ORIGINAL RESEARCH

Adherence to long-term therapies in cystic fibrosis: a French cross-sectional study linking prescribing, dispensing, and hospitalization data

Héloïse Rouzé[1,2]
Marie Viprey[1,2]
Samuel Allemann[2]
Alexandra L Dima ⓘD [2]
Pascal Caillet[3]
Angélique Denis[1]
Stéphanie Poupon-Bourdy[1]
Boubou Camara[4]
Catherine Llerena[5]
Philippe Reix[6]
Isabelle Durieu[2,7]
Quitterie Reynaud[2,7]
Sandrine Touzet[1,2]

[1]Public Health Department, Hospices Civils de Lyon, Lyon, France; [2]HESPER Lab-EA 7425, Université de Lyon-Université Claude Bernard Lyon 1, Lyon, France; [3]Department of Clinical Pharmacology, CHU de Nantes, Nantes, France; [4]Pulmonary Department, Adult CF Center, CHU de Grenoble, Grenoble, France; [5]Pediatric Pulmonology Department, Pediatric CF Center, CHU de Grenoble, Grenoble, France; [6]Pediatric Pulmonology Department, Pediatric CF Center, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, Lyon, France; [7]Department of Internal Medicine, Adult Cystic Fibrosis Care Center, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France

Correspondence: Héloïse Rouzé
Hospices Civils de Lyon, Pôle de Santé Publique, Bâtiment A, 6ème étage, 162 Avenue Lacassagne 69003 Lyon, France
Tel +33 47 211 5132
Email heloise.rouze@chu-lyon.fr

Background: Cystic fibrosis (CF) is a life-shortening genetic condition that usually affects several organs and involves significant treatment burden. Adherence to medication is important for successful CF management.

Objective: To describe medication adherence according to age, therapeutic class, and pharmaceutical form in adults and children followed in four regional CF centers in France.

Methods: We conducted a cross-sectional study with non-transplanted patients followed in two adult and two pediatric centers during 2015 who were covered by the French National Health Insurance (NHI). Sociodemographic, clinical, hospitalization, and prescription data were collected from patient medical records. Medication dispensations were extracted from the regional French NHI database. Adherence was calculated over 12 months using continuous medication availability (CMA) accounting for dose adjustments and hospitalizations. Drug-specific CMA was computed in R with the AdhereR package for each medication prescribed more than 3 months, which was averaged to obtain a composite CMA score (cCMA) for all treatments and per therapeutic class as well as pharmaceutical form for each patient.

Results: A total of 228 patients were included. The number of chronic medications increased with age (r=0.50, p<0.001): a median of 7 medications per patient were prescribed. The mean±SD cCMA was significantly different between age groups (p=0.0098): it was 0.71 ±0.20 for the 0–5 years age group, 0.73±0.16 for 6–11 years, 0.64±0.17 for 12–17 years, 0.57 ±0.23 for 18–25 years, and 0.65±0.20 for the over 25 years age group. cCMA varied significantly according to pharmaceutical forms: the mean±SD cCMA was 0.70±0.21 for oral medications and 0.54±0.28 for inhaled medications (p<0.001).

Conclusion: This study suggests that adherence to medication regimens in CF patients remains suboptimal and varies substantially between age groups and pharmaceutical forms. These variations in adherence should be considered when developing effective strategies to improve adherence.

Keywords: cystic fibrosis, chronic treatment, medication adherence, administrative claims data, prescription data

Background

Cystic fibrosis (CF) is a life-shortening inherited disease that usually affects several organs, although pulmonary disease predominately contributes to morbidity and mortality. In France, the use of new treatment strategies and systematization of early diagnosis since 2002 have led to a significant improvement in survival, and today there are more adult patients than children.[1,2] However, CF remains a chronic

and progressive disease and requires multiple life-long therapies that require daily and time-consuming administration.[3] Treatment generally comprises of the daily intake of pancreatic enzymes, nutritional supplements, airway clearance, physiotherapy, inhaled or nebulized medications (mucolytics, antibiotics, and bronchodilators), and oral medications such as anti-inflammatories and antibiotics, not to mention the management of comorbidities such as CF-related diabetes.[3–5]

The treatment burden of CF raises the question of medication adherence. Published studies have reported adherence that ranges from 35% to 75% according to the age of the population, therapeutic class, and regimen complexity studied, but also the method used to estimate this.[6,7] Furthermore, low adherence is reported to negatively influence health outcomes, such as pulmonary exacerbations,[8–10] health care costs (primarily owing to an increase in hospitalizations),[11,12] and quality of life.[13,14] Published studies used different methods of measurement, such as self-report (a subjective method), electronic measurement or administrative claims data (objective method), and considered different time periods (a few weeks to several months) and populations (children, adults), making comparisons difficult.[6,7] Furthermore, the majority of studies evaluated one or two drugs or therapeutic classes, the most studied class being the drugs of respiratory system,[7] which is only part of the treatment regimen. It therefore seems interesting to investigate the whole CF medication regimen for all ages. The aim of the present study was to describe medication adherence in adults and children followed in four regional CF centers in France, combining prescription data and administrative claims data, and to investigate this according to age, therapeutic class, and pharmaceutical form.

Methods
Design, setting, and sample selection
A multicentre cross-sectional study was conducted among CF patients receiving care in four (two pediatric and two adult) regional CF centers in the Rhône-Alpes region of France during 2015. Inclusion criteria were: documented CF diagnosis by a CF specialist physician, at least one chronic CF treatment prescribed more than 3 months during the follow-up period, covered by the French National Health Insurance (NHI), and living in the Rhône-Alpes region in 2015. Transplanted patients were excluded. All patients registered in the four regional CF centers received an invitation by post to participate in the study. Written informed consent was obtained from adult CF patients and from the parents of children with CF. The study was approved by the ethics committee of the university hospital of Lyon and the French national data protection authority (reference DR 2015 391).

Demographic and clinical data
We extracted the following demographic and clinical data from medical records: gender, age, age at CF diagnosis, context of diagnosis, cystic fibrosis transmembrane conductance regulator (CFTR) genotype, *Pseudomonas aeruginosa* colonization status, presence of CF-related diabetes, body mass index at the last visit to the CF center before 1 January 2015. The FEV_1 collected was the best value during 2014, and was expressed as percentage of the predicted value according to Knudson's reference. Occurrence and total duration of course of intravenous (IV) antibiotic courses, number of outpatient visits in CF centers, and occurrence and total duration of hospitalizations were collected for 2014. Prescription data for medications prescribed more than 3 months (name of drugs, pharmaceutical forms, dosage, and durations of prescription) were collected from the prescription made on the last visit prior to 1 January 2015 and throughout 2015. Parenthood, marital status, and professional situation data were also collected for adult patients. These data were collected in all four CF centers and anonymized before analysis.

Administrative claims data
Administrative claims data were provided by the regional reimbursement database (Extraction, Recherches, Analyses pour un Suivi Medico-Economique, ERASME). This database contains information on all reimbursement data for patients affiliated to the main French NHI living in the Rhône-Alpes area, including drugs and hospitalizations ordered by physicians, for the previous 24-month period.[15] We focused on ten therapeutic classes as follows (drug names are presented in Table S1): drugs for obstructive airways disease (ie, beta-2-adrenoreceptor agonist or glucocorticoid aerosol), mucolytics (dornase alfa), inhaled anti-infectives (ie, colistin or tobramycin), oral anti-infectives (ie, azithromycin or itraconazole), CFTR potentiator (ivafactor), drugs for acid-related disorders, digestive enzymes (lipase and protease), bile acids, vitamins and mineral supplements (ie, calcium or tocopherol), and antidiabetics (insulin and oral hypoglycaemic drugs such as

repaglinide). There is no consensus on the medication threshold defining polypharmacy; thresholds used range from 5 to 10 drugs.[16,17] Herein, a threshold of >7 drugs was used as this is reported elsewhere to be the median number of daily drugs prescribed to CF patients.[3]

Adherence measurement

We derived a measure for adherence combining prescription data and administrative claims data. Administrative claims data provide an objective estimate of adherence for multiple medications, large samples, long follow-up periods, at low cost, and without intrusion.[18,19] We calculated adherence using continuous medication availability (CMA) which evaluates both implementation (to take medication in accordance with the recommended dosing regimen) and persistence (to continue taking it for the recommended duration).[20] We used CMA version 7 to calculate adherence during the prescription period; this is defined as the proportion of days covered by a medication during the observation window (OW; ie, the period for which adherence is calculated), for each individual medication.[21] Briefly, CMA version 7 assumes that dispensed medications are used as prescribed and oversupply from previous dispensing events is finished before a new supply is used.[18] It accounts for dispensing events within the whole follow-up window (FUW; ie, the total period for which relevant medication events are recorded), meaning that oversupply can be carried into the OW. Remaining supply at the end of the OW is excluded. If the first dispensing event during the FUW preceded the first recorded prescription event, we calculated the duration of the supply with the dosage of the first recorded prescription. When patients were hospitalized, we assumed that treatments were supplied by the hospital during the entire hospitalization period, excluding the day of admission, and remaining supplies were extended accordingly. After each prescription change (for example, dosage modification), we recalculated the duration of the remaining supply.

In the present study, the FUW contained all medication events between July 2014 and June 2016, and the OW covered the year 2015 (from 01/01/2015 to 31/12/2015). To adequately estimate adherence for chronic treatments, calculations included only medications prescribed for more than 3 months, with at least one dispensing event during the FUW.

The CMAs of each individual medication could be averaged to obtain a composite CMA (cCMA).[22] In case of one-drug regimen, the cCMA would be equal to the CMA of that individual drug. For each patient, cCMA was obtained for each therapeutic class, for oral and inhaled pharmaceutical form (PO_cCMA and Inhal_cCMA, respectively) and for the entire treatment regimen (overall cCMA). Patients were considered "adherent" if cCMA was 0.80 or above. We used AdhereR, an open-source package for the widely used open-source environment R, to calculate CMA and cCMA.[21,23]

Statistical analyses

Mean and SD or median and (range) for continuous variables and frequency and percentage for categorical variables were used to summarize demographic and clinical characteristics as well as the adherence rate. Chi-square tests were used to compare age and gender between patients included and those who were not included. We analyzed the data according to five age groups consistent with stages of illness and treatment of CF patients: 0–5 years, 6–11 years, 12–17 years, 18–25 years, and 26 or older. Correlations between age and number of medications were assessed by the Spearman's test. We compared cCMA for each therapeutic classes, PO_cCMA, Inhal_cCMA and overall cCMA by age group and pharmaceutical forms using the Kruskal–Wallis test. The significance level was set at 0.05 throughout. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, US).

Results

Patient characteristics

Of the 613 CF patients invited to participate among the 801 followed in the four regional CF centers in 2015, a total of 287 patients consented. Complete refill and medical records could be extracted for 231 patients. Three participants did not have any treatment prescribed for more than 3 months, resulting in a sample of 228 patients composed of 135 children and 93 adults (Figure 1).

There was no significant difference in terms of age between the 228 patients included and the 385 patients who were not included (21.1% versus 14.0% for patients aged 0–5 years; 21.1% versus 23.1% for those aged 6–11 years; 17.1% versus 17.7% for those aged 12–17 years; 14.9% versus 17.9% for those aged 18–25 years, and 25.9% versus 27.3% for those aged 26 years or older; p=0.247) and no significant difference in terms of gender (45.2% versus 47.5%; p=0.571).
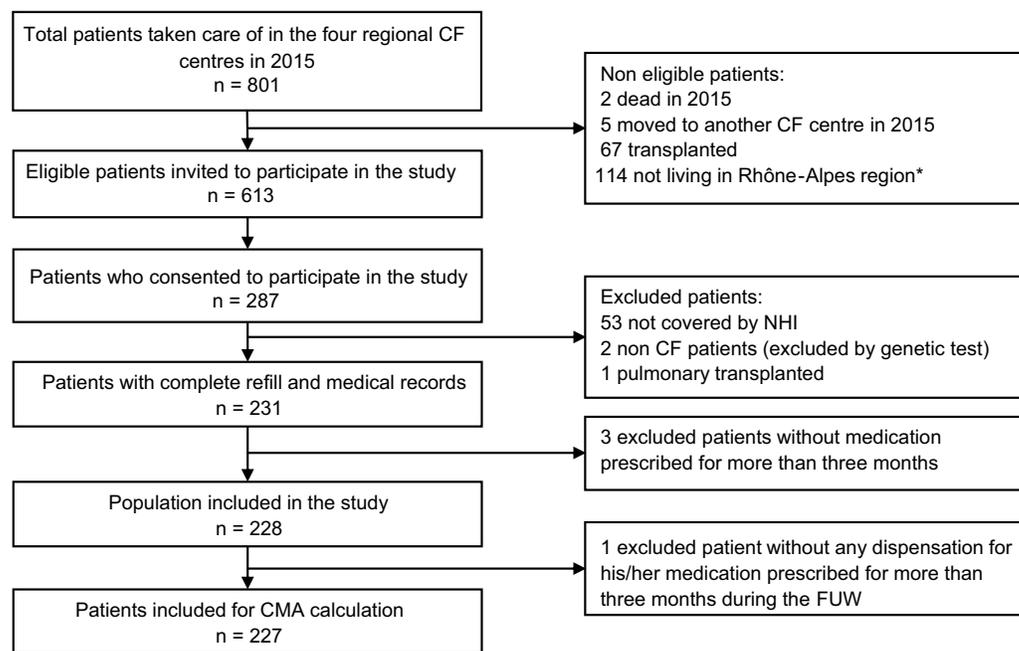
Figure 1 Flow chart for the study.
Note: *No administrative claims data in "ERASME" database.
Abbreviations: CF, cystic fibrosis; NHI, National Health Insurance; FUW, follow-up window (total period for which relevant medication events were recorded); CMA, continuous medication availability (adherence estimation).

Almost all patients of the 0–5 and 6–11 years groups (94/96) were diagnosed before the first year of life versus less than two-thirds of other age groups (81/132). While 12.5% (6/48) of the 6–11 group had one or more IV antibiotic courses in 2014, this rate rose to 43.8% (32/73) of the 12–25 years old and 57.6% (34/59) of the 26 and older group. In parallel, 91.7% (44/48) of the patients aged 6–11 years and 33.9% (20/59) of those aged 26 years or older had mild disease (FEV1% ≥70%). For all groups of patients, mean outpatient visits in CF-center was 4.8 ±2.4 by year. The adult patients aged 18–25 years were mostly students (55.9%), single (72.7%), and without children (94.1%), and those aged 26 years or more were mostly working (83.0%), in a relationship (67.2%) and 30% of them had at least one child (Table 1).

Treatment regimen

The number of chronic medications increased significantly with age from 4 for young children to 9 for adults (r=0.50; $p<0.001$), with a median number of 8 (range 1–15) chronic medications among patients aged 6 and more. Eight or more chronic medications (polypharmacy) were prescribed to 39.6% of patients aged 6–11 years, 53.9% of those aged 12–17 years, 61.8% of those aged 18–25 years, and 66.1% of those aged 26 years or older patients. Digestive

enzymes and vitamins were prescribed in 79–100% of patients. Among inhaled medication prescriptions, 18.8% of patients aged 0–5 years had mucolytics (such as dornase alfa) whereas these drugs were prescribed to 63.9% (115/180) of older patients. For inhaled anti-infectives, the prescription rates were 14.6% in patients aged 0–5 years, 35.4% in those aged 5–11 years, and 68.2% (90/132) in those aged over 11 years; for oral anti-infectives 32.3% (31/96) of those aged 0–11 years and 69.7% (92/132) of older patients had at least one prescription for oral anti-infectives for more than 3 months (Table 2).

Medication adherence

One patient had no dispensation from the beginning of FUW until the end of the OW for any of his medications prescribed for more than 3 months, and therefore CMA was calculated for 227 patients. Sixty-seven patients had at least one prescribed medication that was not dispensed from the beginning of the FUW until the end of the OW. For these medications, no CMA was calculated.

The mean±SD cCMA for all medications (overall cCMA) ranged from 0.57±0.23 to 0.73±0.16, and there was a significant difference between age groups (Table 3 and Figure 2). The proportion of patients classified as adherent (cCMA of 0.80 or above) was 39.6% (19/48) in patients aged

Table 1 Baseline characteristics of the patients according to age (N=228)

	0–5 years old	6–11 years old	12–17 years old	18–25 years old	26 and over
	n=48	n=48	n=39	n=34	n=59
Mean age, years±SD	2.5±1.8	8.5±1.6	15.1±1.67	21.1±2.4	34.5±8.8
Gender, (male/female)	31/17	27/21	20/19	20/14	27/32
Diagnostic pattern, n (%)					
Screening	46 (95.8)	45 (93.8)	4 (10.3)	7 (22.6)	6 (12.4)
Symptoms	2 (4.2)	3 (6.3)	32 (82.0)	24 (77.4)	40 (81.6)
Family history	0	0	3 (7.7)	0	3 (6.1)
Missing data	0	0	0	3	10
Age in years at CF diagnosis, n (%)					
≤1	48 (100)	46 (95.8)	27 (69.2)	21 (61.8)	33 (55.9)
>1	0	2 (4.2)	12 (30.8)	13 (38.2)	26 (44.1)
Mutation n (%)					
Homozygous DeltaF508	20 (41.7)	15 (31.3)	23 (59.0)	15 (44.1)	19 (32.2)
Heterozygous DeltaF508	19 (39.6)	23 (47.9)	14 (35.9)	15 (44.1)	32 (54.2)
Other	9 (27.3)	10 (20.8)	2 (5.1)	4 (11.8)	8 (24.2)
Pseudomonas aeruginosa colonization status, n (%)	1 (2.1)	6 (12.5)	14 (35.9)	15 (44.1)	38 (64.4)
Best forced expiratory volume percent predicted (FEV1%), mean±SD		99±17	95±20	76±21	64±19
Severity of disease (patients >6 years), n(%)					
Mild: FEV1% ≥70%		44 (91.7)	35 (89.7)	23 (67.7)	20 (33.9)
Moderate: 40% ≤ FEV1% <70%		4 (8.3)	4 (10.3)	10 (29.4)	31 (52.5)
Severe: 40% < FEV1%		0	0	1 (2.9)	8 (13.6)
Body mass index[a], n (%)					
Normal[b]	10 (20.8)	15 (31.3)	7 (17.9)	26 (76.5)	50 (84.7)
Subnormal[c]	20 (41.7)	33 (68.7)	32 (82.1)	8 (23.5)	9 (15.3)
CF-related diabetes, n (%)					
Insulin-dependent diabetes	0	0	1 (2.6)	5 (14.7)	10 (16.9)
Non insulin-dependent diabetes	0	0	2 (5.1)	0	4 (6.8)
Glucose intolerance	0	1 (2.1)	12 (30.8)	2 (5.9)	5 (8.5)
IV antibiotics courses in 2014, n (%)					
0	48 (100)	42 (87.5)	21 (53.9)	20 (58.8)	25 (42.4)
1–2	0	6 (12.5)	15 (38.5)	12 (35.3)	25 (42.4)
3+	0	0	3 (7.7)	2 (5.9)	9 (15.3)
Days with IV antibiotics courses,	n=0	n=6	n=18	n=14	n=34
Median (range)		14 (14–50)	15 (5–114)	22 (14–59)	29.5 (11–119)
Outpatient visits in CF-centers in 2014, mean±SD	4.1±1.7	4.1±1.3	5.7±2.9	5.0±2.3	5.0±3.0
Hospitalizations in 2014, n (%)					
0	38 (79.2)	42 (87.5)	28 (71.8)	25 (73.5)	42 (71.2)
1+	10 (20.8)	6 (12.5)	11 (28.2)	9 (26.5)	17 (28.8)
Days in hospital in 2014,	n=10	n=6	n=11	n=9	n=17
Median (range)	3 (2–55)	8 (3–15)	7 (2–43)	5 (4–16)	11 (3–40)

(*Continued*)

Table 1 (Continued).

	0–5 years old	6–11 years old	12–17 years old	18–25 years old	26 and over
	n=48	n=48	n=39	n=34	n=59
Parent with one child or more, n (%)				2 (5.9)	18 (30.5)
Marital status (adults), n (%)					
In a relationship				9 (7.8)	39 (67.2)
Single				24 (72.7)	19 (32.8)
Missing data				1	1
Professionnal situation (adults), n (%)					
Higher professional occupations				2 (5.9)	10 (17.0)
Intermediate professional occupations				3 (8.8)	16 (27.1)
Employees and technical occupations				10 (29.4)	23 (39.0)
Students or Unemployed				19 (55.9)	10 (17.0)

Notes: [a]Body mass index (BMI) for patients over 18 years old or z-score BMI for patient between 2 and 18 years old; no data available for patients under 2 years old. [b]BMI ≥18.5 or z-score BMI≥0. [c]BMI<18.5 or z-score BMI<0.
Abbreviations: CF, cystic fibrosis; IV, intravenous.

Table 2 Description of CF-related treatments for all patients and according to age groups (N=228)

CF long-term Regimen	All patients n=228	0–5 years old n=48	6–11 years old n=48	12–17 years old n=39	18–25 years old n=34	26 and over n=59
Number of drugs prescribed, mean±SD	7.1±3.1	4.2±1.9	6.4±2.4	8.1±2.9	8.7±2.8	8.5±3.1
Number of drugs prescribed median (range)						
All drugs	7 (1–15)	4 (1–8)	7 (1–11)	8 (1–15)	9 (3–14)	9 (1–15)
Oral medications	5 (0–11)	3 (0–7)	5 (1–8)	6 (1–9)	6 (1–9)	6 (0–11)
Inhaled medications	2 (0–6)	1 (0–3)	2 (0–5)	2 (0–6)	2 (1–6)	3 (0–4)
Number of drugs prescribed, n (%)						
0–7 medications	126 (55.3)	46 (95.8)	29 (60.4)	18 (46.1)	13 (38.2)	20 (33.9)
≥8	102 (44.7)	2 (4.2)	19 (39.6)	21 (53.9)	21 (61.8)	39 (66.1)
Prescribed therapeutic class, n (%)						
Oral medication	225 (98.7)	47 (97.9)	48 (100)	39 (100)	34 (100)	58 (98.3)
CFTR potentiator	4 (1.8)	1 (2.1)	1 (2.1)	2 (5.1)	0	0
Antidiabetics	23 (10.1)	0	0	1 (2.6)	6 (17.6)	16 (27.1)
Oral anti-infectives[a]	122 (53.5)	13 (27.1)	18 (37.5)	25 (64.1)	23 (67.6)	44 (74.6)
Digestive enzymes	199 (87.3)	38 (79.2)	42 (87.5)	37 (94.9)	32 (94.1)	51 (86.4)
Vitamins and mineral supplements	216 (94.7)	44 (91.7)	47 (97.9)	39 (100)	32 (94.1)	55 (93.2)
Bile acids	59 (25.9)	2 (4.2)	9 (18.8)	19 (48.7)	14 (41.2)	16 (27.1)
Drugs for acid related disorders	89 (39.0)	20 (41.7)	20 (41.7)	19 (48.7)	12 (35.3)	19 (32.2)
Inhaled medication	187 (82.0)	24 (50.0)	42 (87.5)	36 (92.3)	34 (100)	56 (94.9)
Inhaled anti-infectives[a]	113 (49.6)	7 (14.6)	17 (35.4)	28 (71.8)	24 (70.6)	38 (64.4)
Mucolytics	123 (53.9)	9 (18.8)	29 (60.4)	25 (64.1)	27 (79.4)	34 (57.6)
Drugs for obstructive airways disease	130 (57.3)	15 (31.3)	28 (58.3)	20 (51.3)	21 (61.8)	49 (83.1)

Note: [a]The term "anti-infectives" includes antibiotics, antivirals, and antifungals
Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Table 3 cCMA for all medication, by pharmaceutical form and by therapeutic class for all patients and according to age group (N=227)

cCMA	All patients		0–5 years old		6–11 years old		12–17 years old		18–25 years old		26 and over		p-value
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	p
Overall cCMA	227	0.67±0.20	48	0.71±0.20	48	0.73±0.16	39	0.64±0.17	33	0.57±0.23	59	0.65±0.20	0.0098
PO_cCMA	225	0.70±0.21	47	0.73±0.20	48	0.71±0.28	39	0.69±0.20	33	0.58±0.25	58	0.71±0.21	0.0171
CFTR potentiator	4	0.95±0.04	1	0.97	1	1.00	2	0.92 (0.00)	0	–	0	–	–
Antidiabetics	23	0.78±0.22	0	–	0	–	1	0.78	6	0.72±0.25	16	0.81±0.22	–
Digestive enzymes	199	0.76±0.24	38	0.84±0.23	42	0.85±0.18	37	0.71±0.24	31	0.65±0.23	51	0.73±0.25	<0.0001
Oral anti-infectives	122	0.69±0.28	13	0.68±0.37	18	0.70±0.27	25	0.70±0.28	22	0.61±0.34	44	0.73±0.23	0.7723
Vitamins and mineral supplements	216	0.69±0.24	44	0.74±0.24	47	0.74±0.22	39	0.67±0.25	31	0.58±0.28	55	0.69±0.24	0.0911
Bile acids	59	0.80±0.25	2	1.00±0.00	9	0.76±0.30	19	0.84±0.20	13	0.62±0.34	16	0.89±0.14	0.0347
Drugs for acid related disorders	89	0.67±0.31	20	0.67±0.31	20	0.82±0.21	19	0.66±0.29	12	0.47±0.36	18	0.66±0.33	0.0670
Inhal_cCMA	187	0.54±0.28	24	0.64±0.31	40	0.61±0.24	35	0.45±0.23	32	0.52±0.33	56	0.50±0.26	0.0274
Inhaled anti-infectives	113	0.59±0.29	7	0.91±0.20	17	0.71±0.28	28	0.59±0.27	23	0.56±0.33	38	0.51±0.25	0.0019
Mucolytics	123	0.55±0.31	9	0.70±0.25	29	0.66±0.26	25	0.43±0.28	27	0.61±0.34	33	0.47±0.31	0.0116
Drugs for obstructive airways disease	130	0.51±0.32	15	0.54±0.33	27	0.52±0.28	20	0.44±0.26	19	0.50±0.36	49	0.54±0.35	0.8915

Notes: We used the open-source package AdhereR to calculate cCMAs, and the Kruskal–Wallis test to compare cCMA for each therapeutic classes, PO_cCMA, Inhal_cCMA, and overall cCMA by age group and pharmaceutical forms. The significance level was set at 0.05 throughout. One of the 228 patients had no dispensation during the beginning of FUW until end of OW for any of his medications prescribed for more than 3 months, so CMA calculation was performed for 227 patients.
Abbreviations: cCMA, composite continuous medication availability (CMA average for adherence estimation); overall cCMA, cCMA for the entire treatment regimen; PO_cCMA, cCMA for oral medications only; Inhal_cCMA, cCMA for inhaled medications only; FUW, follow-up window (total period for which relevant medication events were recorded); OW, observation window (period for which adherence was calculated).
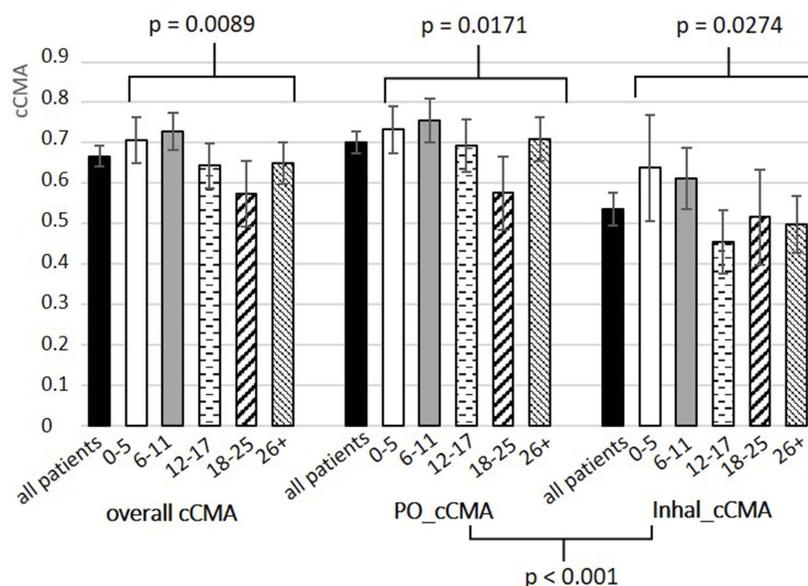
Figure 2 Mean cCMA and 95% confidence interval for all medication (overall cCMA), oral medication (PO_cCMA) and inhaled medication (Inhal_cCMA) according to age.
Notes: We used the open-source package AdhereR to calculate cCMAs, and the Kruskal–Wallis test to compare PO_cCMA, Inhal_cCMA, and overall cCMA by age group and pharmaceutical forms. The significance level was set at 0.05 throughout. One of the 228 patients had no dispensation during the beginning of FUW until end of OW for any of his medications prescribed for more than 3 months, so CMA calculation was performed for 227 patients.
Abbreviations: cCMA, composite continuous medication availability (CMA average for adherence estimation); overall cCMA, cCMA for the entire treatment regimen; PO_cCMA, cCMA for oral medications only; Inhal_cCMA, cCMA for inhaled medications only; FUW, follow-up window (total period for which relevant medication events were recorded); OW, observation window (period for which adherence was calculated).

0–5 years, 37.5% (18/48) in those aged 6–11 years, 20.5% (8/39) in those aged 12–17 years, 21.2% (7/33) in those aged 18–25 years, and 25.4% (15/59) in those aged 26 years or older patients.

There was a significant difference between age groups in mean cCMA for oral medications (PO_cCMA, p=0.0171; Table 3 and Figure 2), particularly for digestive enzymes (p<0.0001), for which 71.1% (27/38) of patients aged 0–5 years, 73.8% (31/42) of those aged 6–11 years, 43.2% (16/37) of those aged 12–17 years, 25.8% (8/31) of those aged 18–25 years, and 47.1% (24/51) of those aged 26 years or older patients had a CMA of 0.80 or above. There was no significant difference in adherence to multivitamins between age groups (p=0.0911; Table 3); the mean±SD cCMA was 0.66±0.26.

Mean cCMAs were significantly different between age groups for inhaled drugs (Inhal_cCMA: p=0.0274; Table 3 and Figure 2); there was a significant difference for mucolytics (p=0.0116) and inhaled anti-infectives (p=0.0019), but not for bronchodilators (p=0.8915). Adherence was significantly lower for inhaled drugs (0.54±0.28) than for oral medication (0.70±0.21, p<0.001; Figure 2).

Regarding inhaled forms of anti-infectives, mean cCMA decreased with age for inhaled forms: in this therapeutic class, mean±SD cCMA was 0.91±0.20 in patients

aged 0–5 years, 0.71±0.28 in those aged 5–11 years, 0.59±0.27 in those aged 12–17 years, 0.56±0.33 in those aged 18–25 years, and 0.51±0.25 in those aged 26 years or older patients (p<0.0001; Table 3), as did the proportion of adherent patients (85.7% (6/7) of patients aged 0–5 years; 47.1% (8/17) of patients aged 6–11 years, 28.6% (8/28) of those aged 12–17 years, 30.4% (7/23) of those aged 18–25 years, and 13.2% (5/38) of those aged 26 years or older patients). Mean±SD cCMA was 0.69±0.28 for oral forms of anti-infectives and did not differ between age groups (p=0.7723; Table 3); less than half (56/122, 45.9%) of patients had a CMA>0.8.

Discussion
The present study found that among adult and pediatric French CF patients, the mean cCMA was 0.67 and for all age groups was above 0.50. These results are consistent with data from the latest targeted literature review, although the study population and the therapeutic classes studied in this study are more extensive.[7] Despite French NHI allows a free providing of all drugs that have been covered in the study, adherence rates do not seem to be notably higher than in countries without this system. The financial barrier does not seem to be the main barrier to adherence.

Adherence varied according to age group, the highest cCMA was found in children it then decreased in adolescents aged and further so in young adults, and finally increased slightly in older adults. This could be attributed to the gradual increase in the autonomy of patients who are supervised in childhood by their parents and then gradually managing their treatment alone. According to Faint et al, disease knowledge of adolescents remained suboptimal shortly before transition to adult care (age 15–17 years) and some adolescents appear to be inadequately prepared to assume the responsibility of managing their CF and making informed decisions about their medical treatment as adults.[24] Moreover, Dziuban et al reported that 42% of teenagers did not feel the need to use their medications in the absence of symptoms, especially for the use of aerosol and nebulization device.[25] This underlines that transition is a pivotal moment to reinforced therapeutic education to enhance young adults adherence.

Adherence also varied between pharmaceutical forms: patients were less adherent to inhaled therapies than oral medications, which is in agreement with previous findings.[11,26] One aspect that could explain this is the more complex management and time-consuming use of inhaled medications, such as inhalation technique, nebulization time, or cleaning devices.[24,27] Furthermore, previous studies have also suggested that CF patients are more likely to be adherent to treatments that offer immediate relief or give rise to immediate consequences in case of non-adherence (eg, abdominal pain or diarrhea for vitamins and digestive enzymes), rather than those that offer more long-term benefits, with considerable motivation and enforcement needed with such treatments.[28] The present study also highlights that among inhaled medications the lowest adherence herein was found for inhaled drugs for obstructive airways disease (bronchodilators and corticosteroids), irrespective of age. This may be because health care professionals undervalue their clinical utility since their effectiveness in CF remains to be demonstrated.[29]

To the best of our knowledge, this is the first study to evaluate medication adherence for chronic treatments used by CF patients of all ages both overall and for therapeutic class. CF is a pathology whose scalability and diversity of care are difficult to compare with other diseases, and whose patient's adherence to one medication cannot reflect adherence to the entire treatment. The second main strength of the study is the use of CMA version 7 to evaluate medication adherence; this is based on both prescription and administrative claims data and allows an objective and reproducible measurement of medication adherence.[21] The calculation accounted also for periods of hospitalization. It has been shown that administrative data allowed measurements closer to reality than self-reports that remains used in many studies.[3,19,30–34] Others opted for electronic adaptive aerosol delivery device or electronic pill-caps, but owing to their cost, patient samples were small and adherence measurements involved only one drug or therapeutic class.[35–39]

The study does, however, have some limitations which can result in over estimation of adherence levels. The first is patient recruitment as less than half of those invited to participate did so. The study may therefore have been affected by selection bias as those who did not consent to participate are possibly those with worse adherence to treatment, and therefore the adherence levels reported in this article should be regarded as conservative estimates. The second limitation is due to the use of an administrative database that may overestimate the real administration of the drug may be lower than medication availability. However, in CF populations such a bias may not be a concern as Modi et al have reported that adherence rates from claims data were better than those estimated by self-report measure substantially inflated by reporting biases and recall problems.[19] Lastly, because of the method of calculation, CMA reflects medication adherence only for drugs with at least one dispensation during the follow-up period. In the present study, 67 patients had at least one medication prescribed that was not dispensed over the beginning of FUW until the end of OW. This may be due in some cases to patient non-adherence for a specific drug during the follow-up period and therefore CMA may be overestimated for overall medication adherence. However, some cases may also be related to the non-initiation of treatment, a dimension of medication adherence not included in this study evaluating both implementation and persistence.

Conclusion

This study suggests that adherence to medication regimens in CF patients remains suboptimal and may vary substantially between age groups and pharmaceutical forms. These variations in adherence should be considered when investigating determinants and when developing effective strategies to improve adherence. Following this study, a bundle of solutions for medication adherence for CF adult patients, co-constructed by a group of patients and health professionals, will be tested in a multicenter, open-label study in our regional CF centers.

Acknowledgments

Author contributions

MV, PC, ADenis, ADima, ID, and ST contributed to the study concept and design and SPB, HR, MV and ST participated in the conduct of the study. All authors contributed to the acquisition of data for the work. HR, MV, ADenis, and SA contributed to the data analysis, and HR, MV, ST, SA, QR, ADenis, ADima, and ID contributed toward drafting. All authors contributed toward critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Supplementary material

Table S1 CF therapeutic medications used in long term by patients of the study

N°	ATC code	ATC denomination	Form	International non-proprietary names (INN)
1	A02	Drugs for acid-related disorders	Oral	Esomeprazole
				Lansoprazole
				Omeprazole
				Pantoprazole
				Sucralfate
2	A05	Bile acids	Oral	Ursodeoxycholic acid
3	A09	Digestives enzymes	Oral	Multienzymes (lipase, protease, etc.)
4	A10	Antidiabetics	Injected	Insulin asparte
				Insulin asparte-protamine
				Insulin detemir
				Insulin glargine
				Insulin glulisine
				Insulin lispro
				Insulin lispro-protamine 1:1
				Insulin lispro-protamine 1:4
			Oral	Repaglinide
5	A11 A12 B02	Vitamins and mineral supplements	Oral	Calcium carbonate
				Calcium, combinations with vitamin D
				Colecalciferol
				Ergocalciferol
				Phytomenadione
				Retinol (vit A)
				Tocopherol (vit E)
6	J01 J02 J04 J05	Oral anti-infectives	Oral	Amoxicilline and beta-lactamase inhibitor
				Azithromycin
				Cefadroxil
				Cefpodoxime
				Ciprofloxacin
				Clarithromycin
				Clofazimine
				Doxycycline
				Erythromycin

(*Continued*)

Table S1 (Continued).

N°	ATC code	ATC denomination	Form	International non-proprietary names (INN)
				Ethambutol
				Itraconazole
				Minocycline
				Moxifloxacin
				Posaconazole
				Pristinamycin
				Sulfamethoxazole and trimethoprim
7		Inhaled anti-infectives	Nebulization	Amphotericin B
				Aztreonam
			Aerosol	Colistin
			Nebulization	
			Aerosol	Tobramycin
			Nebulization	
8	R03	Drugs for obstructive airways disease	Aerosol	Beclometasone
			Aerosol	Budesonide
			Nebulization	
			Aerosol	Fenoterol and ipratropium bromide
				Fluticasone
				Formoterol
				Formoterol and beclometasone
				Formoterol and budesonide
				Indacaterol
			Nebulization	Ipratropium bromide
			Oral	Montelukast
			Injected	Omalizumab
			Nebulization	Salbutamol
			Aerosol	Salmeterol
				Salmeterol and fluticasone
			Oral	Terbutaline
			Nebulization	
9	R05	Mucolytics	Nebulization	Dornase alfa (desoxyribonuclease)
10	R07	CFTR potentiator	Oral	Ivacaftor

Abbreviations: CF, cystic fibrosis ; CFTR, cystic fibrosis transmembrane conductance regulator.