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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ieds20

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To cite this article: Roger S. McIntyre, Rodrigo B. Mansur, Joshua D. Rosenblat & Angela T.H. Kwan (2024) The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS), Expert Opinion on Drug Safety, 23:1, 47-55, DOI: 10.1080/14740338.2023.2295397

To link to this article: https://doi.org/10.1080/14740338.2023.2295397

Published online: 19 Dec 2023.

EXPERT OPINION ON DRUG SAFETY
2024, VOL. 23, NO. 1, 47–55
https://doi.org/10.1080/14740338.2023.2295397

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ORIGINAL RESEARCH

The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS)

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ABSTRACT

Introduction: Recently, the European Medicines Agency (EMA) received reports of suicidal thoughts and self-injury associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) liraglutide and semaglutide.

Research design and methods: Herein, we sought to evaluate suicidality associated with all GLP-1 RAs relative to other glucose-lowering agents currently approved by the United States Food and Drug Administration (FDA). Reports of suicidal ideation, "depression/suicidal", suicidal behavior, suicidal attempts, and completed suicide associated with GLP-1 RA exposure reported to the FDA between 2005 and October 2023 were obtained from the FDA Adverse Event Reporting System (FAERS). We present data using the reporting odds ratio (ROR). The ROR was considered significant when the lower limit of the 95% confidence interval (CI) was greater than 1.0.

Results: Disproportionate reporting of suicidal ideation and "depression/suicidal" was observed with semaglutide and liraglutide. Disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide was not observed for any of the FDA-approved GLP-1 RAs.

Conclusions: Using the Bradford Hill criteria, however, and taking into consideration confounders, no causal link between GLP-1 RAs and suicidality exists.

ARTICLE HISTORY
Received 9 October 2023
Accepted 7 December 2023

KEYWORDS
Glucagon-like peptide 1 (GLP-1); semaglutide; Dulaglutide; Exenatide; liraglutide; lixisenatide; tirzepatide; suicide

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of adults with type 2 diabetes mellitus and obesity [1]. It is reported that the therapeutic effects of this class of agents on metabolic/weight outcomes as well as associated comorbidities have significant positive public health implications [2].

Reports of suicidal thoughts and self-injury associated with semaglutide and liraglutide were recently received by the EMA [3]. An association between GLP-1 RAs and adverse psychiatric outcomes has not hitherto been documented prior to these reports. The increasing prescription of GLP-1 RAs within indication as well as off-label for investigational purposes (e.g. substance- and alcohol-use disorder, major neurocognitive disorders) provides additional impetus to better characterize safety concerns with this class of agents [3–12].

Herein, we sought to evaluate whether disproportionate reporting of suicidality with GLP-1 RAs relative to other glucose-lowering agents using spontaneous adverse events reported to the Food and Drug Administration Adverse Event Reporting System (FAERS). We are not intending to review the overall safety and tolerability of GLP-1 RAs as this has been comprehensively reviewed elsewhere [13].

2. Methods

We obtained data from the United States FAERS which contains reports of post-marketing adverse events to the FDA. We evaluated data beginning in the year 2005 as this year coincides with the FDA approval of the first GLP-1 RA. All GLP-1 RAs that are FDA approved [i.e. Semaglutide (Ozempic, Rybelsus, Wegovy), Dulaglutide (Trulicity), Exenatide (Byetta, Bydureon, Bydureon Bcise), Liraglutide (Saxenda, Victoza), Lixisenatide (Adlyxin), and Tirzepatide] were identified using nonproprietary names [14]. Each GLP-1 agent was then evaluated with respect to suicidal ideation, "depression/suicidal", suicidal behavior, suicidal attempt, and completed suicide.

All adverse events reported to the FAERS between 2005 and October 2023 were obtained (i.e. number of cases *(n)* and total cases of psychiatric disorders *(N)*) (Tables 1 and 2). The reporting odds ratio (ROR) was calculated to assess the disproportionality reporting between cases and non-cases using the formula: odds ratio = (odds of the event in the exposed group)/(odds of the event in the non-exposed group) [15]. In this study, the ROR is the ratio of the odds of the number of

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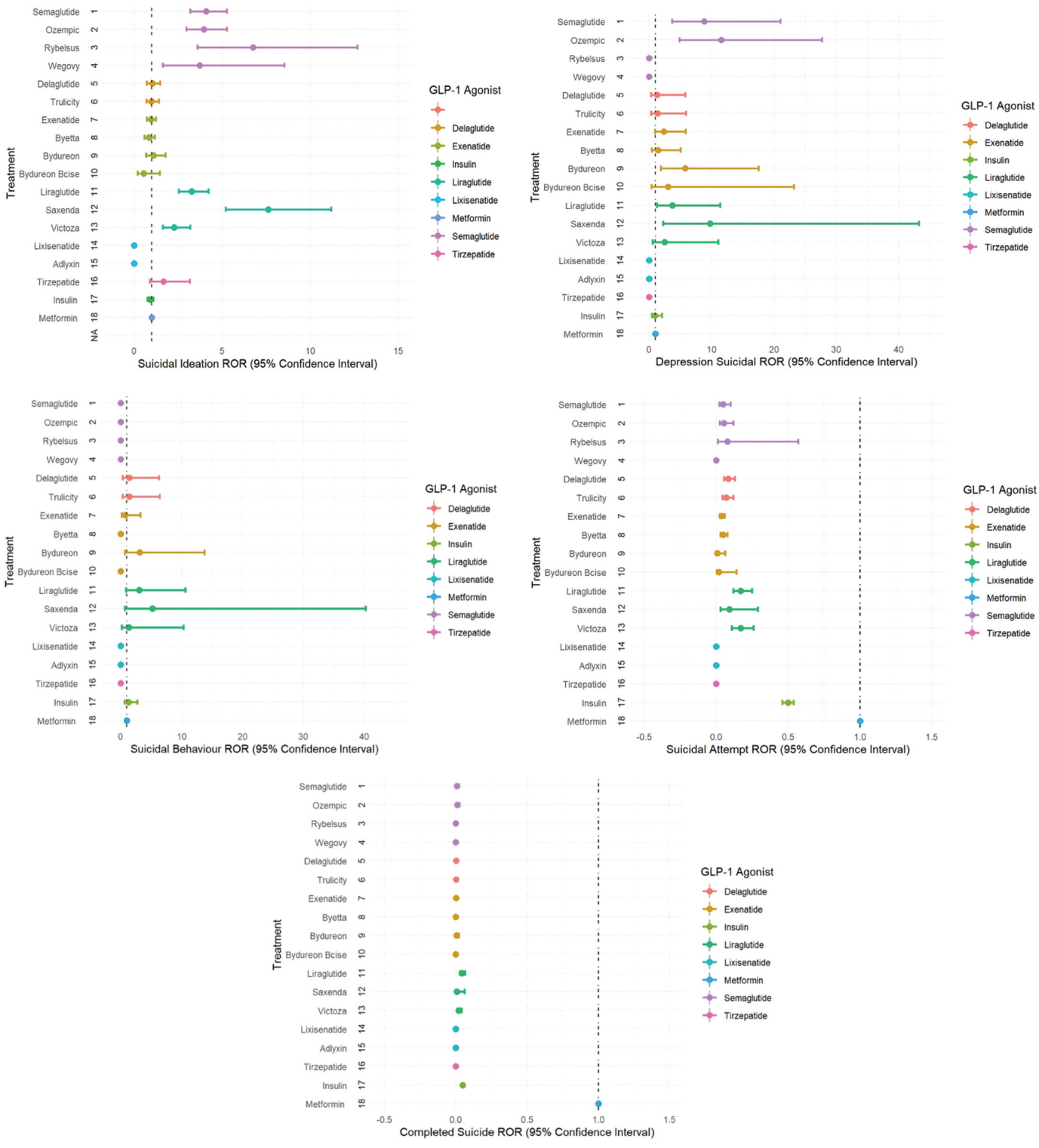

Figure 1. Forest plots: reporting odds ratio (ROR) for psychiatric events with glucagon-like peptide-1 (GLP) receptor agonists versus metformin control.

suicidality events related to GLP-1 RAs compared to metformin (i.e. metformin, metformin hydrochloride, metformin Er 500 Mg and metformin hydrochloride extended-release 500 mg) (Figure 1) and insulin (i.e. insulin aspart, insulin aspart protamine and insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulicine, insulin human, insulin lispro) (Figure 2) as separate controls. The upper and lower 95% confidence intervals (CI) were calculated with an alpha risk of 5% and used to determine statistical significance with a lower 95% CI greater than 1.0 considered to be disproportionate reporting [16]. We chose metformin and insulin as the reference agents for all GLP-1 RAs analyzed. The forest plots were constructed using RStudio version 2023.06.1 + 524 'Desert Sunflower' Release (b51c81cc303d4b52b010767e5b30438beb904641, 25 September 2023) for Windows.

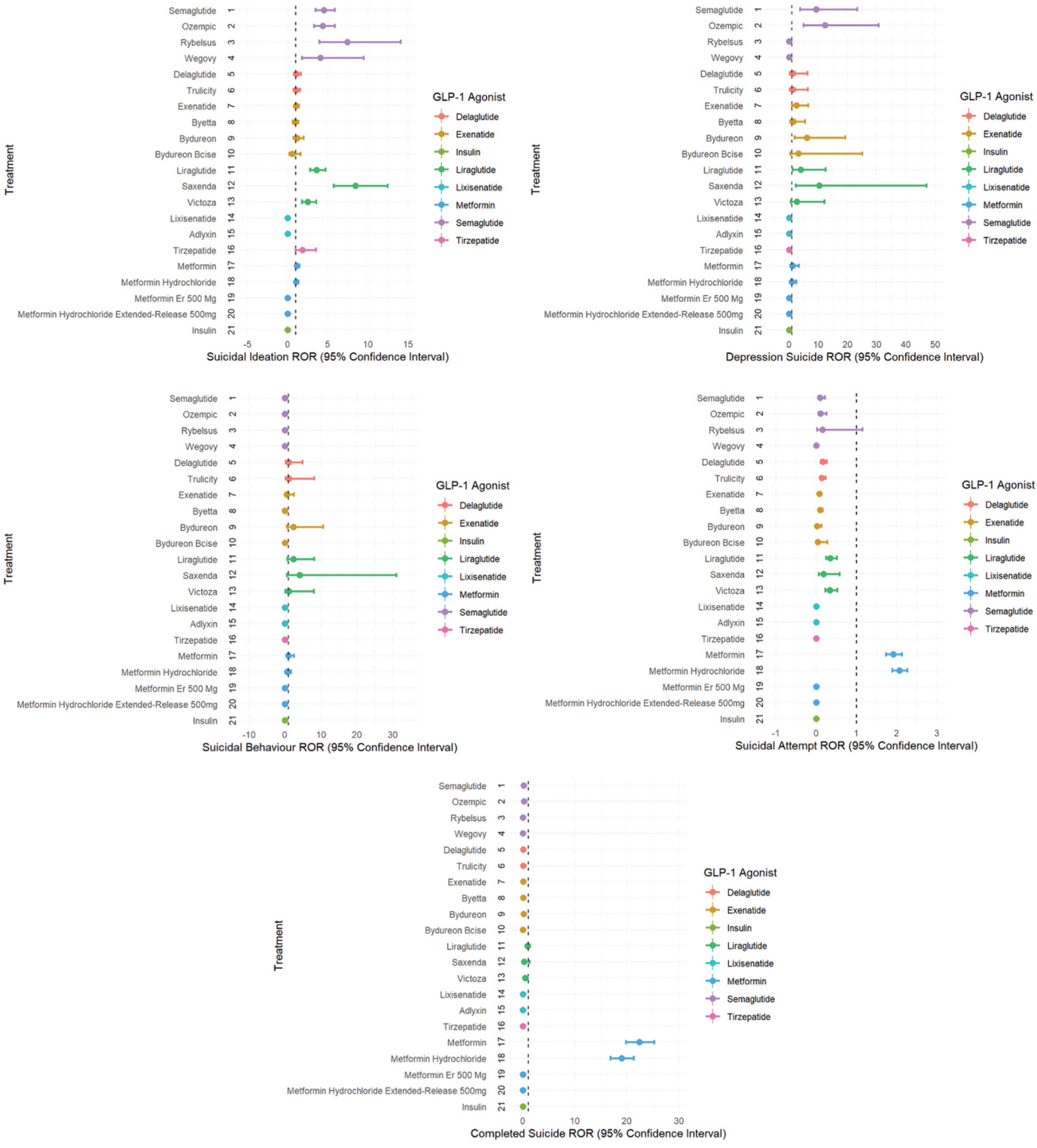

Figure 2. Forest plots: reporting odds ratio (ROR) for psychiatric events with glucagon-like peptide-1 (GLP) receptor agonists versus insulin control.

3. Results

The statistics were performed in Microsoft Excel 2021 and R version 4.3.1. From 2005 to October 2023, there were 315 reports of suicidal ideation, 14 reports of "depression/suicidal", 13 reports of suicidal behavior, 2011 reports of suicidal attempt and 5653 reports of completed suicide with metformin. For insulin, there were 237 reports of suicidal ideation, 11 reports of "depression/suicidal", 14 reports of suicidal behavior, 877 reports of suicidal attempt, and 318 reports of completed suicide. The RORs for each of the GLP-1 RAs were individually compared to metformin (Table 1) and insulin (Table 2) as the controls.

Table 1. Glucagon-like peptide-1 (GLP) receptor agonist-associated suicidality cases identified in the Food and Drug Administration's Adverse Event Reporting System (FAERS), using metformin as the control.

Suicidal Ideation							
GLP-1 Agonist	Number of Cases (n)	Total Cases of Psychiatric Disorders (N)	ROR	95% CI Lower	95% CI Upper	Z statistic	P value
Semaglutide	80	1317	4.08	3.17	5.25	10.94	≤0.0001
Ozempic	59	1003	3.95	2.97	5.25	9.42	≤0.0001
Rybelsus	11	114	6.74	3.59	12.68	5.92	≤0.0001
Wegovy	6	108	3.71	1.62	8.52	3.10	≤0.01
Dulaglutide	35	2189	1.03	0.72	1.46	0.14	0.89
Trulicity	33	2159	0.98	0.68	1.41	0.11	0.91
Exenatide	63	4274	0.95	0.72	1.24	0.41	0.68
Byetta	39	3010	0.83	0.59	1.16	1.10	0.27
Bydureon	17	1005	1.09	0.66	1.78	0.33	0.74
Bydureon Bcise	4	474	0.54	0.20	1.45	1.23	0.22
Liraglutide	76	1546	3.26	2.53	4.22	9.06	≤0.0001
Saxenda	32	297	7.62	5.20	11.18	10.39	≤0.0001
Victoza	40	1151	2.27	1.63	3.18	4.81	≤0.0001
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	10	389	1.67	0.88	3.15	1.57	0.12
Insulin†	237	16,841	0.90	0.76	1.07	1.20	0.23
Metformin† *(control)*	315	20,201	1.00	-	-	-	-
Depression Suicidal							
Semaglutide	8	1317	8.81	3.69	21.04	4.90	≤0.0001
Ozempic	8	1003	11.59	4.85	27.70	5.51	≤0.0001
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	2	2189	1.32	0.30	5.81	0.37	0.71
Trulicity	2	2159	1.34	0.30	5.89	0.38	0.70
Exenatide	7	4274	2.37	0.95	5.86	1.86	0.063
Byetta	3	3010	1.44	0.41	5.01	0.57	0.57
Bydureon	4	1005	5.76	1.89	17.54	3.08	≤0.01
Bydureon Bcise	1	474	3.05	0.40	23.23	1.08	0.28
Liraglutide	4	1546	3.74	1.23	11.38	2.32	≤0.05
Saxenda	2	297	9.78	2.21	43.21	3.01	≤0.01
Victoza	2	1151	2.51	0.57	11.06	1.22	0.22
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Insulin†	11	16,841	0.94	0.43	2.08	0.15	0.88
Metformin† *(control)*	14	20,201	1.00	-	-	-	-
Suicidal Behaviour							
Semaglutide	0	1317	0	-	-	-	-
Ozempic	0	1003	0	-	-	-	-
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	2	2189	1.42	0.32	6.30	0.46	0.64
Trulicity	2	2159	1.44	0.32	6.39	0.48	0.63
Exenatide	2	4274	0.73	0.16	3.22	0.42	0.67
Byetta	0	3010	0	-	-	-	-
Bydureon	2	1005	3.10	0.70	13.74	1.49	0.14
Bydureon Bcise	0	474	0	-	-	-	-
Liraglutide	3	1546	3.02	0.86	10.61	1.72	0.085
Saxenda	1	297	5.25	0.68	40.24	1.60	0.11
Victoza	1	1151	1.35	0.18	10.33	0.29	0.77
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Insulin	14	16,841	1.29	0.61	2.75	0.67	0.51
Metformin *(control)*	13	20,201	1.00	-	-	-	-
Suicidal Attempt							
Semaglutide	7	1317	0.048	0.023	0.10	7.98	≤0.0001
Ozempic	6	1003	0.054	0.024	0.12	7.10	≤0.0001
Rybelsus	1	114	0.080	0.011	0.57	2.51	≤0.05
Wegovy	0	108	0	-	-	-	-
Dulaglutide	20	2189	0.083	0.054	0.13	11.00	≤0.0001
Trulicity	17	2159	0.072	0.044	0.12	10.77	≤0.0001
Exenatide	18	4274	0.038	0.024	0.061	13.75	≤0.0001
Byetta	16	3010	0.048	0.030	0.079	12.03	≤0.0001
Bydureon	1	1005	0.0090	0.0013	0.064	4.71	≤0.0001
Bydureon Bcise	1	474	0.019	0.0027	0.14	3.95	≤0.0001

(*Continued*)

Table 1. (Continued).

Suicidal Ideation

GLP-1 Agonist	Number of Cases (n)	Total Cases of Psychiatric Disorders (N)	ROR	95% CI Lower	95% CI Upper	Z statistic	P value
Liraglutide	29	1546	0.17	0.12	0.25	9.29	≤0.0001
Saxenda	3	297	0.092	0.030	0.29	4.10	≤0.0001
Victoza	21	1151	0.17	0.11	0.26	8.05	≤0.0001
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Insulin[†]	877	16,841	0.50	0.46	0.54	16.69	≤0.0001
Metformin[†] *(control)*	2011	20,201	1.00	-	-	-	-
Completed Suicide							
Semaglutide	4	1317	0.0078	0.0029	0.021	9.68	≤0.0001
Ozempic	4	1003	0.010	0.0039	0.028	9.13	≤0.0001
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	3	2189	0.0035	0.0011	0.011	9.77	≤0.0001
Trulicity	3	2159	0.0036	0.0012	0.011	9.75	≤0.0001
Exenatide	5	4274	0.0030	0.0013	0.0072	12.96	≤0.0001
Byetta	2	3010	0.0017	0.00040	0.0068	9.00	≤0.0001
Bydureon	2	1005	0.0051	0.0013	0.021	7.45	≤0.0001
Bydureon Bcise	0	474	0	-	-	-	-
Liraglutide	26	1546	0.044	0.030	0.065	15.74	≤0.0001
Saxenda	1	297	0.0087	0.0012	0.062	4.74	≤0.0001
Victoza	10	1151	0.023	0.012	0.042	11.92	≤0.0001
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Insulin[†]	318	16,841	0.050	0.044	0.056	51.16	≤0.0001
Metformin[†] *(control)*	5653	20,201	1.00	-	-	-	-

[†]Search terms for metformin included: *'Metformin, Metformin Hydrochloride, Metformin Er 500 Mg, Metformin Hydrochloride Extended-Release 500 mg'* [30].

Table 2. Glucagon-like peptide-1 (GLP) receptor agonist-associated suicidality cases identified in the Food and Drug Administration's Adverse Event Reporting System (FAERS), using insulin as the control.

Suicidal Ideation

GLP-1 Agonist	Number of Cases (n)	Total Cases of Psychiatric Disorders (N)	ROR	95% CI Lower	95% CI Upper	Z statistic	P value
Semaglutide	80	1317	4.53	3.49	5.88	11.39	≤0.0001
Ozempic	59	1003	4.38	3.27	5.87	9.89	≤0.0001
Rybelsus	11	114	7.48	3.97	14.12	6.21	≤0.0001
Wegovy	6	108	4.12	1.79	9.48	3.33	≤0.001
Dulaglutide	35	2189	1.14	0.80	1.63	0.71	0.48
Trulicity	33	2159	1.09	0.75	1.57	0.45	0.65
Exenatide	63	4274	1.05	0.79	1.39	0.33	0.74
Byetta	39	3010	0.92	0.65	1.29	0.48	0.63
Bydureon	17	1005	1.21	0.73	1.98	0.74	0.46
Bydureon Bcise	4	474	0.60	0.22	1.61	1.02	0.31
Liraglutide	76	1546	3.62	2.78	4.72	9.56	≤0.0001
Saxenda	32	297	8.46	5.74	12.48	10.77	≤0.0001
Victoza	40	1151	2.52	1.79	3.55	5.33	≤0.0001
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	10	389	1.85	0.97	3.51	1.88	0.06
Metformin	123	7452	1.18	0.94	1.46	1.45	0.15
Metformin Hydrochloride	192	12749	1.07	0.88	1.30	0.70	0.48
Metformin Er 500 Mg	0	0	0	-	-	-	-
Metformin Hydrochloride Extended-Release 500 mg	0	0	0	-	-	-	-
Insulin[†] *(control)*	237	16,841	1.00	-	-	-	-
Depression Suicidal							
Semaglutide	8	1317	9.35	3.75	23.29	4.80	≤0.0001
Ozempic	8	1003	12.30	4.94	30.65	5.39	≤0.0001
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	2	2189	1.40	0.31	6.32	0.44	0.66
Trulicity	2	2159	1.42	0.31	6.40	0.46	0.65
Exenatide	7	4274	2.51	0.97	6.48	1.90	0.06
Byetta	3	3010	1.53	0.43	5.47	0.65	0.52

(*Continued*)

Table 2. (Continued).

Suicidal Ideation

GLP-1 Agonist	Number of Cases (n)	Total Cases of Psychiatric Disorders (N)	ROR	95% CI Lower	95% CI Upper	Z statistic	P value
Bydureon	4	1005	6.11	1.94	19.24	3.10	≤0.01
Bydureon Bcise	1	474	3.23	0.42	25.11	1.12	0.26
Liraglutide	4	1546	3.97	1.26	12.48	2.36	≤0.05
Saxenda	2	297	10.37	2.29	47.00	3.03	≤0.01
Victoza	2	1151	2.66	0.59	12.03	1.27	0.20
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Metformin	6	7452	1.23	0.46	3.34	0.41	0.68
Metformin Hydrochloride	8	12749	0.96	0.39	2.39	0.09	0.93
Metformin Er 500 Mg	0	0	0	-	-	-	-
Metformin Hydrochloride Extended-Release 500 mg	0	0	0	-	-	-	-
Insulin† *(control)*	11	16,841	1.00	-	-	-	-
Suicidal Behaviour							
Semaglutide	0	1317	0	-	-	-	-
Ozempic	0	1003	0	-	-	-	-
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	2	2189	1.10	0.25	4.84	0.13	0.90
Trulicity	2	2159	1.11	0.25	8.13	0.14	0.89
Exenatide	2	4274	0.56	0.13	2.48	0.76	0.45
Byetta	0	3010	0	-	-	-	-
Bydureon	2	1005	2.40	0.54	10.56	1.16	0.25
Bydureon Bcise	0	474	0	-	-	-	-
Liraglutide	3	1546	2.34	0.67	8.14	1.33	0.18
Saxenda	1	297	4.06	0.53	30.98	1.35	0.18
Victoza	1	1151	1.05	0.14	7.96	0.043	0.97
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Metformin	6	7452	0.97	0.37	2.52	0.07	0.95
Metformin Hydrochloride	7	12749	0.66	0.27	1.64	0.90	0.37
Metformin Er 500 Mg	0	0	0	-	-	-	-
Metformin Hydrochloride Extended-Release 500 mg	0	0	0	-	-	-	-
Insulin* *(control)*	14	16,841	1.00	-	-	-	-
Suicidal Attempt							
Semaglutide	7	1317	0.097	0.046	0.21	6.12	≤0.0001
Ozempic	6	1003	0.11	0.049	0.25	5.38	≤0.0001
Rybelsus	1	114	0.16	0.023	1.15	1.82	0.069
Wegovy	0	108	0	-	-	-	-
Dulaglutide	20	2189	0.17	0.11	0.26	7.85	≤0.0001
Trulicity	17	2159	0.14	0.089	0.23	7.87	≤0.0001
Exenatide	18	4274	0.077	0.048	0.12	10.74	≤0.0001
Byetta	16	3010	0.097	0.059	0.16	9.21	≤0.0001
Bydureon	1	1005	0.018	0.0025	0.13	4.01	≤0.0001
Bydureon Bcise	1	474	0.039	0.01	0.27	3.25	≤0.01
Liraglutide	29	1546	0.35	0.24	0.51	5.54	≤0.0001
Saxenda	3	297	0.19	0.059	0.58	2.90	≤0.01
Victoza	21	1151	0.34	0.22	0.52	4.86	≤0.0001
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Metformin	712	7452	1.92	1.73	2.13	12.46	≤0.0001
Metformin Hydrochloride	1299	12749	2.07	1.89	2.26	15.98	≤0.0001
Metformin Er 500 Mg	0	0	0	-	-	-	-
Metformin Hydrochloride Extended-Release 500 mg	0	0	0	-	-	-	-
Insulin† *(control)*	877	16,841	1.00	-	-	-	-
Completed Suicide							
Semaglutide	4	1317	0.16	0.059	0.43	3.66	≤0.001
Ozempic	4	1003	0.21	0.077	0.56	3.11	≤0.01
Rybelsus	0	114	0	-	-	-	-
Wegovy	0	108	0	-	-	-	-
Dulaglutide	3	2189	0.071	0.023	0.22	4.55	≤0.0001
Trulicity	3	2159	0.072	0.023	0.23	4.53	≤0.0001
Exenatide	5	4274	0.061	0.025	0.15	6.21	≤0.0001
Byetta	2	3010	0.035	0.0086	0.14	4.74	≤0.0001
Bydureon	2	1005	0.10	0.026	0.42	3.19	≤0.01

(*Continued*)

Table 2. (Continued).

Suicidal Ideation

GLP-1 Agonist	Number of Cases (n)	Total Cases of Psychiatric Disorders (N)	ROR	95% CI Lower	95% CI Upper	Z statistic	P value
Bydureon Bcise	0	474	0	-	-	-	-
Liraglutide	26	1546	0.89	0.59	1.33	0.57	0.57
Saxenda	1	297	0.18	0.025	1.25	1.73	0.083
Victoza	10	1151	0.46	0.24	0.86	2.44	≤0.05
Lixisenatide	0	10	0	-	-	-	-
Adlyxin	0	1	0	-	-	-	-
Tirzepatide	0	389	0	-	-	-	-
Metformin	2244	7452	22.39	19.83	25.28	50.15	≤0.0001
Metformin Hydrochloride	3409	12749	18.96	16.86	21.33	49.01	≤0.0001
Metformin Er 500 Mg	0	0	0	-	-	-	-
Metformin Hydrochloride Extended-Release 500 mg	0	0	0	-	-	-	-
Insulin[†] *(control)*	318	16,841	1.00	-	-	-	-

[†]Search terms for insulin *(control)* included: *'Insulin Aspart, Insulin Aspart Protamine and Insulin Aspart, Insulin Degludec, Insulin Detemir, Insulin Glargine, Insulin Glulicine, Insulin Human, Insulin Lispro.'* [31].

3.1. Comparison of GLP-1 RAs to metformin

For the comparison of GLP-1 RAs to metformin as the control, the suicidal ideation RORs were as follows: semaglutide (ROR 4.08, 95% CI 3.17–5.25; $p \leq 0.0001$), dulaglutide (ROR 1.03, 95% CI 0.72–1.46; $p = 0.89$), exenatide (ROR 0.95; 95% CI 0.72–1.24; $p = 0.68$), liraglutide (ROR 3.26; 95% CI 2.53–4.22; $p \leq 0.0001$), lixisenatide (ROR 0), and tirzepatide (ROR 1.67, 95% CI 0.88–3.15, $p = 0.12$), respectively. With respect to "depression/suicidal", the RORs were as follows: semaglutide (ROR 8.81, 95% CI 3.69–21.04; $p \leq 0.0001$), dulaglutide (ROR 1.32, 95% CI 0.30–5.81; $p = 0.71$), exenatide (ROR 2.37; 95% CI 0.95–5.86; $p = 0.063$), liraglutide (ROR 3.74; 95% CI 1.23–11.38; $p \leq 0.05$), lixisenatide (ROR 0), and tirzepatide (ROR 0).

The metformin-controlled suicidal behavior RORs were as follows: semaglutide (ROR 0), dulaglutide (ROR 1.42, 95% CI 0.32–6.30; $p = 0.64$), exenatide (ROR 0.73; 95% CI 0.16–3.22; $p = 0.67$), liraglutide (ROR 3.02; 95% CI 0.86–10.61; $p = 0.085$), lixisenatide (ROR 0), and tirzepatide (ROR 0), respectively. In terms of suicidal attempts, the RORs were as follows: semaglutide (ROR 0.048; 95% CI 0.023–0.10; $p \leq 0.0001$), dulaglutide (ROR 0.083; 95% CI 0.054–0.13; $p \leq 0.0001$), exenatide (ROR 0.038; 95% CI 0.024–0.061; $p \leq 0.0001$), liraglutide (ROR 0.17, 95% CI: 0.12–0.25; $p \leq 0.0001$), lixisenatide (ROR 0), and tirzepatide (ROR 0), respectively. Finally, when considering the metformin-controlled RORs for completed suicide, they were as follows: semaglutide (ROR 0.0078, 95% CI 0.0029–0.021; $p \leq 0.001$), dulaglutide (ROR 0.0035; 95% CI 0.0011–0.011; $p \leq 0.0001$), exenatide (ROR 0.0030; 95% CI 0.0013–0.0072; $p \leq 0.0001$), liraglutide (ROR 0.044, 95% CI 0.030–0.065; $p \leq 0.001$), lixisenatide (ROR 0), and tirzepatide (ROR 0), respectively.

3.2. Comparison of GLP-1 RAs to insulin

When comparing to insulin, the suicidal ideation RORs were as follows: semaglutide (ROR 4.53; 95% CI 3.49–5.88; $p \leq 0.0001$), dulaglutide (ROR 1.14; 95% CI 0.80–1.63; $p = 0.48$), exenatide (ROR 1.05; 95% CI 0.79–1.39; $p = 0.74$), liraglutide (ROR 3.62; 95% CI 2.78–4.72; $p \leq 0.0001$), lixisenatide (ROR 0), and tirzepatide (ROR 1.85; 95% CI: 0.97–3.51; $p = 0.06$), respectively. The ROR for each of the GLP-1 RAs with respect to "depression/suicidal" were as follows: semaglutide (ROR 9.35, 95% CI 3.75–23.29; $p \leq 0.0001$), dulaglutide (ROR 1.40, 95% CI 0.31–6.32; $p = 0.66$), exenatide (ROR 2.51; 95% CI 0.97–6.48; $p = 0.06$), liraglutide (ROR 3.97, 95% CI 1.26–12.48; $p \leq 0.05$), lixisenatide (ROR 0), and tirzepatide (ROR 0).

The ROR for suicidal behavior were as follows: semaglutide (ROR 0), dulaglutide (ROR 1.10, 95% CI 0.25–4.84; $p = 0.90$), exenatide (ROR 0.56; 95% CI 0.13–2.48; $p = 0.45$), liraglutide (ROR 2.34; 95% CI 0.67–8.14; $p = 0.18$), lixisenatide (ROR 0), and tirzepatide (ROR 0), respectively. For suicidal attempt, the respective RORs were semaglutide (ROR 0.097; 95% CI 0.046–0.21; $p \leq 0.0001$), dulaglutide (ROR 0.17; 95% CI 0.11–0.26; $p \leq 0.0001$), exenatide (ROR 0.077; 95% CI 0.048–0.12; $p \leq 0.0001$), liraglutide (0.35, 95% CI: 0.24–0.51; $p \leq 0.0001$), lixisenatide (ROR 0), and tirzepatide (ROR 0). Finally, the ROR for each of the GLP-1 RAs as it pertains to completed suicide were as follows: semaglutide (ROR 0.16, 95% CI 0.059–0.43; $p \leq 0.001$), dulaglutide (ROR 0.071; 95% CI 0.023–0.22; $p \leq 0.0001$), exenatide (ROR 0.061; 95% CI 0.025–0.15; $p \leq 0.0001$), liraglutide (0.89, 95% CI 0.59–1.33; $p = 0.57$), lixisenatide (ROR 0), and tirzepatide (ROR 0).

4. Discussion

Herein, we observed disproportionate reporting of suicidal ideation and "depression/suicidal" with semaglutide and liraglutide when compared to metformin and insulin as separate controls. The remaining GLP-1 RAs (dulaglutide, exenatide, lixisenatide, and tirzepatide) did not show disproportionate reporting of the five psychiatric events evaluated in this study. Furthermore, disproportionate reporting of psychiatric cases, as defined herein, was not observed with metformin when using insulin as the control or with insulin when using metformin as the control.

The well-documented association between type 2 diabetes/obesity and depressive disorders raises the possibility of confounding factors influencing the event of interest herein, i.e. suicidality. The possibility that semaglutide and liraglutide are disproportionately prescribed in persons with depressive disorders, especially in light of reports suggesting potential

antidepressant and pro-cognitive effects, is not known [4,6,17,18]. Causality considerations which represent testable hypotheses include whether GLP-1 RAs are potentially depressogenic, engender and/or exacerbate anhedonia or impulse control in susceptible individuals . This possibility is not mutually exclusive of the potential antidepressant and pro-cognitive effects that are suggested by preclinical and clinical data [19–23].

This analysis is not exempt from methodological limitations. The primary limitation is that FAERS receives spontaneous reporting of adverse events from manufacturers, prescribers, and consumers. Consequently, FAERS cannot be assumed to capture all adverse events. Moreover, FAERS has its own coding system for suicidality (e.g. "depression/suicidal") that may not be identical to other reporting methods. The data captured herein reflect the FAERS and may not apply to international exposure, and the possibility of uneven reporting may have also influenced our findings. Additionally, the reporting process does not include the total prescription volume of the agent/class under scrutiny and consequently more detailed risk hazard cannot be fully ascertained.

It is hypothesized that the extraordinary mainstream and social media attention allocated to GLP-1 RAs, especially semaglutide and liraglutide, may have contributed to an increasing reporting rate relative to other agents. An additional limitation of our method is that we cannot draw any firm conclusions with respect to causality. For example, comprehensive information regarding individual cases, the clinical context, and details surrounding the dose and duration of GLP-1 RA exposure are not sufficiently captured. Furthermore, a plausible mechanism using the Bradford-Hill criteria causally linking GLP-1 RAs to suicidality is also not known.

5. Conclusion

In summary, there is disproportionate reporting of suicidal ideation and depression suicidal to the FAERS for semaglutide and liraglutide. Notwithstanding the association, we are not able to infer any causation between exposure to the foregoing agents and suicidality that aligns with the Bradford-Hill criteria [24]. Moreover, we are not able to ascertain a plausible mechanism that would link exposure specifically to these two agents to suicidality that would not apply to the other agents within this class. Persons receiving GLP-1 RAs for the treatment of diabetes or as part of weight management are differentially affected by psychiatric disorders with known associated risk for suicide, which may have been contributory in reported cases.

Moreover, emerging evidence suggests that GLP-1 RAs may have effects on brain systems that subserve cognition and reward processing, suggesting potential benefits in the treatment of psychiatric disorders and associated hazards (e.g. suicidality) [25–27]. In addition, it is well established that some individuals who receive bariatric surgery may be at risk of new onset or recurrent depression and suicidality, suggesting the phenomenon of suicidality is not etiologically related to a specific agent or class, and instead is an intrinsic risk in this population [28,29].

The EMA has issued a press release announcing the reported cases of GLP-1 RAs and suicidality. It is essential that regulators promptly investigate such cases and efficiently follow-up with additional press releases as to their findings so that the public is informed in a timely and accurate manner [3]. This would assist in reducing the spread of misinformation and/or incomplete information across media platforms. A priority research vista will be to evaluate suicidality ROR associated with glucose-lowering agents, including GLP-1 RAs, in other international databases. Disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide were not observed for any of the FDA-approved GLP-1 RAs. Using the Bradford Hill criteria, however, and taking into consideration confounders, no causal link between GLP-1 RAs and suicidality exists.

Funding

This paper was not funded.

Declaration of interests

RS McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, AbbVie, Atai Life Sciences. Dr. Roger S. McIntyre is a CEO of Braxia Scientific Corp.

RB Mansur has received research grant support from the Canadian Institutes of Health Research (CIHR), the Physicians' Services Incorporated (PSI) Foundation and the Baszucki Brain Research Fund; and support from an Academic Scholars Award from the Department of Psychiatry, University of Toronto.

JD Rosenblat has received research grant support from the Canadian Institute of Health Research (CIHR), Physician Services Inc (PSI) Foundation, Labatt Brain Health Network, Brain and Cognition Discovery Foundation (BCDF), Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund, and Timeposters Fellowship and industry funding for speaker/consultation/research fees from iGan, Boehringer Ingelheim, Janssen, Allergan, Lundbeck, Sunovion, and COMPASS. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contribution statement

All authors (RS McIntyre, JD Rosenblat, RB Mansur, and ATH Kwan) conceptualized, designed, and drafted the manuscript, as well as provided critical review for important intellectual concept and approved the final version to be published. ATH Kwan analyzed and interpreted the data. All authors agree to be accountable for all aspects of the work.

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