






Adherence to disease-specific drug treatment among patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) require lifelong treatment. The aim of the present study was to investigate adherence to disease-specific treatment in patients with PAH or CTEPH.

Methods: The study comprised an adult population diagnosed with PAH (n=384) or CTEPH (n=187) alive in 2016–2017. The study utilised three registries: the Swedish PAH registry, the National Board of Health and Welfare, and Statistics Sweden. Withdrawals from pharmacies of disease-specific oral treatments were studied. Adherence was assessed as: 1) Number of days covered defined as the difference between the total number of daily dosages dispensed and the total number of days covered; and 2) Manual assessment by two persons that independently reviewed each patient's prescription fill history to detect anomalies or patterns of deteriorating or improving adherence over time.

Results: The mean age was 61±16 years, 61% were female and mean time since diagnosis was 4.6 years. Adherence was 62% using the Number of days covered method and 66% by the Manual assessment method. Drug-specific adherence varied from 91% for riociguat to 60% for sildenafil. Good adherence was associated with shorter time since diagnosis in patients with PAH and with lower number of concomitant other chronic treatments in patients with CTEPH. Age, sex, socioeconomic status or number of pulmonary hypertension (PH) treatments were not associated with adherence.

Conclusion: Adherence to oral disease-specific treatment was 60–66% and associated with time since diagnosis and number of concomitant chronic treatments. Sex, age or socioeconomic factors did not affect adherence.

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Adherence to oral ERA and/or PDE-5i/SGC treatment is associated with time since diagnosis, while sex, gender, age and socioeconomic factors do not affect adherence in patients with PAH or CTEPH <https://bit.ly/354NAOQ>

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Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are serious, chronic diseases that require lifelong, disease-specific treatment [1]. The medical treatment is focused on improving symptoms, physical work ability, quality of life and survival. Over the last two decades, new drugs and optimised treatment strategies have increased survival and quality of life [1, 2]. Pulmonary hypertension (PH)-targeted therapies include endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE-5i) and soluble guanylate cyclase stimulators (SGCs), as well as prostacyclin analogues and a prostacyclin receptor agonist [1]. Current guidelines recommend monotherapy or upfront combination therapy, based on risk assessment [1, 3]. Treatment side-effects can make it challenging to motivate patients to follow the prescribed treatment plan over time [4]. Medication adherence as low as 50% has been reported among patients with PAH and CTEPH [5–8]. High age, the number of comorbidities and the integration of a specialist in pharmacology at the outpatient clinic have been shown to correlate with increased treatment adherence [8, 9]. Treatment with monotherapy *versus* combination therapy, on the other side, is showing conflicting results [8, 10]. In a recent Swedish survey, almost all patients with PAH or CTEPH said they understood why they took their drugs, but a third reported that they did not always take them according to the prescription [7]. Concerns about side-effects, reported by half of the study population, likely contributed to the low adherence. Further, a longer elapsed time since diagnosis and start of treatment related to lower self-reported treatment adherence [7].

The aim of the present study was to investigate, by utilising available national registries in Sweden, to what extent patients with PAH or CTEPH adhere to their disease-specific treatment. In addition, concomitant medical treatments and socioeconomic status were investigated.

Methods

The study included a retrospective population comprising patients registered in the Swedish PAH registry [11] with a diagnosis of PAH or CTEPH, aged ≥ 18 years and alive January 2016 through December 2017. In Sweden, individual-level data for all residents can be linked across multiple national databases. This study was based on an interconnection between three available registries: Swedish Pulmonary Arterial Hypertension Register (SPAHR) [11], Socialstyrelsen (the National Board of Health and Welfare) [12] and Statistiska centralbyrån (Statistics Sweden) [13]. Socioeconomic factors including age, education, occupation, family situation and income during 2016 were used for the current analyses. The study complies with the Declaration of Helsinki and was approved by the Regional ethics committee in Lund, Sweden (LU 2016/766).

SPAHR

SPAHR was started in 2008 and constitutes an open continuous register of patients diagnosed with PAH or CTEPH according to the National Institute for Health and Care Excellence (NICE) classification [11]. All Swedish PAH/CTEPH expert centres participate and thus, SPAHR includes >90% of all Swedish patients alive on January 1, 2000 and all subsequent newly diagnosed patients thereafter. SPAHR is approved by the National Board of Health and Welfare and by the Swedish Data Protection Authority. All patients were informed about their participation in SPAHR and had the right to decline.

The National Board of Health and Welfare's pharmaceutical and population registries

The National Board of Health and Welfare's pharmaceutical register covers all medicines that have been dispensed at pharmacies in Sweden. The registration takes place on an individual level. The National Board of Health and Welfare's population register contains information on socioeconomic factors that may affect the ability to pay for the treatment [12].

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)

LISA is part of Statistics Sweden and contains information on marital status, number of children, education level, socioeconomic index, vocational code, employment status, welfare benefits and income for all adult individuals in Sweden [13].

Medical treatment and analyses of adherence

Withdrawals of PH-specific treatments administered from pharmacies in 2016–2017 were studied. For each drug, adherence was assessed as follows.

- 1) "Number of days covered" [14]. This was defined as the difference between the total number of daily dosages dispensed from the pharmacy and the total number of days covered between the first to the last prescription fill. For good adherence, the difference between the dispensed daily dosages and the total number of days had to be one or less than one missed daily dosage per month.

- 2) “Manual assessment” was performed by two persons that independently reviewed each patient’s prescription fill history to detect anomalies or patterns such as deteriorating or improving adherence over time. When the assessments were not in agreement, the results were discussed and a consensus reached.

The studied PH-specific treatments included ERA, PDE-5i and SGCs. Adherence to prostacyclin analogues and the prostacyclin receptor agonist was not analysed due to the individualised dosages that are used for this group of drugs. Less than three concomitant prescription fills during the study period were excluded [14]. If a prescription was not filled for 180 days or more and the patient was on another PH-targeted treatment during that period that could explain why the prescription was not filled, the period was not considered non-adherence. Administration of PH-specific treatments included: ambrisentan and macitentan once daily, bosentan and tadalafil twice daily, and sildenafil and riociguat three times a day.

Other concomitant medical treatments of interest were also studied and allocated as chronic treatment, *e.g.* treatment for chronic diseases with ≥ 3 filled prescriptions in 1 year and as temporary treatment, *e.g.* treatment generally used for temporary diseases and with ≥ 1 filled prescription in a year.

Statistical methods and data management

Descriptive statistics were used to characterise the data. Logistic regression analyses were performed, calculating odds ratios with 95% confidence intervals. All analyses were carried out by use of SAS statistical software (SAS system for Windows 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the study population

A total of 571 patients who were alive 2016–2017 were included in the analyses. Of those, 384 were diagnosed with PAH (idiopathic/hereditary (IPAH/HPAH) $n=201$, associated with connective tissue disease $n=86$, or congenital heart disease $n=66$, or other diseases $n=31$) and 187 with CTEPH. The mean age at time of diagnosis was 56 ± 18 years and at the time of the study 61 ± 16 years; the proportion of women was 61% (table 1). Mean time since diagnosis to study start was 4.6 years.

Half of the population had the highest degree of education as high school and the other half was equally divided between primary school and college/university degree. A majority of the study population was not working, and this was similar in men and women. Forty-five percent were married or had a registered partner and 22% of the households had children living at home, of which 12% were 18 years or older. The disposable household income was slightly below the average Swedish household income (table 1).

Of patients on monotherapy (38%), 49% were treated with PDE-5i or SGCs, and 37% with ERA, while among patients on double therapy (37%), 95% were treated with ERA and PDE-5i or SGCs (table 2). Fifteen per cent did not have a registered prescription fill of a PAH-specific drug, and a majority of those were patients with CTEPH. All patients with CTEPH and 66% of patients with PAH were prescribed anticoagulant treatment.

Treatment adherence

There were 443 patients that filled their prescriptions for ERA or PDE-5i, or a combination of ERA and PDE-5i, ≥ 3 times during the study period and hence, could be included in the analyses of adherence (table 3). Adherence for the whole population was 62% using the Number of days covered method and in the subgroup analyses, 61% for PAH and 64% for CTEPH. Corresponding numbers for the Manual assessment method was 66% for all, 66% for PAH and 67% for CTEPH. Drug-specific adherence for the whole population varied from 91% that filled their prescriptions of riociguat to 60% that filled their prescriptions of sildenafil (table 3). Patients with combination treatment including prostacyclin therapy ($n=66$) had an adherence of 74 and 70% for the Number of days covered and Manual assessment methods, respectively (table 3). The Manual assessment detected more patients that missed two or less dosages per month than Number of days covered (figure 1).

Good adherence to oral PH-specific treatment, assessed by the Manual assessment method, was associated with shorter time since diagnosis in patients with PAH and to lower number of concomitant other chronic treatments in patients with CTEPH (table 4). Age, sex, socioeconomic status or number of PH treatments were not associated with adherence in either group (table 4). In addition, good adherence assessed by the Number of days covered method was also associated with not working in patients with PAH (OR 0.595; 95% CI 0.357–0.991).

Concomitant treatments

Diuretics, β -blockers, statins and calcium channel blockers were the most commonly used chronic concomitant treatments for all patients. Patients with IPAH/HPAH that had a positive vasoreactivity test

at time of diagnosis and who did not receive any other PH-targeted treatment at the time of the present study were not included among those reported using calcium channel blockers as concomitant treatment. Patients with PAH were more often treated with a chronic concomitant treatment than patients with CTEPH (table 5). Antidiabetic drugs and treatment for hypothyroidism were twice as common among patients with PAH as for patients with CTEPH (table 5).

Of temporary treatments, 67% of the patients were treated with antibiotics at least once during the study period and 51% of the patients filled a prescription for a proton pump inhibitor (table 5). Other common drugs were treatments for obstipation and anaemia as well as steroids, asthma inhalers and antifungal crème/solution for external use.

Discussion

The main finding of the present study was that the overall adherence to oral ERA and/or PDE-5i/SGCs treatment was 60–65%. Adherence was associated with time since diagnosis, especially in patients with PAH, and with number of concomitant chronic treatments in patients with CTEPH. Sex, age or socioeconomic factors, such as level of education, income or marital status, did not affect adherence.

TABLE 1 Socioeconomic factors

	All	PAH	CTEPH
Subjects n	571	384	187
Age years	61±16	58±16	67±14
Age men years	64±15	60±15	68±14
Age women years	60±17	58±17	67±15
Sex (women)	349 (61)	269 (70)	80 (43)
Time since diagnosis years	4.6±4.2	4.8±4.4	4.2±3.3
Highest level of education			
Primary school	147 (26)	97 (25)	50 (27)
High school	264 (47)	183 (48)	81 (43)
College/University	147 (26)	93 (24)	54 (29)
Occupation			
Working	152 (27)	103 (27)	49 (26)
<65/≥65 years	135 (89)/17 (11)	98 (95)/5 (5)	37 (76)/12 (24)
Men/women	62 (41)/90 (59)	30 (29)/73 (71)	32 (65)/17 (35)
Not working	419 (73)	281 (73)	138 (73)
<65/≥65 years	149 (36)/270 (64)	126 (45)/155 (55)	23 (17)/115 (83)
Men/women	161 (38)/258 (62)	85 (30)/196 (70)	76 (55)/62 (45)
Marital status			
Married/registered partner	257 (45)	164 (43)	93 (50)
Not married/divorced/widowed	314 (55)	220 (57)	94 (50)
Number of households with children living at home			
0 children in household	447 (78)	286 (74)	161 (86)
1 child in household	70 (12)	56 (15)	14 (7)
2 children in household	38 (7)	32 (8)	6 (3)
≥3 children in household	16 (3)	10 (3)	6 (3)
Number of individual children in different age groups living at home			
0–6 years	31 (19)	25 (19)	6 (18)
7–19 years	80 (48)	67 (51)	13 (38)
≥20 years	55 (33)	40 (30)	15 (44)
Disposable income (kSEK)*			
Individual	202±137	193±134	221±142
Men	234±157	219±166	249±146
Women	181±118	181±116	182±126
Household	340±274	337±290	346±239
Men	361±233	352±239	371±227
Women	327±297	331±309	313±251

Data are presented as mean±SD or n (%), unless otherwise stated. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. #: Average disposable income in Sweden 2016–17 was 360 kSEK (www.scb.se/en/finding-statistics/statistics-by-subject-area/household-finances/income-and-income-distribution/income-and-tax-statistics/pong/tables-and-graphs/income-households-the-entire-country/disposable-income-by-type-of-household-2011-2017/).

TABLE 2 Pulmonary hypertension-specific treatment

	ALL	PAH	CTEPH
Subjects n	571	384	187
Endothelin receptor antagonists	346 (60)	289 (75)	57 (30)
Phosphodiesterase type 5 inhibitors/soluble guanylate cyclase stimulator	370 (65)	265 (69)	105 (56)
Prostacyclin analogues	68 (12)	60 (16)	8 (4)
Single	217 (38)	137 (36)	80 (43)
ERA	80	65	15
PDE-5i/SGC	106	43	63
PRO	2	0	2
CCB	29	29	
Double	214 (37)	175 (46)	39 (21)
ERA+PDE-5i/SGC	204	167	37
ERA+PRO	6	5	1
PDE-5i/SGC+PRO	4	3	1
Triple	56 (10)	52 (14)	4 (2)
ERA+PDE-5i/SGC+PRO	56	52	4
Untreated	84 (15)	20 (5)	64 (35)
Anticoagulants			
Warfarin	349 (61)	180 (47)	169 (90)
Other	92 (16)	74 (19)	18 (10)
Oxygen	52 (9)	37 (10)	15 (8)

Data are presented as n or n (%). PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; ERA: endothelin receptor antagonists; PDE-5i: phosphodiesterase type 5 inhibitors; SGCs: soluble guanylate cyclase stimulator; PRO: prostacyclin analogues; CCB: calcium channel blockers.

The present study used a strict method for treatment adherence, allowing only one missed daily dosage per month to be categorised as low adherence. In support of this method, the overall adherence to PAH treatment found in the study was in good concordance with the self-reported treatment adherence of 57% from the Swedish PAH and CTEPH population that has been published earlier [7]. The patient's perception of adverse side-effects that might occur has been shown to affect the patient's decision whether to take the drugs as prescribed or not [15, 16]. In addition, previous experiences with pharmacological therapies might lead to a lack of motivation to adhere to a treatment [17]. Thus, it is important to address

TABLE 3 Adherence to pulmonary hypertension-specific treatment

	All			PAH			CTEPH		
	Number included	% Adherence (NoDC)	% Adherence (Man)	Number included	% Adherence (NoDC)	% Adherence (Man)	Number included	% Adherence (NoDC)	% Adherence (Man)
ERA									
Ambrisentan	99	87	83	90	87	82	9	89	89
Bosentan	98	71	66	73	71	68	25	72	60
Macitentan	166	84	78	146	82	77	20	95	90
PDE-5i									
Sildenafil	207	60	61	146	61	62	61	59	59
Tadalafil	137	80	74	117	80	74	20	80	75
SGCs									
Riociguat	32	91	91	2	0	0	30	90	90
Single treatment	209	68	65	131	69	66	78	67	63
Double treatment	234	64	59	198	64	58	36	67	67
Oral[#]+PRO	66	74	70	60	73	70	6	83	83

Data are presented as number of patients who filled a prescription and were included in the analyses, and proportion of those with good adherence shown for Number of days covered (NoDC) and Manual assessment (Man) methods. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; ERA: Endothelin receptor antagonists; PDE-5i: Phosphodiesterase type 5 inhibitors; SGCs: Soluble guanylate cyclase stimulator; PRO: prostacyclin therapy. #: Adherence to oral treatment reported.

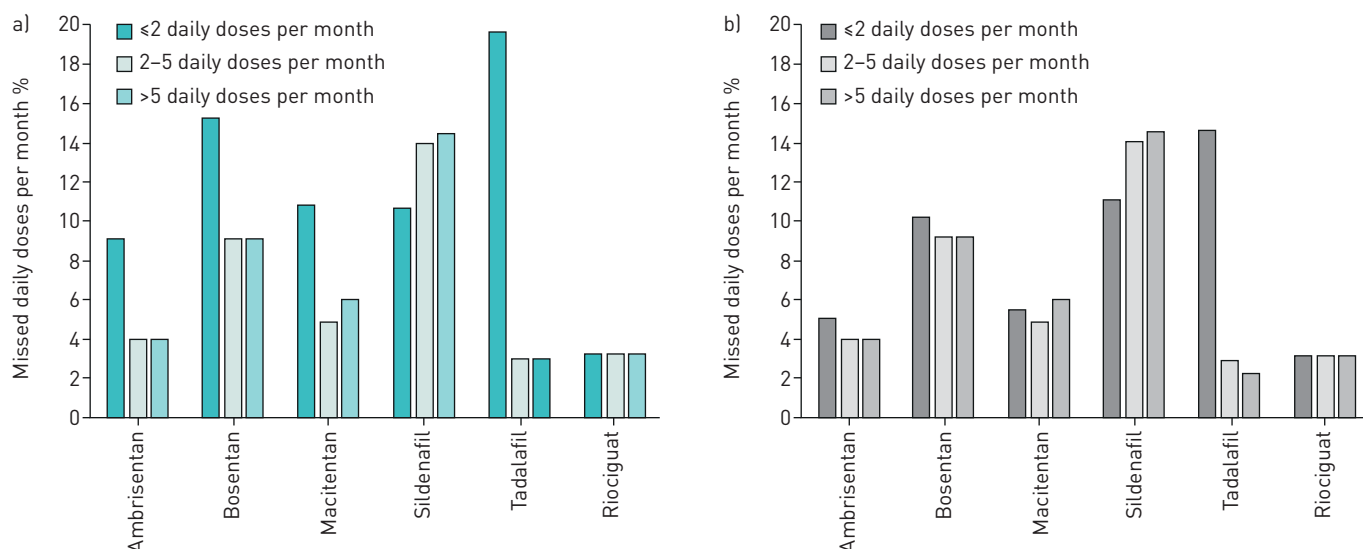


FIGURE 1 Proportion of low adherence by number of missed daily dosages per month shown for the manual assessment (a) and number of days covered (b) methods.

the patient's concerns about a treatment, both at the time of first prescription and at subsequent meetings with the patient [18, 19]. As shown in the present study, as well as in earlier studies, adherence to treatment decreases over time [7, 8].

In the present study, of those who did not meet the criteria of adherence, and with the exception of treatment with sildenafil, approximately half missed two or less daily dosages per month. This might be considered a medium level of adherence, while the quarter that missed more than five daily dosages per month might be at a low level. Patients on sildenafil would then be reckoned as a third in each category of medium, medium-low and low adherence. The effect adherence to PH treatments has on disease progression is not known. Neither is the threshold of adherence that should be considered low. While not taking the medication once or twice in a month might not seem a problem, the present study investigated prescription fill over a 2-year period. Thus, the number of daily dosages not taken represent an average of missed daily dosages per month over a longer period.

TABLE 4 Logistic regression analysis showing the relationship between adherence and explanatory variables

	All	PAH	CTEPH
Subjects n	571	384	187
Sex (female versus male)	0.725 [0.486–1.081]	0.704 [0.434–1.144]	0.808 [0.374–1.746]
Age (continuous)	1.009 [0.997–1.020]	1.010 [0.996–1.024]	1.002 [0.975–1.029]
Age (≤65 years versus >65 years)	0.749 [0.510–1.100]	0.725 [0.461–1.141]	0.870 [0.379–1.995]
Time since diagnosis			
≤1 year versus >1 year	2.036 [1.201–3.454]	1.813 [0.998–3.294]	3.027 [0.948–9.664]
≤2 years versus >2 years	1.912 [1.243–2.943]	1.786 [1.092–2.920]	2.421 [0.978–5.996]
≤3 years versus >3 years	1.933 [1.304–2.864]	1.962 [1.246–3.088]	1.876 [0.850–4.142]
Education (primary/high school versus college/university)	0.930 [0.597–1.448]	1.082 [0.644–1.818]	0.605 [0.256–1.429]
Marital status (married/registered partner versus not married/divorced/widowed)	1.138 [0.774–1.671]	1.120 [0.717–1.751]	1.154 [0.536–2.484]
Children living at home (yes versus no)	0.865 [0.538–1.393]	0.985 [0.579–1.674]	0.515 [0.167–1.589]
Working (yes versus no)	0.782 [0.503–1.216]	0.683 [0.413–1.131]	1.252 [0.487–3.219]
Household income (≤median versus >median[#])	1.142 [0.760–1.717]	1.009 [0.627–1.623]	1.642 [0.740–3.645]
Individual income (≤median versus >median[¶])	0.944 [0.643–1.386]	0.903 [0.578–1.411]	1.114 [0.516–2.404]
Number of PAH treatments (one, two or three)	0.938 [0.705–1.248]	0.880 [0.631–1.227]	1.380 [0.678–2.809]
Number of other treatments – chronic (0 to >8)	1.171 [1.033–1.328]	1.118 [0.969–1.290]	1.430 [1.074–1.905]
Number of other treatments – temporary (0 to >9)	0.945 [0.847–1.055]	0.970 [0.857–1.098]	0.867 [0.678–1.109]

Data are presented as odds ratios and 95% confidence intervals, unless otherwise stated. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. [#]: 360 kSEK; [¶]: 163 kSEK.

TABLE 5 Other concomitant treatment at time of study

	All	PAH	CTEPH
Subjects n	571	384	187
Chronic treatment (≥3 filled prescriptions per year)			
Angiotensin-converting enzyme inhibitors	108 (19)	81 (21)	27 (14)
Angiotensin receptor blockers	101 (18)	65 (17)	36 (19)
β-blockers	226 (40)	156 (41)	70 (37)
Calcium channel blockers	138 (24)	106 (28)	32 (17)
Anti-arrhythmia drugs	82 (14)	61 (16)	21 (11)
Statins	174 (30)	123 (32)	51 (27)
Diuretics	380 (66)	267 (70)	113 (60)
Antidiabetics	80 (14)	67 (17)	13 (7)
Thyroid replacement hormones	88 (15)	69 (18)	19 (10)
Number of patients that filled prescriptions for chronic treatments (≥3 per year)			
0	83 (15)	45 (12)	38 (20)
1	103 (18)	58 (15)	45 (24)
2	114 (20)	78 (20)	36 (19)
3	117 (20)	86 (22)	31 (16)
4	75 (13)	54 (14)	21 (11)
5	51 (9)	42 (11)	9 (5)
≥6	29 (5)	21 (6)	8 (5)
Temporary treatment (≥1 filled prescriptions per year)			
Drugs for anaemia	146 (26)	107 (28)	39 (21)
Antibiotics	384 (67)	275 (72)	109 (58)
Antihistamines	101 (18)	68 (18)	33 (18)
Antiviral drugs	51 (9)	44 (11)	7 (4)
Asthma oral therapy	12 (2)	7 (2)	5 (3)
Asthma inhaler therapy	171 (30)	119 (31)	52 (28)
Antidiarrhoeal drugs	79 (14)	62 (16)	17 (9)
Anti-emetics	61 (11)	52 (14)	9 (5)
Anti-acid drugs	47 (8)	41 (11)	6 (3)
Proton pump inhibitors	294 (51)	219 (57)	75 (40)
Laxatives	204 (36)	143 (37)	61 (32)
Antifungal – oral therapy	2 (<1)	2 (1)	0
Antifungal – cutaneous/solution	191 (33)	142 (37)	49 (26)
Steroids – oral therapy	177 (31)	132 (34)	45 (24)
Number of patients that filled prescriptions for temporary treatments (≥1 per year)			
0	56 (10)	30 (8)	26 (14)
1	79 (14)	43 (11)	36 (19)
2	100 (17)	64 (17)	36 (19)
3	73 (13)	45 (12)	28 (15)
4	92 (16)	69 (18)	23 (12)
≥5	172 (30)	133 (35)	39 (21)

Data are presented as n (%), unless otherwise stated. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

Adherence to PH treatment varied from a 91% adherence to riociguat to a 60% adherence to sildenafil in the present study. However, these results should be interpreted with caution. The use of riociguat was approved in Sweden the year before the present study, and only a small proportion of the patients, and almost all with CTEPH, were treated with it. Both sildenafil and riociguat are prescribed three times a day, a treatment regimen that has previously been associated with low adherence [5, 8, 10, 20]. With riociguat being the only drug in Sweden approved for CTEPH at the present time, this might support a high adherence, at least initially [21]. In addition, riociguat requires more frequent contact with the PAH clinic during the dose-adjustment period, which might also lead to higher adherence. With the exception of riociguat, and in concordance with earlier results, treatments administered once a day had the best adherence [8, 20].

There was no association between adherence and number of PH treatments in the present study. This is in contrast to a previous study by *STUDER et al.* [10] that showed that patients on combination therapy had higher adherence. Study design and treatment regimen probably explain some of the differences. Patients in that study were newly diagnosed, and only a quarter of the identified patients met the inclusion criteria

and were investigated. A majority were treated with monotherapy, in particular PDE-5i, after diagnosis, and at the end of the 12 months the study lasted, 75% were still being treated with only one PH treatment [10]. In the present study, only 38% were treated with monotherapy during the course of the study. Time since diagnosis and number of concomitant chronic drugs were the only investigated variables that showed an association with low adherence in the present study, the latter probably reflecting a higher comorbidity burden [8, 22]. Similar results have been shown in two previous studies using self-reported adherence instruments [7, 8]. However, both those studies showed an association with higher age that was not present in the current study. In addition, GRADY *et al.* [8] showed an association between monotherapy and adherence, while IVARSSON *et al.* [7], similar to the present study, saw no association between either single or combination PH treatment and adherence. The discrepancy between the results might be related to the low proportion of patients on combination therapy in the GRADY *et al.* [8] study.

All patients included in the present study have regular contact with the PAH/CTEPH-expert centres [23], which may have increased their understanding of the PAH disease, improved involvement in treatment decision and supported good medical literacy, factors that have been related to adherence [17, 24]. Building trust between patients, caregivers and staff might affect the patient's health beliefs and attitudes concerning the effectiveness of the treatment [19, 24, 25]. However, this might also have an opposite effect as the healthcare staff feel they know the patient, and thus, information about the disease and the importance of treatment is not repeated regularly, leading to declining adherence over time. In a recent study it was shown that despite agreeing that they received appropriate information, about half of the patients wanted more information [26].

High costs or co-payments for treatment and healthcare have been shown to contribute to poor medication adherence [17, 27]. However, in the present study there was no relation between socioeconomic factors and adherence, despite the household income being at, or slightly lower than, the average disposable income in Sweden. The cost ceiling in the Swedish healthcare system that covers almost all costs related to care, including drug prescriptions, probably contributed to this finding.

The rather high proportion of patients in the present study that filled three or more prescriptions of treatments for other chronic diseases indicates that comorbidities were common in this patient population. In addition, prescriptions for temporary treatments such as antibiotics, proton pump inhibitors and other treatments related to digestive symptoms were also frequently filled. This might be related to side-effects of the PAH-specific drugs or might mirror the comorbidity burden related to increasing mean age of the PAH patients, seen all over the world [28, 29]. The number of patients prescribed antibiotics, about two thirds of the study population, was surprisingly high. One might speculate that some overuse of antibiotics to avoid severe infections in these patients might occur, especially as patients generally contact the primary care service for common colds and infections. The PAH/CTEPH-expert centres are essential for coordinating the contacts with other parts of the healthcare system, such as being accessible for questions from the primary caregivers in the context of these rare diagnoses [30].

A quarter of the patients with PAH had children living at home, and of those, two thirds were 19 years old or younger showing that it is a disease that still affects the young in high proportion [1, 29]. In this study, there was no relation between age, sex or the family situation to treatment adherence. The proportion of patients living alone was higher than in the general Swedish population, a finding in concordance with other reports that divorce is not uncommon in this patient group [31]. However, there was no relation between marital status and adherence in the present study, despite an earlier study showing that spouses want to support treatment adherence to prolong life for their partner [32].

It is obvious that low treatment adherence will contribute to suboptimal clinical benefits. This has further been highlighted by the World Health Organization (WHO), which stated that increasing adherence may have a greater effect on health than any improvement in specific medical treatments [28]. It has been suggested that the best strategy to improve treatment adherence is to involve the patient in the medical decision process and stress the immediate advantages of treatment instead of future complications [17].

Methodological considerations

The adequate sample size in the form of a national cohort of patients alive in 2016–2017 recorded in a register with >90% national coverage is a strength. The proportion of patients with PAH and CTEPH are in alignment with the proportions of patients in the Swedish PAH registry [11]. The analysis of adherence was based on filled prescriptions, and thus, the study has assumed that this reflects the patients actually taking the drug they have collected from the pharmacy. Adherence to prostacyclin analogues and the prostacyclin receptor agonist was not analysed due to the individualised dosages that are used for this group of drugs. In the analysis of other temporary treatments, there is probably a suboptimal reporting of

treatments such as antifungals, antihistamines and treatments for gastrointestinal symptoms, which can be purchased without a prescription in Sweden.

Conclusions

Adherence to oral ERA and/or PDE-5i/SGCs treatment was 60–65% and associated with time since diagnosis and with number of concomitant chronic treatments. Sex, age or socioeconomic factors, such as level of education, income or marital status, did not affect adherence.

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