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Short Communication

Doxofylline Used as Recovery Treatment for Symptomatic Post-Acute Covid-19 Patients – Physician Questionnaire Data

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The country of Georgia reported its first case of SARS-CoV-2 infection on 26 February 2020 and first death from COVID-19 on 4 April 2020 [1]. As of 25 February 2023, there have been 1,825,598 cases, 16,965 deaths, and 1,776,548 people have recovered from COVID-19 [1]. Patients who experience persistent symptoms (e.g., dyspnea, cough, fatigue) extending beyond 3 or 4 weeks from symptom onset are described as having post-acute COVID-19 (or LONG COVID) [2, 3]. This can include people with mild disease who were not hospitalized during the acute phase [2, 3]. Some patients with post-acute COVID-19 may also show radiographic pulmonary abnormalities (e.g., fibrotic changes) and impaired pulmonary function, together with other organ system complications, which can impact their daily functioning and quality of life [2-5]. These reflect the underlying multifactorial pathophysiology and organ-specific sequelae associated with COVID-19, including pulmonary manifestations [3]. The lung function abnormalities present in post-acute COVID-19 patients include reduced diffusing capacity, restrictive abnormalities, and small airways obstruction; these appear to be related to the severity of COVID-19 and are consistent with inflammatory changes occurring in the interstitial compartment of the airways [5]. Effective treatments are needed to aid the recovery of post-acute COVID-19 patients in the community setting. Bronchodilator therapy may be beneficial and result in functional improvements in such patients [6].

Doxofylline is an oral methylxanthine with bronchodilator and anti-inflammatory activities, but with a mechanism of action that is distinct from theophylline [7]. Doxofylline is a safe, effective, and relatively inexpensive drug for the treatment of patients with asthma or COPD [8]. It significantly improves spirometric variables and symptoms including dyspnea and cough in patients with COPD [7, 8]. We hypothesized therefore that doxofylline may have a potential role in the management of patients with post-acute COVID-19.

This retrospective questionnaire study aimed to describe the real-world use of doxofylline in patients with post-acute COVID-19 in Georgia and to gather physicians' perspectives on this drug for symptom relief, improved quality of life, and faster recovery.

38 physicians identified by Eurodrug medical representatives were emailed a questionnaire (see Supplementary Material) to collect information on post-acute COVID-19 patients who had received doxofylline. The questionnaire was completed by 22 physicians (11 general practitioners, 4 infectious disease specialists, 4 tuberculosis specialists, 3 pulmonologists). Information was collected on 70 patients, but 6 patients were excluded from the analysis due to insufficient data. The remaining 64 patients were recovering from mild (20%), moderate (63%), or severe (17%) forms of COVID-19, had a mean age of 60 years, and 58% were female. Table 1 summarizes their demographic characteristics, comorbidities, COVID-19 severity, and the most common symptoms experienced during acute COVID-19 infection.

Table 1: Demographic and clinical characteristics of the COVID-19 patients

	All patients (N=64)
Age, years, mean [range]	60 [28-88]
Females, n (%)	37 (58)
Severity of COVID-19, n (%)	
Mild (non-hospitalized)	13 (20)
Moderate (hospitalized)	40 (63)
Severe/critical (hospitalized + ICU)	11 (17)
COVID-19 confirmation method, n (%)	
PCR	50 (78)
Antibodies in blood	3 (5)
Quick test	11 (17)
Comorbidities*, n (%)	
None	15 (23)
Hypertension	32 (50)
Obesity	10 (16)
Diabetes	9 (14)
Heart failure	8 (13)
Ischemic heart disease	4 (6)
COPD	4 (6)
Respiratory failure	4 (6)
Kidney disease/renal failure	4 (6)
Chronic bronchitis	2 (3)
Asthma	2 (3)
Gastritis	2 (3)
Endofasciitis	2 (3)
Other	14 (22)
COVID-19-related symptoms**, n (%)	
Fever	59 (92)
Shortness of breath	56 (88)
Muscle aches	55 (65)
Fatigue	52 (81)
Tiredness	44 (69)
Wheezing	42 (66)
Dyspnea	35 (55)
Loss of smell/taste	33 (52)
Sore throat	23 (36)
Nausea/vomiting	15 (23)
Diarrhea	13 (20)
Cough	13 (20)
Lung conditions	8 (13)
Runny nose	4 (6)
Headache	3 (5)
Emotional	3 (5)
Desaturation	2 (3)
Other	9 (14)

*Of the 49 patients with comorbidities, 30 (61%) had more than one comorbidity.
**Patients could have more than one symptom.
COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PCR, polymerase chain reaction.

Of the 64 patients, 54 (84%) received the once-daily sustained-release formulation of doxofylline (650 mg), while others received doxofylline 400 mg twice daily. The most common reasons given for prescribing doxofylline were persistent symptoms of dry cough (41%), shortness of breath/dyspnea (23%), paroxysmal cough (18%), wheezing/crackles (11%), bronchospasm (3%), productive cough (2%), and respiratory failure (2%). Doxofylline was prescribed a mean 28.3 days after COVID-19 diagnosis: 0–10 days after diagnosis for 11% of patients, 10–30 days for 44% of patients, and >30 days for 28% of patients. Average treatment duration was 13.3 days (7–30 days). All patients were reported by their physician as improved after doxofylline treatment (versus no change or deterioration) and the most frequently improved symptoms were cough, shortness of breath/dyspnea, and bronchospasm (Fig. 1). Oxygen saturation (SpO_2) levels improved from a mean of 92.4% before doxofylline treatment to 96.7% after treatment; mean improvement 4.4% (n=64). Mean respiratory rate improved from 23.9 to 19.5 breaths/min; mean improvement −4.4 breaths/min (n=26). All participating physicians recommended the use of doxofylline in patients with post-acute COVID-19 for faster recovery, symptom relief, and improved quality of life.

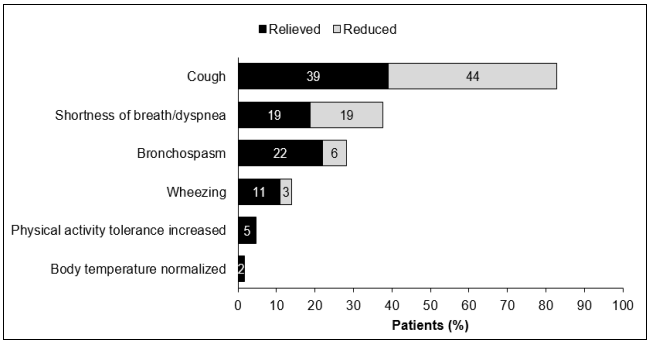

Fig 1: Physician-reported improvements in patient symptoms after doxofylline treatment (n=64)

This retrospective descriptive study was a preliminary exploration of physicians' perspectives on the effectiveness of doxofylline therapy in patients with symptomatic post-acute COVID-19. Doxofylline was used as add-on therapy to other maintenance drugs prescribed for pre-existing comorbidities. Physicians prescribed short-term treatment with doxofylline in the early post-acute phase after COVID-19 and considered that it improved common unresolved respiratory symptoms, especially cough and shortness of breath, and enhanced recovery. Notably, 20% of the doxofylline-treated patients were recovering from mild COVID-19 infection. The low proportion of patients who had been diagnosed with severe COVID-19 in this cohort possibly reflects that more severe patients probably needed more specialist treatment and rehabilitation.

Our findings give no indication of the mechanism of action of doxofylline in this setting or evidence of how the drug contributed to the physician-reported improvements in patients with post-acute COVID-19. However, doxofylline has both bronchodilator and anti-inflammatory properties [7] that may have contributed to beneficial clinical effects observed. Moreover, doxofylline is an oral medication that can be administered once daily and is safe and well tolerated in the treatment of respiratory diseases [8]. Doxofylline has been reported to inhibit lipopolysaccharide-induced inflammatory response (neutrophil infiltration) in mouse lungs and reduces leukocyte infiltration into the airways [7]. Doxofylline has also been shown to inhibit allergen-induced eosinophil infiltration into the lungs of allergic mice and to elicit a steroid-sparing effect in allergic and non-allergic murine models of lung inflammation [7, 9]. Studies in human monocytes have shown that the anti-inflammatory effects of doxofylline are independent of phosphodiesterase inhibition but are related to inhibition of protein kinase C activity [10].

Whilst the results from this pilot investigation are of interest in suggesting doxofylline may have some benefit in reducing respiratory symptoms in patients with post-acute COVID, there are several limitations of this study, including the lack of a control group, no pulmonary function test results or patient-reported outcomes including symptoms, daily functioning, and health-related quality of life. Nonetheless, we feel that the preliminary encouraging results presented may warrant further research to confirm the benefits of doxofylline in the treatment of patients with post-acute COVID-19. A placebo-controlled trial could answer some of the questions that remain, including the optimal time to initiate doxofylline, dose and duration of treatment.

Ethical Statement

This study received ethical approval from the Tbilisi State Medical University Biomedical Research Ethics Committee,

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: I. Chkhaidze, T.Maglakelidze; data collection: T.Maglakelidze; analysis and interpretation of results: I.Chkhaidze, T.Maglakelidze; draft manuscript preparation: I.Chkhaidze. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Keywords: SARS-CoV-2, Doxofylline, COVID-19, Long Covid, Questionnaire

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