Self-reported compliance with drug therapy during the first SARS-CoV-2 Italian lockdown in patients with respiratory disease

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Abstract
Background. Low compliance with drug therapy in patients with chronic respiratory diseases was a well-known issue even before the coronavirus pandemic, but its causes are not yet fully defined.
Objective. To verify the adherence to drug therapy in patients with respiratory disease during the COVID-19 pandemic.
Methods. From June to September 2020, about 700 patients of the Forlanini Hospital who had been unmonitored during the March-May 2020 lockdown in Italy received a questionnaire during the pneumological check-up based on self-reported information on compliance with therapy during lockdown.
Results. 284 out of the 418 returned questionnaires could be used in this study: 179 patients (63.0%) responded positively to the continuation of therapy, 18 (6.3%) reduced the dosage of their medication and 82 (28.9%) interrupted the therapy.
Conclusions. The low percentage of patients that reduced their drug dosage may be due to an increased awareness of drug treatment benefits, and may also be ascribed to the Government healthcare strategy during lockdown.

INTRODUCTION

In Italy, the proportion of patients with obstructive airway disease that comply with their medical treatment for 3 months is 27.3%, while those who continue the correct treatment for 6 and 12 months represent only 13.0% and 8.2% of patients, respectively; these are the lowest compliance rates of all chronic conditions [1]. Although OsMED (the institution that monitors the use of medicines in Italy) has highlighted the low adherence to drug treatment in chronic conditions, especially respiratory conditions such as asthma and COPD (chronic obstructive pulmonary disease), this problem seems not to be a priority of the healthcare community, thus negatively impacting the effectiveness of the respective drug therapy regimes [2]. The option of a single daily inhalation therapy, currently available for asthma and COPD, may lead to an improvement

in compliance, but this remains to be confirmed [3]. Treatment failure of this kind is not solely attributable to patient behavior [4], but it represents a significant risk factor for successful treatment and needs to be investigated.

In general, patient adherence to medication is considered "full adherence" if more than 80% of the prescribed drug is taken, "partial adherence" if the patient takes from 20 to 70%, and "non-adherence" if the patient takes less than 20% of the drug [5]. However, such thresholds are set arbitrarily and proved in any context [6]. In the context of routine clinical practice, assessment of adherence is usually performed with a self-report from patients about their drug therapy [7, 8]. This evaluation is totally subjective and widely influenced by doctor-patient relationship, with a possible overstatement by 20% of the true level of compliance.

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Anonymous, yet self-reporting, surveys may help mitigating such overstatement and may deliver aggregated, helpful information from samples of outpatients. This study exploited such an assessment tool to investigate the adherence to drug therapy in patients with respiratory disease presenting as outpatients after the first Italian lockdown of March-May 2020 due to the COVID-19 pandemic. Main aim of the study was to explore those patients' behavior with respect to therapy adherence during the health crisis that forced many pulmonary divisions to accept only COVID-19 patients. As in many others clinical centers, at the San Camillo-Forlanini Hospital in Rome, the pandemic and accompanying lockdown caused a drastic interruption in both pulmonary outpatient visits and diagnostic examinations for all external users with conditions other than COVID-19. In June 2020, when normal business was resumed with a backlog of nearly 700 check-ups and 400 instrumental examinations, outpatients voluntarily filled in anonymous questionnaires. This study examines compliance with drug therapy during the pandemic as a means of assessing how Government health strategies influenced patient behavior.

MATERIALS AND METHODS

During the 3-month Italian lockdown due to the COVID-19 pandemic, hospital personnel did a telephone selection of all already booked patients together with a selection of indispensable physical or instrumental examinations. With the approval of the San Camillo-Forlanini Hospital Ethical Committee (Prot. n. 888/CE Lazio 1), in June 2020, soon after the end of the lockdown, a voluntary questionnaire was offered for pneumological check-up to booked patients who could not be seen during the lockdown. Questionnaires were anonymously completed by patients, having given informed consent to participate in the research, and handed to nurses before the check-up at the ambulatory clinic at the day hospital for interstitial lung disease (ILD), asthma, COPD, respiratory sleep disorders, smoking cessation and respiratory physiopathology.

The questionnaire included personal data, as well as multiple-choice questions about respiratory disease, continued treatment, respiratory therapy interruption or reduction during lockdown, the reasons for interruption, the medications affected, presence or absence of disease recurrence, the type of the referring physician (whether general doctor, pneumologist, or other clinical professionals), tobacco abuse and the result of a SARS-CoV-2 test, if done.

The completed questionnaire data were digitized and collected in a database after two-step verification of the information. Basic non-parametric statistics tests were applied to all variables: the only continuous variable (age) was analysed using the Mann-Whitney test (with significance set at $p<0.05$); a chi-squared test ($p<0.05$, properly adjusted for multiple comparisons) was applied to all other variables. All data management and processing was performed using the R open-source integrated suite, version 4.0.4 (the R Foundation, (https://www.r-project.org).

RESULTS

In total, 418 questionnaires were collected from June 2020 to September 2020: 39 (9.3%) were not filled out; 33 (7.9%) had been completed by Stop Smoking Clinic patients with or without respiratory disease or tobacco-related symptoms; 58 (13.9%) had been answered by first access patients; and 4 (1%) had been filled out by patients that do not take any medication. The remaining 284 (67.9%) had been completed by patients with respiratory disease who were undergoing drug treatment before lockdown, and these represent the subject of this study.

Since some patients with respiratory disease are still tobacco addicted, we investigated whether there were significant differences between these patients and the smokers without respiratory conditions with respect to the main investigated variables, detailed in *Table 1*. Briefly: Stop Smoking Clinic patients (33 questionnaires/patients) were significantly younger than respondents with respiratory disease (284); there were no statistically significant differences between percentages of women and men in the two groups; the percentage of Stop Smoking Clinic patients who were still smokers (87.9%) was significantly greater than the percentage of smokers within the respiratory disease group (23.6%), the latter including a high percentage of ex-smokers (38.0%), who had stopped for more than one year, and patients who have never smoked (35.6%); out of 67 smoker patients with respiratory conditions, 35 (52.2%) had tried to stop smoking, 31 (88.6%) by themselves, i.e. without any external help, and 4 (11.4%) with the support of the Stop Smoking Clinic.

The analysis on adherence to therapy was conducted on the subgroup of patients with respiratory conditions who were undergoing drug therapy before the lockdown. 284 questionnaires were returned in total from this groups of patients; of these, 5 (1.8%) did not contain information about the follow-on of treatment; 179 (63.0%) reported a positive response to therapy; 18 (6.3%) reported a partial response to therapy; 82 (28.9%) reported the interruption of therapy. Therefore, overall adherence was around 70%, with 63.0% showing full adherence and 6.3% a reduction of drug therapy.

We then proceeded with the characterization of the three groups of patients who CONTINUED (179 patients), INTERRUPTED (82) or REDUCED (18) their treatment.

There were no significant differences between groups as for their age, as well as between women and men.

Statistically significant differences were found between the three groups with respect to tobacco addiction. In particular, among those patients who continued the therapy, there was a greater percentage of ex-smokers than never-smokers, with smokers being the smallest group. The never-smokers represented the highest proportion of those patients who interrupted therapy, followed by a similar percentage of smokers and ex-smokers. Among patients who reduced their therapy, there were no smokers; they were either ex-smokers or never-smokers.

In terms of recurrence of acute episodes of the dis-

Table 1
Main variables self-reported by Stop Smoking Clinic patients and Respiratory disease patients of the San Camillo-Forlanini Hospital, Rome, Italy

Age (years)					
	25° percentile	**Median**	**75° percentile**	*Mean*	*Standard Deviation (SD)*
Stop Smoking Clinic patients	52.8	59.0*	66.3	*59.4*	*11.4*
Respiratory disease patients	58.5	69.0*	75.0	*66.2*	*14.1*
Tobacco addiction					
	Smokers	**Ex-smokers**		**Never smoked**	**NA**
Stop Smoking Clinic patients	29 (87.9%)**	4 (12.1%)**		-	-
Respiratory disease patients	67 (23.6%)**	108 (38.0%)**		101 (35.6%)	8 (2.8%)
Adherence to drug therapy during lockdown among Respiratory disease patients (grouped according to tobacco addiction)					
	Smokers	**Ex-smokers**		**Never smoked**	**NA**
Continued	40 (22.3%)	78 (43.6%)		55 (30.7%)§	6 (3.4%)
Interrupted	24 (29.3%)	19 (23.2%)§		37 (45.1%)	2
Reduced	-	10 (55.6%)		8 (44.4%)	-
Reasons for interruption among Respiratory disease patients who interrupted or reduced the drug therapy					
	"I felt good"	**"Difficulty with GP"**		**Expired treatment plan**	**Other**
Interrupted	42 (51.2%)**	2 (2.4%)		8 (9.8%)	3 (3.7%)
Reduced	7 (38.9%)**	4 (22.2%)		2 (11.1%)	3 (16.7%)

*statistically significant difference (Mann-Whitney, p<0.05).
**statistically significant differences (chi-squared test, p<0.05).
§statistically significant different from the other two groups among the three groups of continued, interrupted and reduced drug therapy (chi-squared test, adjusted p<0.05).
NA = not available.

ease, there were no significant differences between the three groups during lockdown: in all groups the highest proportion of patients showed an absence of recurrence, although this was not statistically significant. Despite this, we noted that the absence of recurrence was most likely found among patients who continued the therapy (79.9%), slightly less in patients who interrupted the treatment (74.4%) and lower in patients who reduced the therapy (66.7%).

With respect to the reasons for interruption, examined in patients who either interrupted or reduced their drug treatment, the two groups showed significant differences in terms of the reported reasons, chosen from those proposed namely: good perception of self-assessed health ("I felt good"), difficulty in interaction with the general practitioner ("difficulty with GP"), expired treatment plans – even though the period of validity had been extended during lockdown – and other or not-reported reasons. The "I felt good" reason was the main justification for interrupting the therapy in a significantly greater proportion of patients than those reporting "difficulty with GP". With respect to an appeal to a healthcare professional during lockdown, up to 80% of questionnaires did not contain information.

Finally, although the questionnaire was self-reported, thus entailing a possible bias, we also aimed at exploring whether the type of disease or the coexistence of more than one respiratory disease correlated with adherence or with the reasons for therapy interruption (Tables 2 and 3). Greater compliance was found in patients who reported two concurrent diseases, in particular chronic bronchitis and asthma (85.7%), and COPD and emphysema (83.3%). Among patients who reported a single respiratory pathology, adherence was 79.4% for COPD, 65.8% for asthma, and 65.4% for pulmonary fibrosis; lower adherence was registered in patients with referred chronic bronchitis (53.9%), emphysema (36.4%), and bronchiectasis (28.6%). Among patients with pulmonary fibrosis, interruption of therapy occurred in 23.1% of cases and reduction in 11.5%. The most frequent reason for an interruption or reduction of therapy was "I felt good" for all pathologies, except for the group with COPD, where the prevailing reason was the reported non-renewal of the treatment plan. Finally, in groups with just one pathology, adherence showed good positive correlation with the lack of recurrence (coefficient of determination of the linear regression $R^2 = 0.62$), which is an intuitive although not obvious result in self-reported data.

DISCUSSION

We found no evidence of a reduction in the compliance with drug therapy during the first SARS-CoV-2 Italian lockdown in patients with respiratory disease. To our knowledge, neither similar studies nor previous data collected at the same clinical center (San Camillo-Forlanini Hospital in Rome, Italy) were available to compare the outcomes of the present study. We could however observe that our findings confirmed what has been published by Kaye et al., even though based on much larger cohorts than ours and on data collected through digital surveys on drug use [9]. Our conclusions are in

Table 2

Respiratory patients of the San Camillo-Forlanini Hospital, Rome, Italy, grouped by type and number of coexisting respiratory pathologies: 19 patients out of 284 did not report on this question, and thus were not included in the Table

	Pathologies		Age (years)		Sex (%)		Adherence (%)			Reasons for interruption (%)				Exacerbations (%)		Smoking (%)		
#	type	N. of patients	mean	SD	M	F	yes	no	partially	good health status	troubles with GP	expired TP	other	yes	no	smoker	former smoker	never smoked
1	Asthma	38	52.1	18.0	34.2	65.8	65.8	26.3	5.3	21.1	0.0	5.3	0.0	5.3	84.2	10.5	21.1	60.5
1	COPD	34	70.7	11.9	52.9	41.2	79.4	17.6	2.9	5.9	2.9	8.8	0.0	2.9	94.1	23.5	47.1	29.4
1	Emphysema	33	68.0	12.3	51.5	45.5	60.6	36.4	3.0	21.2	0.0	6.1	0.0	6.1	81.8	42.4	39.4	18.2
1	Chronic bronchitis	26	72.6	10.0	46.2	50.0	42.3	53.8	3.8	42.3	0.0	0.0	0.0	3.8	76.9	38.5	34.6	26.9
1	Pulmonary fibrosis	26	70.0	14.3	73.1	26.9	65.4	23.1	11.5	11.5	0.0	7.7	3.8	7.7	76.9	15.4	46.2	38.5
1	Bronchiectasis	14	67.8	12.0	21.4	78.6	50.0	28.6	21.4	21.4	7.1	7.1	14.3	14.3	64.3	14.3	21.4	64.3
1	Other	37	65.8	12.2	35.1	56.8	48.6	37.8	5.4	18.9	0.0	8.1	2.7	0.0	73.0	18.9	35.1	37.8
2	Chronic bronchitis & asthma	7	68.7	10.4	28.6	71.4	85.7	14.3	0.0	14.3	0.0	0.0	0.0	14.3	85.7	14.3	14.3	57.1
2	COPD & emphysema	6	69.3	3.8	66.7	33.3	83.3	16.7	0.0	0.0	0.0	16.7	0.0	0.0	100.0	50.0	33.3	16.7
2	Chronic bronchitis & emphysema	5	70.2	9.1	80.0	20.0	60.0	20.0	20.0	0.0	20.0	0.0	0.0	20.0	40.0	40.0	60.0	0.0
2	COPD & asthma	4	64.8	8.8	25.0	75.0	50.0	25.0	25.0	25.0	25.0	0.0	0.0	25.0	75.0	0.0	100.0	0.0
2	Chronic bronchitis and COPD*	2	59; 69		1	1	1	1						1	1		2	
2	Emphysema & pulmonary fibrosis*	2	75; 86			2		2			1			1	1			2
2	Bronchiectasis & pulmonary fibrosis*	2	69; 63		1	1	2							1	1		1	1
2	Chronic bronchitis & pulmonary fibrosis*	1	71			1			1		1			1				1
2	COPD & pulmonary fibrosis*	1	58			1	1							1			1	
2	Emphysema & bronchiectasis*	1	60			1		1						1		1		
2	Chronic bronchitis & bronchiectasis*	1	63			1	1							1			1	
>2	All combinations	14	68.0	11.0	42.9	57.1	71.4	28.6	0.0	0.0	7.1	7.1	7.1	35.7	50.0	35.7	28.6	35.7
>2	At least COPD, asthma & emphysema	6	66.5	9.5	50.0	50.0	83.3	16.7	0.0	0.0	0.0	16.7	0.0	16.7	50.0	50.0	33.3	16.7
>2	At least chronic bronchitis, COPD & asthma	5	64.8	12.0	40.0	60.0	80.0	20.0	0.0	0.0	0.0	20.0	0.0	20.0	40.0	40.0	40.0	20.0

*group formed by 1 or 2 patients only: absolute values are reported instead of percentages.
GP: general practitioner; TP: treatment plan; COPD: chronic obstructive pulmonary disease.
For the sake of space, not available (NA) cases have not been reported.

Table 3
Details of pathologies in respiratory patients of the San Camillo-Forlanini Hospital, Rome, Italy, who self-reported more than two respiratory pathologies

Pathologies		N. of patients	Pathology (%)						
Number	Type		Chronic Bronchitis	COPD	Asthma	Emphysema	Bronchiectasis	Pulmonary fibrosis	Other
>2	All combinations	14	50.0	71.4	64.3	85.7	35.7	35.7	35.7
>2	At least COPD, asthma & emphysema	6	66.7	100.0	100.0	100.0	66.7	16.7	16.7
>2	At least chronic bronchitis, COPD & asthma	5	100.0	100.0	100.0	80.0	60.0	20.0	40.0

COPD: chronic obstructive pulmonary disease.

line with the OsMED report for the 2020 lockdown period too [10], although relevant differences between the studies must be kept in mind: our study was limited to 284 patients, focussed on the lockdown period Mar-May 2020, and used self-reporting questionnaires including – but not limited to – questions on the use of medicines; the OsMED report, instead, analyzed the use of medicines – on the whole Italian territory – in chronic diseases such as COPD and asthma only, and calculated the national per capita consumptions per 10,000 inhabitants per day relating to the pre and post COVID-19-period. More in detail, the OsMED report found no statistically significant differences in drug use between the pre- and during-COVID-19 periods (Jan-Feb 2020 and Mar-Apr 2020 respectively). OsMED attributed this success to the health strategy used to support continuity of care for chronically ill patients, which involved: extending the period of validity of treatment plans; encouraging access to medication by the use of electronic prescriptions; continuously updating relevant information on institutional sites.

Our study findings seem to confirm that, at least within the small sample of outpatients referring to our pulmonary disease division, those measures allowed the continuous delivery of high-quality assistance to patients, proving that an appropriate health strategy can improve patients' awareness of their condition and help maintain an adequate adherence to therapy even in an emergency context. In particular, we were especially interested to know, in view of other possible lockdowns or emergency periods, whether the telephone selection of all the visits already booked during the lockdown period to identify the urgency of performance in presence had proven useful for therapeutic purposes, when used in conjunction with the actions implemented by the Italian National Health Service through digitalization for the continuation of drug therapies.

By analyzing the ex-smokers group, we found that the highest compliance with treatment regimes occurred in those patients with two associated disease conditions (COPD and asthma), as well as in patients with COPD alone. The most common reason for interruption of therapy was "I felt good"; this demonstrates limited knowledge of the patients with respect to the chronic nature of their condition. This problem is already known in the literature, especially in asthmatics, who often interrupt their therapy and show levels of adherence between 16% and 50% [11]. It is important to note the reduction in adherence rates in patients with pulmonary fibrosis, a rare condition monitored in dedicated centers such as the San Camillo-Forlanini Hospital Pulmonology Service, in which medical counseling is only performed in urgent cases using a telephone counseling service organized in conjunction with the Patient Association.

We noted that the smokers in our study were younger than other groups, thus highlighting the importance of greater visibility of the Stop Smoking Clinic set in the Hospital, which is run in collaboration with the pulmonary healthcare service; it has a crucial role in the prevention of smoking-related diseases, and at the same time it is also an integral part of the treatment of pulmonary conditions. Our data revealed that 23.6% of individuals in the group of patients under treatment for pulmonary conditions were still smoking. This finding is similar to those published in an OsMED 2019 report [1] in which 28.5% of patients with asthma and 40.4% of those with COPD were reported as still smoking. Other relevant literature shows that many patients are smokers at the time of diagnosis of a chronic pulmonary disease, and a relatively high percentage of them keep smoking despite their condition, without receiving any therapy for tobacco addiction [12, 13]. Our study revealed that more than half of smokers wanted to try to stop smoking, but without any support. The treatment of tobacco abuse should always be prescribed as an integral part of the respiratory therapy. Further, it should be well kept in mind that, within the still existing context of CO-VID-19 pandemic, smoking increases the probability of severe disease in those who contract COVID-19 [14]. For the National Health Systems, reduction of tobacco abuse would thus mean a significant improvement in clinical outcomes, in reducing lethality and in the optimization of healthcare expenditure. The fact that tobacco abuse increases the impact of COVID-19 should persuade governments to expedite plans to reduce tobacco consumption.

Last on the methodology used in our study, it is worth observing that, despite its intrinsic limitations, the anonymous, self-administered questionnaire used in this study reached a high percentage of respondents

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(90.7%) and represented the fastest way to gather data associated to patients usually belonging to our respiratory service: the data on drug consumption, in fact, which are detectable by local health facilities, would not have allowed us to identify the group of patients of the specific service.

CONCLUSIONS

This investigation confirms that the healthcare strategy applied during the first 2020 SARS-CoV-2 Italian lockdown successfully contributed to maintain the pre-existing level of adherence to drug therapy in patients with respiratory disease. Despite its limitations – among which the small sample of outpatients, the self-reported nature of the data and the relatively short period of the Mar-May 2020 lockdown – the study was helpful to highlight possible improvements in the patients' care. Among emerged criticalities, there remains the need to improve healthcare education in patients, who need to adopt increasingly conscious approaches to chronic disease during the whole pandemic period and afterwards. One helpful means to those approaches might be the use of new digital systems that include a role for pharmacists in the treatment and monitoring of patients with chronic conditions [15].

Consent for publication

The manuscript has not been published or presented elsewhere in part or in entirety, and it is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. All Authors read and understood the Journal's policies, and confirm that neither the manuscript nor the study violate any of these. All Authors read and approved the final manuscript.

Ethics approval and consent to participate

The study has been performed with the approval of the Ethics Committee at S. Camillo-Forlanini Hospital and with the participants' informed consent in compliance with the Helsinki Declaration.

Data statement

All relevant data are reported in the manuscript. Raw data from the survey can be made available by the first Author.

Authors' contribution

Conceptualization and methodology: RP, LDM, AS, DS, CP, GG, CG. Investigation: RP, LDM, AS, DS, CP, GG. Formal analysis: RP, CG. Data interpretation: RP, LDM, AS, DS, CP, GG, CG. Writing – original draft: RP, CG. Writing - Review & Editing: RP, LDM, AS, DS, CP, GG, CG. Project administration: RP.

Conflict of interest statement

The Authors have no conflicts of interest to declare.

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