STUDY REPORT SYNOPSIS

COPVAR
A Cross-sectional study of patients with severe COPD to assess patient perception of symptom variability in MEA countries

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Although Chronic Obstructive Pulmonary Disease (COPD) symptoms have been extensively reviewed in the literature, daily and weekly variation of symptoms and their impact on daily life activities have received less attention, especially in the Middle East and Africa (MEA). No published study in MEA has investigated the fluctuation of COPD symptoms, the COPD treatment patterns and their consistency with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.
This non-interventional study aimed at assessing stable GOLD C and D COPD patient's perception of daily and weekly symptoms variability and their impact on daily activities.
It also explored the current practice in management of stable GOLD C and D COPD patients.

Objectives:

Primary:

- To assess the perception of weekly and daily variability of symptoms in stable GOLD C and D COPD patients and their impact on daily life activities.

Secondary:

- To describe the current treatment practice for the management of GOLD C and D COPD in MEA countries and their adherence to the GOLD 2015 guidelines
- To compare patients' perception of symptoms variability and their impact on activities between categories C and D
- To identify demographic, behavioral and clinical factors associated with symptoms variability

Study design: Non-interventional, cross-sectional multinational multicentre study in 8 MEA countries: Algeria, Egypt, Kuwait, Qatar, South Africa, Saudi Arabia, Turkey, United Arab Emirates (UAE), .

Data source: Data were directly collected from:

- The patients via self-administered validated questionnaires : COPD Assessment Test (CAT), Capacity of Daily Living during the Morning (CDLM), Global Chest Symptoms Questionnaire (GSCQ) and Morning Activities and Symptoms Questionnaires (MASQ) translated in the participating countries local language (Arabic, Turkish, French).
- The investigator via the case report form (CRF) filled during the routine assessment/examination visit of the patients using the patients' personal information, their hospital charts and medical records whenever needed (e.g. last spirometry measures, comorbidities, concomitant medications, COPD exacerbations in the past year…).

Study population:
Patients with Stable GOLD C and GOLD D COPD (according to GOLD 2015)

Planned: 3085 patients: Algeria (800 patients); Egypt (1200 patients); Turkey (810 patients); Kuwait, UAE and Qatar (135 patients); Lebanon and Jordan (200 patients).

Analyzed: 3253 patients; Algeria (711 patients); Egypt (1143 patients); Kuwait (92 patients), Qatar (12 patients); Kingdom of Saudi Arabia (124 patients); Turkey (810 patients); UAE (47 patients), South Africa (314 patients).

Inclusion criteria:

1. Stable COPD GOLD C or D patient under maintenance treatment, over 45 years, who provided signed informed consent;
2. COPD diagnosis documented by spirometry performed in the past 12 months with a ratio of Forced Expiratory Volume in 1 Second (FEV1) to Forced Vital Capacity (FVC) < 0.7 and an FEV1 < 50% predicted.

Exclusion criteria:

1. Patient with an ongoing COPD exacerbation (an exacerbation was defined as worsening of COPD symptoms leading to treatment with antibiotics and/or a short course of oral steroids and/ or hospitalization or emergency room visit);
2. Patient who had experienced an exacerbation in the previous 3 months;
3. History of asthma, allergic rhinitis, lung cancer or any other significant respiratory disease, such as tuberculosis, lung fibrosis or sarcoidosis;
4. Inability to understand the study related questions;
5. Mentally disabled patient or unable to read and write;
6. Pregnant;
7. Current participation in a clinical trial.

Statistical methods:

Statistical analyses were performed using the Full Analysis Set (FAS) defined as all patients whose data have been entered in the database.

All analyses were performed overall and separately for each country (Statistical report for each country is available as stand-alone-document). Results by country are not discussed in this report. Separate study reports are available for Algeria, Turkey, Egypt and South Africa.

The primary and secondary endpoints were described using usual statistics.

- For the primary objective: Description of the score for GCSQ, MASQ, and CDLM questionnaires; Percentage of patients experiencing daily and/or weekly symptoms variability as captured in the CRF and the GCSQ; Percentage of patients whose daily activities were affected by COPD symptoms as captured in the CAT.
- For secondary objectives: Description of the the treatment patterns captured in the CRF; Descriptive statistic of the score for GCSQ, MASQ, and CDLM questionnaires by GOLD C and D category, Percentage of patients experiencing daily and/or weekly symptoms variability as captured in the CRF and the GCSQ by GOLD C and D category.

As the statistical analysis showed a discordance between the GOLD category (C or D) reported in the CRF by the investigator and the GOLD category calculated from the CAT questionnaire (GOLD C if CAT score < 10 and GOLD D if CAT score ≥ 10) at the study visit, all planned analyses were also performed using the re-calculated GOLD category (post-hoc analysis).

- A Multivariate logistic regression was performed to identify demographic, behavioral and clinical factors likely associated with daily and weekly symptoms variability. First, a logistic regression was performed for each factor tested, adjusting on age, sex and country. Then, all factors (in addition to age, sex and country) significantly associated with daily (respectively weekly) symptoms variability at the 20% level were introduced in a model. Backward selection was used to select only the significant factors (at the 5% level). No adjustments were performed for multiple comparison/multiplicity.

- Daily and weekly variations of symptoms were compared between GOLD C and D categories using a Chi square test.
- Therapeutic behaviour in response to symptoms variability was compared between GOLD C and D categories using a Chi square test.
- The MASQ and CDLM were compared between GOLD C and D categories using a Cochran Armitage test.
- The CAT global scores assessed were compared between GOLD C and D categories using Student's t-test. The CAT subscores (8 items) were compared between GOLD C and D categories using a Cochran Armitage test.

Results:

Patients disposition
3253 patients (mean age 64.1±9.4 years, 90% of males) were enrolled in this study: 1143 (35.1%) in Egypt; 810 (24.9%) in Turkey, 711 (21.9%) in Algeria, 314 (9.7%) in South Africa, 124 (3.8%) in KSA, 92 (2.8%) in Kuwait, 47 (1.4%) in UAE, and 12 (0.4%) in Qatar.

Smoking habits and biomass exposure
36.0% of patients were cigarette smokers, 59.7% were ex-smokers and 6.4% were non smokers. Biomass exposure was reported in 25.2% of patients.

Disease history
On average, COPD was diagnosed since 9.0±7.0 years. The mean FEV1/FVC (% predicted) was 53.6±12.7% and the mean FEV1 (% predicted) was 36.8±9.7%. The mean number of exacerbation in the last 12 months was 1.7±1.5 (range: 0-18). Based on the investigator recording, 1240 (38.5%) patients were categorized as GOLD C COPD and 1981 (61.5%) patients as GOLD D. However, this was not found to be concordant with the distribution of patients according to the CAT questionnaire (331 patients, 10.2% with CAT < 10 and 2906 patients, 89.3%, with CAT ≥ 10) (see below).

Comorbidities
Overall, 61.3% of patients had at least one comorbidity including hypertension (41.0%), diabetes mellitus (21.4%), hyperlipidemia (15.9%) and ischemic heart disease (14.6%) for the most frequent.

Primary Study Endpoints

COPD symptoms in the last 7 days
Breathlessness was reported in 84.6% of patients, phlegm in 73.6%, cough in 75.4%, wheezing in 66.9%, and chest tightness in 72.1%.

Daily and weekly symptom variability

- 83.4% of patients reported at least one daily symptom variability, including breathlessness (64.6%), phlegm (52.9%), cough (54.8%), wheezing (52.9%), and chest tightness (56.7%)
- 81.6% of patients reported at least one weekly symptom variability, including breathlessness (62.1%), phlegm (53.8%), cough (54.7%), wheezing (55.3%) and chest tightness (56.6%).

Therapeutic behavior in response to symptom variability
In response to symptom variability, 55.2% of patients continued using the medications in exactly the same way, 46.9% used more of emergency inhaler, and 26.5% varied the dose and/or frequency of regular daily medication.

Global Chest Symptom Questionnaire (GCSQ)
The mean global score of the GCSQ was similar at each time of the day: 1.4±1.1 in the morning, 1.2±0.9 in the afternoon, 1.4±1.1 in the evening, and 1.5±1.1 at night.

Morning Activities and Symptoms Questionnaire (MASQ)
Overall, 10.4% of patients needed help to get out of bed and 2.3% were unable to get out of bed; 55.3% of patients were able to get out of bed in the morning but with some difficulties and 27.9% with moderate to extremely severe difficulties.

Capacity of Daily Living during the Morning (CDLM)
The mean global score was 3.7±1.1 indicating mild to moderate difficulties to carry out morning activities including washing (3.5±1.6), drying with a towel (4.0±1.2), getting dressed (3.9±1.3), eating breakfast (4.0±1.6), walking around home early in the morning after taking medicine (2.9±2.0) and walking around home later in the morning (3.0±1.9).

Results from the CDLM questionnaire showed that:

- 63.7% of patients had difficulty for washing themselves (moderate to severe difficulty in 42% of patients).
- 55.1% of patients had drying difficulty (moderate to severe difficulty in 30.1% of patients).
- 58.7% of patients had difficulty for getting dress (moderate to severe difficulty in 32.9% of patients).
- 44.1% of patients had difficulty for eating breakfast (moderate to severe difficulty 22.7% of patients).
- 69.9% of patients had difficulty for walking around home early in the morning (after taking medicine) (moderate to severe difficulty in 47.6% of patients)
- 71.1% of patients had difficulty for walking around home later in the morning (moderate to severe difficulty 48.0% of patients).

COPD Assessment Test (CAT)
The mean CAT global score assessed by the patient was 20.5±7.9 (ranging from 0 to 40)

- 93.7% of patients were affected by cough (moderate to extremely in 45.8%).
- 93.3% of patients were affected by phlegm (moderate to extremely in 48.1%).
- 93.3% of patients were affected by chest tightness (moderate to extremely in 57.6%).
- 98.2% of patients had breathlessness when walking up a hill or one flight of stairs (moderate to extremely in 77.5%).
- 87.6% of patients were limited doing activities at home (moderate to extremely in 51.2%).
- 79.4% of patients were not confident leaving home despite their lung condition (moderately to extremely not confident in 40.0%).
- 83.2% of patients did not sleep soundly (moderate to extremely in 45.1%).
- 94.3% of patients did not have lots of energy (moderate to extremely in 59.0%).

Secondary Study Endpoints
Current treatment modalities
The most frequent treatment modalities were:

- Long-acting ß2-agonist (LABA) + inhaled corticosteroid (ICS) (as fixed or free combination) in 68.6% of patients
- Long-acting muscarinic antagonist (LAMA) or LAMA + LABA in 67.6% of patients
- Short-acting ß2-agonist (SABA) or Short Acting Muscarinic Antagonist (SAMA) in 58.8% of patients

Statistical analyses by GOLD category according to CAT questionnaire (Post-hoc analysis)
A post-hoc analysis showed that the GOLD C and D categories reported by investigators in the CRF were not concordant (Kappa=0.24 95%CI: 0.21 ; 0.27) with the GOLD C and D category determined using the CAT score. The CAT score showed 331 (10.2%) patients with a CAT score < 10 and 2906 (89.3%) patients with a CAT score ≥ 10. There were 16 patients (0.5%) with missing CAT who were not categorized.

Patients characteristics by GOLD category (according to CAT questionnaire)
Age and anthropometric variables were similar between groups. The proportion of cigarette smokers was slightly lower in GOLD C patients (29.0%) than in GOLD D patients (36.6%) while the proportion of ex-smokers was slightly higher in GOLD C (65.3%) than in GOLD D patients (59.0%).

The time since COPD diagnosis was lower in GOLD C patients (6.6±5.6 years) than in GOLD D patients (9.3±7.1 years). The mean number of exacerbation in the last 12 months was lower in GOLD C than in GOLD D patients (0.9±1.1 versus 1.8±1.5).

The rate of patients with comorbidities was also lower in GOLD C than in GOLD D patients (51.4% versus 62.1%), mainly hypertension (33.8% versus 41.8%). Consequently, the rate of patients taking concomitant therapy was also lower in GOLD C than in GOLD D patients (46.2% versus 56.8%), mainly anti-hypertensive therapy.

Treatment pattern of COPD according to GOLD category (according to CAT questionnaire)
Maintenance treatments for COPD are described by GOLD category in the table below.

	GOLD C N=331	GOLD D N=2906
Inhaled SABA or SAMA	200 (60.4%)	1695 (58.3%)
Inhaled LABA	40 (12.1%)	540 (18.6%)
Inhaled LAMA	215 (65.0%)	1648 (56.7%)
Inhaled LABA + LAMA	20 (6.0%)	297 (10.2%)
ICS	27 (8.2%)	480 (16.5%)
ICS + LABA (Fixed dose combination)	202 (61.0%)	1520 (52.3%)
ICS + LABA (Free combination)	47 (14.2%)	441 (15.2%)
ICS + LAMA	3 (0.9%)	22 (0.8%)
Methylxanthine	46 (13.9%)	807 (27.8%)
PD4 inhibitor	4 (1.2%)	44 (1.5%)
Antibiotics	11 (3.3%)	177 (6.1%)

Influenza vaccination during the last year was reported in 48.0% of GOLD C patients versus 39.4% of GOLD D patients and pneumococcal polysaccharide vaccination in 8.9 and 11.3%, respectively.
Current non-pharmacologic treatment included smoking cessation (28.6% and 29.3% of GOLD C and GOLD D patients, respectively), pulmonary rehabilitation program (5.2% and 6.6%, respectively), physical activity (20.5% and 16.7%, respectively), and oxygen therapy (7.3% versus 15.5%).

Daily and weekly variation of COPD symptoms by GOLD category (as recalculated)
The proportion of patients with daily symptoms variability was lower in GOLD C than in GOLD D patients (76.9% versus 83.9%, P=0.012). This was statistically significant (P<0.001) for breathlessness (51.0% versus 65.7%), cough (40.7% versus 55.9%), wheezing (33.6% versus 54.3%), and chest tightness (30.8% versus 58.7%), but not for phlegm (46.7% versus 53.5%, P=0.092).

Regarding weekly symptom variability, the proportion of patients with weekly symptoms variability was not significantly different between groups (78.3% in GOLD C versus 81.8% for GOLD D, P=0.265). The difference was statistically significant for breathlessness (47.0% versus 63.4%, P<0.001), cough (43.4% versus 55.6%), wheezing (39.1% versus 56.3%), and chest tightness (32.4% versus 58.4%), but not for phlegm (46.5% versus 54.3%, P=0.059).

Factors affecting daily variation in COPD symptoms were the following

- The number of exacerbations
- The GOLD D category
- The time since COPD diagnosis
- Smoking cessation
- Current cigarette smoking
- Biomass exposure

Factors affecting weekly variation in COPD symptoms were the following using recalculated GOLD category

- The number of exacerbations
- The GOLD D category
- The time since COPD diagnosis

Therapeutic behaviour by GOLD category
Relatively more GOLD C patients than GOLD D patients (62.7% versus 54.5%, P=0.005) declared to continue using medications in exactly the same way in response to symptom variability. In addition, 15.9% of GOLD C patients versus 27.9% GOLD D patients (P<0.001) declared to vary the dose and/or frequency of regular medication, and 26.3% versus 49.3%, respectively (P<0.001) to use more emergency inhaler.

GCSQ by GOLD category

- In GOLD C patients, the mean GCSQ score was 0.4±0.6 in the morning, and there was no relevant change on average in the afternoon, in the evening or at night.
- In GOLD D patients, the mean GCSQ score was 1.5±1.0 in the morning, 1.3±0.9 in the afternoon, 1.5±1.1 in the evening, and 1.6±1.2 at night.

MASQ by GOLD category

- GOLD C patients were relatively not or only a little affected to get out of bed as assessed using the MASQ questionnaire.
- In GOLD D patients, 60% had difficulties to get out of bed in the morning including 30.9% with moderate to very severe difficulties.

CDLM by GOLD category

The CDLM mean global score was significantly (P<0.0001) higher in GOLD C (4.6±0.6) patients than in GOLD D (3.5±1.1) patients indicating more difficulty to perform morning activities in GOLD D patients. The most impacted morning activity was walking around home early in the morning after taking medicine (4.2±1.6 in GOLD C patients versus 2.8±2.0 in GOLD D patients, P<0.0001) and walking around home later in the morning (4.1±1.6 in GOLD C patients versus 2.8±1.9 in GOLD D patients, P<0.0001).

All morning activities were significantly (P<0.0001) less difficult to perform in GOLD C than in GOLD D patients.

- Washing was moderately to severely difficult in 5.7% of GOLD C patients versus 46.1% of GOLD D patients.
- Drying was moderately to severely difficult in 1.2% of GOLD C patients versus 33.7% of GOLD D patients.
- Getting dressed was moderately to severely difficult in 1.8% of GOLD C patients versus 36.6% of GOLD D patients.
- Eating breakfast was moderately to severely difficult in 4.6% of GOLD C patients versus 24.8% of GOLD D patients.
- Walking around home early in the morning (after taking medicine) was moderately to severely difficult in 15.2% of GOLD C patients versus 51.3% of GOLD D patients.
- Walking around home later in the morning was moderately to severely difficult in 15.5% of GOLD C patients versus 51.8% of GOLD D patients

CAT by GOLD category

As expected, the mean CAT global score assessed by the patient was significantly (P<0.0001) lower in GOLD C patients (6.8±2.1) than in GOLD D patients (22.0±6.8).

In GOLD C patients, each item was rather graded as mild. Breathlessness when walking up was mild (score 1 or 2) in 61.3% of patients and moderate in 20.8%.

In GOLD D patients, each item was rather graded as moderate to severe (score 3, 4 or 5) including cough (affecting patients moderately to all the time in 50.6% of patients), phlegm (moderately to completely full chest in 52.9%), tight chest (moderately to very tight in 63.9%), breathlessness when walking up (moderately to very breathless in 83.5%, including 28.2% very breathless).

56.9% of patients were moderately to very limited in doing activities at home and 45.3% were moderately to not at all confident leaving at home.

50.2% were moderately to severely affected for sleeping soundly and 65.0% had moderately to no energy at all.