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Letter to the Editor: Discussion on the suicide risk of CCB drugs: based on real-world drug safety surveillance

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To the Editor,

We have read the original article by Richard J. Shaw et al., entitled to 'The relationship between antihypertensive medications and mood disorders: analysis of linked healthcare data for 1.8 million patients' (Shaw et al., 2021) with great interest. The study indicates that there is no evidence that antihypertensive drugs can prevent new episodes of Major Depressive Disorder (MDD). However, we have recently made new discoveries and hope to share them in this paper.

Calcium Channel Blockers (CCBs) are a heterogeneous group of drugs used to treat various cardiovascular diseases, such as angina, hypertension, hypertrophic cardiomyopathy, and supraventricular arrhythmias. They also have potential in reducing proteinuria and providing renal protection, as exemplified by the clear efficacy of dihydropyridine CCBs in non-diabetic hypertension for patients with nephrosis (Sica & Douglas, 2001). With the widespread use of these drugs, concerns have arisen about their safe use. Suicide is a serious public health problem. A previous report by the American Association of Poison Control indicated that cardiovascular drugs are one of the main drugs associated with fatal overdoses, and CCBs are among the most common (Gummin et al., 2020). Whether CCBs induce suicide attempts and behaviors remains a question to be resolved. This study explores this issue based on real-world drug safety surveillance data.

This study obtained report files from the FDA's Adverse Event Reporting System (FAERS) database from the first quarter of 2004 to the first quarter of 2024. The report files were then deduplicated. The study team organized the generic drug names of CCB drugs (Nifedipine, Amlodipine, Nimodipine, Felodipine). The requirements for sorting are as follows: drug entries must be confirmed as CCB drugs, and reports where CCB drugs are judged to be the primary suspects are included. ADRs of suicide, such as Completed Suicide, Suspected Suicide, and Suicide Attempt, were identified.

Based on the principle of disproportionality analysis, four risk signal detection methods (ROR (van Puijenbroek et al., 2002), PRR (Evans, Waller, & Davis, 2001), BPCNN (Bate et al., 1998), and EGBM (Szarfman, Machado, & O'Neill, 2002)) were used in this study. To enhance persuasiveness, for an ADR, only when four algorithms generate positive signals simultaneously, it is considered a positive ADR of CCB drugs. All statistical analyses were conducted using R 4.3.2 software.

From the FAERS database, 3012 reports with Nifedipine as the primary suspect were obtained, with 171 cases (5.7%) of Completed Suicide, 20 cases (0.7%) of Suspected Suicide, and 16 cases (0.5%) of Suicide Attempt; 40 651 reports with Amlodipine as the primary suspect, with 2222 cases (5.5%) of Completed Suicide, 797 cases (2.0%) of Suspected Suicide, and 19 cases (0.4%) of Suicide Attempt; 125 reports with Nimodipine as a suspect, with only 1 report of Completed Suicide; 443 reports with Felodipine as the primary suspect, with 4 cases (0.9%) of Completed Suicide and 5 cases (1.1%) of Suspected Suicide (Table 1).

Based on the four identification methods, Completed Suicide and Suspected Suicide were identified as positive ADRs for Nifedipine, while Suicide Attempt showed positive signals based on three methods (Fig. 1a, 1b); Suicide Attempt and Suspected Suicide were identified as positive ADRs for Amlodipine, while Completed Suicide showed positive signals based on three methods (Fig. 1c, 1d); only two positive signals were detected for Completed Suicide in Nimodipine (Fig. 1e, 1f); Suicide Attempt and Completed Suicide were identified as positive ADRs for Felodipine (Fig. 1g, 1h).

Santunione et al. (2024) suggest that cardiovascular disease is associated with an increased risk of suicide, and drug overdose is a common method they choose for suicide. This seems to emphasize the role of disease rather than drugs. However, this study cannot determine the causal relationship between taking CCB drugs and an increase in suicide intentions among patients with cardiovascular disease or whether cardiovascular disease leads to strong suicide

Table 1. General feature list

Variable	Nifedipine (*N* = 3012)	Amlodipine (*N* = 40 651)	Nimodipine (*N* = 125)	Felodipine (*N* = 443)
Gender				
Female	1789 (59.4%)	19 772 (48.6%)	67 (53.6%)	232 (52.4%)
Male	910 (30.2%)	15 615 (38.4%)	29 (23.2%)	177 (40.0%)
Unknown	313 (10.4%)	5264 (12.9%)	29 (23.2%)	34 (7.7%)
Weight				
<50 kg	131 (4.3%)	685 (1.7%)	1 (0.8%)	5 (1.1%)
>100 kg	98 (3.3%)	1775 (4.4%)		22 (5.0%)
50–100 kg	573 (19.0%)	10 242 (25.2%)	15 (12.0%)	179 (40.4%)
Unknown	2210 (73.4%)	27 949 (68.8%)	109 (87.2%)	237 (53.5%)
AGE				
≤17	96 (3.2%)	869 (2.1%)	3 (2.4%)	3 (0.7%)
≥86	102 (3.4%)	1927 (4.7%)		26 (5.9%)
18–64	1106 (36.7%)	13 082 (32.2%)	53 (42.4%)	103 (23.3%)
65–85	830 (27.6%)	13 162 (32.4%)	20 (16.0%)	181 (40.9%)
Unknown	878 (29.2%)	5264 (12.9%)	29 (23.2%)	34 (7.7%)
Reporter				
Consumer	934 (31.0%)	542 (1.3%)	21 (16.8%)	46 (10.4%)
Healthcare Professional	386 (12.8%)	5219 (12.8%)	59 (47.2%)	20 (4.5%)
Lawyer	3 (0.1%)	91 (0.2%)		
Medical Doctor	739 (24.5%)	3 (0.0%)	19 (15.2%)	128 (28.9%)
Other	733 (24.3%)	7008 (17.3%)	14 (11.2%)	96 (21.7%)
Pharmacist	216 (7.2%)	3621 (8.9%)	17 (13.6%)	73 (16.5%)
Registered Nurse	1 (0.0%)	8 (0.0%)		
ADR				
Completed Suicide	171 (5.7%)	2222 (5.5%)	1 (0.8%)	4 (0.9%)
Suspected Suicide	20 (0.7%)	797 (2.0%)	0 (0.0%)	5 (1.1%)
Suicide Attempt	16 (0.5%)	19 (0.4%)	0 (0.0%)	0 (0.0%)
Top 5 reporting countries				
	United States	United States	United States	United Kingdom
	Japan	United Kingdom	China	United States
	United Kingdom	Canada	Switzerland	China
	Italy	France	Germany	Sweden
	China	Germany	United Kingdom	Germany

ideation followed by the choice of CCB drugs. This study is based on the whole population and identified through disproportionality analysis that most CCB drugs have ADRs related to increased suicide intention or even suicide behavior. The results of multiple methods combined to identify basic trends are consistent. However, the population included in this study is not limited to cardiovascular populations, so the results suggest that the use of CCB drugs may be associated with suicide-related ADRs, which are not specified in FDA labels or even recognized in clinical practice. In summary, this study suggests that for people using CCB drugs, regardless of whether they have cardiovascular disease, psychological support should be strengthened to prevent suicide. The causal relationship and mechanism deserve further research and exploration.

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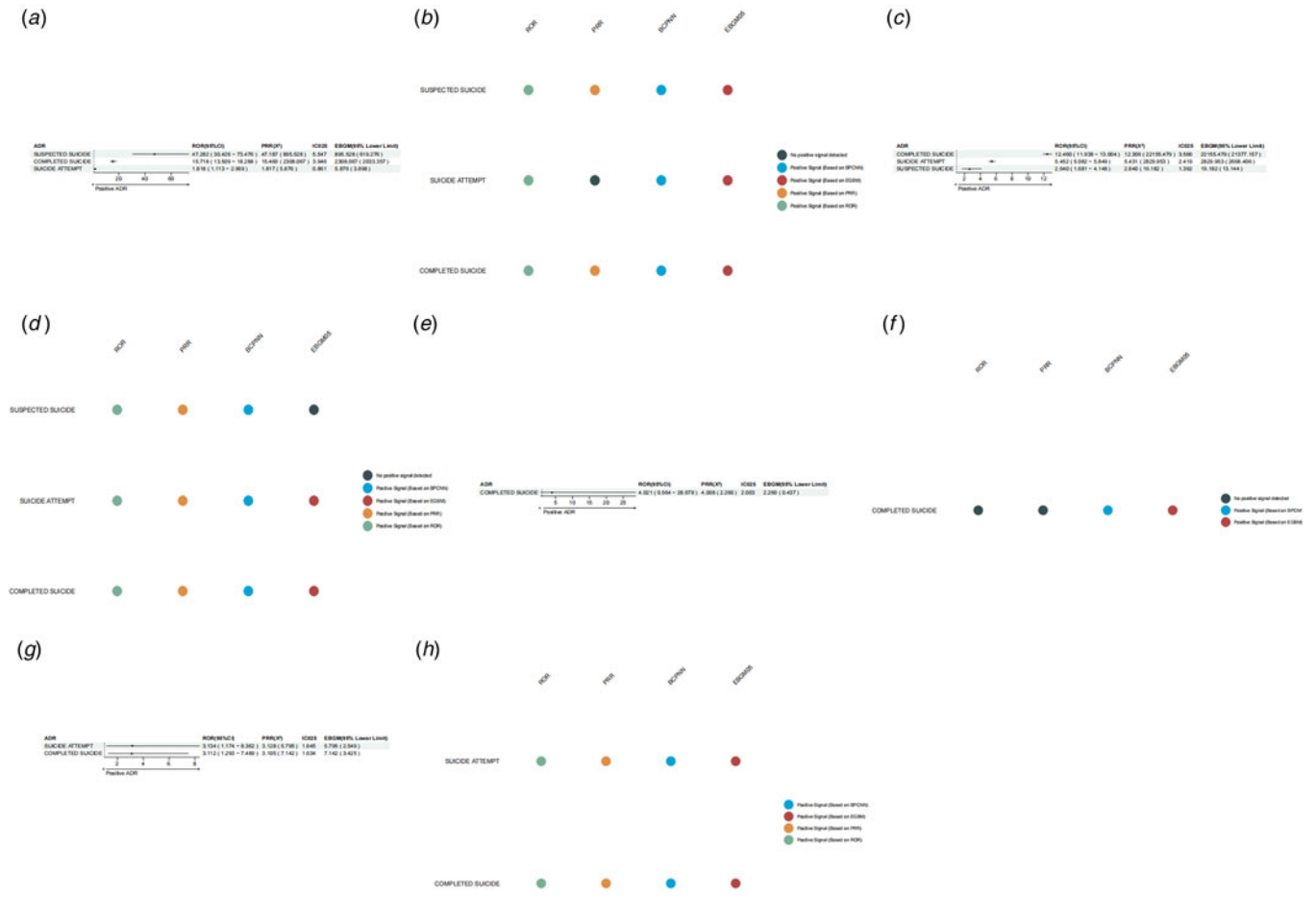

Figure 1. Identification results of positive ADR.

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