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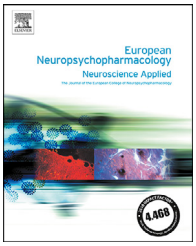

The association between receptor binding affinity and metabolic side effect profile of antipsychotics and major cardio- and cerebrovascular events: A case/non-case study using VigiBase

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Abstract
Antipsychotics (APs) have been associated with major adverse cardio- and cerebrovascular events (MACCE), but the underlying mechanisms are unclear. Our aim was to elucidate the association between APs, stratified for receptor affinity and metabolic side effects (MSE), in the reporting of MACCE. A case/non-case study was conducted using data from the WHO global Individual Case Safety Report (ICSR) database, VigiBase, among all reports associated with an AP. Cases were ICSRs of MACCE, while non-cases were all other adverse drug reactions (ADRs). APs were classified by AP group, the degree of receptor affinity for adrenergic, dopaminergic, muscarinic, histaminic, and serotoninergic receptors and by MSE profile. The strength of the as-

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sociation was estimated with logistic regression and expressed as crude and adjusted reporting odds ratios ($ROR_{adj.}$) with corresponding 95% confidence intervals (95%CIs). We identified 4987 reports of MACCE and 328,907 reports of other ADRs. Atypical APs ($ROR_{adj.}$ 2.46; 95%CI 2.20–2.74) were significantly associated with the reporting of MACCE compared to typical ones. APs with high affinity for Adrenergic alfa-1 ($ROR_{adj.}$ 2.98; 95%CI 1.93–4.59), Histaminic H_1 ($ROR_{adj.}$ 2.31; 95%CI 1.98–2.68), Muscarinic M_1 ($ROR_{adj.}$ 1.87; 95%CI 1.74–2.01), and Serotoninergic 5-HT_{2A} ($ROR_{adj.}$ 3.19; 95%CI 2.07–4.92) were associated with a higher risk of reporting of MACCE compared to low affinity. APs with higher-risk of MSE were associated with higher risk of reporting of MACCE ($ROR_{adj.}$ 1.88; 95%CI 1.73–2.05) compared to the lower-risk. APs with high affinity for Adrenergic alfa-1, Histaminic H_1, Muscarinic M_1, and Serotoninergic 5-HT_{2A} receptors and with high-risk of MSE may explain the occurrence of those events.

1. Introduction

The use of antipsychotics (APs) has increased in the last years worldwide. This drug class is often divided into two groups: (a) typical antipsychotics (TAPs); (b) and atypical antipsychotics (AAPs). TAPs, including for example haloperidol and fluphenazine, are available since the 1950s and have been widely used for decades in the treatment of certain psychiatric disorders. AAPs, introduced since the 1990s, have proven to be more effective in the treatment of negative psychotic symptoms and with lower risk of causing extrapyramidal effects (Gareri et al., 2014; Shin et al., 2015). However, APs use has been linked to several important adverse events, such as metabolic (*e.g.* weight gain, hypercholesterolemia, and diabetes), cerebro/cardiovascular events, and even sudden death (Jackson et al., 2014; Jones et al., 2013; Wang et al., 2006). APs are multi-target drugs, i.e. they are able to bind to different receptors in the human body, which may explain their adverse events profile. TAPs have been linked mostly to extrapyramidal effects, given their antagonism to dopaminergic receptors, whereas AAPs seem to be mostly associated with metabolic and cerebro/cardiovascular events, given their antagonism for adrenergic, serotoninergic, and histaminergic receptors (Shin et al., 2015).

Since 2004, results from clinical trials have shown that olanzapine and risperidone are associated with stroke in the elderly, which resulted in the implementation of several risk minimization strategies by the regulatory bodies (FDA – Food and Drug Administration, and EMA – European Medicines Agency) in 2008 (Szmulewicz et al., 2017; Yu et al., 2016). Since then, several epidemiological studies have investigated this association (Hsu et al., 2017). A recent systematic review identified nine observational studies and estimated that the odds of myocardial infarction (MI) occurrence was 1.88-fold higher (95% Confidence Interval – CI, 1.39–2.54) in antipsychotic users compared to non-users (Michelsen and Meyer, 2007). Another systematic review identified ten studies and estimated a significant increase in the risk of cerebrovascular accident with TAPs [Odds Ratio (OR) = 1.49 (95%CI, 1.24–1.77)] but not with AAPs [OR = 1.31 (95%CI, 0.74–2.30)] (Scigliano and Ronchetti, 2013).

Several mechanisms have been proposed to explain antipsychotic-induced MACCE. Metabolic syndrome, which is linked to weigh gain, increase of glucose, and triglycerides levels, seems to increase the risk of cardiovascular adverse events (Wu et al., 2013). A cohort study has reported that antipsychotics that have been linked with a higher risk of metabolic side effects (*e.g.* clozapine and olanzapine) were associated with increased risk of MACCE [Relative Risk (RR) = 2.82 (95%CI, 1.57–5.05)] (Hsu et al., 2017). The different receptor affinity can also be an explanatory pathway. In preclinical studies, dopaminergic D_3 receptor located in the heart and peripheral vascular system may be related to atherosclerosis formation. Some serotoninergic receptors (*e.g.* 5-HT_{2A}) seem to be activated by antipsychotics at sites of coronary atherosclerosis (Michelsen and Meyer, 2007). A recent case-crossover study has demonstrated a positive association between stroke risk and high M_1 muscarinic [AOR = 1.47 (95%CI, 1.28–1.69)] and α_2 adrenergic [AOR = 1.84 (95%CI, 1.64–2.07)] affinity (Wu et al., 2013).

Despite the association between AP use and MACCE, the underlying pharmacological mechanisms remain unclear. Our main goal was to elucidate the association between antipsychotics, stratified for receptor affinity and MSE profile, in the reporting of MACCE.

2. Experimental procedures

2.1. Setting

The World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, VigiBase, is part of the WHO International Drug Monitoring Programme, which started in 1968, with the aim of identifying possible pharmacovigilance signals as soon as possible. Since 1978, the Uppsala Monitoring Centre (UMC) is responsible for maintaining and developing the VigiBase system, which includes the International Conference on Harmonization (ICH) guideline E2B compatible Individual Case Safety Reports database, the WHO Drug Dictionaries (WHO-DD and -DDE), the medical terminologies WHO Adverse Reaction Terminology (WHO-ART), the International Classification of Diseases (ICD), and the Medical Dictionary for Regulatory Activities (MedDRA) (Lindquist, 2008; Montastruc et al., 2015). The UMC collects all the cases of suspected ADRs spontaneously reported by healthcare professionals, lawyers, manufacturers or patients via the national pharmacovigilance centers. VigiBase contains more than 17 million ICSR collected in over 110 countries. From each ICSR sociodemographic data (*e.g.* age, gender, seriousness of ADR), ADR-related data (*e.g.* descriptive term using MedDRA, date of onset of the reaction, and outcome), and suspected drug (*e.g.* drug name, drug start and stop dates, time to onset, dose, and indication) can be extracted. This database has been used

for data mining studies as well as to investigate drug specific ADRs (Lindquist, 2008).

2.2. Study design

A case/non-case study design in the WHO global ICSR database, VigiBase, including all reports associated with an AP as suspected drug between 1968 and October 2017 was undertaken. Cases were ICSRs of MACCE, while non-cases were all ICSRs containing other ADRs. As a composite endpoint, MACCE included cerebrovascular events (stroke and transient ischemic attack), MI, and cardiovascular death (Kittle et al., 2017; Lincoff et al., 2007; Tsai et al., 2015) and was defined using MedDRA Preferred Terms (Supplementary material – Table S1). Reports with missing values on age and gender were excluded.

2.3. Definition of exposure

APs were identified using the WHO Anatomical Therapeutic Chemical (ATC) classification (ATC codes N05A, excluding N05AN01 – lithium) and divided into two groups: TAPs and AAPs. The first group included 55 drugs, whereas the second one included 37 drugs.

APs were classified by different receptor binding affinity and MSE profile. The degree of receptor affinity was studied for adrenergic (alfa-1 and alfa-2), dopamine (D_1, D_2, D_3 and D_4), histamine (H_1), muscarinic (M_1, M_2, M_3, M_4 and M_5) and serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7) receptors. The binding affinities of each receptor were defined using the constant of affinity (K_a) and retrieved from Psychoactive Drug Screening Program funded by the National Institute of Mental Health (http://pdsp.med.unc.edu). Receptor affinity was categorized in three groups: low affinity (> 1,000 nM), intermediate affinity (10–1000 nM), and high affinity (< 10 nM) (Risselada, 2012). These ranges were depicted in a gradient color, with distinction of (partial) agonist and antagonist. Data were only available for 30 drugs out of the 92 initially identified (Supplementary material – Table S2). MSE profiles were studied using data from previous literature, where APs were divided according to their risk of causing weight gain and increased levels of glucose and lipids (Risselada, 2012; Szmulewicz et al., 2017). APs were categorized in three groups: low-risk if they only caused weight gain; intermediate-risk if they caused weight gain plus increased levels of glucose or lipids; and high-risk if they caused weight gain and increased levels of glucose and lipids. For the full list of the antipsychotics included in each group, see Supplementary material – Table S3.

2.4. Covariates

From each ICSR, data on age, sex, region, reporter type, and reporting year was extracted. Age was categorized in four groups: 0–17 years old, 18–44 years old, 45–64 years old, and aged 65 or older. Reporter type was divided into four categories: healthcare professionals, consumer or non-healthcare professionals, manufacturer, and other. Time periods were categorized into three groups: 1968–2009, 2010–2012, and 2013–2017.

2.5. Data analysis

The unit of analysis in this study was the ICSR. Characteristics of the cases and non-cases were analyzed using Chi-square test (age, sex, region, and reporting year). The association between reporting of MACCE and type of AP used (typical vs. atypical) was assessed using logistic regression analysis and expressed as Reporting Odds Ratio (ROR) with 95% confidence intervals (95%CI). The crude ROR was defined as a ratio of the odds of exposure in reports of cases and non-cases, and then adjusted for sex, age, region and reporting year. TAPs were used as reference group. The analysis was also stratified based on sex and age groups, which are important effect modifiers when studying cardio- and cerebrovascular diseases. Receptor affinity was classified as "higher receptor affinity" when the value was < 10 nM, as "intermediate affinity" when the value was between 10 and 1000 nM, and as "lower receptor affinity" when the value was >1000 nM (reference group). MSE profile was classified into high-, intermediate- and low-risk (reference) groups. Two sensitivity analyses were performed: (a) the first one where only reports from Europe and other regions were included, as Americas accounted for the majority of cases; (b) and a second one, where only healthcare professionals' reports were included.

3. Results

3.1. Study population

By October 2017, out of the total 11,751,594 reports filled in VigiBase, there were 333,894 (2.8%) ICSRs, where APs were suspected drugs. Among these reports, 4,987 (1.5%) cases of MACCE and 328,907 non-cases (all other ADRs) were identified. Of the 4987 reports of MACCE, 2409 (48.3%) reported MI, 1496 (30.0%) reported cerebrovascular events (*e.g.* stroke and transient ischemic attack) and 1176 (23.6%) reported cardiovascular death (Fig. 1).

The characteristics for MACCE-cases and non-cases are presented in Table 1. Cases of MACCE reports were more often from male older patients and reports came predominantly from the Americas (*n*=3,028; 60.7%).

3.2. Association between antipsychotics and reporting of MACCE

Clozapine was the most frequently suspected drug among MACCE cases (*n*=1,919; 38.5%), followed by quetiapine (*n*=901; 18.1%), olanzapine (*n*=785; 15.7%) and risperidone (*n*=411; 8.2%).

AAPs were statistically significantly associated with reporting of MACCE ($ROR_{adj.}$ 2.46; 95%CI 2.20–2.74) when compared to TAPs. Ziprasidone ($ROR_{adj.}$ 3.14; 95%CI 2.49–3.97), olanzapine ($ROR_{adj.}$ 2.64; 95%CI 2.22–3.15), and clozapine ($ROR_{adj.}$ 2.64; 95%CI 2.24–3.12) were associated with higher reporting of MACCE compared to haloperidol (Table 2).

3.3. Association between antipsychotic receptor binding affinity and reporting of MACCE

When assessing the effect of receptor binding affinity and risk of MACCE, we found that the increase in the degree of affinity for adrenergic alfa-1 (High – $ROR_{adj.}$ 2.98; 95%CI 1.93–4.59; Intermediate – $ROR_{adj.}$ 2.74; 95%CI 1.78–4.22), histaminic H_1 (High – $ROR_{adj.}$ 2.31; 95%CI 1.98–2.68; Intermediate – $ROR_{adj.}$ 1.64; 95%CI 1.40–1.92), muscarinic M_1 (High – $ROR_{adj.}$ 1.87; 95%CI 1.74–2.01; Intermediate – $ROR_{adj.}$ 1.20;

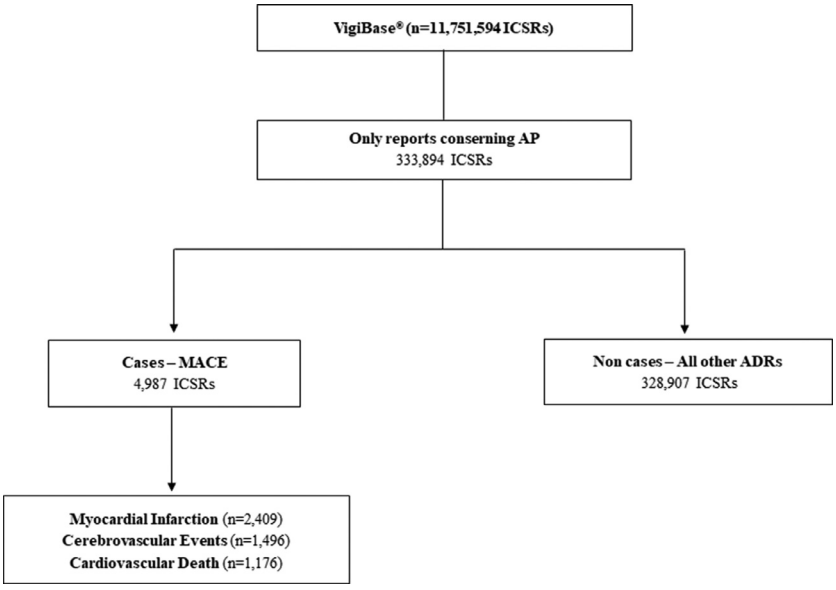

Fig. 1 The study flowchart.

Table 1. Baseline characteristics of the study population.

Characteristics	Total ICSRs (n=333,894)	
	Cases(n=4987)	Non cases(n=328,907)
Sex, n (%)		
Female	2133 (42.8)	156,725 (47.7)
Male	2854 (57.2)	172,182 (52.3)
Age, n (%)		
0 - 17 years	45 (0.9)	20,691 (6.3)
18 - 64 years	3636 (72.9)	262,919 (79.9)
65 - 74 years	583 (11.7)	23,209 (7.1)
Aged 75 or older	723 (14.5)	22,088 (6.7)
Region, n (%)		
Americas	3028 (60.7)	146,043 (44.4)
Europe	1487 (29.8)	119,352 (36.3)
Others	472 (9.5)	63,512 (19.3)
Reporter type, n (%)		
Healthcare professionals	3150 (76.1)	181,887 (67.6)
Consumer or non-healthcare professional	856 (20.7)	44,049 (16.4)
Manufacturer	73 (1.8)	3347 (1.2)
Other	63 (1.5)	39,939 (14.8)
Reporting year, n (%)		
1968 - 2009	1230 (24.7)	135,947 (41.3)
2010 - 2012	2103 (42.2)	79,292 (24.1)
2013 - 2017	1654 (33.2)	113,668 (34.6)

Abbreviation: CI - Confidence Interval; ROR - Reporting Odds Ratio,
*statistically significant (p<0.05).

95%CI 1.10-1.31), and serotoninergic 5-HT_{2A} (High - $ROR_{adj.}$ 3.19; 95%CI 2.07-4.92; Intermediate - $ROR_{adj.}$ 2.20; 95%CI 1.42-3.39), were associated with higher frequency of MACCE compared to low affinity (Table 3).

MACCE reporting rates seem to be related to adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} receptors antagonism given the heat map presented in the Supplementary material - Table S2.

When analyzing the contribution of sex in the reporting of MACCE and receptor binding affinity, we found that the increase in the degree of affinity for adrenergic alfa-1, histaminic H_1, and serotoninergic 5-HT_{2A} were associ-

Table 2. Association between reports of MACCE and exposure to antipsychotics.

	Cases (n=4987)	Non cases (n=328,907)	Crude ROR (95%CI)	Adjusted ROR (95%CI)[a]
***Type of APs*, *n* (%)**				
Typical	347 (7.0)	52479 (16.0)	Ref.	Ref.
Atypical	4640 (93.0)	276428 (84.0)	2.54 (2.28-2.83)*	2.46 (2.20-2.74)*
***Individual APs*, *n* (%)**				
Haloperidol	153 (3.1)	20138 (6.1)	Ref.	Ref.
Clozapine	1919 (38.5)	91543 (27.8)	2.76 (2.34-3.26)*	2.64 (2.24-3.12)*
Olanzapine	785 (15.7)	40386 (12.3)	2.56 (2.15-3.05)*	2.64 (2.22-3.15)*
Risperidone	411 (8.2)	35901 (10.9)	1.51 (1.25-1.82)*	1.66 (1.37-2.00)*
Quetiapine	901 (18.1)	51681 (15.7)	2.30 (1.93-2.73)*	1.90 (1.60-2.27)*
Aripiprazole	248 (5.0)	23672 (7.2)	1.38 (1.13-1.69)*	1.51 (1.23-1.85)*
Ziprasidone	143 (2.9)	6053 (1.8)	3.11 (2.47-3.91)*	3.14 (2.49-3.97)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval.
[a] adjusted for age, sex, region, reporter type, and reporting year.
* statistically significant (p<0.05).

Table 3. Reporting odds ratio of MACCE and the receptor binding affinity.

	Cases	Non cases	Crude ROR(95%CI)	Adjusted ROR(95%CI)[a]
***Adrenergic alfa-1*, *n* (%)**				
Low	21 (0.4)	5116 (1.6)	Ref.	Ref.
Intermediate	2297 (47.2)	149733 (47.6)	3.74 (2.43-5.75)*	2.74 (1.78-4.22)*
High	2546 (52.3)	159460 (50.7)	3.89 (2.53-5.98)*	2.98 (1.93-4.59)*
***Adrenergic alfa-2*, *n* (%)**				
Low	1094 (22.5)	80889 (25.7)	Ref.	Ref.
Intermediate	3228 (66.4)	180598 (57.5)	1.32 (1.23-1.42)*	1.46 (1.36-1.57)*
High	542 (11.1)	52822 (16.8)	0.76 (0.68-0.84)*	0.96 (0.86-1.06)
***Dopaminergic D_1*, *n* (%)**				
Low	1197 (24.6)	82708 (26.3)	Ref.	Ref.
Intermediate	3622 (74.5)	225206 (71.7)	1.11 (1.04-1.19)*	1.24 (1.15-1.32)*
High	45 (0.9)	6395 (2.0)	0.49 (0.36-0.66)*	0.58 (0.43-0.79)*
***Dopaminergic D_2*, *n* (%)**				
Low	901 (18.5)	51681 (16.4)	Ref.	Ref.
Intermediate	2783 (57.2)	141547 (45.0)	1.13 (1.05-1.22)*	1.34 (1.24-1.45)*
High	1180 (24.3)	121081 (38.5)	0.56 (0.51-0.61)*	0.74 (0.67-0.81)*
***Dopaminergic D_3*, *n* (%)**				
Low	901 (19.0)	51681 (17.2)	Ref.	Ref.
Intermediate	2754 (58.0)	135955 (45.3)	1.16 (1.08-1.25)*	1.40 (1.29-1.51)*
High	1097 (23.1)	112381 (37.5)	0.56 (0.51-0.61)*	0.73 (0.67-0.80)*
***Dopaminergic D_4*, *n* (%)**				
Low	925 (19.0)	57366 (18.3)	Ref.	Ref.
Intermediate	3722 (76.5)	229372 (73.0)	1.01 (0.94-1.08)	1.20 (1.11-1.29)*
High	217 (4.5)	27571 (8.8)	0.49 (0.42-0.57)*	0.58 (0.50-0.68)*
***Histamine H_1*, *n* (%)**				
Low	185 (3.8)	25937 (8.3)	Ref.	Ref.
Intermediate	982 (20.2)	86842 (27.6)	1.59 (1.35-1.86)*	1.64 (1.40-1.92)*
High	3697 (76.0)	201530 (64.1)	2.57 (2.22-2.98)*	2.31 (1.98-2.68)*
***Muscarinic M_1*, *n* (%)**				
Low	1132 (36.5)	113312 (36.5)	Ref.	Ref.
Intermediate	996 (20.6)	64982 (20.9)	1.53 (1.41-1.67)*	1.20 (1.10-1.31)*
High	2704 (56.0)	131929 (42.5)	2.05 (1.91-2.20)*	1.87 (1.74-2.01)*
***Muscarinic M_2*, *n* (%)**				
Low	1017 (21.7)	96551 (32.9)	Ref.	Ref.
Intermediate	3680 (78.3)	196487 (67.1)	1.78 (1.66-1.91)*	1.55 (1.44-1.66)*
High	0 (0.0)	0 (0.0)	NE	NE

(*continued on next page*)

Table 3. (*continued*)

	Cases	Non cases	Crude ROR(95%CI)	Adjusted ROR(95%CI)[a]
Muscarinic M_3, n (%)				
Low	1925 (40.7)	148851 (50.6)	Ref.	Ref.
Intermediate	2799 (59.3)	145230 (49.4)	1.49 (1.41-1.58)*	1.52 (1.43-1.61)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_4, n (%)				
Low	1003 (21.4)	93229 (32.3)	Ref.	Ref.
Intermediate	3675 (78.6)	195220 (67.7)	1.75 (1.63-1.88)	1.52 (1.41-1.63)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_5, n (%)				
Low	1746 (37.3)	123505 (42.8)	Ref.	Ref.
Intermediate	2932 (62.7)	164944 (57.2)	1.26 (1.19-1.34)*	1.29 (1.21-1.37)*
High	0 (0.0)	0 (0.0)	NE	NE
Serotoninergic 5-HT_{1A}, n (%)				
Low	1029 (21.2)	80834 (25.7)	Ref.	Ref.
Intermediate	3557 (73.1)	206911 (65.8)	1.35 (1.26-1.45)*	1.24 (1.15-1.33)*
High	278 (5.7)	26564 (8.5)	0.82 (0.72-0.94)*	0.85 (0.74-0.98)*
Serotoninergic 5-HT_{1B}, n (%)				
Low	936 (20.0)	60353 (21.0)	Ref.	Ref.
Intermediate	3609 (77.0)	220473 (76.9)	1.06 (0.98-1.14)	1.25 (1.16-1.34)*
High	143 (3.0)	6053 (2.1)	1.52 (1.28-1.82)*	1.79 (1.49-2.14)*
Serotoninergic 5-HT_{2A}, n (%)				
Low	21 (0.4)	5116 (1.6)	Ref.	Ref.
Intermediate	1379 (28.4)	105594 (33.6)	3.18 (2.07-4.90)*	2.20 (1.42-3.39)*
High	3464 (71.2)	203599 (64.8)	4.15 (2.70-6.37)*	3.19 (2.07-4.92)*
Serotoninergic 5-HT_{2C}, n (%)				
Low	1094 (22.5)	80506 (25.7)	Ref.	Ref.
Intermediate	3555 (73.2)	220855 (70.6)	1.19 (1.11-1.27)*	1.36 (1.27-1.46)*
High	206 (4.2)	11490 (3.7)	1.32 (1.14-1.53)*	1.51 (1.30-1.76)*
Serotoninergic 5-HT_6, n (%)				
Low	1492 (31.6)	113204 (38.3)	Ref.	Ref.
Intermediate	3204 (67.8)	180510 (61.2)	1.35 (1.27-1.43)*	1.41 (1.32-1.50)*
High	27 (0.6)	1548 (0.5)	1.32 (0.90-1.94)	1.79 (1.21-2.64)*
Serotoninergic 5-HT_7, n (%)				
Low	4 (0.1)	2616 (0.9)	Ref.	Ref.
Intermediate	4156 (87.7)	248474 (83.6)	10.94 (4.10-29.18)*	9.30 (3.48-24.83)*
High	578 (12.2)	46143 (15.5)	8.19 (3.06-21.92)*	7.95 (2.97-21.30)*

Abbreviation: ROR - Reporting Odds Ratio; CI - Confidence Interval; NE - Not estimable.
[a] adjusted for age, sex region, reporter type, and reporting year.
* statistically significant ($p<0.05$).

ated with higher frequency of MACCE in men compared to women (adrenergic alfa-1 - men: High - $ROR_{adj.}$ 3.62; 95%CI 1.50-8.74; Intermediate - $ROR_{adj.}$ 3.06; 95%CI 1.27-7.41 vs women: High - n $ROR_{adj.}$ 2.93; 95%CI 1.38-6.21; Intermediate - $ROR_{adj.}$ 2.40; 95%CI 1.13-5.08; histaminic H1 - men: High - $ROR_{adj.}$ 4.31; 95%CI 3.17-5.84; Intermediate - $ROR_{adj.}$ 2.63; 95%CI 1.91-3.62 vs women: High - $ROR_{adj.}$ 2.41; 95%CI 1.84-3.16; Intermediate - $ROR_{adj.}$ 1.80;95%CI 1.36-2.38; serotoninergic 5-HT2A - men: High - $ROR_{adj.}$ 3.78; 95%CI 1.57-9.13; Intermediate - $ROR_{adj.}$ 2.40; 95%CI 0.99-5.83 vs women: High - $ROR_{adj.}$ 2.70; 95%CI 1.27-5.71; Intermediate - $ROR_{adj.}$ 2.58; 95%CI 1.22-5.48). On the other hand, we found that there were no differences between reporting of MACCE and receptor binding affinity within the different age groups (Supplementary material - Table S10).

3.4. Association between antipsychotics' metabolic side effects profile and reporting of MACCE

APs associated with intermediate- and high-risk of metabolic side effects ($ROR_{adj.}$ 1.33; 95%CI 1.21-1.46 and $ROR_{adj.}$ 1.88; 95%CI 1.73-2.05, respectively) were associated with higher reporting of MACCE compared to low-risk ones (Table 4).

3.5. Sensitivity analyses

Results were consistent after excluding reports from the Americas (adjusted ROR for the association between different groups of APs and reporting of MACCE was 2.21, 95%CI 1.91-2.56) and when restricting the analysis to healthcare

Table 4. Reporting odds ratio of MACCE and the different metabolic side effects profile of antipsychotics.

	Cases(n=4,848)	Non cases(n=309,852)	Crude ROR(95%CI)	Adjusted ROR (95%CI)[a]
***Low-risk of MSE*, *n* (%)**	656 (13.5)	68022 (22.0)	Ref.	Ref.
Intermediate-risk of MSE	1433 (29.6)	100600 (32.5)	1.48 (1.35-1.62)*	1.33 (1.21-1.46)*
High-risk of MSE	2759 (56.9)	141230 (45.6)	2.03 (1.86-2.21)*	1.88 (1.73-2.05)*

Abbreviation: CI – Confidence Interval; MSE – Metabolic Side Effects; ROR – Reporting Odds Ratio.
[a] adjusted for age, sex region, reporter type, and reporting year.
* statistically significant ($p<0.05$).

professionals' reports only (adjusted ROR 2.66, 95%CI 2.29-3.09). Furthermore, there were no major differences with the main analysis with respect to the results of the antipsychotics' receptor binding affinity and MSE profile

4. Discussion

In this study, we found an increased frequency of ICSRs AAPs being a suspected drug group in relation to the reporting of MACCE compared with other ADR reports. Our findings also suggest that a high affinity to some receptors, like adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A}, as well as a high MSE profile could explain the occurrence of such events.

The association between AP use and MACCE occurrence has been described for over a decade in the literature. In 2004, clinical trials have shown that olanzapine and risperidone were associated with an increased risk of stroke among the elderly. From 2008, this risk was generalized to all APs and several risk minimization measures were implemented (Steinberg and Lyketsos, 2012; Sultana et al., 2016; Szmulewicz et al., 2017). Our findings have shown that there is a 2.5-fold increased risk of MACCE reports with AAPs being the suspected drug group compared to TAPs. This is in line with recognized data that antipsychotic-induced cardiovascular adverse events are commonly linked to AAPs (Wu et al., 2013).

In our study, MACCE definition included three main conditions: cerebrovascular events, MI, and cardiovascular death. Cardiovascular diseases are multifactorial conditions and, therefore, multiple mechanisms can be proposed as possible explanations, such as the degree of receptor affinity. We found that an increased degree of affinity for adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} receptors were associated with higher reporting of MACCE. All these receptors seem to play a role in the cardiovascular system. Adrenergic receptors are a part of our sympathetic system and are normally associated with vasoconstriction, whereas muscarinic receptors act in the opposite direction stimulating a vagal response (vasodilatation and decrease in the heart rate and in the conduction velocity in the atrioventricular node). Interestingly, both types of receptors also seem to play a role in metabolic disorders, such as eating disorder. Histaminic receptors located in the brain are responsible, among others, for the regulation of feeding rhythms and energy metabolism (Olten and Bloch, 2018; Polcwiartek et al., 2016; Wu et al., 2013). Therefore, we hypothesized that APs with a high affinity for such receptors may cause: (a) tachycardia as a result of the blockage of muscarinic M_1; (b) reflex tachycardia as a result of the blockage of adrenergic alfa-1; (c) metabolic syndrome (*e.g.* weight gain, increased glucose and lipid levels) given the blockage of histaminic H_1. Increased affinity for serotoninergic 5-HT_{2A} receptor may be another possible pathway by which antipsychotics, especially atypical ones, could be linked to MACCE, because this receptor is normally present in the membrane of platelets and, therefore, could lead to major bleedings (*e.g.* intracranial bleedings) (Verdel et al., 2011). A study undertaken by Verdel et al. (2011) has shown that APs with medium- and high-affinity for 5-HT_{2A} receptor were associated with a higher risk of cerebral hemorrhage. Wu et al. (2013) have also found an association between stroke and high muscarinic M_1 and adrenergic α_2 receptors' affinity. A current meta-regression by Olten et al. (2018) showed that high affinity for M_1, H_1, and M_4 receptors were associated with weight gain in AP users, which may contribute to the development of metabolic syndrome Olten and Bloch, 2018.

Conversely, obesity, diabetes and hypercholesterolemia are well known risk factors for cardiovascular diseases. APs with intermediate- and high-risk of metabolic side effects were associated with more frequent reporting of MACCE. This is in line with findings from a study conducted by Szmulewicz et al., 2017, who have shown that older adult patients using APs may face a higher incidence of major cardiovascular events than those using a low-risk regimen during long-term follow-up. These results support our findings from the receptor affinity analysis showing, that APs with high affinity for receptors involved in metabolic syndrome are a possible pathway for MACCE development.

Studies from our research group have also shown the existence of a time relationship between drug use and event occurrence. Knol et al. (2008) have shown that current users (defined as those finalizing a prescription within 7 days of the index date) had a 60% greater risk of pneumonia compared to non-users. They also showed that greater risk had an inversely proportional relationship to duration of treatment. Later in 2011, another study has demonstrated the same results, where current users seem to be at higher risk when compared to non-users (Verdel et al., 2011).

To our knowledge this is the first study assessing the role of receptor affinity and MSE profile in antipsychotic-induced MACCE using data from the global pharmacovigilance database, VigiBase. Results from this study suggest that different pathways could lead to MACCE occurrence depending on the degree of receptor affinity and MSE profile. However, given that atypical APs are normally more consumed than typical ones, more attention should be given to

high affinity to serotoninergic receptors, like 5-HT_{2A} and to APs associated with a high-risk of metabolic side effects.

This study has some limitations worth acknowledging. First, data were obtained through spontaneous reporting without any additional clinical assessment or qualitative validation by the authors. Second, the Weber effect, *i.e.* severe ADRs or the ones not listed in the Summary of Product Characteristics are more likely to be reported. Third, reporting bias could be present, either by under- or over-reporting. Fourth, the APs were introduced in the market in different time points depending on the country, which may have introduced selection bias. Fifth, the different indications, doses, and durations of treatment were not assessed, which may influence the reporting of the outcome. Given that was not possible to distinguish the different age groups in the pediatric population, it was not possible to assess their contribution to the association between the reporting of MACCE and receptor binding affinity. Additionally, there was also no available data on doses and drug plasma concentrations, which are likely to modulate receptor binding affinity. Finally, it was not possible to adjust for other potential confounders, such as comorbidities, and lifestyle variables.

5. Conclusion

The reporting of MACCE was disproportionally associated with atypical APs use, when compared to typical ones. We also have shown that increased degree of affinity for adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} were associated with higher reporting of MACCE and as well as APs with intermediate- and high-risk of metabolic side effects. Future studies with prospective designs are needed to confirm these hypotheses.

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Contributors

JPA conceived and designed the study; analyzed the data; and drafted, finalized and submitted the manuscript; FAC contributed to the study design and reviewed all drafts of the manuscript; TE helped on design, data interpretation and reviewed the manuscript; HGM and PS conceived the design of the study, the interpretation of the study findings, provided guidance on writing the manuscript and critically reviewed all drafts of the manuscript.

Conflict of interest

Authors have no conflict of interest to disclose of financial, personal or of any other nature that may bias the work.

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Disclaimer

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Supplementary materials

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