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SCIENTIFIC INVESTIGATIONS

Insomnia and suicide as reported adverse effects of second-generation antipsychotics and mood stabilizers

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Study Objectives: Insomnia and suicide ideation/behavior/death (SIB) are common in psychiatric disorders. There is evidence that clozapine and lithium have antisuicidal properties and beneficial effects on sleep. We investigated the reported odds of spontaneously reported psychiatric adverse drug reactions of insomnia and SIB in adults for second-generation antipsychotics (SGAs) and mood stabilizers compared to clozapine and lithium, respectively.

Methods: We searched the U.S. Food & Drug Administration Adverse Event Reporting System from inception through February 2021 for which an SGA or mood stabilizer was the suspected agent of a psychiatric adverse drug reaction.

Results: We investigated 10 SGAs and 5 mood stabilizers. Compared to clozapine, other SGAs were associated with a significantly increased reported odds of insomnia (reported odds ratio [rOR] = 2.41–9.70) and SIB (rOR = 1.18–2.72). Compared to lithium, there was a significantly increased reported odds of SIB (rOR = 1.17–1.70) for other mood stabilizers and odds of insomnia (rOR = 1.66) for lamotrigine. The insomnia and SIB rORs for SGAs and mood stabilizers were positively correlated.

Conclusions: Our results are consistent with evidence for antisuicidal properties of clozapine and lithium. Findings also raise the possibility of beneficial effects on sleep as one potential pathway underlying the antisuicidal properties for these agents. Future studies are needed to identify underlying biological mechanisms that contribute to these associations.

Keywords: clozapine, lithium, antipsychotics, mood stabilizers, insomnia, suicide, adverse drug reaction

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BRIEF SUMMARY

Current Knowledge/Study Rationale: There is evidence that clozapine and lithium have antisuicidal properties, but the mechanism(s) for this association are unclear. This study investigated spontaneously reported psychiatric adverse drug reactions for insomnia and suicidal ideation and behavior in adults for second-generation antipsychotics and mood stabilizers compared to clozapine and lithium, respectively.

Study Impact: This study provides evidence for antisuicidal properties of clozapine and lithium using pharmacovigilance data. Findings also raise the possibility of beneficial effects on sleep as one potential pathway underlying the antisuicidal properties for these agents.

INTRODUCTION

Insomnia and suicide ideation/behavior/death (SIB) are common in psychiatric disorders. Among psychotropic medications, there is evidence that clozapine and lithium have antisuicidal properties. Clozapine is the only antipsychotic with an indication for suicide prevention in schizophrenia from the U.S. Food & Drug Administration (FDA).[1] There is evidence from nationwide register-based cohort studies of all individuals with schizophrenia in Finland and Sweden that clozapine was the only antipsychotic consistently associated with significantly decreased risk of suicide attempt and suicide death.[2] A large Danish incidence cohort of patients with nonaffective psychosis also found significantly decreased risk of suicide death during current use of clozapine.[3] In the international suicide prevention trial (InterSePT) of 980 patients with schizophrenia at increased risk for suicide, clozapine (vs olanzapine) was associated with significantly less SIB.[4] In that trial, insomnia was reported significantly less frequently in patients treated with clozapine vs olanzapine (20% vs 33%). This finding is consistent with evidence that sedation is a common adverse effect of treatment with clozapine.[5,6]

Similarly, there is evidence that lithium is associated with significantly decreased risk of suicide death in bipolar disorder from a Finnish nationwide cohort study[7] and decreased suicide death in randomized controlled trials in mood disorders[8] and that lithium concentrations in drinking water reduced suicide death.[9] Although sedation is reported less frequently with lithium (compared to clozapine and other agents), there is evidence for potential beneficial effects on sleep, including better sleep efficiency and longer sleep duration[10] and decreased rapid eye movement sleep and increased rapid eye movement sleep latency.[11,12] There is also evidence that a morning chronotype is associated with response to maintenance treatment with lithium in bipolar disorder.[13,14]

The mechanisms underlying antisuicidal properties of clozapine and lithium remain unclear. Potential hypotheses include decreased impulsive-aggressive behaviors, decreased anxiety,

and decreased depression.[15,16] A nonmutually exclusive hypothesis is that effects on insomnia and sleep behavior may mediate the antisuicidal effects of clozapine and lithium. There is evidence in both schizophrenia and mood disorders that insomnia is associated with increased SIB.[17–21] However, no previous studies have specifically investigated whether improvement in insomnia is associated with decreased SIB during treatment with either clozapine or lithium. Furthermore, to our knowledge, no previous studies have systematically investigated risks of insomnia and SIB as reported adverse effects of second-generation antipsychotics (SGAs) and mood stabilizers. The purpose of the present study was to investigate the prevalence of spontaneously reported psychiatric adverse drug reactions (ADRs) of insomnia and SIB in adults for SGAs and mood stabilizers and the reported odds of insomnia and SIB compared to clozapine and lithium, respectively.

METHODS

Data sources

The FDA Adverse Event Reporting System (FAERS) is a publicly available database that contains adverse event and medication error reports, as well as product quality complaints resulting in adverse events that were submitted to the FDA. These reports are voluntarily submitted by both health care professionals and consumers. Manufacturers receiving these reports are required to send them to the FDA. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation for Pharmaceuticals for Human Use (ICH E2B). Adverse events are coded using terms in the Medical Dictionary for Regulatory Activities. We included all reports in FAERS from inception in 1968 through February 2021 for which either an SGA or mood stabilizer was the suspected agent of a psychiatric adverse event.

Procedures

Spontaneously reported psychiatric adverse events related to insomnia and SIB were identified by searching each SGA and mood stabilizer in FAERS. We included data on adults aged 18–64 years for all SGAs or mood stabilizers with at least 500 psychiatric adverse event reports, as treatment in older adults may be confounded by an increased prevalence of general medical conditions. "Psychiatric Disorders" was included as the primary reaction group in the search results for individual SGAs and mood stabilizers. Specific adverse events in the FAERS database are based on the Medical Dictionary for Regulatory Activities preferred terms. "Insomnia" was the specific reaction in FAERS counted as a possible insomnia adverse event. The following reactions listed in FAERS were counted as possible SIB adverse events: "suicidal ideation," "suicide attempt," and "completed suicide." We combined the data from both generic and brand formulations, as well as oral and long-acting injectable (but not short-acting intramuscular) forms of each SGA. Data on the total number of psychiatric adverse events and the number of insomnia and SIB adverse events for each SGA and mood stabilizer were extracted by one author (B.J.M.) and independently verified by the other author (W.V.M.).

Statistical analysis

For each agent, we first calculated the proportion of ADRs for insomnia and SIB by dividing the number of insomnia and SIB ADRs by the total number of psychiatric ADRs, respectively. For SGAs, we then calculated reported odds ratios (rORs) and 95% confidence intervals for insomnia and SIB ADRs relative to clozapine. We chose clozapine as the comparator antipsychotic because of evidence for decreased SIB and increased sedation with this agent. For mood stabilizers, we calculated rORs and 95% confidence intervals for insomnia and SIB ADRs relative to lithium. We chose lithium as the comparator mood stabilizer because of evidence for decreased SIB and potential beneficial effects on sleep with this agent. For both SGAs and mood stabilizers, separately, we also calculated the bivariate correlation coefficient (Pearson's r) between the insomnia rOR and the SIB rOR. P values were considered statistically significant at the $\alpha = 0.05$ level if the 95% confidence interval for the OR excluded 1.00. All statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX).

RESULTS

We investigated psychiatric ADRs for 10 different SGAs and 5 different mood stabilizers. For SGAs, data were not included for cariprazine, iloperidone, and lumateperone due to the low number of psychiatric ADRs. For the other SGAs, 74,577 psychiatric adverse events were reported, including 8,157 insomnia ADRs and 16,790 SIB ADRs. Therefore, insomnia ADRs comprised 11% and SIB ADRs comprised 23% of the psychiatric ADRs. For individual SGAs, the prevalence of insomnia ADRs ranged from 3%–23%, and the prevalence of SIB ADRs ranged from 16%–33%. Notably, clozapine had the lowest prevalence of both insomnia (3%) and SIB (16%) ADRs among all included SGAs. As shown in **Table 1**, compared to clozapine, all of the other SGAs were associated with a significantly increased reported odds of insomnia (rOR = 2.41–9.70) and SIB (rOR = 1.18–2.72) ADRs, including quetiapine, olanzapine, risperidone, aripiprazole, paliperidone, ziprasidone, lurasidone, asenapine, and brexpiprazole. After excluding one extreme outlier (quetiapine), the insomnia and SIB rORs for each SGA were correlated at the trend level (**Figure 1A**; $r = .66$, $P = .053$).

For the mood stabilizers, 25,724 psychiatric adverse events were reported, including 1,822 insomnia ADRs and 8,306 SIB ADRs. Therefore, insomnia ADRs comprised 7% and SIB ADRs comprised 32% of the psychiatric ADRs. For mood stabilizers, the prevalence of insomnia ADRs ranged from 5.6%–9.0%, and the prevalence of SIB ADRs ranged from 27%–38%. Notably, lithium had the lowest prevalence of both insomnia (5.6%) and SIB (27%) ADRs among all included mood stabilizers. As shown in **Table 1**, compared to lithium there was a significantly increased reported odds of insomnia (rOR = 1.66) for lamotrigine and nonsignificantly increased reported odds of insomnia for valproic acid, carbamazepine,

Table 1—Reported odds ratios for insomnia and suicide ideation/behavior/death as adverse drug reactions for individual second-generation antipsychotics and mood stabilizers, relative to clozapine and lithium.

Class and Agent	Psychiatric Adverse Event								
	Total	Insomnia				Suicide Ideation/Behavior/Death			
		% ADR	n	rOR	95% CI	% ADR	n	rOR	95% CI
Antipsychotic									
Clozapine	10,321	3.0	309	1.00	Reference	15.5	1,599	1.00	Reference
Olanzapine	13,500	6.9	933	2.41	2.11–2.74	24.8	3,346	1.80	1.68–1.92
Paliperidone	5,024	7.4	371	2.58	2.21–3.02	17.8	894	1.18	1.08–1.29
Risperidone	12,165	8.4	1,027	2.98	2.62–3.04	22.5	2,736	1.58	1.48–1.69
Lurasidone	1,939	9.7	188	3.48	2.88–4.86	32.0	621	2.57	2.30–2.87
Brexpiprazole	744	10.3	77	3.74	2.88–4.86	19.1	142	1.28	1.06–1.56
Aripiprazole	11,824	11.0	1,297	3.99	3.52–4.53	20.8	2,460	1.43	1.37–1.54
Asenapine	1,122	11.8	132	4.32	3.49–5.35	33.3	374	2.72	2.38–3.12
Ziprasidone	3,282	13.6	445	5.08	4.37–5.91	31.0	1,016	2.45	2.23–2.68
Quetiapine	14,656	23.0	3,378	9.70	8.61–10.94	24.6	3,602	1.77	1.67–1.90
Mood stabilizer									
Lithium	4,825	5.6	271	1.00	Reference	26.8	1,292	1.00	Reference
Carbemazepine	4,272	5.9	253	1.06	0.89–1.26	29.9	1,277	1.18	1.06–1.28
Valproic acid	5,985	6.3	378	1.13	0.96–1.33	30.2	1,805	1.18	1.09–1.28
Oxcarbazepine	1,834	6.8	125	1.23	0.99–1.53	30.2	553	1.17	1.05–1.33
Lamotrigine	8,808	9.0	795	1.66	1.45–1.92	38.4	3,379	1.70	1.58–1.84

ADR = adverse drug reaction, CI = confidence interval, rOR = reported odds ratio.

and oxcarbazepine (rOR = 1.06–1.23). Compared to lithium, there was a significantly increased reported odds of SIB (rOR = 1.17–1.70) for all other mood stabilizers. Furthermore, the insomnia and SIB rORs for each mood stabilizer were significantly, positively correlated (**Figure 1B;** $r = .97$, $P = .005$).

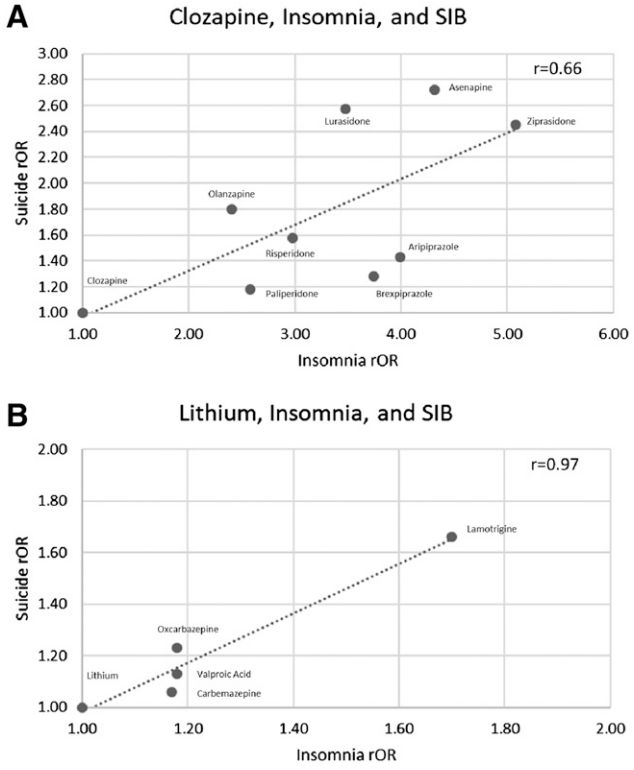
DISCUSSION

In the FAERS database we found that compared to clozapine all other SGAs were associated with a significantly increased reported odds of insomnia (rOR = 2.41–9.70) and SIB (rOR = 1.18–2.72) ADRs. Compared to lithium there was a significantly increased reported odds of SIB (rOR = 1.17–1.70) for all other mood stabilizers, as well as an increased reported odds for insomnia (rOR = 1.06–1.66), although the latter finding was only significant for lamotrigine. Furthermore, the insomnia and SIB rORs were positively correlated for both clozapine and lithium.

There are several strengths to the present study. To our knowledge, ours is the first study to systematically investigate the prevalence of insomnia and SIB ADRs for individual SGAs and mood stabilizers. The use of the large FAERS database permitted indirect "head-to-head" comparisons between different SGAs and mood stabilizers. It is reassuring that our findings were consistent for both clozapine and lithium, given other evidence for antisuicidal properties for these agents, which supports the validity of the present findings. As with any study utilizing a public pharmacovigilance database, there are limitations. The FDA does not verify reports submitted to FAERS and does not require the establishment of a causal relationship between the agent and adverse events. The assessment of psychiatric symptoms, including insomnia and SIB, by nonpsychiatric clinicians also represents an important potential source of bias. Furthermore, reports may be submitted by health care professionals or patients, so there is a risk of misclassification of psychiatric ADRs. Importantly, given the prevalence of insomnia and SIB in patients taking SGAs and/or mood stabilizers, it is also possible that some adverse events were misattributed to the drug rather than the illness itself. Duplicate reporting as well as potential underreporting of adverse events are also possible. Individual-level data in the FAERS database are limited, which could shed light on other potential confounding or moderating factors.

Although the available pharmacovigilance data do not permit causal inferences, it is nevertheless intriguing that for both clozapine and lithium the insomnia and SIB rORs were positively correlated. To our knowledge, no previous studies have specifically investigated whether improvement in insomnia is associated with decreased SIB during treatment with either clozapine or lithium. However, there is evidence that insomnia and other sleep disturbances—including nightmares, hypersomnia, snoring or coughing, pain, and lower sleep efficiency—prospectively predict SIB.[17,22,23] A systematic review and meta-analysis found that insomnia was associated with suicide ideation, attempt, and death with small-to-medium effect sizes (Cohen's d = 0.45, 0.38, and 0.30, respectively).[17] In that review, compared to insomnia, nightmares were associated with suicide ideation with a similar

Figure 1—Correlation between reported odds ratios for insomnia and suicide ideation/behavior/death as adverse drug reactions for individual second-generation antipsychotics and mood stabilizers, relative to clozapine and lithium, respectively.



(A) Second-generation antipsychotics. **(B)** Mood stabilizers. rOR = reported odds ratio, SIB = suicide ideation/behavior/death.

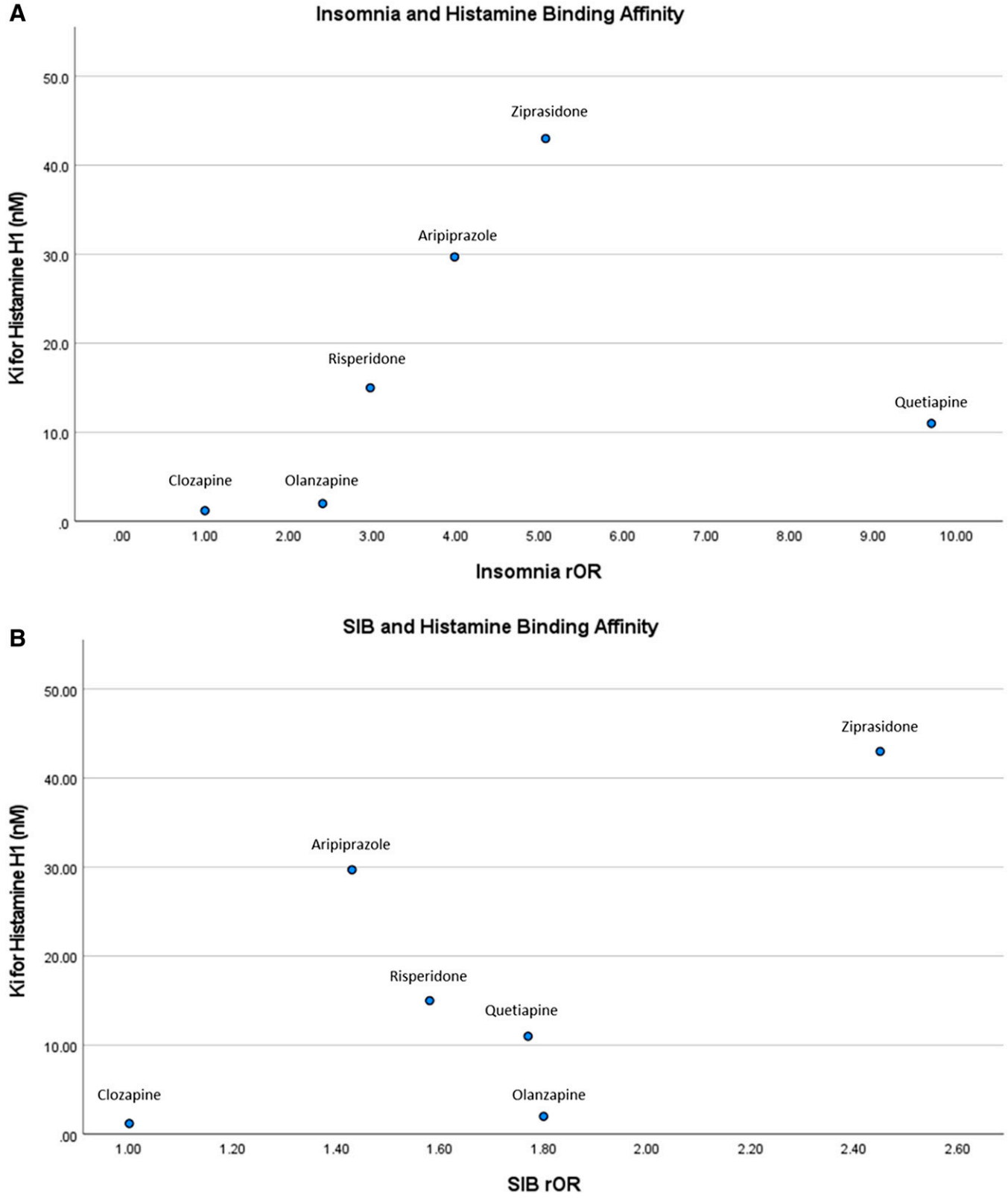
effect size (d = 0.40) and even larger effect sizes for suicide attempt (d = 0.60) and suicide death (0.50), but findings were limited by a small number of studies. In the same review, hypersomnia was not associated with suicide ideation or attempt, but in one study of 247 residents of a retirement community hypersomnia was associated with suicide death with a large effect size (d = 0.84). Replication of this finding in other cohorts, including patients with psychiatric disorders, appears warranted.

The mechanism(s) by which clozapine and lithium are associated with decreased suicide are likely complex and multifactorial, and the associated literature in this area is quite modest. Regarding lithium, most evidence has focused on glycogen synthase kinase-3, as this enzyme modulates multiple systems associated with suicide and is inhibited by lithium.[24] Compared to other antipsychotics, clozapine has a unique (and broad) pharmacologic profile. Clozapine significantly increases peripheral norepinephrine levels—to a greater extent than other antipsychotics—which may contribute to beneficial effects on mood and, therefore, decreased suicide.[25] Another potential mechanism whereby clozapine may decrease suicide is (indirectly) through reduction in comorbid substance use. Finally, our data raise the (relatively straightforward) possibility that improvements in insomnia—likely through histamine H1 receptor antagonism—directly contribute to decreased SIB with clozapine and lithium. Interestingly, using published[26] histamine H1 receptor affinity data for six antipsychotics—aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone—the inhibition constant for histamine H1 was positively correlated with the insomnia rOR in our study ($r = .27$; Figure 2), suggesting that greater histamine H1 affinity was associated with a lower reported odds of insomnia. After excluding one outlier (quetiapine), the inhibition constant for histamine was significantly, positively correlated with the insomnia rOR ($r = .95$, $P = .13$). Furthermore, the inhibition constant for histamine H1 was positively correlated with the SIB rOR ($r = .65$, $P = .17$; Figure 2). These findings support the plausibility that antihistamine effects of clozapine may contribute to decreased insomnia and SIB.

Hyperarousal has been nominated as a candidate biomarker that may mediate associations between insomnia and SIB. Natural language processing of hospital discharge records found that terms linked to arousal such as "vigilance" or "reactivity" were positively associated with suicide death.[27] A recent meta-analysis of prospective clinical risk factors of suicide death found an OR = 1.29 for the Research Domain Criteria (RDoC) arousal domain.[28] Hyperarousal has also been reported to lead to urgency of action expressed as response inhibition deficits in executive functioning,[29,30] thereby leading to a risk of suicide.[31,32] The pupillary light reflex test is a potential practical measure of physiologic arousal. Measurement of the pupillary light reflex can be completed by a self-contained handheld device, providing data about pupillary constriction, which is proximally controlled by acetylcholine, and pupillary dilation, which is proximally controlled by norepinephrine,[33] and both these systems contribute to central nervous system arousal.[34] In studies of patients with either schizophrenia or major depressive disorder we found that the mean constriction velocity during the pupillary light reflex test was associated with both insomnia and SIB.[35,36] Future studies in patients treated with clozapine and lithium are needed to explicate potential mechanisms for the changes in sleep and SIB with these agents. For example, a next step would be to conduct a longitudinal study of changes in insomnia (using a standardized instrument), hyperarousal (as indexed by an objective measure of physiologic arousal such as pupillometry and/or heart rate variability), and SIB (also using a standardized instrument) following initiation of treatment with clozapine or lithium.

In conclusion, our results are consistent with other evidence for antisuicidal properties and potential beneficial effects on sleep for clozapine and lithium. Correlation between insomnia and suicide rORs raises the possibility that beneficial effects on sleep are one potential pathway underlying the antisuicidal properties for these agents. Nevertheless, the present findings are intended to be hypothesis-generating and should be interpreted with caution in light of inherent limitations of pharmacovigilance data and are not ready for adoption into clinical care. Future longitudinal studies in this area are needed to explicate potential underlying biological mechanisms that contribute to these associations. Findings also affirm the use of clozapine and lithium in relevant patient populations at high risk for suicide.

Figure 2—Correlation between antihistamine H1 receptor binding affinity and reported odds ratios for insomnia or suicide ideation/behavior/death as adverse drug reactions for individual second-generation antipsychotics, relative to clozapine.



Ki = inhibition constant, rOR = reported odds ratio, SIB = suicide ideation/behavior/death.

ABBREVIATIONS

ADR, adverse drug reaction
FAERS, FDA Adverse Event Reporting System
FDA, U.S. Food & Drug Administration
rOR, reported odds ratio
SGA, second-generation antipsychotic
SIB, suicide ideation/behavior/death

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at Augusta University. Dr. Miller has nothing to disclose for the work under consideration. In the past 12 months, Dr. Miller received research support from Augusta University, the National Institute of Mental Health, and the Stanley Medical Research Institute; participated in advisory boards for Boehringer Ingelheim; and received honoraria from Atheneum, Clearview Healthcare Partners, and *Psychiatric Times*. Dr. McCall has nothing to disclose for the work under consideration. In the past 12 months, Dr. McCall has received honoraria from Wolters Kluwer Publishing, CME Outfitters, and Anthem Inc. and research support from Merck and MECTA Corp. and is a scientific advisor for Sage Therapeutics, Janssen, Jazz, and Idorsia.