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Research paper

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: A replication study using reports to the World Health Organization pharmacovigilance database (VigiBase®)

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ABSTRACT

Introduction: Reports of suicidality associated with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been reported to the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). We previously reported an increased reporting odds ratio (ROR) of some measures of suicidality with semaglutide and liraglutide using the FDA Adverse Event Reporting System (FAERS). Notwithstanding the increased ROR, causality between GLP-1 RAs exposure and any aspect of suicidality is not established.

Research design and methods: The analysis herein aims to extend a previous analysis of the FAERS by evaluating the ROR for suicidality reported to the World Health Organization (WHO) Pharmacovigilance Database (VigiBase). We aimed to characterize the ROR of suicidality associated with GLP-1 RAs, as extrapolated from spontaneous reports. As per our previous report, the ROR was considered significant when the lower limit of the 95 % confidence (CI) was >1.0.

Results: We searched VigiBase reports from inception to January 2024. The RORs for suicidal ideation were significantly increased for semaglutide (5.82), liraglutide (4.03) and tirzepatide (2.25). For "depression/suicidal", the ROR was significantly increased for semaglutide (14.74) and liraglutide (5.86); and for suicidal behaviour, the ROR was significantly increased for semaglutide (6.52) and liraglutide (3.90). However, for suicide attempts, the ROR was significantly decreased for semaglutide (0.11), dulaglutide (0.075), exenatide (0.047) and liraglutide (0.15). For completed suicide, the ROR was also significantly decreased for semaglutide (0.01), dulaglutide (0.003), exenatide (0.002) and liraglutide (0.008).

Conclusion: Unlike our previous report with FAERS, a mixed pattern of ROR emerged in the WHO VigiBase with respect to suicidality and exposure to select GLP-RAs. Causation between GLP-1 RA exposure and suicidality (either increased or decreased) cannot be ascertained from ROR data.

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1. Introduction

We previously reported an increased reporting odds ratio (ROR) with the glucagon-like peptide 1 receptor agonists (GLP-1 RAs) semaglutide and liraglutide for suicidal ideation and "depression/suicidal" (McIntyre et al., 2023a). The impetus for the aforementioned analysis was provided by reports to European and United States (US) regulators of suicidality associated with GLP-1 RAs (EMA statement on ongoing review of GLP-1 receptor agonists, 2024). Subsequently, the US Food and Drug Administration (FDA) reported that a causal link between GLP-1 RAs and suicidality does not currently exist (Center for Drug Evaluation, Research, 2024). In addition, a recent retrospective cohort study of an electronic health records database reported that amongst persons with overweight/obesity or type II diabetes mellitus (T2DM), semaglutide was significantly associated with a lower risk for incident and recurrent suicidal ideation (Wang et al., 2024).

For the analysis herein, we aim to extend our previous analysis of the FDA Adverse Event Reporting System (FAERS) by evaluating suicidality associated with GLP-1 RAs reported to the World Health Organization Global Pharmacovigilance Database (WHO VigiBase) (McIntyre et al., 2023a). The overarching aim of this analysis is to provide a fuller reporting of increased or decreased suicidality associated with GLP-1 RAs.

2. Methods

We evaluated reports of "suicidal ideation, depression/suicidal, suicidal behaviour, suicide attempt and completed suicide" to the WHO VigiBase as part of an observational retrospective analysis conducted in January 2024. Each of the aforementioned categories reflect the coding system within the WHO VigiBase.

The GLP-1 RAs we chose and report herein were identical to those we previously reported using the FAERS (McIntyre et al., 2023a). All GLP-1 RAs that are FDA approved include Semaglutide (Ozempic, Rybelsus, Wegovy), Dulaglutide (Trulicity), Exenatide (Byettta, Bydureon, Bydureon Bcise), Liraglutide (Saxenda, Victoza), Lixisenatide (Adlyxin) and Tirzepatide (Mounjaro, Zepbound).

All events pertaining to suicidality reported to the WHO VigiBase up until January 2024 were obtained **(**Table 1**)**. Additionally, as per our previous analysis, we determined the reporting odds ratio (ROR) as follows: odds ratio = (odds of the event in the exposed group) / (odds of the event in the non-exposed group) (McIntyre et al., 2023a). To allow comparison to our previous report, we used metformin as the reference agent.

Also, identical to our prior publication, the upper and lower 95 % CI were calculated with an alpha risk of 5 % to determine statistical significance. As done prior, we used a lower 95 % CI >1.0 as consideration for disproportionate reporting. We also used the identical software for analysis, where we used Microsoft Excel 2021 and R version 4.3.1 as well as RStudio Windows version 2023.06.1 + 524 "Desert Sunflower" Release (b51c81cc303d4b52b010767e5b30438beb904641, 2023-09-25) for Windows to create the forest plots.

3. Results

From inception to January 2024, we identified 89 reports in the WHO VigiBase of suicidal ideation, 4 reports of depression suicidal, 3 reports of suicidal behaviour, 359 reports of suicidal attempt and 2178 reports of completed suicide associated with metformin **(**Table 1**;** Fig. 1**).** When no cases were reported for a particular category, we present the ROR as 0.

3.1. Comparison of GLP-1 RAs in the WHO VigiBase to metformin

When compared to metformin, the ROR for suicidal ideation for each of the selected GLP-1 RAs were: semaglutide (ROR 5.82, 95 % CI 4.46–7.60, $p \leq 0.0001$), dulaglutide (0.96, 95 % CI 0.63–1.45, $p = 0.84$), exenatide (0.95, 95 % CI 0.67–1.34, $p = 0.77$), liraglutide (4.03, 95 % CI 3.05–5.33, $p \leq 0.0001$), lixisenatide (ROR 0) and tirzepatide (2.25, 95 % CI 1.29–3.91, $p = 0.0042$). For the category "depression/suicidal", the RORs were: semaglutide (14.74, 95 % CI 4.98–43.61, $p \leq 0.0001$), dulaglutide 1.42, 95 % CI 0.26–7.77, $p = 0.68$), exenatide (2.40, 95 % CI 0.68–8.50, $p = 0.18$), liraglutide (5.86, 95 % CI 1.76–19.49, $p = 0.0039$), lixisenatide (ROR 0) and tirzepatide (ROR 0).

With respect to the category suicidal behaviour, RORs were: semaglutide (6.52, 95 % CI 1.63–26.08, $p = 0.0081$), dulaglutide (1.90, 95 % CI 0.32–11.36, $p = 0.48$), exenatide (ROR 0), liraglutide (3.90, 95 % CI 0.87–17.45, $p = 0.075$), lixisenatide (ROR 0) and tirzepatide (ROR 0). In addition, the RORs compared to metformin for suicide attempt were: semaglutide (0.11, 95 % CI 0.064–0.20, $p \leq 0.0001$), dulaglutide (0.075, 95 % CI 0.040–0.14, $p \leq 0.0001$), exenatide (0.047, 95 % CI 0.026–0.085, $p \leq 0.0001$), liraglutide (0.15, 95 % CI 0.093–0.24, $p \leq 0.0001$), lixisenatide (ROR 0) and tirzepatide (ROR 0), respectively.

Reports of completed suicide and GLP-1 RAs revealed a different pattern. For example, the RORs were: semaglutide (0.010, 95 % CI 0.0055–0.019, $p \leq 0.0001$), dulaglutide (0.0027, 95 % CI 0.0009–0.0083, $p \leq 0.0001$), exenatide (0.0015, 95 % CI 0.0005–0.0047, $p \leq 0.0001$), liraglutide (0.0083, 95 % CI 0.0043–0.016, $p \leq 0.0001$), lixisenatide (ROR 0) and tirzepatide (ROR 0)..

4. Discussion

A mixed pattern of ROR emerged from the WHO VigiBase with respect to ROR for suicidality and exposure to GLP-1 RAs. Significantly increased ROR for some GLP-1 RAs for suicidal ideation and suicidal behaviour were noted, while significant reductions for some (and overlapping) GLP-1 RAs were noted for suicide attempts and completed suicide. The results we obtained using the WHO VigiBase partially comports with our previous report from the FAERS, with the additional and separate finding being decreased reporting of suicide attempt and completed suicide associated with some GLP-1 RAs in the WHO VigiBase (McIntyre et al., 2023a). In addition, our results also align with a separate WHO Vigibase analysis that was delimited to semaglutide and liraglutide that reported an increase in aspects of suicidality (Schoretsanitis et al., 2024).

Our mixed results of increased suicidal ideation with select GLP-1 RAs yet decrease in suicide do not lend themselves to simple reconciliation and likely multiple factors are explanatory. For example, the presence of comorbid psychiatric disorders may partially explain the differences across aspects of suicidality. In addition, although suicidal ideation and suicidal behaviour are related, they are different behavioural and neurobiological constructs wherein suicidal behaviour cannot be simplified as a eventuality in persons with prominent suicidal ideation. Hence, it is not uncommon for interventions to have differential effects across aspects of suicidality (Mann et al., 2021).

Results from two pharmacoepidemiological studies in the US and Europe observed a significant reduction in measures of suicidality associated with GLP-1 RAs (Wang et al., 2024; Wium-Andersen et al., 2022). Moreover, the emergence or worsening of suicidality has not been reported to be significantly increased in studies with GLP-1 RAs in the treatment of alcohol use-, depressive- and bipolar disorders as well as Parkinson's Disease; each of which are associated with suicidality (Antonsen et al., 2018; Klausen et al., 2022; Chen et al., 2023; Cooper et al., 2023; Mansur et al., 2017; McGarry et al., 2024; O'Neil et al., 2017; McIntyre et al., 2023b; McIntyre et al., 2020). Moreover, worsening of suicidality has not been reported when GLP-1 RAs are prescribed to mitigate psychotropic drug-related weight gain in persons with serious mental illness (McIntyre et al., 2024). The foregoing observations are in accordance with other lines of evidence indicating GLP-1 RAs target molecular and cellular systems that may benefit dimensions of psychopathology (e.g., cognition) (McIntyre et al., 2013; Weina et al.,

Table 1
Glucagon-like peptide-1 (GLP) receptor agonist-associated suicidality cases identified in the WHO VigiBase, 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 (i.e., Ozempic, Rybelsus, Wegovy)	150	2100	5.82	4.46	7.60	12.93	≤ 0.0001
Dulaglutide (i.e., Trulicity)	30	2400	0.96	0.63	1.45	0.20	0.84
Exenatide (i.e., Byetta, Bydureon, Bydureon Bcise)	53	4276	0.95	0.67	1.34	0.30	0.77
Liraglutide (i.e., Saxenda, Victoza)	118	2335	4.03	3.05	5.33	9.78	≤ 0.0001
Lixisenatide (i.e., Adlyxin)	0	20	0	–	–	–	–
Tirzepatide	15	520	2.25	1.29	3.91	2.86	0.0042
Insulin[†]	39	2975	1.01	0.69	1.47	0.028	0.98
Metformin *(control)*	89	6825	1.00	–	–	–	–
Depression Suicidal							
Semaglutide (i.e., Ozempic, Rybelsus, Wegovy)	18	2100	14.74	4.98	43.61	4.86	≤ 0.0001
Dulaglutide (i.e., Trulicity)	2	2400	1.42	0.26	7.77	0.41	0.68
Exenatide (i.e., Byetta, Bydureon, Bydureon Bcise)	6	4276	2.40	0.68	8.50	1.35	0.18
Liraglutide (i.e., Saxenda, Victoza)	8	2335	5.86	1.76	19.49	2.89	0.0039
Lixisenatide (i.e., Adlyxin)	0	20	0	–	–	–	–
Tirzepatide	0	520	0	–	–	–	–
Insulin[†]	2	2975	1.15	0.21	6.27	0.16	0.87
Metformin *(control)*	4	6825	1.00	–	–	–	–
Suicidal Behaviour							
Semaglutide (i.e., Ozempic, Rybelsus, Wegovy)	6	2100	6.52	1.63	26.08	2.65	0.0081
Dulaglutide (i.e., Trulicity)	2	2400	1.90	0.32	11.36	0.70	0.48
Exenatide (i.e., Byetta, Bydureon, Bydureon Bcise)	0	4276	0	–	–	–	–
Liraglutide (i.e., Saxenda, Victoza)	4	2335	3.90	0.87	17.45	1.78	0.075
Lixisenatide (i.e., Adlyxin)	0	20	0	–	–	–	–
Tirzepatide	0	520	0	–	–	–	–
Insulin[†]	5	2975	3.83	0.91	16.03	1.84	0.066
Metformin *(control)*	3	6825	1.00	–	–	–	–
Suicide Attempt							
Semaglutide (i.e., Ozempic, Rybelsus, Wegovy)	13	2100	0.11	0.064	0.20	7.72	≤ 0.0001
Dulaglutide (i.e., Trulicity)	10	2400	0.075	0.040	0.14	8.04	≤ 0.0001
Exenatide (i.e., Byetta, Bydureon, Bydureon Bcise)	11	4276	0.047	0.026	0.085	10.01	≤ 0.0001
Liraglutide (i.e., Saxenda, Victoza)	19	2335	0.15	0.093	0.24	8.08	≤ 0.0001
Lixisenatide (i.e., Adlyxin)	0	20	0	–	–	–	–
Tirzepatide	0	520	0	–	–	–	–
Insulin[†]	62	2975	0.38	0.29	0.50	6.88	≤ 0.0001
Metformin *(control)*	359	6825	1.00	–	–	–	–
Completed Suicide							
Semaglutide (i.e., Ozempic, Rybelsus, Wegovy)	10	2100	0.010	0.0055	0.019	14.42	≤ 0.0001
Dulaglutide (i.e., Trulicity)	3	2400	0.0027	0.0009	0.0083	10.25	≤ 0.0001
Exenatide (i.e., Byetta, Bydureon, Bydureon Bcise)	3	4276	0.0015	0.0005	0.0047	11.25	≤ 0.0001
Liraglutide (i.e., Saxenda, Victoza)	9	2335	0.0083	0.0043	0.016	14.32	≤ 0.0001
Lixisenatide (i.e., Adlyxin)	0	20	0	–	–	–	–
Tirzepatide	0	520	0	–	–	–	–
Insulin[†]	28	2975	0.020	0.014	0.030	20.34	≤ 0.0001
Metformin *(control)*	2178	6825	1.00	–	–	–	–

† Search term for insulin included the active ingredient "insulin human" (VigiAccess, 2024).

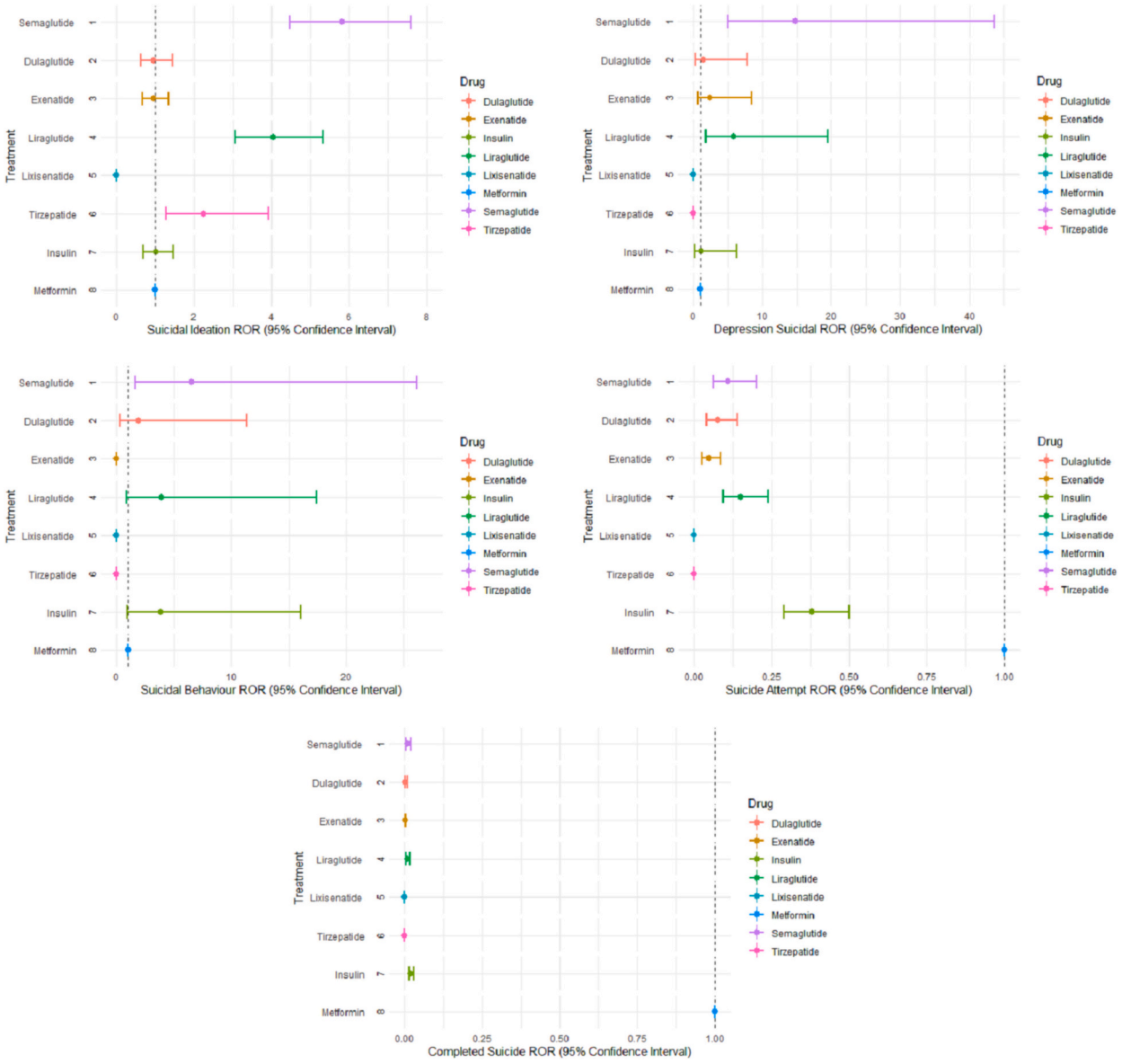

Fig. 1. Forest plots: reporting odds ratio (ROR) for psychiatric events with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) versus metformin control.

2018; Yang et al., 2022; Ridout et al., 2022; Çiçekli et al., 2022).

Confounding interpretation of pharmacovigilance reporting of suicidality associated with GLP-1 RAs is the well-established risk of suicide documented in persons living with mood disorders, obesity and metabolic disorders (McIntyre et al., 2023b; McIntyre et al., 2020; Maj et al., 2020). For example, meta-analytic data have documented a bidirectional relationship between aspects of suicidality and T2DM as well as a higher rate of suicidality in persons living with polycystic ovarian syndrome (Renaud-Charest et al., 2024; Hsu et al., 2024). It remains a testable hypothesis that the increased risk of suicidality in persons prescribed GLP-1 RAs may be partially mediated by the presence of other medical conditions that increase risk of suicide (McIntyre, 2024). A non-competing hypothesis to be tested is the possibility that in a subgroup of persons prescribed GLP-1 RAs, a causal relationship to suicidality does exist and the elevated report of suicidal ideation and behaviour is not adequately or completely explained by confounding factors. For example, the possibility has not been disproven that GLP-1 RAs effects on brain systems and/or psychological reactions to weight loss (which may be discordant with patient expectation) and/or other biological systems affected by GLP-1 RAs directly, or indirectly, by weight change may adversely affect brain health, similar to what is reported in some people receiving bariatric surgery (Miller-Matero et al., 2023).

The limitations of the WHO VigiBase are that it is dependent on spontaneous reporting of cases that have not been subjected to systematic verification. Relatedly, we do not have comprehensive or specific information on persons' past medical and psychiatric history which may confound some of our results. We also chose metformin as our control, as has been done for other analyses which allows comparison of results, it is possible that results of our analysis would be different with another comparator (Schoretsanitis et al., 2024). In addition, the absence of contextual factors prevent any determination of cause and effect analyses or conclusions. Consequently, as with the FAERS, a causative effect between GLP-1 RAs or increased or decreased suicidality

cannot be established. It is possible that increased reporting may be a function of other factors including the confound of mental illness overrepresented in persons with obesity and/or metabolic disorders as well as the media discourse surrounding this class of medications (Liu et al., 2022; Liu et al., 2021; Jawad et al., 2022). Also, we did not have information as it relates to whether persons were prescribed GLP-1 RAs for obesity, T2DM or both. We assume that most were prescribed these agents for T2DM in light of the fact the diabetic indication preceded obesity indication and these agents are prescribed more often to persons with T2DM. Using electronic health records, it was separately reported that the lack of association between GLP-1 RAs and suicidality was observed in both diabetic and obesity populations. It is noteworthy that obesity dosing of GLP-1 RAs is typically higher than antidiabetic dosing, which in the Wang et al. analysis was associated with a lower suicidality risk (Wang et al., 2024). In addition, we did not investigate whether the weight loss potential of the agents is a moderator of any of the events we observed.

5. Conclusion

Similar to our previous report to the FAERS, we observed higher ROR for some aspects of suicidality with semaglutide, liraglutide and tirzepatide. We also observed a significantly lower ROR for suicide attempts and completed suicide for semaglutide, dulaglutide, exenatide and liraglutide. As mentioned previously, causal effects cannot be established using pharmacovigilance databases such as the FAERS or WHO VigiBase (Fedak et al., 2015).

The preponderance of extant data evaluating suicidality and GLP-1 RAs integrating pharmacoepidemiology, randomized controlled trials, safety/neuropsychiatric side effect reporting and results from pharmacovigilance do not establish a causal link between GLP-1 RAs and suicidality. Whether GLP-1 RAs lower suicidality remains a testable hypothesis and priority research vista. The increasing prescription of GLP-1 RAs in the general population as well as in the psychiatric population, where they are additionally used to mitigate weight and metabolic consequences of concomitant psychiatric medication, is informed by up-to-date safety information including but not limited to the use of real world pharmacovigilance (McIntyre et al., 2024). Future research vistas should aim to identify data points that fulfill Bradford Hill Criteria to inform putative cause and effect of GLP-1 RAs and suicidality (McIntyre, 2024). In the interim, practitioners should be vigilant for the risk of psychiatric disorders and suicidality which is heightened in persons who would be candidates for GLP-1 RAs (e.g., obesity, T2DM) and educate and evaluate patients for emergence or worsening of suicidality in the presence of GLP-1 RA exposure.

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Author contributions

All authors (ATH Kwan, JD Rosenblat, RB Mansur and RS McIntyre) conceptualized, designed and drafted the manuscript as well as provided critical review for important intellectual concept and approved the final version to be published (Taeho Greg Rhee, Kayla M. Teopiz, Bing Cao, Sabrina Wong, Gia Han Le, Roger Ho). ATH Kwan analyzed and interpreted the data. All authors agree to be accountable for all aspects of the work.

CRediT authorship contribution statement

Roger S. McIntyre: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Rodrigo B. Mansur:** Writing – review & editing. **Joshua D. Rosenblat:** Writing – review & editing. **Taeho Greg Rhee:** Writing – review & editing. **Bing Cao:** Writing – review & editing. **Kayla M. Teopiz:** Writing – review & editing. **Sabrina Wong:** Writing – review & editing. **Gia Han Le:** Writing – review & editing. **Roger Ho:** Writing – review & editing. **Angela T.H. Kwan:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

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Dr. Taeho Greg Rhee serves as a review committee member for Patient-Centered Outcomes Research Institute (PCORI) and Substance Abuse and Mental Health Services Administration (SAMHSA) and has received honoraria payments from PCORI and SAMHSA. Dr. Rhee has also served as a stakeholder/consultant for PCORI and received consulting fees from PCORI. Dr. Rhee serves as an advisory committee member for International Alliance of Mental Health Research Funders (IAMHRF). Dr. Rhee is currently a co-Editor-in-Chief of Mental Health Science and has received honorarium payments annually from the publisher, John Wiley & Sons, Inc.

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Data availability statement

The data presented in this study is available on request from the corresponding author.

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