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Pharmacovigilance Analysis of Adverse Psychiatric Events and Suicidality Reported for Roflumilast, an Add-On COPD Therapy

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ABSTRACT

Aims: Roflumilast is a phosphodiesterase-4-inhibitor used as add-on therapy to long-acting bronchodilators in chronic obstructive pulmonary disease. Although roflumilast is well tolerated, there have been concerns regarding psychiatric problems, including suicide tendencies. This study aims to identify and characterize signals of adverse psychiatric events reported for roflumilast in the US FDA Adverse Event Reporting System (FAERS).

Study design: Retrospective pharmacovigilance analysis.

Place and Duration of Study: Adverse event reports submitted to FAERS from October 1997 through September 2012.

Methodology: Multi-item Gamma Poisson Shrinker data-mining algorithm was applied to adverse psychiatric events (APE) that were submitted to the FAERS (3Q1997-3Q2012). Empirical Bayes Geometric Mean (EBGM) and 95% confidence interval (EB05-EB95) were calculated for roflumilast-associated APE compared to all drugs in FAERS. The following Preferred Terms of the MedDRA terminology were used to define the outcome of interest: "anxiety", "depressed mood", "depression", "insomnia", "suicide attempt", and "suicidal ideation". Signals with $EB05 \geq 2$ are considered significant disproportional reporting (\geq twice that expected) of APE.

Results: 126 reports of APE were identified for roflumilast, corresponding to mutually non-exclusive events of insomnia (n=53), anxiety (n=38), depression (n=36), suicidal ideation (n=30), depressed mood (n=8), and suicide attempt (n=6). EBGM (EB05-EB95) were: APE, 3.55 (3.06-4.11); insomnia, 4.55 (3.62-5.66); anxiety, 2.96 (2.26-3.82); depression, 2.88 (2.19-3.75); suicidal ideation, 5.65 (4.16-7.52); depressed mood, 3.90 (2.20-6.53); and suicide attempt, 1.66 (0.86-2.95).

Conclusion: Roflumilast is associated with higher than expected reporting of APE, including suicidal thoughts, but not suicide attempts. **Given the inherent confounding and bias limitations of spontaneous reporting systems,** pharmacoepidemiologic studies are required to test these hypotheses; meanwhile, prescribers should consider alternative add-on therapies to patients with past or present depression or suicidality.

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Keywords: Roflumilast; Adverse Event Reporting System; FAERS; Suicide; Psychiatric Events; COPD; Pharmacovigilance.

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18 **1. INTRODUCTION**

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20 Roflumilast is a novel orally-administered phosphodiesterase-4 inhibitor approved in
21 February 2011 for maintenance therapy in individuals with severe chronic obstructive
22 pulmonary disease (COPD) who have frequent exacerbations that are not well controlled by
23 long acting bronchodilators alone [1]. Data from clinical trials and unpublished spontaneous
24 reporting sources in the United Kingdom (UK) raised concerns about roflumilast-associated
25 psychiatric problems, including suicidal thoughts, suicide attempts and completed suicides
26 [2-4]. Anxiety, depression, insomnia, and suicidality are the most common psychiatric events
27 observed with roflumilast therapy in clinical trials [4]. The incidence rates from clinical trials
28 are estimated to be 1%-10% for insomnia; 0.1%-1% for anxiety; and 0.01%-0.1% for
29 depression and suicidality [4]. Reports of suicidality prompted the UK Medicines and
30 Healthcare products Regulatory Agency (MHRA) to issue pertinent warnings to healthcare
31 professionals in January 2013. **In particular, three cases of completed suicides occurred in
32 men exposed to roflumilast who did not have a known history of depression and two cases
33 of suicidal attempts in women** [2-3].

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35 There is no published pharmacovigilance analysis of roflumilast-associated psychiatric
36 events, and this study evaluates this potential association by signal detection and
37 characterization using spontaneously reported adverse events in the US FDA Adverse Event
38 Reporting System (FAERS).

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40 **2. METHODOLOGY**

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42 **2.1 Data Source**

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44 Adverse event reports submitted to the FAERS from October 1, 1997 through September 30,
45 2012 are used to conduct a retrospective pharmacovigilance analysis of roflumilast-
46 associated adverse psychiatric events. The FAERS is a spontaneous reporting system of
47 adverse events for all medicinal products approved for marketing in the US. It is an important
48 source of postmarketing safety signal detection and assessment for marketed products. The
49 database structure has been described elsewhere [5].

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51 **2.2 Exposure and Outcome Definition**

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53 Roflumilast was identified by the generic name in the classification system of the World
54 Health Organizations' Anatomical Therapeutic Chemical (ATC, January 2012). Reports with
55 roflumilast's role in APE occurrence defined as concomitant, primary or secondary suspect
56 are included. Psychiatric events were identified by the Preferred Term (PT) hierarchy of the
57 Medical Dictionary for Regulatory Activities (MedDRA 16.0, March 2013). The following PTs
58 were used to reflect adverse psychiatric events (APE) in conformism with the events
59 reported in clinical trials: "anxiety", "depressed mood", "depression", "insomnia", "suicidal
60 ideation" and "suicide attempt".

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62 **2.3 Statistical Analysis**

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64 Statistical analyses are conducted using Empirica Signal (7.3, November 2011, Oracle USA
65 Inc., Redwood, CA). Multi-item Gamma Poisson Shrinker (MGPS) disproportionality
66 algorithm was applied to test the hypothesis of disproportional reporting of APE for
67 roflumilast compared to other drug-event combinations in FAERS. Empirical Bayes
68 Geometric Mean (EBGM) values and corresponding 95% confidence intervals (EB05-EB95)
69 are reported for roflumilast-associated APE. Roflumilast-APE combinations with $EB05 \geq 2$
70 are considered significant disproportional reporting (at least twice that expected) of APE.

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72 In addition, signal sector mapping is applied to describe APE signals relative to other signals
73 detected for roflumilast. In signal sector maps, tile color is controlled by the EB05 value, and
74 PT box size displayed by System Organ Class (SOC) is controlled by whether Public Health
75 Impact (PHI) score is calculated for individual PT. Tiles with larger size have larger PHI
76 score. PHI score takes into account the distribution of PT regardless of its association with a
77 particular drug, thus, tile size for a particular PT is stable across sector maps for different
78 drugs. The score is the product of the number of times the PT occurred in serious events
79 and the proportion of reports with the PT that are serious. Furthermore, additional analysis
80 was restricted to reporting period of 1 February 2011-30 September 2012 to characterize
81 signals during the period following roflumilast introduction to market (28 February 2011).
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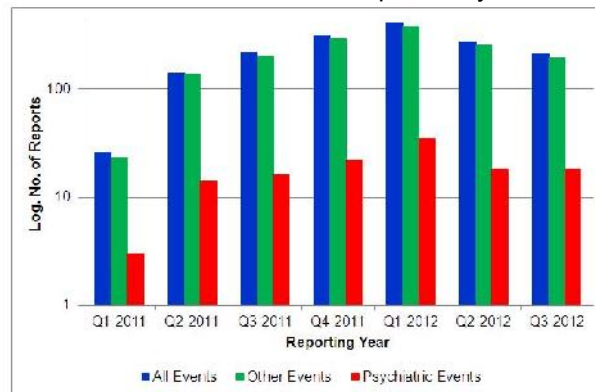
83 3. RESULTS

84 3.1 Overview of APE Reports

85 A total of 1,605 adverse event reports were submitted for roflumilast during the reporting
86 period, 7.8% of total reports were for APE (n=126). Each APE report could include >1
87 psychiatric PT. There were 53 insomnia reports; 38 anxiety reports; 36 depression reports;
88 30 suicidal ideations; 8 depressed mood reports; and 6 suicide attempts. Figure 1 depicts
89 reporting trend of APE in relation to other events reported for roflumilast. The trend for APE
90 was consistent with overall events and peaked one year after product approval (Q1 2012).
91 Characteristics of APE reports are described in table 1. The majority of roflumilast users who
92 experienced APE were men with a median age of 67 years, in whom the drug had a primary
93 role in APE occurrence with most indications being for COPD. On average, 27% and 19% of
94 reported APE has occurred after 30 days and within 1 day of starting roflumilast,
95 respectively. About 48% of reports indicated patients had 3-10 concomitantly administered
96 medications; however, 27% of occurred APE was reported in patients without concomitant
97 exposure to other medications.
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101 None of patients recovered from the reported events. Vast majority of reported APE were
102 classified as serious events that were reported within 15 days of event happening. One APE
103 report might have >1 serious event, e.g., a report of hospitalization might also include
104 intervention or subsequent disability. Most of serious events were unclassified, followed by
105 requirement for medical or pharmacological intervention and hospitalization. Only 6 APE
106 reports contributed to patient's death, corresponding to about 6% of all reported serious
107 APE. Half of reported APE were domestic (within the US), and half came from overseas
108 (mainly Germany), with approximately 47% of reported events submitted by healthcare
109 professionals. Only about 17% of the events were reported by roflumilast users.



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Figure 1. Trend of adverse event reports submitted for roflumilast

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Table 1. Characteristics of adverse psychiatric events reported for roflumilast

Characteristic of report	Distribution (N=126)
Patient's age in years, median (minimum, maximum)	67 (40, 94) n=113
Patient's sex	
Male	68 (54)
Female	57 (45.2)
Unknown	1 (0.8)
Drug role in event occurring	
Primary suspect	114 (90)
Secondary suspect	7 (6.0)
Concomitant	5 (4.0)
Clinical indication	
Chronic obstructive pulmonary disease	100 (79.4)
Unspecified lung disorder	9 (7.1)
Emphysema	6 (4.7)
Asthma	5 (4.0)
Chronic bronchitis	3 (2.4)
Respiratory failure	2 (1.6)
Bronchiectasis	1 (0.8)
Duration of therapy (days)	
0-1	24 (19)
2-7	26 (20.7)
8-14	14 (11.1)
15-30	14 (11.1)
31-180	34 (27)
Unknown	14 (11.1)
Number of concomitant drugs	
None	34 (27)
One	9 (7.1)
Two	8 (6.3)
3-10	60 (47.6)
>10	15 (12)
Serious event	107 (85)
Serious event type (percentage of serious events) ^a	
Unspecified serious event	71(66.3)
Required intervention	41 (38.3)
Hospitalization	34 (31.2)
Life-threatening	8 (7.5)
Disability	7 (6.5)
Death	6 (5.6)
Report type	
Expedited	84 (66.7)
Periodic	28 (22.2)
Direct	14 (11.1)
Report source	
Prescriber	59 (46.8)
Unspecified source	22 (17.5)
Consumer	21 (16.7)
Manufacturer	16 (12.7)
Clinical study	8 (6.3)
Reporting country	
United States	63 (50)

Germany	61 (48.4)
Denmark	1 (0.8)
Brazil	1 (0.8)
Reporting year	
Q1 2011	3 (2.4)
Q2 2011	14 (11.1)
Q3 2011	16 (12.7)
Q4 2011	22 (17.4)
Q1 2012	35 (27.8)
Q2 2012	18 (14.3)
Q3 2012	18 (14.3)

114 ^a One report might include more than one serious event
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116 3.2 Overview of Suicidality Reports

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118 Thirty six suicidality events were reported for roflumilast, corresponding to 30 reports of
119 suicidal ideation and 6 reports of suicide attempts. Consistent with all APE reports, reporting
120 trend for suicidality was the highest during the first quarter of 2012. Table 2 shows the
121 characteristics of these reports. Men experienced most of suicidality events, with relatively
122 older patients reported suicide attempts compared to those with suicidal ideations. Majority
123 of suicidal ideation reports and all of suicide attempt reports indicated roflumilast to be the
124 primary suspect in event occurrence and used for COPD treatment. Approximately fourth of
125 suicidal thoughts occurred after first week of roflumilast exposure, and half of suicide
126 attempts occurred within first day of therapy with roflumilast. About 37% and 50% of suicidal
127 ideation and suicide attempt reports respectively reported concurrent exposure to 3-10
128 medications at the time of exposure to roflumilast and event occurrence. About 37% of
129 suicidal thoughts and third of suicide attempts did not report concomitant exposure to other
130 drugs.

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132 Almost all of suicidality reports were serious events, the majority however, was unclassified
133 and unlike other APE, none contributed to patient's death; nevertheless, about 13% of
134 suicidal ideation and 33% of attempts were life-threatening. Moreover, majority of suicidal
135 ideations was periodically reported every quarter, compared to suicide attempts which were
136 submitted within 15 days of experiencing the events. About 43% and half of suicidal ideation
137 and suicide attempts were reported by healthcare professionals. Ten percent of suicidal
138 thoughts were reported by consumers. None of suicide attempts were reported by roflumilast
139 users; however, 50% of suicide attempts didn't include reporting source. Preponderance of
140 suicidal ideation reports and half of those for suicide attempt were from the US; the rest was
141 from Germany.

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143 **Table 2. Characteristics of suicidality events reported for roflumilast**

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Characteristic of report	Suicidal ideation (N=30)	Suicide attempt (N=6)
Patient's age in years, median (minimum, maximum)	67 (45, 94) n=26	70 (67, 78) n=5
Patient's sex		
Male	20 (66.7)	5 (83.3)
Female	10 (33.3)	1 (16.7)
Drug role in event occurring		
Primary suspect	24 (80)	6 (100)
Secondary suspect	6 (20)	0

Clinical indication		
Chronic obstructive pulmonary disease	28 (93.4)	6 (100)
Chronic bronchitis	1 (3.3)	0
Respiratory failure	1 (3.3)	0
Duration of therapy (days)		
0-1	2 (6.6)	3 (50)
2-7	7 (23.3)	0
8-14	8 (26.7)	2 (33.3)
15-30	3 (10)	0
31-180	5 (16.7)	1 (16.7)
Unknown	5 (16.7)	0
Number of concomitant drugs		
None	11 (36.7)	2 (33.3)
One	3 (10)	1 (16.7)
Two	2 (6.6)	0
3-10	11 (36.7)	3 (50)
>10	3 (10)	0
Serious event	29 (96.7)	6 (100)
Serious event type (percentage of serious events) ^a		
Unspecified serious event	24 (80)	4 (66.6)
Required intervention	18 (60)	2 (33.3)
Hospitalization	4 (13.3)	2 (33.3)
Life-threatening	4 (13.3)	2 (33.3)
Disability	1 (3.3)	2 (33.3)
Report type		
Expedited	13 (43.3)	4 (66.6)
Periodic	14 (46.7)	1 (16.7)
Direct	3 (10)	1 (16.7)
Report source		
Prescriber	13 (43.3)	3 (50)
Unspecified source	0	3 (50)
Consumer	3 (10)	0
Manufacturer	12 (40)	0
Clinical study	2 (6.7)	0
Reporting country		
United States	19 (63.3)	3 (50)
Germany	11 (36.7)	3 (50)
Reporting year		
Q2 2011	5 (16.7)	0
Q3 2011	1 (3.3)	1 (16.7)
Q4 2011	7 (23.3)	2 (33.3)
Q1 2012	12 (40)	3 (50)
Q2 2012	2 (6.7)	0
Q3 2012	3 (10)	0

^a One report might include more than one serious event

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3.3 MGPS Disproportionality Analysis Results

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Disproportionality analysis results are described in table 3 and figure 2. Roflumilast is significantly associated with 3.55 times more likely reporting of APE than expected compared to all drug-event combinations in FAERS between 1997-2012 (EBGM, 3.55; EB05-EB95, 3.06-4.11). Among APE reports, significant signals were detected for insomnia (EBGM, 4.55; EB05-EB95, 3.62-5.66), anxiety (EBGM, 2.96; EB05-EB95, 2.26-3.82),

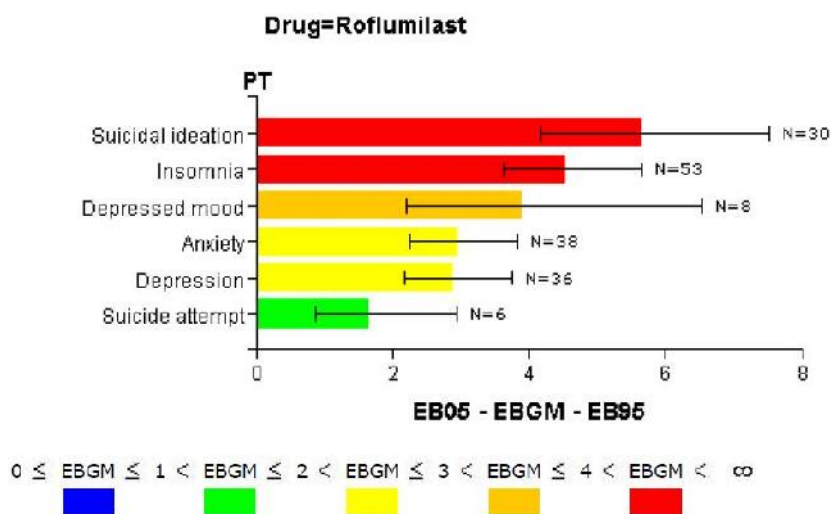
154 depression (EBGM, 2.88; EB05-EB95, 2.19-3.75) and depressed mood (EBGM, 3.90; EB05-
 155 EB95, 2.20-6.53). Among suicidality reports, Roflumilast was significantly associated with
 156 disproportional reporting of suicidal ideation (EBGM, 5.65; EB05-EB95, 4.16-7.52), but not
 157 with suicide attempt (EBGM, 1.66; EB05-EB95, 0.86-2.95).

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Table 3. Disproportionality analysis of APE and suicidality reported for roflumilast

Event MedDRA PT	No. of reports	EBGM (EB05-EB95)	
		1997-2012	2011-2012
All adverse psychiatric events	126 ^a	3.55 (3.06-4.11)	1.00 (0.86-1.16)
Insomnia	53	4.55 (3.62-5.66)	0.95 (0.83-1.09)
Anxiety	38	2.96 (2.26-3.82)	0.95 (0.82-1.09)
Depression	36	2.88 (2.19-3.75)	0.95 (0.82-1.09)
Suicidal ideation	30	5.65 (4.16-7.52)	0.94 (0.81-1.09)
Depressed mood	8	3.90 (2.20-6.53)	0.93 (0.79-1.09)
Suicide attempt	6	1.66 (0.86-2.95)	0.93 (0.79-1.09)

161 ^a One report might have more than one psychiatric event.
 162 APE= Adverse psychiatric events
 163 EBGM= Empirical Bayes Geometric Mean
 164 MedDRA PT= Medical dictionary for regulatory activities, preferred term
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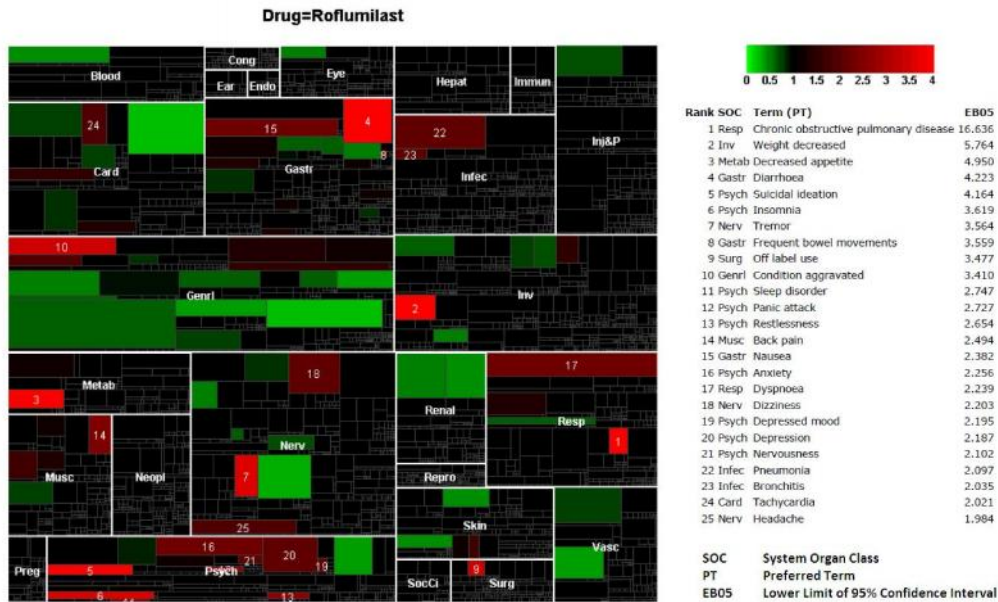
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Figure 2. Signals of adverse psychiatric events detected for roflumilast

Figure 3 shows the distribution of top 25 signals detected for roflumilast depicted by SOC, PT, and relative PHI score. Suicidal ideation ranked the fifth detected score, and depression and anxiety had the largest PHI scores among psychological SOC. Strongest signals were found for weight loss and gastrointestinal events.

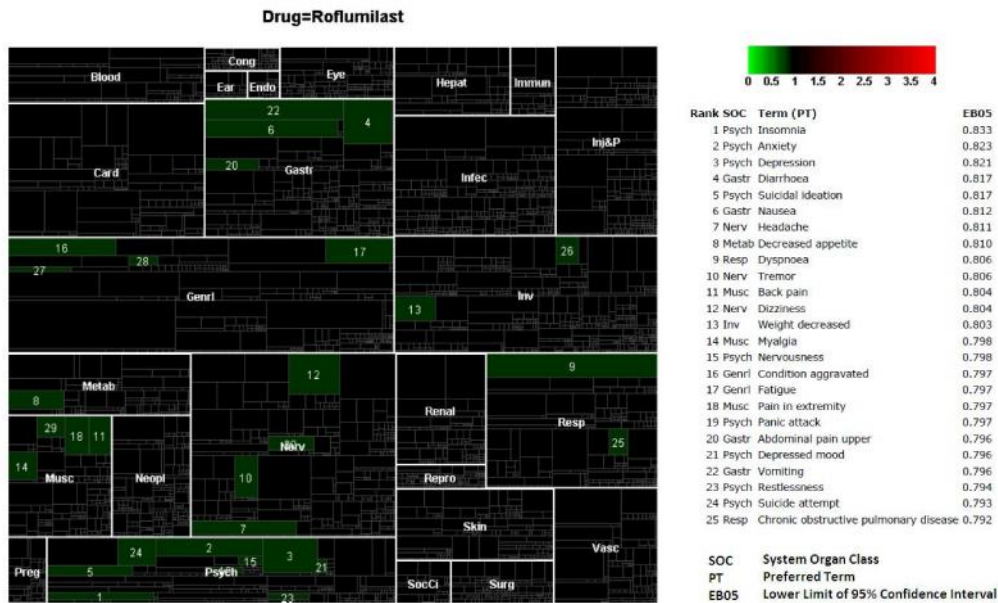
In addition, restricting analysis to post-approval reporting period of 2011-2012 didn't yield signals of APE (EBGM, 1.00; EB05-EB95, 0.86-1.16), nor other adverse events (Figure 4).

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Figure 3. Sector map of top 25 safety signals detected for roflumilast



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Figure 4. Sector map of top 25 roflumilast-event associations during 2011-2012 period

4. DISCUSSION

The potential association between roflumilast and APE, including suicidality has been an issue with considerable deliberations at regulatory agencies, and there is no known published pharmacovigilance report evaluating this issue. This pharmacovigilance analysis of spontaneously reported APE subsequent to treatment with roflumilast suggests that

194 roflumilast is associated with APE and suicidal ideation, but not suicide attempts. The
195 findings are consistent with what is known from clinical studies, including signals for adverse
196 events other than APE, e.g., gastrointestinal events and weight loss (Figure 3) [3]. In clinical
197 trials, nausea, diarrhea, headache, and weight loss were the most frequently encountered
198 side effects of treatment with roflumilast, which resulted in drug withdrawal in 9%-16% of
199 patients [6].

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201 Nonetheless, the findings should be carefully interpreted in light of the inherent limitations of
202 spontaneously reported safety data. There is a high likelihood the detected signals are
203 biased estimates because of confounding by indication, where reported events are
204 associated with drug indications; comorbidities; or concomitant medications (73% of reported
205 APE had ≥ 1 drug exposure further to roflumilast). Additionally, reporting of APE events
206 increased within the first year of roflumilast introduction to market, and peaked in the first
207 quarter of 2012, just around the timing of regulatory safety communication by the MHRA, an
208 incident that could contribute to reporting bias and subsequent over-reporting at that time.

209
210 Absence of APE signal after restricting analyses to one year after roflumilast introduction to
211 market might be attributed to masking effect, where another drug or group of drugs have a
212 disproportionately large number of APE events, which makes APE appears more common for
213 that drug or group of drugs and less detected in roflumilast. However, this proposition might
214 not be true when no signal was detected for events other than APE (Figure 4). It might be
215 advisable to conduct similar analyses by restricting data after roflumilast approval only after
216 considerable amount of reporting data is available, e.g. 5years.

217
218 COPD is a debilitating chronic condition with significant morbidity and poor quality of life
219 burdens. Psychological comorbidities, including depression are increasingly prevalent in
220 individuals with COPD; estimates of coexisting COPD and depression exceed 40% [7].
221 Further, the severity of depression is correlated with exacerbation frequencies and increased
222 risk of suicidal ideation [8]. Compared to individuals without COPD, those with COPD are
223 significantly associated with suicidal behavior, including suicide attempt [9].

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225 **5. CONCLUSION**

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227 Roflumilast is an effective novel add-on therapy to long-acting bronchodilators, including
228 long-acting beta-agonists and long-acting muscarinic-antagonists to reduce inflammation
229 and exacerbations [1-3]; and this study should be viewed as a hypothesis generating
230 exercise, and such hypothesis should be tested by more robust pharmacoepidemiologic
231 studies to better characterize the benefit/risk profile of roflumilast. Meanwhile, and in tandem
232 with regulatory recommendations [4], prescribers should consider alternative add-on
233 therapies to patients with past or present depression or suicidality.

234

235 **COMPETING INTERESTS**

236

237 Author has declared that no competing interests exist.

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239 **REFERENCES**

240

- 241 1. Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis,
242 management, and prevention of chronic obstructive pulmonary disease. Updated 2013.
243 Accessed 13 June 2013. Available: <http://www.goldcopd.org>.
- 244 2. Giembycz MA, Field SK. Roflumilast: first phosphodiesterase 4 inhibitor approved for
245 treatment of COPD. *Drug Des Devel Ther.* 2010;4:147-158.

- 246 3. Beghè B, Rabe KF, Fabbri LM. Phosphodiesterase-4 inhibitor therapy for lung diseases.
247 *Am J Respir Crit Care Med* 2013. Epub ahead of print. Published May 8, 2013. DOI:
248 10.1164/RCCM.201301-0021PP
- 249 4. Medicines and Healthcare products Regulatory Agency. Roflumilast: risk of suicidal
250 behaviour. Drug Safety Update. 2013;6(6):S2. Accessed 13 June 2013. Available:
251 <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/>.
- 252 5. Ali AK. Pharmacovigilance Analysis of Adverse Event Reports for Aliskiren
253 Hemifumarate, A First-in-Class Direct Renin Inhibitor. *Ther Clin Risk Manag.*
254 2011;7:337-344.
- 255 6. Pinner NA, Hamilton LA, Hughes A. Roflumilast: A Phosphodiesterase-4 Inhibitor for
256 The Treatment of Severe Chronic Obstructive Pulmonary Disease. *Clin Ther.*
257 2012;34(1):56-66.
- 258 7. Stage KB, Middelboe T, Stage TB, Sørensen CH. Depression in COPD—Management
259 and Quality of Life Considerations. *Int J Chron Obstruct Pulmon Dis.* 2006;1(3):315-320.
- 260 8. Sekiduka-Kumano T, Kawayama T, Ito K, Shoji Y, Matsunaga K, Okamoto M, Edakuni
261 N, Imaoka H, Uchimura N, Hoshino T. Positive Association between The Plasma Levels
262 of 5-Hydroxyindoleacetic Acid and The Severity of Depression in Patients with Chronic
263 Obstructive Pulmonary Disease. *BMC Psychiatry.* 2013;13:159.
- 264 9. Goodwin RD. Is COPD Associated with Suicide Behavior? *J Psychiatr Res.*
265 2011;45(9):1269-1271.

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