen gerelateerd aan het spijsverteringskanaal en metabolisme werden het meest gebruikt en vertegenwoordigden ongeveer 61% van de populatie. Ongeveer 41% van de deelnemers gebruikte corticosteroïden en 26% gebruikte anti-infectiemiddelen 3-6 maanden na besmetting. Van alle deelnemers gebruikte ongeveer 38% analgetica en medicijnen gerelateerd aan het ademhalingssysteem. 31 van de 95 deelnemers gebruikten geen medicatie. Op basis van de statische analyse bleek dat deelnemers die medicijnen gebruikten voor constipatie, diabetes, antitrombotische- en antibacteriële middelen, een statistisch significante vermindering van de ernst van de vermoeidheid hadden.

Conclusie

Onze resultaten suggereren dat medicijnen tegen constipatie, diabetes, antitrombotische- en antibacteriële middelen die 3-6 maanden na een doorgemaakte corona-besmetting door long COVID patiënten worden gebruikt, de ernst van vermoeidheid verminderen.

Trefwoorden

Long COVID; vermoeidheid, medicatie-evaluatie; ATC-classificatie

Abstract

Background

After recovery from acute SARS-CoV-2 infection, some individuals experience long COVID that manifests as prolonged acute COVID symptoms or the development of new symptoms. According to research, long COVID can negatively affect patients quality of life, causing physical limitations and mental health disruption. The underlying biological mechanism of long COVID is currently not fully understood; hence there is a lack of consensus on diagnosis and treatment options. To date, research is scarce describing the correlation between medication use and long COVID. In this study, we aimed to identify the medication use of long COVID patients and evaluate the impact of medication use on fatigue.

Methods

Data used in this study is collected from the Precision Medicine for more Oxygen - COVID-19 (P4O2 COVID-19) study. P4O2 includes 95 participants aged between 40-65 years, recruited from COVID-19 outpatient clinics in five different hospitals in the Netherlands. We collected sociodemographic data, medication data at 3-6 months after acute COVID-19 infection, and fatigue severity scale questionnaire data to perform our analysis. To identify the medication use of participants systematically, ATC (Anatomical Therapeutic Chemical) classification system is used to code the medication, after which descriptive analysis is conducted. The correlation between medication use and fatigue severity is examined by performing logistic regression analysis.

Results

A total of 95 participants aged between 40-65 were included in this study. Most participants were obese, ex-smokers, and had a mild SARS-CoV-2 infection. An overview of medication use was obtained by analyzing the data using R Studio. Medications related to the alimentary tract and metabolism were most commonly used and represented about 61% of the sample. Notably, about 41% used corticosteroids and 26% used anti-infective agents 3-6 months after infection. Of all participants, approximately 38% used analgesics and medications related to the respiratory system. 31 of 95 did not use any medication. Based on the statical analysis, it was found that

participants using medications for constipation, diabetes, antithrombotic agents, and antibacterials for systemic use had statistically significant reductions in fatigue severity.

Conclusion

These results suggest that medications for constipation, diabetes, antithrombotic agents, and antibacterials used by long covid patients 3-6 months after SARS-CoV-2 infection reduce fatigue severity.

Keywords

Long COVID; fatigue, medication evaluation; ATC classification

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been confirmed in approximately 754 million people worldwide, with an estimated 6.8 million deaths [1]. COVID-19 can manifest in a wide range of symptoms, including asymptomatic, mild, severe and even death. The most common symptoms during an acute infection are fever, cough, dyspnea, muscle pain, headache, sore throat, chest pain, and abdominal pain [2]. The majority of affected individuals develop a mild illness that will resolve spontaneously. However, some will develop serious complications resulting in severe SARS-CoV-2 infection requiring hospitalization, particularly older adults and patients with underlying health conditions (e.g., diabetes mellitus, obesity, and serious cardiac conditions).

Some individuals exhibit prolonged acute COVID symptoms or develop new symptoms after microbiological recovery from the initial SARS-CoV-2 infection. Long COVID or Post-Acute Sequelae of SARS-CoV-2 (PASC) is characterized by persistent or newly developed symptoms typically within three months after the initial infection [3]. A broad range of symptoms describe long COVID; the most common symptoms include fatigue, dyspnea, and cognitive dysfunction [4]. Long COVID symptoms are likely to negatively impact everyday functioning by affecting multiple biological systems, e.g., respiratory, cardiovascular, neurological, or musculoskeletal [5]. The severity of the symptoms varies between individuals, but they usually ameliorate over time. However, research has shown that long COVID negatively affects patients quality of life by causing physical limitations and mental health disruption [6]. Moreover, long COVID may negatively impact patients' social lives by causing inability to return to work, dysfunctional social relations, and social stigma [7,8]. The underlying biological mechanisms behind long COVID are mostly hypothetical and not fully understood yet [9]. Consequently, there is currently a lack of consensus on diagnosis and treatment options. Continued research is needed to provide better care and support for those affected by long COVID.

To our knowledge, only a few works in the literature describe the correlation between medication use during acute SARS-CoV-2 infection and the development of long COVID. It is reported that the use of immunosuppressants such as glucocorticoids during an acute SARS-CoV-2 infection may prolong the recovery of patients [10]. In another study, it's suggested that the use of certain antiviral medications such as Remdesivir and monoclonal antibodies will reduce the risk of hospitalization and improve outcomes in some patients with COVID-19 [11]. To fill this literature gap, additional studies to understand the impact of medications on long COVID are required. Furthermore, the high unmet medical need and the demand of long COVID patients for treating their multiple symptoms can drive healthcare providers to challenging conditions. Currently, the general management of long COVID includes supportive care whereby outstanding symptoms such as pain, inflammation, or insomnia are considered. Therefore, the goal of the treatment is to relieve symptoms and improve patients ability to function in daily life. However, there are currently no registered medications that can treat the underlying long COVID cause [12]. Since drug development is a time-consuming process, the most useful strategy is to investigate whether existing medications can benefit the treatment of long COVID. In this study, we aimed to evaluate the medication usage of long COVID patients and evaluate the impact of medications on fatigue. We analyzed data from P4O2 COVID-19 cohort to examine whether there are differences in the severity of long COVID (fatigue) regarding medication usage.

Methods

Study design

P4O2 (Precision Medicine for more Oxygen) is a multicenter prospective observational cohort study. The aim of P4O2 is to define the risk for developing lung disease and to find (bio)markers that predict the development of lung disease early on in the process. For the P4O2 COVID-19 cohort, participants were recruited from post-COVID outpatient clinics from five different hospitals within The Netherlands, including Amsterdam University Medical Centre (Amsterdam UMC, location AMC and VUmc), Leiden University Medical Centre (LUMC), VieCurie medical centre and Spaarne Gasthuis. All participants provided informed consent before collecting any data. P4O2 was approved by the medical ethical review board of the Amsterdam University Medical Centers. Participants were invited for two study visits at the hospital: 3-6 months after the SARS-CoV-2 infection and 9-12 months after visit 1.

Participants

The inclusion criteria for the study population were as follows: 1) participants were aged between 40 and 65 years, 2) confirmed SARS-CoV-2 infection (real-time polymerase chain reaction (qPCR), serology tests or a CO-RADS score 4/5), 3) a post-COVID outpatient clinic visit appointment, 3) the ability to provide informed consent, 4) access to internet and understanding of the Dutch language.

Enrollment of study participants occurred between May 2021 and August 2022. The second study visits are taking place and will end in June 2023.

Patients were excluded from participation when they were unable to provide informed consent, had a history or suspicion of inability to cooperate adequately, participated in any other study involving investigational or marketed products concomitantly or within four weeks prior to entry into the study or during the study, investigator's uncertainty about the willingness or ability of the patient to comply with the protocol requirements, and patients with a terminal illness.

Data collection

All study participants underwent the following study procedures: clinical evaluation, pulmonary function tests, questionnaires, and assessment of pre- and post-COVID-19 health status.
During the participants' visit, medication history and sociodemographic data, including age, gender, BMI, ethnicity, and comorbidities, were collected. Patients were asked to fill out questionnaires describing their health characteristics, including Fatigue Severity Scale (FSS) [13], among others. The assessment of the pre-and post-COVID-19 health status of participants was also conducted.

Medication use

To describe medication use systematically, the WHO ATC (Anatomical Therapeutic Chemical) classification is used to code the medication during study visit 1 [14]. This classification system groups the active medical substances according to the organ or system on which they act and also according to their therapeutic, pharmacologic, and chemical characteristics. Each medication is linked to corresponding ATC codes and categorized according to the 14 main ATC-classes; alimentary tract and metabolism, blood and blood forming organs, cardiovascular system, dermatologicals, genito urinary system and sex hormones, systemic hormonal preparations, excl. sex hormones and insulins, anti-infective for systemic use, antineoplastic and immunomodulating agents, musculo-skeletal system, nervous system, antiparasitic products, insecticides and repellents, sensory organs, and various resources.

Outcomes

The study outcome included the FSS score, as fatigue is the most commonly reported long COVID symptom. The FSS is a validated questionnaire that measures fatigue effects on daily functioning in patients. A score of 4 shows that fatigue influences the daily functioning of subjects. We have therefore divided the FSS scores into two categories for our analyses: the non-problematic fatigue (<4) and the problematic fatigue (≥ 4) category.

Statistical analysis

Characteristics of patients were described using mean ± standard deviation for continuous variables and frequency and percentage for categorical variables. The medication use overview is shown in Table 2.

Logistic regression models were fitted to the outcome according to classes of the ATC classification system of interest. Odds ratio (OR) and confidence intervals (95%CI) were calculated. A p-value below 0.05 was considered statistically significant. All models were adjusted for differences in baseline characteristics between groups, including age (continuous), sex (categorical), BMI (continuous), and the number of comorbidities (continuous). All analyses were conducted using R software and R Studio software version 2022.12.0+353.

Results

We included 95 participants of the P4O2 COVID-19 during study visit one. The demographic characteristics of participants are shown in table 1. The mean age of the participants was 54 years (standard deviation 6 years), 48 (50.33%) were men and 76.1% (N = 67) were of Caucasian ethnicity. More than half of the study population were obese (52.1%, N = 49), and 37.2% (N = 35) were overweight. The majority of the participants (54.3%, N = 51) were former smokers, and 4.3% (N = 4) were current smokers. According to the WHO classification, most participants (N = 59/95) had mild SARS-CoV-2 infection, whereas 27,4% (N = 26) had a severe infection. Overall, the majority (N = 85/95) were hospitalized for acute SARS-CoV-2 infection of which a third (30,5%, N = 29) were admitted to the ICU. A third of the participants (31,6%, N = 30) were unvaccinated, 26,3% (N = 25) had a single vaccination dose and 42.1% (N = 40) had 2 or more vaccination doses.

Table 1. Demographic and clinical characteristics of study population.

Characteristics	**No. (N=95)**
Age (years) Female Male	54,14 ± 6,18 47 (49.47%) 48 (50.53%)
BMI	
Healthy weight (18-25 kg/m2) Overweight (25-30 kg/m2) Obese (>30 kg/m2)	10/94 (10.6%) 35/94 (37.2%) 49/94 (52.1%)
Ethnicity	
Caucasian African Asian Latin-American Other	67/88 (76.1%) 7/88 (8.0%) 5/88 (5.7%) 3/88 (3.4%) 6/88 (6.8%)
Level of education	

Secondary education	18/78 (23.1%)
Vocational education	33/78 (42.3%)
Bachelor	19/78 (24.4%)
Master	8/78 (10.3%)
Smoking status	
Current smoker	4/94 (4.3%)
Ex-smoker	51/94 (54.3%)
Never smoker	39/94 (41.5%)
WHO disease severity classification	
Ambulatory	10/95 (10.5%)
Mild	59/95 (62.1%)
Severe	26/95 (27.4%)
Hospital admission for acute COVID-19	
Hospitalized	85 (89.5%)
Hospitalized in ICU	29 (30.5%)
COVID-19 vaccination status	
No	30 (31.6%)
Yes, 1 dose	25 (26.3%)
Yes, 2 or more doses	40 (42.1%)

BMI = body mass index. In the case of missing data, the number of patients for whom data is available will be indicated. Continues variables are described as mean ± standard deviation and categorical as N (% of N). N = number of participants.

Medication use of the study population at 3-6 months after SARS-CoV-2 infection was categorized according to ATC classification. Table 2 demonstrates the anatomical groups and pharmacological/ therapeutic subgroups that correspond to the reported medications. Of all participants, 32.6% (N = 31) did not use any medication. Medications for the alimentary tract and metabolism were most commonly used and represented 61.1% (N = 58) of the sample, whereas vitamins and mineral supplements represented 12.6% (N = 12) and 25.3% (N = 24) respectively. Notably, almost half of the participants (49.5%, N = 47) used medications for blood and blood forming organs. 41.1% (N = 39) of the participants used medication related to the cardiovascular system. In the dermatologicals, genito urinary system and sex hormones, antiparasitic products, insecticides and repellents groups, we found no significant difference between users and nonusers. In the category of systemic hormonal preparations (excl. sex hormones and insulins) we found that 41.1% (N = 39) use corticosteroids. We also found that 26.3% (N = 25) of the participants used anti-infective for systemic use. Immunosuppressants were taken by approximately a quarter of the participants (24.2%, N = 23). Medicines affecting nervous system represented 51.6% (N = 49), of which 37.9% (N = 36) were analgesics and 20% (N = 19) were psycholeptics. Among the respiratory system agents, the use of drugs for obstructive airway diseases was the highest (24.2%, N = 23) by the participants. This was followed by cough and cold preparation agents (17.9%, N = 17). Only 8.4% (N = 8) of the study population were found to use medications related to sensory organs. Of all, 20% (N = 19) used medications for various indications.

Table 2. ATC classification of medication used by the study population at 3-6 months after SARS-CoV-2 infection.

Code	Class of medication	No. (N=95)	%
A	**Alimentary tract and metabolism**	**58/95**	**61.1%**
A02	Drugs for acid-related disorders	28/95	29.5%
A04	Antiemetics and antinauseants	3/95	3.2%
A06	Drugs for constipation	24/95	25.3%
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	15/95	15.8%
A10	Drugs used in diabetes	28/95	29.5%
A11	Vitamins	12/95	12.6%
A12	Mineral supplements	24/95	25.3%
B	**Blood and blood forming organs**	**47/95**	**49.5%**
B01	Antithrombotic agents	38/95	40.0%
B02	Blood substitutes and perfusion solutions	19/95	20.0%
C	**Cardiovascular system**	**39/95**	**41.1%**
C01	Cardiac therapy	13/95	13.7%
C02	Antihypertensives	8/95	8.4%
C03	Diuretics	24/95	25.3%
C07	Beta blocking agents	11/95	11.6%
C08	Calcium blocking agents	10/95	10.5%
C09	Agents acting on the renin-angiotensin system	11/95	11.6%
C10	Lipid modifying agents	12/95	12.6%
D	**Dermatologicals**	**4/95**	**4.2%**
G	**Genito urinary system and sex hormones**	**1/95**	**1.1%**
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**42/95**	**44.2%**
H02	Corticosteroids for systemic use	39/95	41.1%
H03	Thyroid therapy	3/95	3.2%
J	**Anti-infective for systemic use**	**25/95**	**26.3%**
J01	Antibacterials for systemic use	20/95	21.1%
J02	Antimycotics for systemic use	4/95	4.2%
J05	Antivirals for systemic use	4/95	4.2%
J06	Immune sera and immunoglobulins	4/95	4.2%
L	**Antineoplastic and immunomodulating agents**	**24/95**	**25,3%**
L04	Immunosuppressants	23/95	24.2%
M	**Musculo-skeletal system**	**21/95**	**22.1%**
M01	Anti-inflammatory and anti-rheumatic agents	9/95	9.5%
M03	Muscle relaxants	7/95	7.4%
N	**Nervous system**	**49/95**	**51.6%**
N01	Anesthetics	12/95	12.6%
N02	Analgesics	36/95	37.9%
N03	Anti-epileptics	3/95	3.2%
N05	Psycholeptics	19/95	20.0%
N06	Psychoanaleptics	7/95	7.4%
P	**Antiparasitic products, insecticides and repellents**	**3/95**	**3.2%**
R	**Respiratory system**	**36/95**	**37.9%**
R01	Nasal preparations	3/95	3.2%
R03	Drugs for obstructive airway diseases	23/95	24.2%
R05	Cough and cold preparations	17/95	17.9%
R06	Antihistamines for systemic use	7/95	7.4%

S	**Sensory organs**	**8/95**	**8.4%**
S01	Opthalmologicals	7/95	7.4%
V	**Various**	**19/95**	20.0%
V03	All other therapeutic products	4/95	4.2%
V06	General nutrients	12/95	12.6%
V08	Contrast media	12/95	12.6%
	No medication use at 3-6 months after SARS-CoV-2 infection	31/95	32.6%

Bold values are ATC classification of anatomical groups. Other values are ATC classification of pharmacological/therapeutic subgroups. Results are presented as N, % of N. N = number of participants.

Table 3 shows the association between medication use and fatigue 3-6 months after SARS-CoV-2 infection. For this analysis we selected medication groups that were applicable for at least 20% of the study population. Our results demonstrated that participants who took medication from the selected medication groups had a lower FSS score than participants who did not. Both the adjusted and unadjusted OR showed a statistically significant reduction in FSS score for medications used for constipation 0.26 (95%CI: 0.07-0.91), medications used in diabetes 0.23 (95%CI: 0.06-0.81), antithrombotic agents 0.30 (95%CI: 0.10-0.90), and antibacterials for systemic use 0.12 (95%CI: 0.02-0.55).

Table 3. Association between medication use and fatigue 3-6 months after SARS-CoV-2 infection.

Code	Class of medication	Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
A06	Drugs for constipation	0.32 (0.10-1.02)	**0.049**	0.26 (0.07-0.91)	**0.035**
A10	Drugs used in diabetes	0.29 (0.09-0.89)	**0.029**	0.23 (0.06-0.81)	**0.023**
A12	Mineral supplements	0.45 (0.14-1.49)	0.174	0.29 (0.07-1.11)	0.068
B01	Antithrombotic agents	0.32 (0.11-0.91)	**0.032**	0.30 (0.10-0.90)	**0.032**
C03	Diuretics	0.34 (0.10-1.19)	0.082	0.30 (0.07-1.18)	0.082
H02	Corticosteroids for systemic use	0.80 (0.27-2.55)	0.691	0.81 (0.26-2.67)	0.713
J01	Antibacterials for systemic use	0.16 (0.04-0.63)	**0.010**	0.12 (0.02-0.55)	**0.008**
L04	Immunosuppressants	0.38 (0.11-1.43)	0.136	0.31 (0.08-1.27)	0.098
N02	Analgesics	0.54 (0.19-1.51)	0.233	0.51 (0.17-1.51)	0.217
N05	Psycholeptics	0.71 (0.23-2.50)	0.572	0.64 (0.18-2.41)	0.491
R03	Drugs for obstructive airway diseases	0.86 (0.28-2.99)	0.802	0.70 (0.21-2.59)	0.574

Bold values are statistically significant. FSS scores dichotomized using 4 as a cutoff value (<4 non problematic fatigue, ≥4 problematic fatigue). Model adjusted for: age, gender, BMI and number of comorbidies. Bold values are statistically significant.

Discussion

The P4O2 COVID-19 study aims to define the risk for developing lung disease and to find (bio)markers that predict the development of lung disease early on in the process. It includes 95 participants recruited from post COVID outpatient clinics from five different hospitals in the Netherlands. As part of the study procedure, long COVID symptoms of participants were investigated and sociodemographic and clinical data were collected. In the present study we used data collected by the P4O2 COVID-19 study to evaluate the medication usage of participants 3-6 months after SARS-CoV-2 infection and to evaluate the impact of medications on fatigue.

Our results demonstrated that many participants used corticosteroids (41.1%, N = 39) and anti-infective agents (26.3%, N = 25) 3-6 months after SARS-CoV-2 infection. To the best of our knowledge, this study is the first to describe the medication usage of long COVID patients 3-6 months after SARS-CoV-2 infection. We think that antibacterials are excessively prescribed to this group to compensate for the immune system dysregulation caused by COVID-19 [15]. Further studies are needed to investigate the patern of medication use in long COVID patients. In addition, analgesics and medications related to the respiratory system were frequently used by the participants (37.9%, N = 36). This is expected given that long COVID patients often experience pain and respiratory problems [16]. As mentioned before, there are currently no medications approved for the treatment of long COVID symptoms. Therefore, the safety and effectiveness of medications need to be further evaluated [17].

Furthermore, our results demonstrated that participants taking corticosteroids had a lower FSS score than patients who did not (adjusted OR 0.81, 95%CI: 0.26-2.67). Many studies have studied and analyzed the occurrence of fatigue in long COVID-19 patients. In a study conducted in India by Goel et al., it was found that corticosteroids accelerate the recovery from long COVID symptoms [18]. This result is in line with our findings. Our results revealed that the use of medications for constipation, diabetes, antithrombotics, and antibacterials was significantly associated with a reduction in FSS scores. This suggests that medication use between participants may contribute to the variation in FSS scores between participants.

Additionally, previous research investigated the effect of dietary l-carnitine supplementation on fatigue [19]. The trimethylated amino acid L-carnitine, which shares structural similarities with choline, is required as a cofactor to transform long-chain free fatty acids into acylcarnitine and transport them to the mitochondrial matrix. The researchers suggested that intake of those supplements may decrease fatigue in long COVID patients. Moreover, in a meta analysis from China by Li et al., the efficacy and safety of Lianhua Qingwen (Chinese herb) combined with Western medicine for the treatment of patients with COVID-19 were evaluated [20]. Researchers found a positive effect of Lianhuaqingwen capsules in reducing long COVID symptoms.

The strength of this study is that this research is the first to investigate the effect of medication use on fatigue. Besides that, fatigue severity is measured using a standardized and validated questionnaire (Fatigue Severity Scale questionnaire). The data was corrected using standardized protocols that added validity to our results. Another strength was that participants were recruited from five different hospitals in the Netherlands. The difference in geographical locations of the hospitals allowed for a heterogeneous sample.

This study has potential limitations. The first limitation is the absence of a comparison group, which makes it difficult to determine if the observed effects are truly caused by the intervention (ATC codes). Another limitation of the present study is that we were unable to collect information on the duration of therapy or indications for medications, which could have impacted the results and should be considered when interpreting the findings. Moreover, the ATC classification system is used to identify medication use systematically. Although widely accepted, this method suffers from certain limitations. For instance, medications with multiple indications are assigned to just one ATC code, which prevents correctly grouping them into primary and subgroups that suit the individual patient.

In spite of these limitations, the current study provides a valuable evidence on the impact of medication usage on fatigue severity. It would be beneficial to conduct more research on this topic with a larger study population and a comparison group. Moreover, this study can be extended with data from study visit 2 to examine the long-term impact of medication on fatigue severity. Additionally, It would be beneficial look at the medication use related to the respiratory system and the therapy duration. According to the Amsterdam UMC COVID-19 respiratory therapy protocol, salbutamol and ipratropium can be prescribed in case of dyspnea. This study included participants having asthma and/or COPD as co-morbidities. However, we found that some patients were still using salbutamol. Due to the lack of information about the start of the therapy we considered medications related to the respiratory system a whole group. This is also the case for medications for other chronic disorders. While evaluating the effect of medication use on long COVID symptoms, the present study acknowledges the limitation of not differentiating between medications prescribed for symptom relief and those prescribed for other medical indications. This lack of distinction may have implications for the interpretation of study results and should be considered in future research. Additionally, the study recommends that therapy duration be taken into account to avoid potential complications or adverse effects from prolonged medication use.

Conclusion

Based on our study, which specifically investigated the impact of medication use on long COVID symptoms, it can be concluded that medications for constipation, diabetes, antithrombotic agents, and antibacterials may be effective in reducing fatigue levels in long COVID patients. These

medications may have a positive impact on the quality of life for long COVID patients and help them to better manage their daily activities.

In conclusion, our study provides valuable insight into the most common medications used by long COVID patients and the potential impact of medication therapy on fatigue. Nevertheless, further research is needed to investigate the optimal use and duration of medication therapy for long COVID patients. By taking into account the study limitations, clinicians can use our findings to develop more effective and personalized treatment regimens for long COVID patients, which may ultimately lead to improved clinical outcomes and quality of life.

References

1. World Health Organization. (n.d.). Who coronavirus (COVID-19) dashboard. World Health Organization. Retrieved February 5, 2023, from https://covid19.who.int/
2. Weng, L.-M., Su, X., & Wang, X.-Q. (2021). Pain symptoms in patients with coronavirus disease (COVID-19): A literature review. Journal of Pain Research, Volume 14, 147–159. https://doi.org/10.2147/jpr.s269206
3. Long covid. RIVM. (n.d.). Retrieved February 5, 2023, from https://www.rivm.nl/en/coronavirus-covid-19/long-covid
4. World Health Organization. (n.d.). Post covid-19 condition (long covid). World Health Organization. Retrieved February 5, 2023, from https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition
5. Notarte, K. I., Catahay, J. A., Velasco, J. V., Pastrana, A., Ver, A. T., Pangilinan, F. C., Peligro, P. J., Casimiro, M., Guerrero, J. J., Gellaco, M. M., Lippi, G., Henry, B. M., & Fernández-de-las-Peñas, C. (2022). Impact of covid-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. EClinicalMedicine, 53, 101624. https://doi.org/10.1016/j.eclinm.2022.101624
6. Smith, P., Charafeddine, R., Drieskens, S., Pauw, R. D., Ridder , K. D., Demarest, S., & Cauteren, D. van. (n.d.). COVIMPACT studie - COVID-19 infectie en de lichamelijke, geestelijke en sociale gevolgen op lange termijn : resultaten van 3 en 6 maanden opvolging na infectie. https://doi.org/https://doi.org/10.25608/pcm4-w474
7. Aghaei, A., Zhang, R., Taylor, S., Tam, C.-C., Yang, C.-H., Li, X., & Qiao, S. (2022). Social life of females with persistent COVID-19 symptoms: A qualitative study. International Journal of Environmental Research and Public Health, 19(15), 9076. https://doi.org/10.3390/ijerph19159076
8. Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long covid: Major findings, mechanisms and recommendations. Nature Reviews Microbiology. https://doi.org/10.1038/s41579-022-00846-2
9. Singh, Jaspreet and Singh, Jagandeep, COVID-19 and Its Impact on Society (April 3, 2020). Electronic Research Journal of Social Sciences and Humanities, Vol 2: Issue I, 2020 , Available at SSRN: https://ssrn.com/abstract=3567837
10. Patel, P., Ochieng, P., & Shetty, A. (2022). Another sequalae of COVID? - not so fast! C62. EXPANDING OUR INSIGHT INTO COVID-19. https://doi.org/10.1164/ajrccm-conference.2022.205.1_meetingabstracts.a4565
11. COVID-Team, F. I. I. (2023, January 17). Remdesivir alone or in combination with monoclonal antibodies as an early treatment to prevent severe COVID-19 in patients with mild/moderate

disease at high risk of progression: A single centre, real-life study. MDPI. Retrieved February 13, 2023, from https://www.mdpi.com/2076-393X/11/2/200

12. Jarrott, B., Head, R., Pringle, K. G., Lumbers, E. R., & Martin, J. H. (2022). “long covid”—a hypothesis for understanding the biological basis and pharmacological treatment strategy. Pharmacology Research & Perspectives, 10(1). https://doi.org/10.1002/prp2.911
13. Shahid, A., Wilkinson, K., Marcu, S., & Shapiro, C. M. (2011). Fatigue severity scale (FSS). STOP, THAT and One Hundred Other Sleep Scales, 167–168. https://doi.org/10.1007/978-1-4419-9893-4_35
14. Nahler, G. (2009). Anatomical Therapeutic Chemical Classification system (ATC). Dictionary of Pharmaceutical Medicine, 8–8. https://doi.org/10.1007/978-3-211-89836-9_64
15. Abdelhafiz AS, Fouad MA, Sayed-Ahmed MM, Kamel MM, Ali A, Fouda M, Khalil MA, Abdel-Moneim AS, Kamal LM. Upregulation of FOXP3 is associated with severity of hypoxia and poor outcomes in COVID-19 patients. Virology. 2021 Nov;563:74-81. doi: 10.1016/j.virol.2021.08.012. Epub 2021 Aug 28. PMID: 34478955; PMCID: PMC8397927.
16. Merikanto, I., Dauvilliers, Y., Chung, F., Wing, Y. K., De Gennaro, L., Holzinger, B., Bjorvatn, B., Morin, C. M., Penzel, T., Benedict, C., Koscec Bjelajac, A., Chan, N. Y., Espie, C. A., Hrubos-Strøm, H., Inoue, Y., Korman, M., Landtblom, A. M., Léger, D., Matsui, K., … Partinen, M. (2022). Sleep symptoms are essential features of long-covid– comparing healthy controls with covid-19 cases of different severity in the international covid sleep study (icoss-ii). Journal of Sleep Research, 32(1). https://doi.org/10.1111/jsr.13754
17. Garg, M., Maralakunte, M., Garg, S., Dhooria, S., Sehgal, I., Bhalla, A. S., Vijayvergiya, R., Grover, S., Bhatia, V., Jagia, P., Bhalla, A., Suri, V., Goyal, M., Agarwal, R., Puri, G. D., & Sandhu, M. S. (2021). The conundrum of ‘long-covid-19’: A narrative review. International Journal of General Medicine, Volume 14, 2491–2506. https://doi.org/10.2147/ijgm.s316708
18. Goel, N., Goyal, N., Nagaraja, R., & Kumar, R. (2021). Systemic corticosteroids for management of ‘long-COVID’: An evaluation after 3 months of treatment. Monaldi Archives for Chest Disease. https://doi.org/10.4081/monaldi.2021.1981
19. Vaziri-harami, R., & Delkash, P. (2022). Can l-carnitine reduce post-covid-19 fatigue? Annals of Medicine & Surgery, 73. https://doi.org/10.1016/j.amsu.2021.103145
20. Li, Y., Xiao, P., Liu, N., & Zhang, Z. (2022). Efficacy and safety of Chinese medicine Lianhua Qingwen for treating covid-19: An updated meta-analysis. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.888820