

Research article

Teodor T. Postolache*, Deborah R. Medoff, Clayton H. Brown, Li Juan Fang, Sanjaya K. Upadhyaya, Christopher A. Lowry, Michael Miller, Julie A. Kreyenbuhl

Lipophilic vs. hydrophilic statins and psychiatric hospitalizations and emergency room visits in US Veterans with schizophrenia and bipolar disorder

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Abstract

Objective – Psychiatric hospitalizations and emergency department (ED) visits are costly, stigmatizing, and often ineffective. Given the immune and kynurenine activation in bipolar disorder (BD) and schizophrenia, as well as the immune-modulatory effects of statins, we aimed to compare the relative risk (RRs) of psychiatric hospitalizations and ED visits between individuals prescribed lipophilic vs. hydrophilic statins vs. no statins. We hypothesized

(a) reduced rates of hospitalization and ER utilization with statins versus no statins and (b) differences in outcomes between statins, as lipophilia increases the capability to penetrate the blood–brain barrier with potentially beneficial neuroimmune, antioxidant, neuroprotective, neurotrophic, and endothelial stabilizing effects, and, in contrast, potentially detrimental decreases in brain cholesterol concentrations leading to serotonergic dysfunction, changes in membrane lipid composition, thus affecting ion channels and receptors.

Methods – We used VA service utilization data from October 1, 2010 to September 30, 2015. The RRs for psychiatric hospitalization and ED visits, were estimated using robust Poisson regression analyses. The number of individuals analyzed was 683,129.

Results – Individuals with schizophrenia and BD who received prescriptions for either lipophilic or hydrophilic statins had a lower RR of psychiatric hospitalization or ED visits relative to nonstatin controls. Hydrophilic statins were significantly associated with lower RRs of psychiatric

* **Corresponding author: Teodor T. Postolache**, VISN 5 Capitol Health Care Network Mental Illness Research Education and Clinical Center (MIRECC), U.S. Department of Veterans Affairs, Baltimore, MD 21201, United States of America; Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), U.S. Department of Veterans Affairs, Aurora, CO 80045, United States of America; Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America; Military and Veteran Microbiome: Consortium for Research and Education (MVM-CoRE), U.S. Department of Veterans Affairs, Denver, CO 80045, United States of America, e-mail: tpostola@som.umaryland.edu

Deborah R. Medoff: VISN 5 Capitol Health Care Network Mental Illness Research Education and Clinical Center (MIRECC), Baltimore, MD 21201, United States of America; Department of Psychiatry, Division of Psychiatric Services Research, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America, e-mail: dmedoff@som.umaryland.edu

Clayton H. Brown: VISN 5 Capitol Health Care Network Mental Illness Research Education and Clinical Center (MIRECC), Baltimore, MD 21201, United States of America; Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America, e-mail: clbrown@som.umaryland.edu

Li Juan Fang: Department of Psychiatry, Division of Psychiatric Services Research, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America, e-mail: LFang@som.umaryland.edu

Sanjaya K. Upadhyaya: Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America, e-mail: medsanup400@gmail.com

Christopher A. Lowry: Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), U.S. Department of Veterans Affairs, Aurora, CO 80045, United States of America; Military and Veteran Microbiome: Consortium for Research and Education (MVM-CoRE), U.S. Department of Veterans Affairs, Denver, CO 80045, United States of America; Department of Integrative Physiology, Center for Neuroscience, Center for Microbial Exploration, University of Colorado Boulder, Boulder, CO 80309, United States of America; Department of Physical Medicine and Rehabilitation, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States of America, e-mail: christopher.lowry@colorado.edu

Michael Miller: Department of Medicine, VAMC Baltimore and University of Maryland School of Medicine, Baltimore, Maryland 21201, United States of America, e-mail: mmiller@som.umaryland.edu

Julie A. Kreyenbuhl: VISN 5 Capitol Health Care Network Mental Illness Research Education and Clinical Center (MIRECC), Baltimore, MD 21201, United States of America; Department of Psychiatry, Division of Psychiatric Services Research, University of Maryland School of Medicine, Baltimore, MD 21201, United States of America, e-mail: Julie.Kreyenbuhl@va.gov

hospitalization but not of ED visits, compared to lipophilic statins.

Conclusion – The reduction in psychiatric hospitalizations in statin users (vs. nonusers) should be interpreted cautiously, as it carries a high risk of confounding by indication. While the lower RR of psychiatric hospitalizations in hydrophilic statins relative to the lipophilic statins is relatively bias free, the finding bears replication in a specifically designed study. If replicated, important clinical implications for personalizing statin treatment in patients with mental illness, investigating add-on statins for improved therapeutic control, and mechanistic exploration for identifying new treatment targets are natural next steps.

Keywords: statins, lipophilia, hospitalization, schizophrenia, bipolar

1 Introduction

1.1 Psychiatric hospitalizations and emergency room visits

Psychiatric hospitalizations represent markers of instability in severe mental illness and of insufficient therapeutic control, and are economically burdensome and stigmatizing. Even if multifactorial, they are most commonly driven by dangerousness to self or others and psychotic decompensation combined with the lack of social support in the community [1]. Inpatient hospitalization often fails to fulfill its main rationale, suicide risk management, as the discharge from the inpatient unit brings with it a substantially elevated potential for suicidal behavior [2,3]. In addition to psychiatric inpatient hospitalization, the use of Psychiatry Emergency Departments (ED) in the United States (US) is responsible for substantially increasing costs of health care [4,5] and diverting funds from services that would be expected to have a potentially more impactful contribution to quality care and preventative services. This is particularly true for the care of US Veterans, considering that the Veterans Health Administration (VHA) serves a population with considerable mental health needs [6] and has steeply increasing costs [7]. The top 10% of utilizers of psychiatric inpatient [8] and emergency services [9] are responsible for a disproportionately high share of healthcare costs. In the VHA system, understanding the clinical, social, and economic factors driving the utilization of psychiatric emergency services has relied on the availability and the analysis

of administrative data [10,11] and has identified severe mental illness, personality disorders, substance use disorders, utilization of detox services, and homelessness as dominant predictive variables [12–14]. All in all, it is common knowledge for anyone who either worked or studied psychiatric emergency services that the reason for psychiatric hospitalization is the evaluation and management of acute suicide risk [2]. Thus, to a certain degree, psychiatric hospitalization also serves as a proxy measure of suicide risk. While important everywhere, in US Veterans, in particular, death by suicide and its prevention are the indisputable #1 priority. According to the latest available yearly report (2020), the 2018 age- and gender-adjusted rate of suicide in US Veterans was 27.5 per 100,000, 50% higher than in the US general population, as it has been each year since 2013–2014 [15]. In Veterans with mental health or substance use disorders, the 2018 rate was significantly twice, at 57.2 per 100,000. More than 17 Veterans are prematurely lost to suicide each day, with guns being the lethal means for 41.9% of female Veteran suicides and 69.4% of male Veteran suicide deaths.

1.2 Medications for medical conditions affect psychiatric condition

Comorbidity with medical illness often leads to worsening of the course of mental illness. However, there is a potential of the medical treatment per se to worsen mental health, directly (e.g., systemic corticosteroids decompensating mood disorders) or through interactions with psychiatric medication (e.g., thiazide diuretics for hypertension dramatically increasing lithium serum levels and causing toxicity in patients with bipolar disorder, or the commonly prescribed seizure medication phenytoin lowering the levels of clozapine in patients with schizophrenia and inducing a recurrence or exacerbation of psychosis).

Yet, there are circumstances when a specific medical treatment could have a beneficial effect on mental health. Examples include beta-blockers for anxiety, certain calcium blockers as mood stabilizers, certain alpha-adrenergic blockers on nightmares (prazosin), and others.

1.3 Statins

1.3.1 Pleiotropic effects

Statins, one of the most prescribed groups of medications worldwide, have been increasingly recognized as having

therapeutic value for a variety of conditions beyond their original metabolic and cardiovascular indication [16]. Early, when the main data were anecdotal and observational, there were concerns that statin may worsen mood and cognition and have a negative impact on neuropsychiatric conditions and potentially elevate the suicide risk via the association between very low levels of serum cholesterol and suicide. With the emergence of case-control, longitudinal, and especially randomized controlled studies and their meta-analyses, the opposite picture emerged, i.e., that statins as a group are cognitively, affectively, and behaviorally safe and that they show beneficial effects in the treatment of mood disorders, schizophrenia, and cognitive disorders. These positive effects appear to be based on statins' pleiotropic effects including multiple immune regulatory actions and antioxidant properties [17,18], as well as endothelial stabilizing [19] and neuroprotective effects [20,21]. Statins reduce NADPH oxidase and superoxide generation, inhibit the negative regulation of nitric oxide, increase free radical scavenging, decrease inflammatory cell transmigration from blood to tissue, inhibit the NLRP3 inflammasome, and reduce metalloproteinase expression [22–27]. Notably, evidence also suggests that statins facilitate PI3K-Akt signaling [28,29] and crosstalk with peroxisome proliferator-activated receptor (PPAR) signaling [30]. In addition, within the brain, statins are potent inducers of axonal and neurite outgrowth; in fact, among more than 50,000 small molecules previously implicated in axonal outgrowth, statins were the most effective [31]. Activation of the Akt signal transduction and RhoA prenylation underlie the statin-dependent neurite outgrowth, which may account for the effects of statins to promote structural repair of injury and to reduce excitotoxicity, leading to the establishment, and maintenance of short- and long-distance connectivity with following injury. Consistently, high-dose simvastatin, a highly lipophilic statin, leads to less brain atrophy than a placebo-control group using serial volumetric MRIs in patients with the prototypical autoimmune disease of the brain-multiple sclerosis (MS).

1.3.2 Statins are beneficial for medical conditions characterized by inflammation

Statins have favorable long-term effects in individuals with medical conditions characterized by increased inflammation, both in medical conditions with increased inflammation primarily within the brain and in medical conditions with increased inflammation primarily in the periphery. For instance, sustained statin pretreatment and continuation

lead to decreased mortality following traumatic brain injury (TBI; a condition in which inflammation plays a strong dual role of providing surveillance and removal of necrotic tissue, and also, being a negative prognostic indicator and a local mediator of pathophysiology leading to prolonged symptomatology, delayed healing, and limited functional recovery), as well as a more rapid hospitalization discharge, decreased depression post-TBI, and improved functional recovery at 12 months post-injury [32]. In patients with allergies, statin use is associated with a decreased risk of asthma-related ED visits [33,34] and/or hospitalizations [33]. Statins have also demonstrated benefit across autoimmune conditions, particularly, in MS [35].

1.3.3 Inflammation and immune-mediated conditions – links with mental illness and suicidal behavior

The involvement of inflammation in mental illness [36], including schizophrenia [37–40], bipolar disorder [41], and suicidal behavior [42–45], has been increasingly recognized. For instance, individuals with schizophrenia have a peripheral blood elevation of interleukin (IL) 6, IL-1 β , and transforming growth factor- β 1 (TFG- β 1) [28], and, centrally, have molecular and visual markers of microglia activation relative to healthy controls [29], leading to ongoing vulnerability to immunological challenges and psychological stress. Immune-mediated clinical conditions implicated in schizophrenia have included infections, autoimmune disease, and atopy [46]. Similarly, suicidal behavior – a common driver of ED visits and hospitalizations – has also been associated with infections, with either specific microbial agents, such as *Toxoplasma gondii*, [47–51] or nonspecific microbial agents [52,53], allergy [54], and allergen exposure [55–57]. As illustrated in both preclinical and clinical studies, statins manifest a potent antimicrobial action across a broad spectrum of intracellular pathogens, including viruses, bacteria, protozoa, and fungi, interfering with the host mevalonate pathways and compromising the microbial immune evasion. Statin administration prolongs survival in certain infectious diseases by protecting from the overly intense and prolonged immune response, in addition to promoting host defense [58].

1.3.4 Statins in depression

Given the considerable overlap among elements of the immune, oxidative stress, excitotoxic, endothelial, and immune

regulatory dysfunction in severe mental illness and reversal of these effects with statins, promising reports on experimental/animal models and early clinical data using statins for augmentation of classical psychotropic agents became increasingly attractive. While heterogeneous and far from definitive, increasingly compelling data exist in support of with distinct clinical and physiopathological benefits with the use of statins; with increasingly sophisticated and well-sized studies, the earlier concerns about potentially major negative effects of statins are slowly receding. For example, awareness of successful augmentation of antidepressant effects in major depression (MD) by statins begins to emerge, starting with a small meta-analysis [59] (3 studies on 165 participants), followed by a meta-analysis of 36 randomized placebo-controlled studies of anti-inflammatory add-on interventions including 7 randomized placebo-controlled studies on 1,576 participants [60]. This was further confirmed by a large meta-analysis of multiple anti-inflammatory approaches by Bai et al., including 30 studies, and 1,610 participants, including 3 randomized controlled trials of statins with 166 participants [61]. In the most recent meta-analysis of randomized clinical trials on 5 studies and 389 participants, De Giorgi et al. reported significant benefits of add-on statins at 8 and 12 weeks of treatment. In comparing statins, simvastatin, the most lipophilic compound, demonstrated a stronger antidepressant capability than atorvastatin [62]. This was consistent with a previous study on the antidepressant effect of statin in post coronary artery bypass graft with mild-moderate clinical depression, demonstrating a greater efficacy of simvastatin over atorvastatin [63].

1.3.5 Statins in schizophrenia

In schizophrenia, a meta-analysis of 5 RCTs (with 236 adult participants with schizophrenia, neuroleptic treated) found improvement in positive and negative symptom scores with an add-on statin vs. placebo [64]. A larger meta-analysis (70 studies, 4,104 participants) also including other potential anti-inflammatory add-on interventions confirmed a significant, yet small, improvement in positive and negative symptom scores (7.1%) with statins relative to placebo [65]. In contrast, another meta-analysis (56 studies, 4,327 participants) found no significant benefit from an add-on statin [66]. Shen et al. [67] embarked on an ambitious meta-analysis not only to evaluate if statins improved negative or positive symptoms but also to see if different classes of statins have differential effects, if different types of antipsychotics combined with statins had a different effect, and finally, to measure the effect of the duration of

treatment with statins. At week 12, a significant difference emerged in both positive and negative symptoms between the statin antipsychotic group vs. the placebo antipsychotic group. In terms of differences between statins, simvastatin manifested the strongest effect for both positive and negative symptoms, and it was the routine antipsychotics, rather than the new-generation antipsychotics, that showed improvement in both positive and negative symptoms [67]. The authors explained their finding in terms of both statins (simvastatin [68], atorvastatin, rosuvastatin, pravastatin, and lovastatin [69,70]), and antipsychotics (strongest with risperidone [and quetiapine] and weakest for haloperidol and clozapine) being P-gp substrates of P-glycoprotein 1 (P-gp), also called ATP-binding cassette sub-family B member 1 (ABCB1). Antipsychotic agents interact with statins through competition for P-gp transport. Being co-substrates, the lower affinity antipsychotics and statins will result in reciprocal greater access to the CNS; the results indeed supported a considerable component of the effect of statins on negative symptoms to be the result of interactions between statins and the type of the antipsychotic.

What could explain the beneficial effect of statins in schizophrenia reported by the majority of the meta-analyses published to date, in particular in regard to domains that are so resilient to neuroleptic treatment, such as negative symptoms and cognitive deficits? Indeed, negative symptoms and cognitive deficits in schizophrenia are the two symptomatic domains least responsive to treatment and most contributory to functional deficits in individuals with the illness. Immune activation has been increasingly identified in individuals with schizophrenia, and, in particular, proinflammatory signals are associated with the severity of cognitive dysfunction and negative symptoms [71,72] with likely disruptive effects on synaptic signaling, neurogenesis, neuroprotection, axonal/neurite growth, and thus connectivity [73]. In addition, oxidative stress, in part a consequence of a proinflammatory and excitotoxic milieu, disrupts parvalbumin interneurons. The disruption of these interneurons localized in the cortex and hippocampus, known to have an increased vulnerability to oxidative stress, may centrally contribute to the production of cognitive dysfunction and negative symptoms [74]. In addition, executive dysfunction in schizophrenia is also, in part, a consequence of increased oxidative stress, as illustrated peripherally by several molecular systems, such as glutathione/GSH and, centrally, via reduced neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) [75]. All these targets, the oxidative stress, neuroinflammation, neuroprotective and neurotrophic deficits, and molecular inflammation cascades are engaged and modulated by statins [76,77].

1.3.6 Statins in bipolar disorder

Similarly, individuals with bipolar disorder also have clinical and preclinical evidence for immune dysregulation, with the elevation of proinflammatory cytokines relative to psychiatric and normal controls, including IL-6, tumor necrosis factor (TNF)- α , IL-1 β , soluble receptor of TNF-type 1 (STNFR1), and soluble interleukin-2 receptor (sIL-2R) [78–84]. Isolated reports have been confirmed in a recent systematic review/meta-analysis that documented a “trait-like” elevation of proinflammatory signals during both mania and depression episodes, reverting to normal values after return to euthymia [85]. Of functional importance, the markers of immune activation are positively associated with cognitive status, as well as neuroanatomical changes [86–90]. Yet not all studies have found evidence of neuroinflammation in BD [91]. In contrast with the classical view of bipolar disorder being in principle an episodic condition with full restoration to normality, there is evidence that residual mood and cognitive symptoms, functional impairment, decreased quality of life, and psychosocial disability exist even when the condition is appropriately treated [92,93]. Moreover, there is evidence for bipolar disorder being a progressive condition, often in the context of nonadherence and inappropriate treatment resulting in highly recurrent mood episodes, incomplete interepisodic remission, progressive cognitive impairment, and functional decline [94–96], with specific neurobiological underpinnings characterizing different stages and longitudinal progression of bipolar disorder (“neuroprogression”) [97–102]. Of relevance for possible treatment targeting by statins, neuroprogression has been linked to enhanced oxidative stress, breakdown of the neurotrophic support, mitochondrial dysfunction, and decreased cellular resilience, in part as a result of persistent and cascading immune dysfunction [99,100,103,104], leading to the loss of neuroprotection, excitotoxicity, apoptosis, and loss of cortical volume. Yet not all studies agree with the neuroprogression hypothesis in bipolar disorder, in particular with the accelerated cognitive decline with aging [100,105].

1.4 The tryptophan degradation and the kynurenine pathway

Immune activation and stress lead to activation of enzymatic systems such as indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO), resulting in increased production of kynurenines and decreased tryptophan [106].

Mitigating potential pathogenic effects of infection, the decrease of tryptophan affects multiplication of microbes, preventing unchecked invasion of the organism, and kynurenine production is immune regulatory, preventing unremitting inflammation. Kynurenine can cross the blood–brain barrier (BBB) freely and is degraded to molecules produced locally without the capability to freely cross the BBB. These have excitotoxic effects (e.g., quinolinic acid [QA]) or inhibitory effects (kynurenic acid [KA]) on brain structure or function. Suicidal behavior is associated with elevations in kynurenine [107] and QA [108,109], while schizophrenia [110,111] and BD with history of psychotic episodes [112] are associated with elevations of KA. More recently, positive associations between cognitive deficits in schizophrenia and QA in schizophrenia have been reported, suggesting a state of excitotoxic necrosis as the basis of these symptoms, highly relevant for functioning, rehabilitation, and prevention of suicidal behavior in schizophrenia [113]. Dysregulation of the kynurenine pathway has also been implicated in BD and its progression [114], as well as state severity of depression in patients with bipolar disorder [115].

1.5 Statins: Anti-inflammatory and immune regulatory effects

Statins generally decrease, in a concentration-dependent manner, the production of neopterin and degradation of tryptophan in *ex vivo* models, such as peripheral blood mononuclear cells (PBMCs) stimulated by IFN-gamma, concanavalin A (ConA), and phytohemagglutinin (PHA) [116]. In patients with suspected stable angina pectoris who are taking statin therapy after angiography, increased neopterin level is associated with the increased risk of acute myocardial infarction (AMI) [117]. Consistent with these findings, in patients with acute coronary syndrome (ACS), higher neopterin levels predict the increased long-term risk of death and nonfatal coronary events. In these patients, high-dose statin treatment reduces neopterin levels, while decreasing coronary mortality and nonfatal coronary events [118]. Statins inhibit the cellular proliferation of PBMCs induced by different antigens, such as T–B polyclonal stimuli and *Staphylococcus aureus* enterotoxin A (SEA) [119].

However, not all studies have concordant results. For instance, in one clinical longitudinal study, statins led to decreased C-reactive protein (CRP) levels, but had no effect on neopterin levels and autoantibody titers (such as antinuclear antibodies) [120]. Furthermore, a double-blind placebo-controlled randomized trial of statin administration found no significant change in inflammation biomarkers (neopterin, CRP) [121].

Statins also manifest immune-modulatory effects by activating regulatory T cells (Tregs). For example, in a murine model of tumor growth, statins activate Treg and increase the production of the immune regulatory markers IL-10 and TGF- β 1 [122]. Statins reduce the number and increase the suppressive function of Treg cells in animal experimental models of chronic immune activation [123] and in humans with or without immune-mediated conditions [124]. The production of Tregs is linked with the production of reactive oxygen species (ROS) geared at a minimum toward eliminating pathogens, at most, to regulate the balance between proinflammatory and regulatory arms of the immune response [125]. This has a narrow regulatory window as specifically unopposed ROS production can suppress regulatory T cell production in favor of proinflammatory reactions, or alternatively, very little ROS production may also impair the differentiation, stability, and suppressive function of Tregs [125].

Statins not only reduce the production of kynurenine but also actively limit the effects of kynurenine's main excitotoxic metabolite, QA. For example, in a model of QA-induced neurotoxicity in rats, statins significantly decrease the excitotoxic effect of QA, levels of markers of oxidative stress, and proinflammatory cytokines (such as TNF- α) as well as striatal lesion volume [126]. In another study, statins appear to have a neuroprotective effect in excitotoxic rodent seizure models. Specifically, atorvastatin significantly reduced QA-induced clonic and/or tonic seizures and prevented cell death induced by QA in the hippocampus [127]. Atorvastatin also counteracts the decrease in glutamate uptake triggered by QA and prevents the QA-induced decrease in protein kinase B (PKB, or Akt) phosphorylation [128].

1.6 Lipophilic vs. hydrophilic statins

Statins are characterized by different degrees of lipophilicity and divided into lipophilic and hydrophilic categories. While both groups have a similar efficacy in reducing cardiovascular and general mortality and overall side effects [129], the lipophilic statins cross more readily the BBB [130] and thus raise the hope that they could have a more pronounced local anti-inflammatory, antioxidant, neuroprotective, and endothelial-stabilizing effect within the CNS, and lead to improvement in conditions with clear primary brain localization of pathological processes. On the other hand, their potential toxic effects on cellular lipid components of membranes in affecting transmembrane

receptors and channels, and other deleterious molecular effects within the brain could offset, at least partially, the beneficial CNS effects of statins [76,77].

1.7 Rationale and hypotheses

The increasing understanding of immune dysregulation across diagnostic categories of mental illness, including MD, BD, schizophrenia, and dementias (of Alzheimer's type, vascular type), has been the number one rationale to consider using add-on statins, especially in individuals who already have medical indications. Indeed, several meta-analyses, increasingly including randomized clinical trials (RCT), support the clinically beneficial effects of add-on statins in depression and schizophrenia, although meta-analytic and RCT exceptions exist. Similarly, statins appear to have been beneficial in cognitive disorders by slowing cognitive decline [131], reducing the risk of dementia [132], improving Mini-Mental scores, and slowing deterioration on neuropsychiatric inventory deficit scores [133].

A large population-based study on Danish nationals with MD treated with selective serotonin reuptake inhibitors (SSRIs) found a reduced hazard of psychiatric hospitalizations with concurrent statin use compared to a no statin treatment group (hazard ratio, 0.75; 0.64–0.75) [134]. To our knowledge, there is no equivalent study on hospital contacts in schizophrenia and BD. We now aimed to fill this gap. We went one step further: Because lipophilic statins and hydrophilic statins differ in terms of their ability to cross the BBB (specifically lipophilic statins being able to cross more readily the BBB, thus having effects also on the CNS, and not only peripherally, as the hydrophilic statins), we engaged the aim of comparing the two statin categories on their ability to prevent psychiatric hospitalizations and ED visits when added on to antipsychotic treatment (in schizophrenia and bipolar individuals) and mood stabilizer treatment (in bipolar individuals). In doing so, we intended to minimize confounding by indication and to take a first step in the direction of personalizing the choice of statins for individuals with mental health problems. We used VA administrative data on ER visits and psychiatric hospitalizations as well as VA pharmacy data. We hypothesized that add-on statins will be protective relative to no statin control and that differences between lipophilic and hydrophilic statins will emerge (two-tailed hypothesis). Psychiatric hospitalization and ED visits were pair-wise compared among the three statin prescription groups (lipophilic,

hydrophilic, and none) separately in antipsychotic-treated individuals with schizophrenia, as well as antipsychotic- or mood stabilizer-treated individuals with BD, using robust Poisson regressions.

2 Methods

2.1 Overall design

Overall, this is a hypothesis-testing observational study using VA health care service utilization data from October 1, 2010 to September 30, 2015, including demographic, diagnostic, hospitalization, and ED visits, and all outpatient prescription medications dispensed from VA pharmacies, as reported in a recent publication using a similar methodology with the same dataset [135].

2.2 Data sources

This study used data on health services maintained at the U.S. Department of Veterans Affairs' (VA) Corporate Data Warehouse (CDW). The study period was between October 1, 2010 and September 30, 2015. All healthcare inpatient and outpatient workloads provided to Veterans in VA hospitals and outpatient clinics across the US were included. Hospitalizations that occurred in non-VA hospitals were included via the VA fee base files.

Ethical approval: This study was approved by the Institutional Review Board of the University of Maryland School of Medicine. The conducted research is not related to either human or animal use.

Informed consent: Institutional Review Board of the University of Maryland School of Medicine approved a waiver of informed consent because we used only extant administrative data.

2.3 Sample selection

We selected all VA health records, which had, during the study period, at least one outpatient or inpatient ICD-9-CM code for schizophrenia (295×) or BD (code disorder (ICD-9-CM code of 296.0–1, 296.4–8). If other serious mental illness codes (296.×, 297.×, 298.×) were present,

we assigned the diagnosis that was present during the majority of encounters in the study period. A total of 683,129 participants were included in this study. Among them, 185,449 were individuals with schizophrenia treated with antipsychotics, 211,412 were individuals with BD treated with antipsychotics and 286,268 were patients with BD treated with mood stabilizers.

2.4 Medications

Incident treatment episodes were constructed from prescription records. Lipophilic statins included prescriptions for simvastatin, atorvastatin, pitavastatin, and lovastatin. The hydrophilic statins included rosuvastatin, pravastatin, and fluvastatin. A total of 69.69% of individuals in the entire population during the duration of the study had at least one statin prescription dispensed at a VA pharmacy, with most commonly dispensed lipophilic statins being simvastatin (in 33.16% of individuals) followed by atorvastatin (18.07%), hydrophilic statins pravastatin (9.49%), and rosuvastatin (7.76%). Lovastatin, pitavastatin, and fluvastatin were seldomly dispensed (combined less than 2%). A treatment episode was defined as a continuous time interval of medication possession from the specific date of the incident prescription until the first prescribing time gap between prescriptions of more than 15 days. Gaps of at least 16 days past the expected refill date were considered clinically significant and consequently were interpreted as a discontinuation of a prescribed medication. Imperfect adherence was defined as gaps of 2 weeks or less, was considered clinically irrelevant and was ignored.

2.5 Outcomes

To help identify the average effect of each medication, we examined only incident prescribing episodes, defined here as no prescriptions for the same medication in the 6 months before the designated episode start date. To ensure sufficient numbers of individuals prescribed a medication with an adequate exposure period were available for analysis, we retained only those medications that had at least 100 individuals with schizophrenia or BD with episodes lasting at least 3 months. To facilitate the identification of episodes lasting at least 3 months, we limited analyses to episodes with start dates between April 1, 2011, and March 31, 2015.

2.6 Comparisons

We examined the relative risk (RR) of psychiatric hospitalization and ED visit during incident prescription episodes comparing lipophilic to hydrophilic statins, and also each statin group to a “no statin” control group. In each of the three analyses by diagnosis-psychiatric medication, the control group (no statin – “none”) consisted of all other nonpsychiatric incident medication episodes – excluding those for hydrophilic or lipophilic statins – that lasted 3 or more months for at least 100 individuals.

We only included patients who received a prescription of primary psychotropic medication during the 6 months before the start of the prescription episode. Individuals with schizophrenia were excluded if they did not have an antipsychotic prescription in the 6 months before the start of any episode, and individuals with BD were excluded if they were not on a mood stabilizer or antipsychotic during this period. As such, we performed three separate analyses for each outcome – one for patients with schizophrenia treated with antipsychotics, one for BD patients treated with antipsychotics, and one for BD patients treated with mood stabilizers.

2.7 Statistical analyses

We analyzed the data with the Statistical Analysis System (SAS) Version 9.4, Cary, NC. Robust Poisson regression [136] was used to estimate the RR of psychiatric hospitalization and ED visits comparing incident episodes of lipophilic vs. hydrophilic statin use and each statin vs. the “other” control group episodes. Robust Poisson regression provides accurate standard error estimates when the outcome is binary by using robust (“sandwich”) standard errors. The robust standard errors also account for within-individual correlation among repeated prescription episodes. In those with schizophrenia and those with BD on antipsychotic medication, we adjusted for age, gender, race, ever married, prior psychiatric hospitalization or ED visits, posttraumatic stress disorder (y/n), alcohol use disorder (y/n), other substance use disorder (y/n), antipsychotic coverage, mood stabilizer (y/n), and antidepressant (y/n) in the prior 6 months. In the group of bipolar individuals on mood stabilizers, all the covariates were identical, with the exception of antipsychotic coverage being replaced with antipsychotic (y/n) and mood stabilizer (y/n) being replaced with mood stabilizer coverage. A parallel analysis was performed to estimate RR of ED visits in the 6 months after the prescription episode began.

3 Results

3.1 Descriptive results

The participants with schizophrenia with antipsychotic medication had the mean (SD) age of 58.67 (9.99) years. The majority of these participants were men (91.66%) and white (60.13%; Table 1). The participants with BD on antipsychotic medication had the mean age (SD) of 54.77 (11.29) years. The majority of these participants were men (82.35%) and white (80.18%; Table 2). Their demographic composition was very similar to that of the bipolar participants on a mood stabilizer (Table 3).

3.2 Hypothesis testing analysis

The RR of psychiatric hospitalization was higher in those prescribed lipophilic statins in comparison to those prescribed hydrophilic statins in all three diagnosis X treatment groups, in individuals with schizophrenia on antipsychotic medication (RR = 1.11; CI, 1.0007–1.23; $p = 0.048$), in individuals with BD on antipsychotic medication (RR = 1.22; CI, 1.09–1.36; $p = 0.001$), and in individuals with BD on mood stabilizers (RR = 1.18; CI, 1.06–1.32; $p = 0.002$; Table 4). The RR of psychiatric hospitalization was lower in those prescribed either statin (lipophilic vs. hydrophilic) than in the control “no statin” group (Table 4).

After adjustment, there were no statistical differences in the RR for ED visits between lipophilic and hydrophilic statins in all three diagnosis X treatment groups, in individuals with schizophrenia on antipsychotic medication (RR = 1.07; CI, 0.83–1.36; $p = 0.61$), in individuals with BD on antipsychotic medication (RR = 1.26; CI, 0.97–1.63; $p = 0.08$), and in individuals with BD on mood stabilizers (RR = 1.16; CI, 0.92–1.46; $p = 0.2$). The differences between each statin group and control “no statin” group were robust, with lower RR of ER visits in those on either statin group relative to controls (see Table 5).

4 Discussion

4.1 Key results in context

The add-on of either lipophilic or hydrophilic statin prescription to US Veterans diagnosed with and treated for

Table 1: Description of individuals with schizophrenia on antipsychotic medication

Schizophrenia with antipsychotic	Whole		Lipophilic		Hydrophilic		None	
	<i>N</i> = 185,449	SD or %	<i>N</i> = 11,293	SD or %	<i>N</i> = 4,759	SD or %	<i>N</i> = 169,397	SD or %
Mean age SD	58.67	9.99	58.49	9.5	58.18	9.38	58.7	10.03
Male	169,985	91.66%	10,480	92.80%	4,388	92.20%	155,117	91.57%
Race								
White	111,513	60.13%	7,007	62.05%	2,893	60.79%	101,613	59.99%
Non-white	65,446	35.29%	3,761	33.30%	1,642	34.50%	6,0043	35.45%
Missing	8,490	4.58%	525	4.65%	224	4.71%	7,741	4.57%
Ever married	124,317	67.04%	7,514	66.54%	3,279	68.90%	11,3524	67.02%
With service percentage \geq 50%	102,312	55.17%	6,149	54.45%	2,661	55.92%	93,502	55.20%
Fiscal year								
FY11	24,502	13.21%	997	8.83%	893	18.76%	22,612	13.35%
FY12	49,032	26.44%	1,660	14.70%	2,250	47.28%	45,122	26.64%
FY13	47,452	25.59%	3,903	34.56%	843	17.71%	42,706	25.21%
FY14	43,940	23.69%	3,371	29.85%	547	11.49%	40,022	23.63%
FY15	20,523	11.07%	1,362	12.06%	226	4.75%	18,935	11.18%
Psychiatric condition								
Major depression	45,121	24.33%	2,613	23.14%	1,081	22.71%	41,427	24.46%
PTSD	33,771	18.21%	1,913	16.94%	838	17.61%	31,020	18.31%
Alcohol use disorder	36,316	19.58%	1,792	15.87%	731	15.36%	33,793	19.95%
Other substance use disorder	34,198	18.44%	1,671	14.80%	660	13.87%	31,867	18.81%
Psychiatric medication use								
Prescribed ATP	185,449	100%	11,293	100%	4,759	100%	169,397	100%
Antipsychotics coverage \geq 80%	104,434	56.31%	6,431	56.95%	2,857	60.03%	95,146	56.17%
Prescribed clozapine	7,473	4.03%	411	3.64%	159	3.34%	6,903	4.08%
Prescribed mood stabilizer medication	75,709	40.82%	4,204	37.23%	1,829	38.43%	69,676	41.13%
Mood stabilizer medication coverage \geq 80%	37,797	20.38%	2,155	19.08%	942	19.79%	34,700	20.48%
Prescribed antidepressant	118,310	63.80%	7,094	62.82%	3,044	63.96%	108,172	63.86%
Prescribed anti-anxiety medication	77,130	41.59%	4,309	38.16%	1,873	39.36%	70,948	41.88%
Prescribed substance use disorder medication	8,957	4.83%	430	3.81%	175	3.68%	8,352	4.93%
Service use								
Hospitalized for somatic reason	34,769	18.75%	1,557	13.79%	590	12.40%	32,622	19.26%
Emergency room use	65,965	35.57%	3,241	28.70%	1,263	26.54%	61,461	36.28%
PRRC visits	15.41	2.38	14.59	2.26	16.5	2.59	15.43	2.38
MHICM visits	13	4.22	12.2	3.78	12.45	3.72	13.07	4.26
Other mental health outpatient visits	12.8	7.63	12.6	7.07	13.48	7.12	12.79	7.68
Substance use visits	8.69	1.39	7.07	1.06	7.68	1.08	8.81	1.43
Somatic outpatient visits	18.36	18.22	16.55	15.79	17.15	16.43	18.5	18.44
Somatic outpatient visits during 3M post	11.57	11.56	10.06	9.74	9.45	9.56	11.7	11.74
Carlson comorbidity index								
0	71,235	38.41%	4,007	35.48%	1,700	35.72%	57,702	34.06%
1	63,409	34.19%	2,762	24.46%	1,220	25.64%	46,823	27.64%
2+	50,805	27.40%	9.5	58.49	9.38	58.18	10.03	58.7

FY: Fiscal year in which incident medication episode began; PTSD: posttraumatic stress disorder; ATP: prescribed antipsychotic; PRRC: count of psychosocial rehabilitation and recovery center visits; MHICM: count of mental health intensive case management visits.

BD or schizophrenia was associated with a lower RR of psychiatric hospitalizations or ED visits as previously reported for patients with MD treated with SSRIs [134].

The add-on hydrophilic statins prescribed to individuals with BD and schizophrenia had a lower RR of psychiatric hospitalizations, but not of ED visits, than the lipophilic

Table 2: Description of individuals with BD on antipsychotic medication

Bipolar with antipsychotic	Whole		Lipophilic		Hydrophilic		None	
	N = 211,412	SD or %	N = 13,292	SD or %	N = 5,326	SD or %	N = 192,794	SD or %
Mean age SD	54.77	11.29	55.93	10.37	56.11	10.12	54.65	11.37
Male	174,106	82.35%	11,424	85.95%	4,519	84.85%	158,163	82.04%
Race								
White	169,511	80.18%	10,919	82.15%	4,397	82.56%	154,195	79.98%
Non-white	34,040	16.1%	1,843	13.87%	737	13.84%	31,460	16.32%
Missing	7,861	3.72%	530	3.99%	192	3.60%	7,139	3.70%
Ever married	178,906	84.62%	11,373	85.56%	4,644	87.19%	162,889	84.49%
With service percentage $\geq 50\%$	93,123	44.05%	5,654	42.54%	2,226	41.79%	85,243	44.21%
Fiscal year								
FY11	25,504	12.06%	1,151	8.66%	1,041	19.55%	23,312	12.09%
FY12	53,920	25.5%	1,864	14.02%	2,374	44.57%	49,682	25.77%
FY13	54,168	25.62%	4,729	35.58%	1,018	19.11%	48,421	25.12%
FY14	52,605	24.88%	3,931	29.57%	637	11.96%	48,037	24.92%
FY15	25,215	11.93%	1,617	12.17%	256	4.81%	23,342	12.11%
Psychiatric condition								
Major depression	81,864	38.72%	4,732	35.60%	1,846	34.66%	75,286	39.05%
PTSD	79,552	37.63%	4,483	33.73%	1,827	34.30%	73,242	37.99%
Alcohol use disorder	56,951	26.94%	3,016	22.69%	1,118	20.99%	52,817	27.40%
Other substance use disorder	50,489	23.88%	2,530	19.03%	980	18.40%	46,979	24.37%
Psychiatric medication use								
Prescribed ATP	211,412	100%	13,292	100%	5,326	100%	192,794	100%
Antipsychotics coverage $\geq 80\%$	90,831	42.96%	6,001	45.15%	2,491	46.77%	82,339	42.71%
Prescribed clozapine	361	0.17%	16	0.12%	8	0.15%	337	0.17%
Prescribed mood stabilizer medication	137,213	64.9%	8,426	63.39%	3,435	64.49%	125,352	65.02%
Mood stabilizer medication coverage $\geq 80\%$	65,707	31.08%	4,239	31.89%	1,725	32.39%	59,743	30.99%
Prescribed antidepressant	159,677	75.53%	9,834	73.98%	3,970	74.54%	145,873	75.66%
Prescribed anti-anxiety medication	111,319	52.66%	6,459	48.59%	2,718	51.03%	102,142	52.98%
Prescribed substance use disorder medication	22,158	10.48%	1,129	8.49%	440	8.26%	20,589	10.68%
Service use								
Hospitalized for somatic reason	36,434	17.23%	1,748	13.15%	628	11.79%	34,058	17.67%
Emergency room use	76,432	36.15%	3,905	29.38%	1,474	27.68%	71,053	36.85%
PRRC visits	8.93	0.92	8.42	0.88	9.1	0.94	8.96	0.92
MHICM visits	6.36	0.96	5.82	0.83	5.51	0.8	6.42	0.97
Other mental health outpatient visits	14.37	8.76	13.18	7.7	12.18	7.23	14.5	8.88
Substance use visits	11.11	2.37	10	1.89	9.09	1.63	11.23	2.43
Somatic outpatient visits	18	18.96	16.47	16.27	16.33	16.98	18.12	19.2
Somatic outpatient visits during 3M post	11.88	12.15	10.29	9.9	9.91	9.89	12.01	12.37
Carlson comorbidity index								
0	96,283	45.54%	6,139	46.19%	2,337	43.88%	87,807	45.54%
1	67,107	31.74%	4,316	32.47%	1,815	34.08%	60,976	31.63%
2+	48,022	22.71%	2,837	21.34%	1,174	22.04%	44,011	22.83%

FY: Fiscal year in which incident medication episode began; PTSD: posttraumatic stress disorder; ATP: prescribed antipsychotic; PRRC: count of psychosocial rehabilitation and recovery center visits; MHICM: count of mental health intensive case management visits.

statin prescription in the same clinical groups. Although no similar comparisons between lipophilic and hydrophilic statins have been undertaken, to our knowledge, the results of a protective effect of statin use on hospitalization

rates were consistent with one study nested in Danish registers showing that statin (simvastatin) treated patients with citalopram had fewer hospital contact than patients treated with SSRI alone [137]. The results are also consistent

Table 3: Description of individuals with BD on mood-stabilizer medication

Bipolar with mood stabilizer	Whole		Lipophilic		Hydrophilic		Other	
	N = 286,268	SD or %	N = 18,267	SD or %	N = 7,307	SD or %	N = 260,694	SD or %
Mean age SD	55.41	11.34	56.8	10.3	56.87	10.13	55.28	11.43
Male	238,625	83.36%	15,976	87.46%	6,302	86.25%	216,347	82.99%
Race								
White	233,821	81.68%	15,221	83.33%	6,104	83.54%	21,2496	81.51%
Non-white	41,238	14.41%	2308	12.63%	898	12.29%	38,032	14.59%
Missing	11,209	3.92%	738	4.04%	305	4.17%	10,166	3.9%
Ever married	246,998	86.28%	15,971	87.43%	6502	88.98%	224,525	86.13%
With service percentage \geq 50%	126,007	44.02%	7867	43.07%	2,990	40.92%	115,150	44.17%
Fiscal year								
FY11	32,946	11.51%	1,454	7.96%	1,418	19.41%	30,074	11.54%
FY12	71,876	25.11%	2,478	13.57%	3,346	45.79%	66,052	25.34%
FY13	73,489	25.67%	6,626	36.27%	1,269	17.37%	65,594	25.16%
FY14	73,066	25.52%	5,457	29.87%	896	12.26%	66,713	25.59%
FY15	34,891	12.19%	2,252	12.33%	378	5.17%	32,261	12.38%
Psychiatric condition								
Major depression	109,158	38.13%	6,404	35.06%	2,503	34.25%	10,0251	38.46%
PTSD	100,897	35.25%	5,878	32.18%	2,314	31.67%	92,705	35.56%
Alcohol use disorder	69,117	24.14%	3,678	20.13%	1,366	18.69%	64,073	24.58%
Other substance use disorder	59,663	20.84%	2,964	16.23%	1,072	14.67%	55,627	21.34%
Psychiatric medication use								
Prescribed ATP	137,213	47.93%	8,426	46.13%	3,435	47.01%	125,352	48.08%
Antipsychotics coverage \geq 80%	60,215	21.03%	3,909	21.4%	1,600	21.9%	54,706	20.98%
Prescribed clozapine	277	0.1%	13	0.07%	4	0.05%	260	0.1%
Prescribed mood stabilizer medication	286,268	100%	18,267	100%	7,307	100%	260,694	100%
Mood stabilizer medication coverage \geq 80%	129,612	45.28%	8,582	46.98%	3,489	47.75%	117,541	45.09%
Prescribed antidepressant	211,314	73.82%	13,191	72.21%	5,299	72.52%	192,824	73.97%
Prescribed anti-anxiety medication	142,628	49.82%	8,294	45.4%	3,471	47.5%	130,863	50.2%
Prescribed substance use disorder medication	26,805	9.36%	1,309	7.17%	519	7.1%	24,977	9.58%
Service use								
Hospitalized for somatic reason	49,987	17.46%	2470	13.52%	907	12.41%	46,610	17.88%
Emergency room use	101,884	35.59%	5441	29.79%	2050	28.06%	94,393	36.21%
PRRC visits	7.7	0.71	7.45	0.68	7.27	0.61	7.73	0.71
MHICM visits	5.17	0.64	4.61	0.54	4.58	0.55	5.22	0.65
Other mental health outpatient visits	13.71	7.96	12.2	6.83	11.36	6.38	13.87	8.08
Substance use visits	10.65	2.16	9.67	1.65	8.92	1.4	10.76	2.22
Somatic outpatient visits	18.45	19.88	16.63	17.21	16.95	17.85	18.59	20.12
Somatic outpatient visits during 3M post	12.2	12.64	10.61	10.52	10.42	10.51	12.33	12.85
Carlson comorbidity index								
0	125,230	43.75%	7,964	43.6%	3,035	41.54%	114,231	43.82%
1	90,077	31.47%	5,947	32.56%	2,461	33.68%	81,669	31.33%
2+	70,961	24.79%	4,356	23.85%	1,811	24.78%	64,794	24.85%

FY: Fiscal year in which incident medication episode began; PTSD: posttraumatic stress disorder; ATP: prescribed antipsychotic; PRRC: count of Psychosocial Rehabilitation and Recovery Center visits; MHICM: count of Mental Health Intensive Case Management visits.

with a military study, revealing the increased risk of developing schizophrenia symptoms in nonpersistent statin users vs. persistent statin users [131]. It is important to keep

in mind that the majority of studies of positive effects of statins on depression, schizophrenia, and on a delay of Alzheimer's disease onset were based on lipophilic statins,

Table 4: Inpatient psychiatric hospitalization in individuals with schizophrenia and bipolar disorder; comparison between lipophilic, hydrophilic, and no statin groups

Label	Relative risk	Mean		L'Beta estimate	Standard error	Alpha	L'Beta		Chi-square	p
		Confidence limit					Confidence limit			
Lipophilic vs. hydrophilic										
Schizophrenia with antipsychotic	1.11	1.0007	1.23	0.1	0.05	0.05	0.0007	0.21	3.89	0.048
BD with antipsychotic	1.22	1.09	1.36	0.2	0.06	0.05	0.08	0.31	11.42	<0.001
BD with mood stabilizer	1.18	1.06	1.32	0.17	0.05	0.05	0.06	0.27	9.37	0.002
Lipophilic vs. none										
Schizophrenia with antipsychotic	0.81	0.77	0.86	-0.21	0.03	0.05	-0.26	-0.16	59.84	<0.001
BD with antipsychotic	0.85	0.80	0.89	-0.17	0.03	0.05	-0.22	-0.11	36.88	<0.001
BD with mood stabilizer	0.83	0.79	0.88	-0.18	0.03	0.05	-0.23	-0.13	49.31	<0.001
Hydrophilic vs. none										
Schizophrenia with antipsychotic	0.73	0.67	0.80	-0.31	0.05	0.05	-0.40	-0.22	47.16	<0.001
BD with antipsychotic	0.70	0.63	0.77	-0.36	0.05	0.05	-0.46	-0.26	50.07	<0.001
BD with mood stabilizer	0.70	0.64	0.77	-0.35	0.05	0.05	-0.44	-0.26	53.89	<0.001

BD: bipolar disorder.

and an elevated risk of suicidal ideation with statin (a common reason for psychiatric hospitalizations) has been also reported in lipophilic statin use only [138]. Yet direct comparisons between two statin categories have seldomly, if at all, been undertaken. Mild cognitive impairment [139,140] and sleep disturbances [141,142], both a consequence as well as a possible contributor to poor therapeutic control, occurred more commonly with lipophilic rather than hydrophilic statin administration, suggesting

that brain penetrance may engage mechanisms that could offset, in part, anti-inflammatory, antioxidant, and endothelial positive effects of statins, perhaps via lowering cholesterol in the neuronal membranes and impairing channel and receptor function and/or mitochondrial function. However, this has to be interpreted with skepticism, as recent meta-analyses have not found any significant cognitive impairment of statin use with mild cognitive deficits [143,144] or with sleep efficiency or duration [145].

Table 5: Psychiatric emergency department visit in individuals with schizophrenia and bipolar disorder; comparison between lipophilic, hydrophilic, and no statin groups

Label	Relative risk	Mean		L'Beta estimate	Standard error	Alpha	L'Beta		Chi-square	p
		Confidence limit					Confidence limit			
Lipophilic vs. hydrophilic										
Schizophrenia with antipsychotic	1.07	0.83	1.36	0.06	0.13	0.05	-0.18	0.31	0.27	0.61
BD with antipsychotic	1.26	0.97	1.63	0.23	0.13	0.05	-0.03	0.49	3.11	0.08
BD with mood stabilizer	1.16	0.92	1.46	0.15	0.12	0.05	-0.08	0.38	1.63	0.2
Lipophilic vs. none										
Schizophrenia with antipsychotic	0.76	0.67	0.87	-0.27	0.07	0.05	-0.41	-0.14	16.44	<0.001
BD with antipsychotic	0.83	0.74	0.94	-0.18	0.06	0.05	-0.31	-0.06	8.44	0.004
BD with mood stabilizer	0.79	0.71	0.89	-0.23	0.06	0.05	-0.35	-0.12	16.09	<0.001
Hydrophilic vs. none										
Schizophrenia with antipsychotic	0.71	0.58	0.88	-0.34	0.11	0.05	-0.55	-0.13	10.03	0.002
BD with antipsychotic	0.66	0.53	0.83	-0.41	0.12	0.05	-0.64	-0.19	12.93	<0.001
BD with mood stabilizer	0.68	0.56	0.83	-0.38	0.1	0.05	-0.58	-0.18	14.09	<0.001

BD: bipolar disorder.

4.2 Confounding by indication

In comparisons between statins and no statins, there is a likely confounding by indication based on comorbidity with metabolic and cardiovascular conditions that may affect the response to medication, alter the risk of self-harm, and alter the risk of psychiatric hospitalization and ED visits. Methods to weigh, balance, or adjust for potential sources of bias, e.g., propensity score-matched analyses as in the supplemental material presented in the study by Kohler *et al.* [134], are deemed to remain incomplete without including the specific indications for statin treatment, such as low-density lipoprotein and total cholesterol measurement. Thus, our current comparison between statins and no statins, as Kohler's finding in MD, should be received with considerable skepticism. Yet the comparison of lipophilic and hydrophilic statin minimizes bias [16] and may lead to an important decision point in those individuals who have schizophrenia or BD and meet the criteria to initiate or restart the statin treatment.

4.3 Statin effects on cognition and cognitive disorders

Cognitive deficits, as well as negative symptoms, are strongly predictive of functioning and course in schizophrenia and bipolar disorder and, although to a limited degree, are modifiable with add-on statin treatment [76,77]. Theoretically, statins could be particularly promising for cognitive deficits in individuals with schizophrenia and bipolar disorder as they have been reported by some (but not all) studies on cognitive deficits in the context of aging (age-related cognitive decline) and dementia. For instance, in community-dwelling adults, slower cognitive decline [131] and fewer white matter abnormalities [146] have been associated with statin treatment.

Wong *et al.* (2013) performed a systematic review of 20 uncontrolled studies on 4 million participants and identified a mild beneficial effect in Alzheimer's dementia and all dementias. Similarly, Song *et al.* (2013), via a meta-analysis of 11 longitudinal cohort studies and 57,020 participants, with positive heterogeneity and no evidence of bias, identified an approximately 40% decreased risk of dementia with the use of statins [132]. At the same time, Swiger *et al.* found in a meta-analysis of 11 studies with 23,443 individuals [144] enrolled in RCTs and prospective cohort studies identified a 29% protective effect of statins at the long term (>1 year), while there were no immediate benefits at a short term (<1 year). Most recently, the meta-

analysis of Xuan *et al.* (2020) on exclusively RCTs (nine studies) and 1,489 participants, uncovered a statistical improvement in cognitive function by Mini-Mental score and a reduced progression of worsening based on the Neuropsychiatric Inventory Questionnaire, but with no differences in other measures [133].

In a recent large study, bipolar individuals using neurocognitive testing belonging to four cognitive domains, statin users and nonusers did not differ in regard to cognitive function [15]. The authors concluded that statins neither improve nor deteriorate cognitive functioning in bipolar patients [147]. They suggested that inherent cognitive deterioration secondary to bipolar disorder, i.e., "neuroprogression" [105,148], and aging per se [100] outweigh the beneficial effects of statin treatment.

Statins have been linked also with mild cognitive impairment [149–151], findings that stand in full opposition to those reporting a delayed decline in cognitive function in older adults [149–151], with several studies that found no significant association [143,144]. Of relevance and congruent with our current report, clinical trials of hydrophilic statins did not elicit any cognitive deficits [76], while lipophilic studies were associated with mild cognitive impairment [139,140].

4.4 Biological mechanisms potentially contributing to our key results

4.4.1 Immune modulatory effects

Statins increase the number and increase the suppressive function of Treg cells in animal experimental models of chronic immune activation [123], clinically both in the presence and in the absence of immune-mediated conditions [124]. In addition, an increasing number of randomized controlled studies and meta-analyses support substantial benefits of statins as add-on interventions in various mental health conditions. The benefits of statins in mental health have been attributed to several molecular, cellular, and system effects, including modulating inflammation and endothelial function and reducing oxidative stress [18]. In particular, for the diagnostic categories analyzed in this project, the immunoregulatory effects of statins specifically engage and modulate proinflammatory targets associated with cognitive dysfunction and negative symptoms [71,72], key determinants of functioning in schizophrenia. In addition, statins have been reported to modulate molecular and cellular signatures involved in the trait-like immune activation during mania

and depression in BD [85] as well as the progressive immune dysfunction [99,100,103,104] linked with the cognitive and functional decline in “neuroprogressive” cases of BD [97–102]. Most importantly, in conditions of acute neuro-adversity known to be downstream mediated by systemic inflammation and oxidative stress, statins have an overall immunoregulatory effect. For instance, in a murine model of TBI, atorvastatin significantly increases the proportion of regulatory T cells (Tregs) in both the periphery (spleen) and the brain and simultaneously increases their main immunoregulatory effectors – anti-inflammatory cytokines such as IL-10 and TGF- β 1 [152], with the reduction in histopathology and functional recovery.

4.4.2 Antimicrobial effects

Statins are also potent add-on antimicrobial agents by interfering with mechanisms that pathogens use to evade the immune response and preventing immune overactivation and unremitting activation, which might have an important role in preventing reactivation of latent infections, such as chronic toxoplasmosis, implicated in schizophrenia [153] or suicidal behavior in individuals with schizophrenia [51] or with recurrent mood disorders [49,154].

4.4.3 Potential mechanisms for lipophilic vs. hydrophilic divergence

What mechanisms could underlie the difference in outcome between the lipophilic and hydrophilic statins? First, cognitive dysfunction may be elevated in the group of statins with penetrance in the brain, potentially through affecting neurotransmitter receptors, ion channels (via changes in the cholesterol component of lipid membranes), or, as in Alzheimer’s Dementia, induction of axonal degeneration due to deprivation of cholesterol as shown in cultured neurons [155]. Furthermore, a much more intense lowering of brain cholesterol by the lipophilic statins – with no cholesterol intake possible from outside the CNS – may affect brain serotonin synthesis, thus impulsivity, aggression, anxiety, violent ideation, and thus increased risk for self-directed violence [156–158], and, in response, ED visits and psychiatric hospitalizations.

In addition, another interactive effect is possible, i.e., local intense antioxidant effect by lipophilic statins within the CNS may adversely affect the TH₁ immune pressure on intracellular pathogens such as CMV or *Toxoplasma*

gondii, which may result in reactivation of the pathogens and loss of therapeutic control. Furthermore, the plunging of brain ROS levels could also affect the maturation and function of Tregs, with reduced mediation of immunomodulatory signals (such as IL-10) and overshooting of inflammatory reactions promoting, among other mechanisms, persistent microglia hyperreactivity. For instance, in cell cultures, TNF- α upregulation and microglia activation [159,160] and induction of the mitochondrial apoptotic pathways, time and dose-dependent, have been reported with lovastatin [161].

4.4.4 Panorgan endothelial-stabilizing effects of statins

Furthermore, the effects of statins on stabilizing endothelial function [19] could be, in conjunction with their peripheral anti-inflammatory effect, the most important mechanisms for symptomatic, functional, and behavioral effects of statins, and thus, the effect on brain and behavior would primarily take place via diffuse vascular mechanisms. This has been best documented for rosuvastatin, the most commonly prescribed hydrophilic statin in our sample, given its potency and vascular tropism, and devoid of the added toxicity of penetration of brain parenchyma with lipophilic statins, such as the toxic effects on brain mitochondrial pathways.

Several molecular underexplored mechanisms could underlie the effects of statins. As autophagy-related pathway impairment has been reported in schizophrenia [162], it is possible that statin-mediated neuroprotection is based, at least in part, on restored autophagic mechanisms as robustly reported for rosuvastatin (the most prescribed hydrophilic statin) in Parkinson’s disease [163].

4.4.5 Statin kinetic interactions with psychotropic medications

First, coupling between a specific psychotropic agent and a specific statin may lead to interactions at the level of the cytochrome system involved in their metabolism resulting in blood level changes on the psychotropic, or of the statin. For instance, fluvastatin (lipophilic) and rosuvastatin are metabolized via CYP 2C9 and all others (with the exception of pravastatin) via CYP 3A4 [164]. Pravastatin is eliminated renally with minimal metabolism at the CYP system [165]. For example, the mood stabilizer carbamazepine is a strong inducer of the CYP 3A4 and thus is expected decrease the blood level of most

statins, bringing it below the high-dose requirement that appears clinically necessary for effectively augmenting psychotropic medications or protecting cognitive function. On the other hand, the SSRI fluvoxamine, used almost exclusively in obsessive compulsive disorder (OCD), a condition often comorbid with schizophrenia, is a potent inhibitor of CYP 3A4, and thus resulting in considerable increases in levels for the majority of statins (thus meeting the high-dose requirements established for positive psychiatric effects based on early clinical impression, or, alternatively, contributing to toxicity and statin discontinuation). This combination may put a patient at a major risk for myopathy, liver and kidney toxicity, situations that for many patients practically represent an early end of statin treatment effects based on early clinical impression. Other potential interactions between statins and antipsychotics are based on competition for P-glycoprotein 1 (a BBB transporter guarding brain molecular access) and, being both substrates, act additively or synergistically for achieving a higher concentration in the CNS, leading to increased efficacy or amplified side effects [76]. This interaction is likely statin and antipsychotic specific based on specific P-glycoprotein 1 affinity (e.g., high for risperidone and low for clozapine or haloperidol) and, with advanced knowledge, amenable to deliberate statin by psychotropic coupling. These effects and specific interactions should be taken into considerations in future studies using machine learning to weigh potential effect modifiers and confounders among statin groups, individual statins, and statin/psychotropic combinations to identify sources of heterogeneity in clinical benefits.

4.4.6 Strength

We utilized a systematic data mining approach and yet a focused hypothesis-driven stance. The lipophilic vs. hydrophilic comparison is based on a dichotomy, central vs. peripheral effects, and known capability to cross the BBB. This comparison minimizes confounding and reduces bias.

4.4.7 Limitations

The generalizability might be relatively limited. We analyzed prescriptions (i.e., picking up the prescription) and not adherence based on actually taking the medications. We have not taken into consideration the relative potency of statins, the duration of administration, degree of adherence, and dosage (e.g., by accounting for a “dose-

equivalent” across specific statins). The few studies that considered these variables suggested advantages for long duration and high dosages [166,167].

Time-varying confounders, such as interactions with psychiatric medications, have not been analyzed, and time-invariant confounders such as genetic factors and lifestyle characteristics could have biased our study. Observational design and the use of health services encounter data rather than clinical data, not weighing the statin vs. no statins groups, and the lack of biomarker measurements represents other limitations of the study.

In future studies, it will be relevant to measure markers of inflammation such as proinflammatory and anti-inflammatory cytokines, CRP, chemokines, neopterin measures of oxidative stress, markers of endothelial function, microRNA involved in proinflammatory and anti-inflammatory responses, physiological measurements of endothelial function, glucocorticosteroid measurement to consider effects of stress, acute and chronic, especially on TDO and immune function, tryptophan, kynurenine and molecules of the kynurenine pathway, precursors of dopamine affected by inflammation (phenylalanine, tyrosine, and their ratio), liver function tests (to monitor and account for statin toxicity), and of course, lipid profiles, especially total cholesterol, LDL cholesterol, and triglycerides. For large studies nested in electronic medical records, or for long-term monitoring, perhaps the most accessible and relevant clinical parameters are routine hematological laboratory results implicated in inflammation, such as WBC, neutrophil count, neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio. The neutrophil:lymphocyte ratio (NLR) has been reported to be elevated in acute relapse in schizophrenia [168] and bipolar disorder [169], in particular in functionally relevant cognitive dysfunction and functional deterioration, as well as in increased suicide risk in euthymic bipolar individuals [170]. In tight experimental conditions, pretreatment with statins has been shown to prevent elevated NLR [171] after experimental stroke in rodents.

Future studies could be classified into two broad categories – studies of patients who have both metabolic/cardiovascular indications and psychiatric indications and, probably at a later stage, studies on individuals who have only psychiatric indications, with incomplete responses to psychotropic medication. The outcome of the interventions could be psychiatric admissions (as done in this article), psychiatric instability (perhaps as a composite measure, including parameters related to stability–instability of mental illness, such as admissions, emergency room visits, need to increase medication dosages or replace medications,

notable changes in the level of functioning [academic, occupational, activities of daily living, maintaining relationships], trouble with the law, loss of housing, remission, relapse, or recurrence of substance abuse, and nonadherence with psychiatric medications and follow-up, and with larger samples – suicide attempts, episodes of violence, or, with even larger samples – mandating multicenter collaboration – death by suicide). Either by design, or by analysis (adjustment, stratification, postrandomization weighing), the intervention and control groups (statin vs. no statin randomization, and lipophilic vs. hydrophilic statin) would have to take into account demographic factors (age and gender), metabolic/cardiovascular indications of statins, substance use, psychiatric diagnosis (schizophrenia or bipolar I), its severity and treatment, and history of immune-mediated conditions (autoimmune, allergic, severe or persistent infections, and TBI). In particular, baseline markers of immune activation could represent criteria of inclusion (i.e., in line with the idea that inflammation must be present to be valuable to modulate it) or stratification. Machine learning paradigms could be employed for both weighing factors that may contribute to the outcome, analyzing heterogeneity of effects (i.e., what combination of demographic, clinical, and pharmacological factors predict the strongest effect size, or in contrast little or no benefit, or side effects of statin treatment). In essence, it will be important to know not only if statins have benefits, but also which categories of statins, which dosages, and what durations manifest the greatest psychiatric benefits, and what are the broad characteristics of patients most likely to benefit from statin add-on treatment.

4.4.8 Implications and future plans

In sum, this study identified that while both subgroups of statins are associated with lower RR of psychiatric hospitalization and ED visits, hydrophilic statins were advantageous in reducing the risk of psychiatric hospitalizations compared to lipophilic studies. The difference between hydrophilic and lipophilic statins was relatively small, and yet, given the proportion of individuals who are taking statins, this small effect may result in public health implications given the large number of individuals struggling with mental health issues, the increased metabolic and cardiovascular morbidity, and mortality in patients with severe mental illness.

Given the high proportion of Veterans with the history of mental illness who are being treated with a statin, the augmentation of psychotropic treatment in schizophrenia and BD with an individualized statin may have broad positive consequences. Understanding not only if

statins help therapeutic controls but also what are the demographic, clinical, and pharmacologic characteristics of subgroups of patients who would benefit the most, and by which specific statin regimen (considering the lipophilia, potency, dose, and individual pharmacokinetic properties) is necessary. These efforts may lead to improved therapeutic control by repurposing statins as an add-on intervention in individuals in mental health treatment.

5 Conclusion

As pharmacological agents that engage multiple molecular targets implicated in onset, severity, and poor therapeutic control in schizophrenia and BD, personalized statin augmentation may become a salient, efficient, and nonstigmatizing intervention for reducing ER visits and hospitalization, achieving and sustaining remission, and maximizing functional recovery.

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