"Screening for drug misusers in exacerbated chronic obstructive pulmonary disease (COPD) patients."

Authors

Eman M Mahmoud [1] **Zeinab Abdou Mohammed** [2]

Abeer El hawary [3] **Dalia Ans Ibrahim** [4]

[1] **Port Said Universiy**

[2] **Assistant professor of toxicology faculty of medicine**

Zagazig University

[3] **Assistant professor of Chest diseases faculty of medicine**

Zagazig University

[4] **Assistant professor of Chest medicine Zagazig University**

Abstract:

Background: Even though treatment   ıronic obstructive pulmonary disease (COPD) has improved, COPD exacerbation-related complications remain challenging. One related factor is substance use/abuse .Generally there is a rising concern about COPD with substance use to decrease the burden on health care because of substance use associated complications We, therefor aimed to asses the secondary morbidity, frequency of exacerbation and the need for Mechanical ventilation related to substance misuse in chronic obstructive lung disease patients .

Methods and Material: This is cohort population –based   study on 50 acute exacerbated COPD patients who were admitted to intensive care unit of Chest department, Zagazig University Hospitals during the period from February 2021to march 2022. After taking an informed consent from them they were classified into two groups Drug abusers group and non drug abusers group

Results: In between drug abusers group, opioids were the most prevalent misused substance (63%)). Also there was statistical significance difference between both patients groups as regards frequency of exacerbation, drug abusers significantly associated with higher rate of exacerbation, higher type II respiratory failure and higher rate of need for MV

Conclusions: Diagnosis of substance misuse was associated with increased risk of respiratory failure, increased frequency of exacerbation and the need for mechanical ventilation.

Key-words: COPD, respiratory failure, drug abuse, opiates

Introduction: COPD is the third cause of death all over the world. COPD phenotype (if there is emphysema or chronic bronchitis, overlap with asthma, moderate/severe exacerbations etc.), determine the mortality outcomes. [1]

Injection drug use has found to be associated with COPD [2] Despite the fact that people who inject drugs (PWID)   have a very high smoking prevalence. [3]

For COPD patients, quitting smoking is a standard of therapy. [4] Indeed, quitting smoking has shown positive results in reducing airway obstruction and COPD consequences. [5] Smoking with COPD is not just confined to cigarettes; it can

also take the form of smokeless tobacco, pipe tobacco, and cigars. [6] Inflammatory markers for COPD have increased with the use of alcohol, marijuana, and other licit and illicit substances. [7] Studies have found that substance use increases the hospitalisation, complications, and death associated with chronic diseases. [8] Unpleasant psychosensory feelings of pain and anxiety are usually prevalent with COPD. It's unknown whether adults with COPD use over-the-counter medications, such as sedatives and opioids, to treat these symptoms or for other purposes. [9] The negative effects of abusing those medications include anxiety, restlessness, [10] lead to catastrophic actions [11].

Quantifying the secondary morbidity, frequency of exacerbations, and need for mechanical ventilation in patients with chronic obstructive lung disease is the goal of this study

Subjects and Methods:

Design and Setting

This cross-sectional study included 50 men and women with acutely exacerbated COPD who were admitted by acute exacerbation to the chest intensive care unit at Zagazig University Hospitals, Egypt, between February 2021 and March 2022. Their ages ranged from 47 to 78 years.

The study was approved by the Zagazig University institutional review board (Zu-IRB No.6308/22/1/2019). Written informed consent was obtained from each participant.

Exclusion criteria: COPD patients with obvious strong cause for exacerbation (pneumonia, pneumothorax, MI).

I. Clinical evaluation:

1. Clinical diagnosis included medical history (smoking, cough, expectoration, progressive dyspnea, drug used…), irreversible airflow obstruction on spirometry, physical examination and chest X-ray examination.

2. ECG for all patients, Echocardiography if indicated to evaluate the cardiac condition.

3. ABG (Arterial blood gases) evaluation.

II. Laboratory Investigations.

II.A. General Laboratory Investigation:

All Participate were subjected to routine lab investigations.

II. B. Toxicological Laboratory investigation:

II-B.1. Screening for drug abuse in urine specimen using Rapid dipstick:

The one-venture screen test board ABON Multi-Drug was used to evaluate urine tests for drug abuse, which included tramadol, narcotics, tetrahydrocannabinol (THC), amphetamine, barbiturate, benzodiazepines, cocaine, and ethanol. The test was considered sure if appearance of two lines (a tinted line in the control region [C] and another shaded line in the test region [T] for a specific medicine), negative if one line just appeared (a toned line in the control line region [C] yet no line in the test line district [T] for a specific drug), or invalid on the off chance that there was no line in the control line area [C]).

II- B.2. Confirmation in a blood sample of drug abuse.

Blood tests were gathered from patients utilizing aseptic method and safeguards. An ethylenediaminetetraacetic corrosive (EDTA)-sealed tube was used to collect three milliliters of blood for the test. These models were set apart with the patients' information and were held under controlled conditions at - 20°C until be run on the device to investigate for presence of unlawful medication use.Confirmation for drug abuse in blood specimen.

Methods

• RANDOX Evidence Investigator Biochip Immunanalyser (machine id: EI-13286) Semiautomated benchtop immunoanalyser in Zagazig college poison control focus lab; Zagazig University Hospital, Egypt. This analyzer obliges concurrent discovery of various medication metabolites from a solitary example. The framework is unit based and accommodates every one of the vital parts like the chips, synthetic substances, calibrators and creating specialists.

The center effectively provided the Randox Kits and controls used in the study. The device used to detect drug abuse in blood samples for.

• The Randox drug of abuse (DOA) pack contains 10 milliliters of form, 10 milliliters of test diluents, 9 milliliters of calibrators, 54 biochips, 10 milliliters of luminal-EV841 and 10 milliliters of peroxide, 10 milliliters of phosphate cradle (pH 7.2), 20 milliliters of Tris cushioned saline (pH 7.4) containing Control one and control two are the two modules that make up the gadget quality control. These controls are lyophilized powder controls. The controls hold a comparative reach and assortment of analytes pursued for inside the pack

at two unique centers levels, which cover the eliminate ranges. . [12] Nuve NF200 centrifuges were utilized. A Sam Lab Egypt CO provided double deionized water• The Randox Kits and controls used in the study were effectively offered by the center.. The device used for detecting drug abuse in the blood sample for.

Specimen acquisition and processing

• 3 ml blood sample was collected from patients using aseptic technique and precautions dispensed into an (EDTA) preserved tube and at -20°C until investigated on the device.

Tests

Sample preparation

Sample preparation was done according to the instructions. [12] .Controls and pack were taken out the refrigeration unit to arrive at temperature room. Each jug of the calibrators and controls contained 1 mL of deionized water, which was then placed on an ABC powerhouse for 30 minutes. The named blood tests after allowed to thaw out to temperature room were centrifuged using a Nuve NF200 at 13000rpm for 10 minutes. 50µl of test diluent bringing about a four-overlay weakening. The biochip transporters were eliminated from their bundling, mathematically named and afterward positioned on the transporter holder. [13] Adjust the thermo-shaker prior to start. the test by around 30 min to permit temp to reach 25◦ as per the directions of the exhibit framework.

Analysis:

Analysis was performed according to the instructions, 120µl of measure diluent was been pipetted into every single biochip well of the biochip carriers followed with sixty µl of reconstituted, controls, calibrators and organized model, into their different wells. After that, 120 l of shape (a protein known as a neutralizer) was pipetted into each well. After that, the biochip transporter holder that was holding the biochip transporters was moved into the canteen shaker, where it was heated to 25 °C and spun at 330 rpm for 30 minutes. During that time, the sign reagent, which consisted of peroxide and luminol in a 1:1 ratio, was prepared, placed in a darkened compartment, and then blended for 15 minutes on a powerhouse. Subsequent to bring forth the abundance blends in each biochip carrier were killed and the biochip carriers were washed using the wash support course of action. The wash cycle included 6 fast flushes and six 2-minute sprinkles. The biochip transporters were filled with wash cushion

solution following the final wash and drenching to prevent the biochips from drying out. The biochip carriers were been arranged independently for imaging. The expecting carriers were been covered by aluminum foil to safeguard them from light transparency. Preceding imaging the biochip, carrier was been tapped onto dry paper towel to deduct waiting wash pad. After that, 250 mL of the working sign reagent was added to each biochip well, covered to prevent light from entering, and left for two minutes. The biochip transporter was then loaded into the Randox Evidence Investigator for imaging at that point. The photos were normally acknowledged and dealt with by the item. Change twists were been set up for every medicine or drug pack and the results were been displayed as spotlights and these were recorded on the result sheet. Prior to acknowledging the results of the examples, both results of quality control were confirmed in accordance with manufacturer details and quality confirmation information. Table (1) shows the Randox hints that were used as the cut-off values for the analysis.

Table (1) shows the cut-off values applied to the analysis were as per Randox recommendations:

Analyte	Cut-off level (ng/mL)
Amphetamines	25
Barbiturates	50
Benzodiazepine	50
Buprenorphine	1
Tetrahydrocannibinol	10
Benzoylecgonine	50
3,4- Methylenedioxymethamphetamine	60
Methadone	25
Methamphetamine	50
Opiates	25

Sample Size Calculation

Test size computation was conveyed utilizing the accompanying equation [14] .: n=Z2 X P (1P)d2, where d is the absolute precision of 5%, P is the expected prevalence from the literature, and z is the standard normal variate with a type of error of 5% (P.05). A range of 50 to 124 was thought to be a sufficient sample size. Therefore, 50 participants were included in the study. Microsoft Excel was used to code and analyze the historical, medical, and investigational data. After

that, for analysis, they were imported into the software program Statistical Package for the Social Sciences (SPSS version 20.0). Quantitative continues group represents by mean SD, while qualitative numbers and percentages are used to represent qualitative variables; The Chi square test (X2) examines the association and difference of a qualitative variable. The distinctions between quantitative free gatherings by t test. For results that were highly significant, we assigned a P value of 0.001 and a P value of 0.05, respectively.

Results:

Both groups (Drug abusers and non-drug abusers) matched according to age, sex, and smoking habit

and associated co-morbidities.

Table 2: demographic data distribution among studied group regarding sex and smoking.

			Abusers	Non abusers	
Age			59.89±7.41	62.96±7.62	0.169
Sex	Male	N	13	18	
		%	68.4%	58.1%	
	Female	N	6	13	0.46
		%	31.6%	41.9%	
Smoking	Yes	N	16	14	
		%	84.2%	45.2%	
	No	N	3	17	0.006*
		%	15.8%	54.8%	
Total		N	19	31	
		%	100.0%	100.0%	

Table 2: Shows that there was no significant difference between addicted and non addicted COPD

patients regarding age ,sex while a significant difference was detected as regard smoking

(p=0.006)Both groups (Drug abusers and non-drug abusers groups) were matched as regards age,

7

sex, and smoking habit and associated co-morbidities. The mean age was (62.96±7.6 versus 59.89±7.41 years) in group 1 and group 2 respectively. In group I and group Π, male patients were (58.1% versus 68.4%).

Table 3: Shows that, opioids were the most prevelant addicted substance (63%) while methadone was the least abused substance among addicted patients (5.3%)

Table 3: type of drug abuse between studied groups,

Drug	N	% from total	% from drug abusers
Tramadol	9	18.0	47.4
Opioids	12	24.0	63.2
Barbiturate	4	8.0	21.1
Amphetamine	3	6.0	15.8
THC	9	18.0	47.4
Benzodiazepine	5	10.0	26.3
Methamph	2	4.0	10.5

Table 3: Shows that, opioids were the most prevelant addicted substance (63%) while methadone was the least abused substance among addicted patients (5.3%)

Table 4: Comparison of general lab investigation (complete blood count, liver function test, kidney function test and random blood glucose test between two groups.

		Drug abuse	Non abusers	P
PH		7.27±0.06	7.23±0.04	0.022*
Paco2		88.0±17.3	93.29±7.12	0.137
Pao2		48.0±7.71	51.51±8.32	0.143
Hco3		41.05±8.03	42.87±4.47	0.308
O2_Sat		64.47±9.35	69.48±12.25	0.133
WBCs		14.53±3.68	15.79±5.26	0.366
Hb		13.37±1.98	13.04±2.21	0.598
ALT		38.94±13.87	42.64±14.16	0.503
AST		30.10±10.54	32.38±11.1	0.543
Alb		3.15±0.28	3.04±0.19	0.134
Cr		1.0±0.22	1.12±0.38	0.089
Urea		21.1±8.12	23.29±7.79	0.394
RBS		135.57±42.6	190.51±64.85	0.007*
Total	N	19	31	
	%	100.0%	100.0%	

Table 4: Shows that There was significant difference between two group regarding PH .Addicted cases significantly associated with acidic PH (P=0.022) , lower RBS(P=0.007)

Table 5: frequency of COPD exacerbation between two groups:

			Drug abuser	Non abuser	P
Frequency of Exacerbation	I	N	4	18	
		%	21.1%	58.1%	
	II	N	8	11	0.007*
		%	42.1%	35.5%	
	III	N	7	2	
		%	36.8%	6.5%	
Total		N	19	31	
		%	100.0%	100.0%	

Table 5: Shows that Addicted cases significantly associated with higher rate of exacerbation(P= **0.007**)

Table 6: Causes of COPD exacerbation between two groups

Cause of exacerbation		Drug abuser	Non	P
Tracheobronchial Infection	N	9	16	
	%	47.36%	51.6%	.041
CHF	N	3	5	
	%	15.7 %	16.1%	
	N	0	3	
PE	%	0.0%	9.7%	
Smoking	N	0	3	
	%	0.0%	9.7%	
Unknown	N	7	4	
	%	36.9%	12.9%	
	N	19	31	
	%	100.0%	100.0%	

Table 6: Shows that   Addicted cases significantly associated with higher unknown cause of exacerbation (p= **0.041***)

11

Table 7: comparison of types of Respiratory Failure between two groups:

			Drug abuse	Non	P
Type of RF	II	N	13	5	
		%	68.5%	16.2%	
	I	N	6	26	0.0001**
		%	31.5%	83.8%	
	Total	N	19	31	
		%	100.0%	100.0%	

Table 7: shows that Addicted cases significantly associated with higher rate of MV (p=**0.0006**)
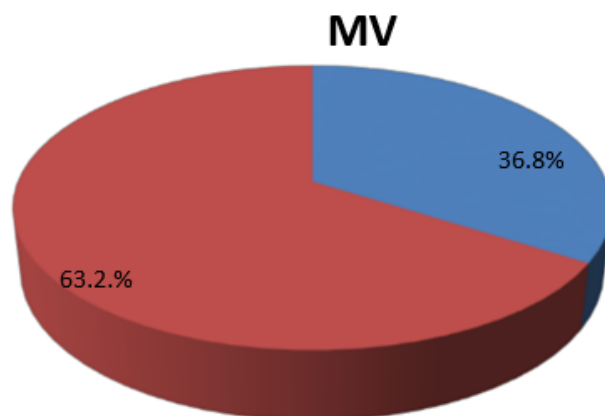
Figure (1)

MV

36.8%

63.2.%

Figure (1) illustrates that there was a statistical significant difference between both patients' groups regarding the need for mechanical ventilation (MV). Drug abuse patients were significantly associated with high rate of MV.

Discussion:

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity in the majority of people worldwide. [15] It is strongly linked to smoking tobacco, [16] and it is especially common in heroin users. [17]

Patients in treatment for substance abuse have been found to have high rates of asthma and chronic obstructive pulmonary disease (COPD). [18]The strategy for substance abuse is significant, with respiratory health more unfortunate in those smoke heroin[17]. A recent cross-sectional study of substance abuse by inhalation found a high prevalence of asthma–COPD overlap syndrome (15%) and COPD (35%) [19]

In the general population of most countries, Chronic obstructive pulmonary disease (COPD) causes substantial morbidity and mortality [15] It is associated strongly with tobacco smoking,[16]and is especially prevalent among people who use illicit opioids such as heroin. [17].

Opioids may contribute to the respiratory disease, by several mechanisms including increased airway resistance, as an irritant stimulating histamine release and suppression of neural respiratory drive. [20]

In Egypt, 10.4% of the populace is evaluated to mishandle drugs, which is roughly twofold the world normal. [21]

This cross sectional study was conducted on 50 acute exacerbated COPD patients

who were admitted to the chest intensive care unit at Zagazig University Hospitals in Egypt and were between the ages of 47 and 78. They were divided into two groups: the drug abusers group and the non-drug abusers group. There was no statistically significant difference found between the two groups in terms of age, sex, while there was a significant difference as regard smoking (table 2). Whereas 45.2% of non-drug abusers were smokers, 84.2. This is consistent with a review by Guydish et al., [22]Where the prevalence of smoking in treatment programs of addiction, were 85.1% in OMUs.

Additionally, this is consistent with a Macmurdo et al, Study that found that patients with a diagnosis of substance abuse of any kind were significantly more likely to use tobacco (OR 3.89 95% CI: 3.82–3.96, p < 0.001). [11]

In a study by Tan et al., included 878 cases over the age of 40 years, the commonness of tobacco smoking was 73%.He reported the impacts of tobacco and marijuana use in patients with COPD, and deteriorate respiratory side effects increment with simultaneous utilization of marijane and tobacco together. [23]

Maheta et al , reported that high smoking rates in patients on methadone substitution and they have high commonness of both asthma and COPD. [8]

We found opioids were the most common manhandled substance (63%) while Methamp was the least- one among dependent patients (10.5%) ,(table 3) this is steady with Macmurdo etal found that opiate abuse was the most prevalent diagnosis among patients who had a history of substance abuse (Table 2).. [11]

On the other hand Carlos et al., found that Cocaine is the most generally utilized unlawful medication and the most frequent cause of drug-related deaths reported by clinical analysts. [24]

Across the globe, Cannabis is the most usually utilized illegal medication, especially among teenagers. Moreover, a new Egyptian review exhibited that 20% of patients with substance use disorders (SUD) creating COPD, and added

that the most predominant chronic drug use was weed (63%) while narcotic was lesser

Across the globe, Cannabis is the most commonly used illicit drug, particularly among adolescents. Furthermore, a recent Egyptian study demonstrated that 20% of patients with substance use disorders (SUD) developed COPD, Also cannabis was the most prevalent one (63%) and opioid was the lesser (27%) . [25]

The analyzed data shows that, cannabis abuse is the second prevalent substance that misused by COPD cases, it is 18% from total cohort and 47.4% from drug abuse group. (Table 2).

Our study reported that, COPD exacerbation in drug abuse group significantly associated with unknown cause (36.9%), while in non-drug abuse group is due to trachea-bronchial infection (51.6%), (Table 6.) The frequency of exacerbation and ICU admission is significantly higher among COPD cases with drug abuse rather than others without; 42.1 and 36.8% opposite to 35.5 and 6.5% respectively (Table 5). This consistent with Guerrero et al documented that substance abuse was linked to a significantly higher risk of a 30-day readmission as well as an increased risk of multiple readmission events. Patients with COPD have previously been found to have a 30-day readmission as an independent predictor of one-year mortality.. [26]

Vozoris et al., Study the relationship between new benzodiazepine utilization in COPD cases with respiratory system. He tracked down that, the clients of benzodiazepine were at higher danger for trauma centre visits; (RR 1.92, 95% CI 1.69–2.18) and for outpatients' respiratory compounding; (RR 1.45, 95% CI 1.36–1.54), and for, in correlation with non-clients' gathering. Also, the hospitalization hazard from pneumonia or COPD expanded in clients' gathering as opposed to non-client one; (RR 1.09, 95% CI 1.00–1.20). [27] Also Palmer et al.,in an example of medication misusers (current or past) than controls that have never utilized medications demonstrated a more prominent of respiratory infections when adapted to smoking status. The middle amount of SABA and ICS solutions was significantly higher in drug misusers and eventually, increased exacerbation and mortality . [28]

In our study drug abuse cases associated significantly with a higher incidence of type II respiratory failure (table 7); this is consistent with Kevin et al., where respiratory failure is a frequent complication of drug abuse. Drugs can also complicated by respiratory failure via causing pulmonary pathology or inhbitig

respiratory pump function . Poly-substance overdoses are common, and complications related to these drugs should be anticipate .deppression of respiratory pump function may result from inhibition of central nervous system (CNS) (suppression of the medulla oblongata, stroke or seizures) or fatigue of respiratory muscle (increased respiratory workload, metabolic acidosis).. [28]

The current work demonstrates that, the prevalence of drug abuse among exacerbated COPD cases that were admitted to ICU was 38 % (19 cases of 50); most of them (63.2%; 12 of 19 cases) needed mechanical ventilation (MV) support (fig .1). This is in agreement with large recent study from health care system of 211,880 cases, and evaluated the prevalence of SUD among different chronic disease morbidity, on which 35% of COPD patients showed substance abuse. Moreover, the prevalence of hospitalization was significantly higher in the group that used drugs than in the other group that did not have a history of SUD. [29]

This study has several limitations, the most important is a small sample size (n=50), another limitation is related to subjects; hence all of them were admitted in ICU with inability to communicate with them for further detailed history about drug misuse and source of the abuse substance (legal or illegal). However, our study highlights the problem of drug misuse among COPD cases. As well as, pointed to how it significantly associated with an increased rate of MV use and repeated ICU admissions..

Conclusion

In conclusion, the prevalence of Abuse to different drug substance was higher among COPD exacerbation case especially those admitted to intensive care units, most of them get used on opioid drugs, the cause of exacerbation was unknown, and the frequency of exacerbation more than one time was higher.

References:

1-Global Initiative for Chronic Obstructive Lung Disease, 2018. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2018 Report). Retrieved from https://goldcopd.org/wp-content/uploads/2017/ 11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (Accessed on 18 May 2019). .

2-Crothers, K., Butt, A.A., Gibert, C.L., Rodriguez-Barradas, M.C., Crystal, S., Justice, A.C., Veterans Aging Cohort 5 Project Team, 2006. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest 130, 1326–1333.

3-Clarke, J.G., Stein, M.D., McGarry, K.A., Gogineni, A., 2001. Interest in smoking cessation among injection drug users. Am. J. Addict. 10, 159–166.

4-Strassmann, R.; Bausch, B.; Spaar, A.; Kleijnen, J.; Braendli, O.; Puhan, M.A. Smoking cessation interventions in COPD: A network meta-analysis of randomised trials. Eur. Res. J. 2009, 34, 634–640. [CrossRef]

5-Godtfredsen, N.S.; Lam, T.H.; Hansel, T.T.; Leon, M.; Gray, N.; Dresler, C.; Burns, D.; Prescott, E.; Vestbo, J. COPD-related morbidity and mortality after smoking cessation: Status of the evidence. *Eur. Res. J.* 2008, *32*, 844–853. [CrossRef]

6- Chang, C.M.; Corey, C.G.; Rostron, B.L.; Apelberg, B.J. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health* 2015, *15*, 390. [CrossRef]

7-Wu, L.-T.; Zhu, H.; Ghitza, U.E. Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: Results from electronic health records data. Drug Alcohol. Depend. 2018, 192, 316–323. [CrossRef]

8-Mehta, S.; Parmar, N.; Kelleher, M.; Jolley, C.J.; White, P.; Durbaba, S.; Ashworth, M. COPD and asthma in patients with opioid dependency: A cross-sectional study in primary care. *NPJ Prim. Care Respir. Med.* 2020, *30*, 4. [CrossRef]

9-☐ Thakur, E.R.; Sansgiry, S.; Petersen, N.J.; Stanley, M.; Kunik, M.E.; Naik, A.D.; Cully, J.A. Cognitive and perceptual factors, not disease severity, are linked with anxiety in COPD: Results from a cross-sectional study. *Int. J. Behav. Med.* 2018, *25*, 74–84. [CrossRef]

10-Viglino, D.; Daoust, R.; Bailly, S.; Faivre-Pierret, C.; Charif, I.; Roustit, M.; Paquet, J.; Debaty, G.; Pépin, J.-L.; Maignan, M. Opioid drug use in emergency and adverse outcomes among patients with chronic obstructive pulmonary disease: A multicenter observational study. *Sci. Rep.* 2020, *10*, 5038. [CrossRef]

11-Macmurdo, M.; Lopez, R.; Udeh, B.; Zein, J. Beyond tobacco–the secondary impact of substance misuse in chronic obstructive lung disease. J. Asthma 2020, 1–12. [CrossRef]

12- Drugs of Abuse Array I Whole Blood Plus. Available from: http://www.randox.com/drugs-of-abuse-array-i-plus-quality-control/.   Accessed 12 March 2016.

13- Hansmeyer, C. G. near-body drugs of abuse testing in a post mortem medico-legal population in south africaAfrica: a pilot study. A research report submitted to the Faculty of Health Sciences, University of the Rabie Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine. 2016; 54-59.

14.NHS. National Services Scotland. ISD Scotland Publications. Drug Misuse Statistics

15- Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;370:765-73 . doi:10.1016/S0140-6736(07)61380-4

16-Raherison C, Girodet P-O. Epidemiology of COPD. *Eur Respir Rev* 2009;18:213–21. doi:10.1183/09059180.00003609

17- Furlong J, Peat R, Young R. Prevalence of COPD in heroin smokers screened at substance misuse clinics. *Eur Respir J* 2016;48.

18- Palmer, F. et al. Prevalence of common chronic respiratory diseases in drug misusers: a cohort study. Prim. Care Respir. J. 21, 377–383 (2012).

19- Burhan, H. Et al. Screening heroin smokers attending community drug services for COPD. Chest 155, 279–287 (2019).

20- Royal College of Physicians. The National Review of asthma deaths: why asthma still https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills (London, 2014).

21- M, Shaker NM, Gaber E, et al. Prevalence updates of substance use among Egyptian adolescents. Middle East Curr Psychiatry . 2020 ;27:4. https://doi.org/10.1186/s43045-019-0013-8

22-Guydish J, Passalacqua E, Pagano A, et al. An international systematic review of smoking prevalence in addiction treatment. Addiction 2016;111:220–30.

23-Tan WC, Lo C, Jong A, Xing L, FitzGerald MJ, Vollmer WM, Buist SA, Sin DD. Marijuana and chronic obstructive lung disease: a population-based study. Cmaj. 2009 (8):814-20

24.   Carlos S, Restrepo, MD , Carrillo JA, ,et al . Pulmonary Complications from Cocaine and Cocaine-basedSubstances: Imaging Manifestations RadioGraphics 2007; 27:941–956 ● Published online

25-WHO (2010) ATLAS of substance use disorders resources for the prevention and treatment of substance use disorders (SUD) country profile. Egypt

26- Guerrero M, Crisafulli E, Liapikou A, et al. Readmission for Acute Exacerbation within 30 Days of Discharge Is Associated with a Subsequent Progressive Increase in Mortality Risk in COPD Patients: A Long-Term Observational Study. Loukides S, ed. PLoS One 2016;11(3):e0150737. doi:10.1371/journal.pone.015073

27-Vozoris NT, Fischer HD, Wang X, et al. . Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. European Respiratory Journal. 2014 ;44; 44(2):332-40.

28-Palmera F, Jaffraya M , Moffata M,et al. . Prevalence of common chronic respiratory diseases in drug misusers: a cohort study Prim Care Respir J 2012

29- LT, Zhu H, Ghitza UE. Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: Results from electronic health records data. Drug and alcohol dependence. 2018 ;192:316-23.