Brain-penetrant calcium channel blockers for psychiatric use: revisiting the evidence for benefit

Authors: David M. Kern [1], Justin Bohn [1], Michael Maher [2], Dmytro Dymshyts [1], Azza Shoaibi [1]

[1] Janssen Research & Development, LLC, Global Epidemiology Organization

[2] Janssen Research & Development, LLC, Neuroscience

Background: A recently published study of electronic health records (EHRs) reported that use of brain-penetrant calcium channel blockers (BP-CCBs) compared with use of non-brain-penetrant CCBs (NP-CCBs), drugs typically used to treat hypertension, was associated with a reduced incidence of multiple neuropsychiatric outcomes [1]. If results can be replicated, it could mean a new pathway worth exploring for effective neuropsychiatric treatments. However, the study had several limitations, including limited control for confounding and post-index follow-up requirements, which threatened the validity of the results. The objective of this study was to use best practices in pharmacoepidemiology to assess the association between new use of BP-CCBs and the incidence of bipolar disorder, major depression (MDD), schizophrenia and schizoaffective disorder.

Methods: New users of BP CCBs and NP CCBs were identified in 9 claims and EHR databases from across the globe (e.g., Merative MarketScan, Japan Medical Data Center). First use of a CCB was the index date. At-risk period began 1 day after index, during which time to bipolar disorder, MDD, schizophrenia, and schizoaffective disorder cases were captured separately. Both on-treatment (OT) and intention-to-treat (ITT) analyses were conducted. Propensity scores were used to control for observed confounding, including all diagnosed comorbid conditions, all prior and concomitant medication use, demographics, and other variables found in the observational data sources. Cox models were used to analyze the time to incident neuropsychiatric disorder in each of the groups; hazard ratios (HRs) compared BP group to the NP group. Negative control outcomes (N=180) were used to calibrate estimates, confidence intervals and p-values to account for residual confounding. Study diagnostics were used to assess the validity of the analysis.

Results: There were 1.2 million BP-CCB patients and 9.3 million NP-CCB patients identified across all databases, with 881,758 million matched in each group. For the outcome of incident MDD in the ITT design, HRs (95% CIs) ranged from 0.96 (0.59, 1.57) to 1.08 (0.96, 1.21) with a meta-analysis HR of 1.02

(0.97, 1.08) (**Figure 1)**. Meta-analytic HRs for bipolar disorder [1.04 (0.96, 1.13)], schizophrenia [1.05 (0.94, 1.18)], and schizoaffective disorder [1.04 (0.87, 1.23)] showed similar null effects. The OT analysis was largely consistent: MDD [1.01 (0.96, 1.06)], bipolar [1.05 (0.86, 1.27)], schizophrenia [1.09 (0.87, 1.38)], schizoaffective [1.00 (0.71, 1.40)].

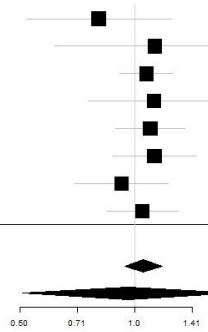
Conclusions: There was no evidence of an association with use of BP-CCB compared with NP-CCB use and incidence of any of the neuropsychiatric conditions of interest. Results were consistent across databases and study designs.

Figures

Figure 1. Primary analysis using ITT design for each of the four outcomes

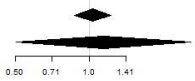
(A) Schizophrenia

Data Source	BP CCBs N	NP CCBs N	BP CCBs Events	NP CCBs Events	BP CCBs IR	NP CCBs IR	Hazard Ratio (95% CI)
IQVIA Australia LPD	157	157	<5	<5	<24.1	<24.9	--
IQVIA German DA	38,288	38,288	38	50	0.3	0.4	0.80 (0.52, 1.24)
IQVIA PharMetrics Plus	104,057	104,057	60	53	0.3	0.2	1.13 (0.62, 2.06)
Japan Medical Data Center	44,054	44,054	355	312	2.8	2.5	1.07 (0.91, 1.26)
Merative MarketScan CCAE	173,560	173,560	109	98	0.2	0.2	1.12 (0.75, 1.67)
Merative MarketScan MDCD	20,842	20,842	192	184	2.7	2.6	1.10 (0.89, 1.35)
Merative MarketScan MDCR	85,141	85,141	129	124	0.4	0.4	1.12 (0.87, 1.44)
Optum Pan-Therapeutic EHR	275,789	275,789	824	884	0.7	0.8	0.92 (0.70, 1.22)
Optum Clinformatics DoD	167,341	167,341	283	273	0.5	0.4	1.05 (0.84, 1.29)
Primary analysis (all SDM ≤ 0.20)							**1.05 (0.94, 1.18)**
Sensitivity analysis (all SDM ≤ 0.10)							**0.96 (0.51, 1.82)**



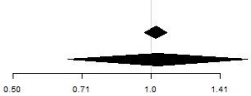
(B) Schizoaffective disorder

Data Source	BP CCBs N	NP CCBs N	BP CCBs Events	NP CCBs Events	BP CCBs IR	NP CCBs IR	Hazard Ratio (95% CI)
IQVIA Australia LPD	157	157	<5	<5	<24.1	<24.9	--
IQVIA German DA	38,288	38,288	14	17	0.1	0.1	0.87 (0.42, 1.79)
IQVIA PharMetrics Plus	104,057	104,057	40	43	0.2	0.2	0.93 (0.49, 1.76)
Japan Medical Data Center	44,054	44,054	16	9	0.1	0.1	1.67 (0.73, 3.84)
Merative MarketScan CCAE	173,560	173,560	80	55	0.1	0.1	1.46 (0.94, 2.29)
Merative MarketScan MDCD	20,842	20,842	106	113	1.5	1.6	0.98 (0.75, 1.29)
Merative MarketScan MDCR	85,141	85,141	39	41	0.1	0.1	1.04 (0.67, 1.62)
Optum Pan-Therapeutic EHR	275,789	275,789	407	432	0.3	0.4	0.93 (0.69, 1.25)
Optum Clinformatics DoD	167,341	167,341	128	133	0.2	0.2	0.96 (0.73, 1.27)
Primary analysis (all SDM ≤ 0.20)							**1.04 (0.87, 1.23)**
Sensitivity analysis (all SDM ≤ 0.10)							**1.14 (0.50, 2.60)**



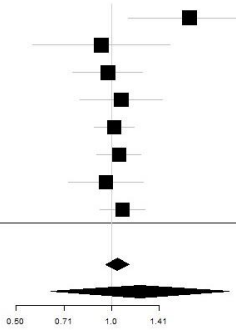
(C) Major depressive disorder

Data Source	BP CCBs N	NP CCBs N	BP CCBs Events	NP CCBs Events	BP CCBs IR	NP CCBs IR	Hazard Ratio (95% CI)
IQVIA Australia LPD	157	157	<5	<5	<24.3	<25.2	--
IQVIA German DA	38,288	38,288	4249	4170	33.8	34.1	1.08 (0.96, 1.21)
IQVIA PharMetrics Plus	104,057	104,057	7807	8102	38.8	40.5	0.96 (0.59, 1.54)
Japan Medical Data Center	44,054	44,054	1711	1567	13.8	12.6	1.03 (0.95, 1.13)
Merative MarketScan CCAE	173,560	173,560	14720	14661	27.8	28.0	1.01 (0.76, 1.35)
Merative MarketScan MDCD	20,842	20,842	4003	4163	69.4	72.0	1.00 (0.93, 1.07)
Merative MarketScan MDCR	85,141	85,141	8177	8506	27.8	27.2	1.04 (0.98, 1.10)
Optum Pan-Therapeutic EHR	275,789	275,789	37805	38617	36.3	37.9	0.96 (0.74, 1.26)
Optum Clinformatics DoD	167,341	167,341	22265	22375	40.4	41.5	1.01 (0.88, 1.15)
Primary analysis (all SDM ≤ 0.20)							**1.02 (0.97, 1.08)**
Sensitivity analysis (all SDM ≤ 0.10)							**1.03 (0.66, 1.62)**



(D) Bipolar disorder

Data Source	BP CCBs N	NP CCBs N	BP CCBs Events	NP CCBs Events	BP CCBs IR	NP CCBs IR	Hazard Ratio (95% CI)
IQVIA Australia LPD	157	157	<5	<5	<24.1	<24.9	--
IQVIA German DA	38,288	38,288	55	33	0.4	0.2	1.76 (1.13, 2.76)
IQVIA PharMetrics Plus	104,045	104,045	327	351	1.5	1.6	0.93 (0.56, 1.53)
Japan Medical Data Center	44,054	44,054	127	123	1.0	1.0	0.97 (0.76, 1.25)
Merative MarketScan CCAE	173,544	173,544	866	813	1.5	1.4	1.07 (0.79, 1.45)
Merative MarketScan MDCD	20,826	20,826	415	425	5.9	6.0	1.02 (0.88, 1.18)
Merative MarketScan MDCR	85,135	85,135	327	335	1.0	1.0	1.06 (0.90, 1.24)
Optum Pan-Therapeutic EHR	275,588	275,588	2193	2255	1.9	2.0	0.96 (0.73, 1.26)
Optum Clinformatics DoD	167,327	167,327	938	877	1.5	1.4	1.08 (0.92, 1.28)
Primary analysis (all SDM ≤ 0.20)							**1.04 (0.96, 1.13)**
Sensitivity analysis (all SDM ≤ 0.10)							**1.23 (0.64, 2.35)**



Events occurring in fewer than 5 patients are reported as "<5" in accordance with data use agreements.
***Abbreviations**: IR, incidence rate (per 1,000 person-years); CI, confidence interval; BP CCBs, brain penetrant calcium channel blockers; NP CCBs, non-brain penetrant calcium channel blockers*

References

1. Colbourne L, Harrison PJ. Brain-penetrant calcium channel blockers are associated with a reduced incidence of neuropsychiatric disorders. Mol Psychiatry [Internet]. 2022/05/27. 2022;27(9):3904–12. Available from: https://www.ncbi.nlm.nih.gov/pubmed/35618884