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THESIS

«Antipsychotics and the risk for pneumonia: Disproportionality analysis in the FDA adverse events spontaneous reporting system database»

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ABSTRACT

Aim: An association between antipsychotic drugs and pneumonia has been demonstrated in several studies, however, the risk for pneumonia caused by specific antipsychotics has not been extensively studied. The aim of this study was to detect a potential safety signal of antipsychotics and reporting pneumonia analysing the FDA adverse events spontaneous reporting system (FAERS) database and to investigate possible receptor/transporter mechanisms involved.

Method: A disproportionality analysis was performed using the OpenVigil2.1.-MedDRA interface including data from 2004 to 2019. The main outcome was 'infective pneumonia' and the secondary outcome was 'pneumonia aspiration'. Adjusted reporting odd ratio (aROR) was calculated for 20 FDA approved antipsychotics. The pharmacodynamic profile of antipsychotics was extracted from PDSP and IUPHAR/BPS databases and receptor/transporter occupancy was calculated. The Pearson correlation coefficient (r) was used to investigate the relationship between aROR and receptor/transporter occupancy.

Results: Disproportionality signals for reporting both outcomes were identified for clozapine [infective pneumonia: aROR 3.7 (95% CI: 3.27 – 4.18), pneumonia aspiration: aROR 1.42 (95% CI: 1.12 – 1.81)], olanzapine [infective pneumonia: aROR 1.33 (95% CI: 1.16 – 1.53), pneumonia aspiration: aROR 1.39 (95% CI: 1.08 – 1.79)] and also for the use of multiple antipsychotics compared to single antipsychotic use [infective pneumonia: aROR 1.22 (95% CI: 1.09 – 1.37), pneumonia aspiration: aROR 1.92 (95% CI: 1.61 – 2.28)]. A significant correlation coefficient was identified only for the 5-HT3 receptor and the risk for 'infective pneumonia' ($r = 0.98$, $p = 0.001651$) while the muscarinic receptors M4 ($r=0.75$, $p=0.019$), M2 ($r=0.73$, $p=0.027$), M1 ($r=0.72$, $p=0.029$) demonstrated strong but not significant correlations after adjustments to Bonferroni correction.

Conclusion: An association between clozapine and olanzapine and the risk for reporting pneumonia was identified while higher degrees of occupancy on 5-HT3 and muscarinic receptors may be a possible pharmacological mechanism. Additionally, multiple antipsychotics use was linked with an increase in pneumonia-related reporting. Considering the limitations of disproportionality analysis more

pharmacovigilance data and clinical causality assessment is needed to validate this potential safety signal.

ΠΕΡΙΛΗΨΗ

Στόχος: Η σχέση μεταξύ αντιψυχωσικών και πνευμονίας έχει επισημανθεί σε διάφορες μελέτες, παρόλα αυτά ο κίνδυνος εμφάνισης πνευμονίας για μεμονωμένα αντιψυχωσικά δεν έχει μελετηθεί εκτενώς. Ο στόχος της μελέτης αυτής ήταν η ανίχνευση πιθανού σήματος για τα αντιψυχωσικά και την πνευμονίας χρησιμοποιώντας δεδομένα από την βάση ανεπιθύμητων ενεργειών FAERS και η διερεύνηση πιθανών εμπλεκόμενων μηχανισμών μεσολαβούμενων από υποδοχείς/μεταφορείς.

Μέθοδος: Διενεργήθηκε ανάλυση δυσαναλογίας χρησιμοποιώντας δεδομένα από το 2004 έως το 2019 για την πρόσβαση στα οποία χρησιμοποιήθηκε το περιβάλλον OpenVigil2.1 – MedDRA. Ως κύρια έκβαση μελετήθηκε η λοιμώδης πνευμονία (infective pneumonia) και ως δευτερεύουσα η πνευμονία από εισρόφηση (pneumonia aspiration) . Το adjusted reporting odd ratio (aROR, προσαρμοσμένος αναφερόμενος λόγος αναλογιών) υπολογίστηκε για 20 εγκεκριμένα από τον FDA αντιψυχωσικά. Για τον υπολογισμό της κατάληψης των υποδοχέων/μεταφορέων το φαρμακοδυναμικό προφίλ των αντιψυχωσικών εξήχθη από τις βάσεις PDSP και UPHAR/BPS. Ο συντελεστής συσχέτισης (r) του Pearson χρησιμοποιήθηκε για την διερεύνηση της σχέσης μεταξύ aROR και κατάληψης των υποδοχέων.

Αποτελέσματα: Σήμα δυσαναλογίας στις αναφορές και των δύο υπό μελέτη εκβάσεων ανιχνεύτηκε για την κλοζαπίνη [infective pneumonia: aROR 3.7 (95% CI: 3.27 – 4.18), pneumonia aspiration: aROR 1.42 (95% CI: 1.12 – 1.81)] και την ολανζαπίνη [infective pneumonia: aROR 1.33 (95% CI: 1.16 – 1.53), pneumonia aspiration: aROR 1.39 (95% CI: 1.08 – 1.79)] όπως επίσης και για την χρήση πολλαπλών αντιψυχωσικών συγκριτικά με τη χρήση ενός αντιψυχωσικού [infective pneumonia: aROR 1.22 (95% CI: 1.09 – 1.37), pneumonia aspiration: aROR 1.92 (95% CI: 1.61 – 2.28)]. Στατιστικά σημαντικός συντελεστής συσχέτισης (r) βρέθηκε για τον 5-HT3 υποδοχέα και την έκβαση ‘infective pneumonia’ ($r = 0.98$, $p = 0.001651$) ενώ οι μουσκαρινικοί υποδοχείς M4 ($r=0.75$, $p=0.019$), M2 ($r=0.73$, $p=0.027$), M1 ($r=0.72$, $p=0.029$) έδειξαν ισχυρή αλλά όχι σημαντική συσχέτιση μετά από τη διόρθωση κατά Bonferroni.

Συμπέρασμα: Ανιχνεύτηκε συσχέτιση μεταξύ κλοζαπίνης και ολανζαπίνης και των αναφορών πνευμονίας με την υψηλή συγγένεια για τον 5-HT3 υποδοχέα και τους

μουσκαρινικούς υποδοχείς να αποτελούν ένα πιθανό μηχανισμό. Επιπλέον, η χρήση πολλαπλών αντιψυχωσικών ομοίως συσχετίστηκε με αυξημένο αριθμό αναφορών για πνευμονία. Λαμβάνοντας υπόψιν τους περιορισμούς των αναλύσεων δυσαναλογίας, περισσότερα δεδομένα χρειάζονται για να αποδείξουν αιτιακή σχέση μεταξύ αντιψυχωσικών και πνευμονίας.

ABBREVIATIONS

AP(s)	Antipsychotic(s)
EPS	Extrapyramidal symptoms
FGA(s)	First Generation Antipsychotic(s)
SGA(s)	Second Generation Antipsychotic(s)
D2R	Dopamine-2-Receptor
WHO	World Health Organisation
PV	Pharmacovigilance
SP	Spontaneous reporting
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio
CI	Confidence Interval
AE(s)	Adverse Event(s)
AR(s)	Adverse Reaction(s)
RCT(s)	Randomised Controlled Trial(s)
DPA	Disproportionality analysis
F_U	Unbound drug fraction
C_U	Total unbound drug concentration
C_T	Total drug concentration in blood
MW	Molecular weight

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1. PHARMACOVIGILANCE

1.1. Definition

According to the World Health Organisation (WHO) Pharmacovigilance (PV) is 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'.

The aims of PV are to optimise the use of medicines and encourage prudent use minimising any potential risk to the patient and the public, detect problems related to the use of medicines and communicate the findings in a timely manner, ameliorate public health and safety, provide reliable data for the assessment of the risk-benefit profile of medicines and promote understanding, education and clinical training and its effective communication to the public.[1]

1.2. The need for Pharmacovigilance

No medicine is harm-free that is why it is important to monitor their effects, intended and not, so that any risk-benefit assessment can be performed based on high quality data. Particularly with new products, early identification of ADRs and predisposing risk factors is crucial. Before the approval of a pharmaceutical product a great quantity of data has been gathered on the efficacy and safety of said product via non-clinical and clinical trials demonstrating that the benefits outweigh any potential risks. However, non-clinical trials are not predictive for all potential safety outcomes in humans and clinical trials are mainly designed to access efficacy rather that answer specific safety questions. Furthermore, the population included in clinical trials differ significantly from the real-world users which might be vulnerable populations such as the elderly, pregnant women and children. Even the biggest, well-designed clinical trials are unable to identify rare ADRs due to the limited number of participants (low statistical power) and duration. Thus, it is not uncommon for drugs to be withdrawn from the market due to ADRs unknown at the time of approval. Drug discontinuation is not the only action to be taken when new data concerning drug safety emerge. Changing the label, issuing a warning, requiring complimentary data from the manufacturer are common practices implemented by regulatory authorities. It is thus becoming clearer that post-marketing surveillance of drugs is important for patients, physicians,

pharmacological industry and authorities to promptly recognise any new ADRs and ensure patients safety when a product is available to a larger more versatile population.[2]

1.3. Surveillance systems

Spontaneous reporting (SR) is the cornerstone of PV and its success depends on the rates of reporting of suspected ADRs by all parties involved. According to WHO SR is defined as ‘A system whereby case reports of adverse drug events are voluntarily submitted by health professionals, pharmaceutical companies or consumers to the national pharmacovigilance centre’.[3]

SR is a means of passive surveillance and a signal identified through this process is mostly hypothesis generating and requires further investigation using active surveillance programmes. Systematic literature reviews and meta-analyses of available evidence, epidemiological studies or RCTs designed to answer specific drug safety related hypotheses, case control networks, hospital-based intensive monitoring systems and record linkage systems are a few forms of available active monitoring. Data collection from social media is also a growing area. However, there methods are time and money consuming and bare their own limitations.[3,4]

1.4. ADRs reporting databases and data mining tools

There are several databases (national and international) designed for post-marketing drug surveillance. Some examples are:

- VigiBase (WHO for International Drug Monitoring (Uppsala Monitoring Centre)) [5],
- EudraVigilance (European Medicines Agency) [6],
- FAERS (US Food and Drug Administration (FDA) Adverse Event Reporting System) [7],
- VAERS (US Food and Drug Administration (FDA) Vaccine Adverse Event Reporting System) [8],
- Canada Vigilance adverse reaction online database [9],
- DAEN (Australian Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications) [10]

These databases contain reports from patients, physicians and manufacturers as well as data from medical literature about possible ADRs. Due to the wide variety of medical products available, facilitation of the reporting process for consumers and medical professionals (voluntary reporting) and current regulatory guidelines for manufacturers (mandatory reporting) these databases have grown exponentially over the last few years making data mining tools indispensable in the detection of possible safety signal.[2,4]

1.5. Strengths of studies using PV databases

Modern PV databases contain a great volume of information that can be relatively easily accessed. The size of data extracted allows for even rare ADRs to be recorded and analysed. The pharmaceuticals industry is an international industry, and most pharmaceutical product are approved and used in multiple countries. This calls for PV strategies to be implemented in an international level. The major databases mention in paragraph1.4. meet this demand making international nature one of PV main strengths. Another important advantage of PV studies is that they are based on real-world data incorporating a wide range of age groups (e.g. the elderly, children) and patients with multiple comorbidities and polypharmacy that would most probably be

excluded from RCTs. Additionally, these versatile groups of patients are studied in everyday real-world circumstances in contrary to RCTs. [4,11]

1.6. Limitations of studies using PV databases

There are several inherited limitations of studies relying on data from spontaneous reporting systems. Unfortunately, under-reporting and selective reporting are patterns commonly witnessed.[12] A review by Hazell et al. estimated that only 6% of events get reported resulting in under-reporting.[13] However, it is generally admitted that under-reporting does not affect the validity of the end-result when comparing drugs of the same therapeutic class, indication, circulating in the same country at the same period of time (e.g. antipsychotics).[14] On the other hand, reporting rates may vary depending on the reporter, the drug, the AE or time thus resulting in selective reporting with ADRs of high perceived severity more likely being reported.[11,12] Data quality may also be an issue. Missing, incorrect or vague information, duplicate reports (same report directly from physicians or consumers and indirectly from manufacturers), reported event being due to treated condition, another condition or another drug are common in pharmacovigilance databases and are generally referred to as information bias.[4,15] Even though information bias does not prevent data analysis since drug and event information are available missing data regarding clinical information, indication, age, sex, comedications, evolution, type of report and reporter, country, specific doses or treatment dates limit complementary analyses and confounding assessment (confounding by indication or co-prescription bias, protopathic bias, baseline risk).[11] Furthermore, reports included in a PV database might date many years in the past. As a result, several parameters such as changes in reporting requirements, coding dictionaries for products and/or events, data entry and coding processes, inconsistent database structure architecture and malicious reporting and spam must be considered. Moreover, multiple databases accept reports of different origin which may be subjects of different national reporting requirements. Temporal bias including the 'Weber effect' and 'notoriety effect' will be presented in paragraph 4.4 so that their influence on disproportionality measures can be further discussed. The above mentioned limitations should be considered when reviewing results from PV studies. [15]

2. ANTIPSYCHOTIC MEDICATION

2.1. Indications

Antipsychotics (APs) are substances used for the treatment and management of multiple psychiatric disorders. When first introduced APs were used to treat psychosis and since then they have been approved for numerous indications. These indications include schizophrenia and schizoaffective disorders, acute mania, major depressive disorder with psychotic features, delusional disorder, sever agitation, Tourette disorder, borderline personality disorder, dementia and delirium, substance induced psychotic disorder, childhood schizophrenia as well as other indications such as Huntington disease, Parkinson disease, Lesch-Nyhan syndrome, pervasive developmental disorder where APs are not considered as the first line of treatment.[16,17] Off-label APs use is also trending mostly in conditions with limited approved therapeutic options such as dementia -related psychosis.[18]

2.2. Antipsychotics: groups and mechanism of action

Commonly, APs are further classified into two subgroups, classic /typical /conventional /first-generation and atypical /second-generation APs. All clinically effective APs are Dopamine-2-Receptor (D2R) antagonists with different receptor affinities. Further ingroup classification for typical APs is mainly according to their chemical structure (e.g. Phenothiazines, Butyrophenones etc) while atypical APs are classified according to their pharmacological properties.[16] When first introduced, the term ‘atypical’ was used to refer to new effective antipsychotic agents associated with less extrapyramidal symptoms (EPS). The first atypical AP was clozapine and since then all newly introduced APs are characterized as ‘atypical’ regardless of their mechanism of action and safety profile. As a result, the number of new molecular entities under the term ‘atypical APs’ has significantly increased in recent years with atypical APs being a heterogenous group that does not share a common pharmacodynamic, clinical and safety profile. In fact, the narrow definition of atypicality based on D2R antagonism and EPS minimisation applied to only few of the APs widely considered as atypical. Subsequently, the term ‘atypical’ has been broadened to accommodate other treats such as transient elevation in prolactin levels, efficacy in treating positive as well as

negative symptoms of schizophrenia, a mechanism of action that involves serotonin 2A and –2C antagonism and/or mesolimbic specificity over nigrostriatal dopamine neurons, and efficacy in treating resistant schizophrenia.[19–21] In fact, SGAs have additional properties compared to FGA including serotonin 2A antagonism and 1A agonism, serotonin and/or norepinephrine reuptake inhibition, histamine, muscarinic cholinergic and alpha-adrenergic antagonism. The degree of affinity and receptor occupancy of each SGA with the aforementioned receptors varies and thus their overall profile.[22]

2.3. Antipsychotics classification according to the ATC Classification System

The Anatomical Therapeutic Chemical Classification System (ATC) is a tool for drug utilization monitoring and research in order to improve quality of drug use. In the ATC classification system active drug substances are classified in a hierarchy with five distinct levels. An anatomical/pharmacological group (1st level) which is further divided into 2nd levels either pharmacological or therapeutic groups. The 3rd and 4th levels are chemical, pharmacological or therapeutical subgroups and lastly the 5th level is the chemical substance. Consequently, APs are classified as N05A (3rd level, therapeutic subgroup). [23]

Figure 2—1: ATC Classification of antipsychotics, WHO Collaborating Centre for Drug Statistics Methodology

Further subdivision of the APs (N05A) is based on chemical subgroup and chemical structure:

Phenothiazines with aliphatic side-chain		
N05AA	01	chlorpromazine
N05AA	02	levomepromazine
N05AA	03	promazine
N05AA	04	acepromazine
N05AA	05	triflupromazine
N05AA	06	cyamemazine
N05AA	07	chlorproethazine
Phenothiazines with piperazine structure		
N05AB	01	dixyrazine
N05AB	02	fluphenazine
N05AB	03	perphenazine
N05AB	04	prochlorperazine
N05AB	05	thiopropazate
N05AB	06	trifluoperazine
N05AB	07	acetophenazine
N05AB	08	thioproperazine
N05AB	09	butaperazine
N05AB	10	perazine
Phenothiazines with piperidine structure		
N05AC	01	periciazine
N05AC	02	thioridazine
N05AC	03	mesoridazine
N05AC	04	pipotiazine
Butyrophenone derivatives		
N05AD	01	haloperidol
N05AD	02	trifluperidol
N05AD	03	melperone
N05AD	04	moperone
N05AD	05	pipamperone
N05AD	06	bromperidol
N05AD	07	benperidol
N05AD	08	droperidol
N05AD	09	fluanisone
Indole derivatives		
N05AE	01	oxypertine
N05AE	02	molindone
N05AE	03	sertindole
N05AE	04	ziprasidone
N05AE	05	lurasidone

Thioxanthene derivatives		
N05AF	01	flupentixol
N05AF	02	clopenthixol
N05AF	03	chlorprothixene
N05AF	04	tiotixene
N05AF	05	zuclopenthixol
Diphenylbutylpiperidine derivatives		
N05AG	01	fluspirilene
N05AG	02	pimozide
N05AG	03	penfluridol
Diazepines, oxazepines, thiazepines & oxepines		
N05AH	01	loxapine
N05AH	02	clozapine
N05AH	03	olanzapine
N05AH	04	quetiapine
N05AH	05	asenapine
N05AH	06	clotiapine
Benzamides		
N05AL	01	sulpiride
N05AL	02	sultopride
N05AL	03	tiapride
N05AL	04	remoxipride
N05AL	05	amisulpride
N05AL	06	veralipride
N05AL	07	levosulpiride
Lithium		
N05AN	01	lithium
Other antipsychotics		
N05AX	07	prothipendyl
N05AX	08	risperidone
N05AX	10	mosapramine
N05AX	11	zotepine
N05AX	12	aripiprazole
N05AX	13	paliperidone
N05AX	14	iloperidone
N05AX	15	cariprazine
N05AX	16	brexpiprazole
N05AX	17	pimavanserin

Table 2—1: ATC (Level 5) Antipsychotics classification - Guidelines for ATC classification and DDD assignment 2020.

2.4. Adverse Drug Reactions

APs therapeutical effect if mainly achieved via D2R blockage in the mesolimbic pathway while the blockage of receptor in other locations as well as interaction with other type of receptors result in ADRs. The blockage of D2R in the nigrostriatal pathway results in movements abnormalities known as Extrapyramidal Symptoms (EPS). There are four main categories of EPS reported with APs: pseudoparkinsonism, akathisia, acute dystonic reactions and tardive dyskinesia. These adverse events are more common with FGAs. Blockade of D2R in the tuberoinfundibular pathway is associated with hyperprolactinemia. Patients with elevated prolactin levels may remain asymptomatic or demonstrated gynecomastia, galactorrhoea, oligomenorrhea or amenorrhea, sexual dysfunction, acne, hirsutism, infertility and loss of bone mineral density resulting in osteoporosis and increased risk of hip fracture. Metabolic adverse events (weight gain, glycaemic abnormalities and dyslipidaemia) are also common with APs, most commonly SGAs. Sedation is a common dose-related side effect of APs and many patients develop tolerance to the sedative effect over time. Orthostatic hypotension is an antiadrenergic (a1) side effect and careful dose titration might help patients develop tolerance to this side effect as well. Anticholinergic effects including dry mouth, blurred vision, urinary retention and constipation are common with APs and might result in other problems such as tooth decay, falls, accidents or gastrointestinal obstruction. Agranulocytosis is the drop of granulocytes below the critical number of 500 cells per mm^3 that can lead to potentially fatal infections. This side effect is associated with clozapine and according to the FDA patients taking clozapine should monitor their absolute neutrophil count regularly. All APs may contribute to prolongation of QTc interval which may result in fatal cardiac arrythmias. All APs may lower the seizure threshold and should be administered with caution to patients with history of seizures or organic brain damage. Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic, life-threatening complication of treatment with APs that affects 0.01 – 0.02% of patients exposed and is characterized by fever, severe muscle rigidity and autonomic and mental status changes. The estimated mortality rate is 10%.[24–26] In 2005, the FDA issued a warning for atypical antipsychotics, which was further extended in 2008 to conventional antipsychotics as well, and their association with an increased risk of mortality in elderly patients treated

for dementia-related psychosis (off-label use) mostly due to heart related events or infections (primarily pneumonia).[27,28]

All above mention side effects might present with different frequencies with different FGAs and SGAs.

2.5. Serious Adverse Events

Some ADRs might be associated and thus easily predicted with a well-known molecular pathway with which a drug interacts. However, many adverse events with a more complex or unknown mechanism are unpredictable and can only be recognised after systematic analysis.

A serious adverse event is defined as a medical occurrence (at any dose) that causes death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or is a congenital anomaly or birth defect.

A 2019 meta-analysis of RCTs of APs aiming to examine whether APs contribute to the observed increased morbidity and mortality in patients with severe mental illness identified an increased risk of serious somatic AEs in patients treated with APs compared to controls. This analysis provides randomised evidence that APs can induce or aggravate serious somatic disorders. Approximately 20% of patients with a serious somatic AE died and the causes of death with the highest absolute difference between APs and placebo were pneumonia, overdose, injury, cerebrovascular disorder and pneumonia aspiration.[29]

As pneumonia and aspiration pneumonia were between the most common causes of mortality between patients treated with APs it seems as an association worth further investigation.

3. THE BURDEN OF PNEUMONIA

Regardless of being a preventable and curable disease, pneumonia remains an important cause of morbidity and mortality. Between 2010 - 2012, in the United States, the annual incidence of community-acquired pneumonia requiring hospitalization was 24.8 (CI 95%, 23.5 to 26.1) cases per 10,000 adults.[30] Tong et al. examined US insurance records to determine the annual frequency of pneumonia during 2008 – 2014 and the costs associated with index pneumonia events during 2013 – 2014 estimating that 4.9 million patients suffer from pneumonia annually in the US, resulting in US$ 13.4 billion in costs related to the index episode.[31–34] In 2017, pneumonia and influenza were the 8th leading cause of death accounting for 55,672 (2%) of total deaths, showing a significant increase (5.9%) comparing to 2016 with most of the people affected being adults.[35]

1. Diseases of heart (heart disease)
2. Malignant neoplasms (cancer)
3. Accidents (unintentional injuries)
4. Chronic lower respiratory diseases
5. Cerebrovascular diseases (stroke)
6. Alzheimer disease
7. Diabetes mellitus (diabetes)
8. Influenza and pneumonia
9. Nephritis, nephrotic syndrome and nephrosis (kidney disease)
10. Intentional self-harm (suicide)
11. Chronic liver disease and cirrhosis
12. Septicaemia
13. Essential hypertension and hypertensive renal disease (hypertension)
14. Parkinson disease
15. Pneumonitis due to solids and liquids

Table 3—1: Final data on United States 15 leading causes of death in 2017, https://www.cdc.gov/nchs/products/index.htm.

4. DISPROPORTIONALITY ANALYSIS

4.1. Disproportionality analysis

Disproportionality assessment is one of multiple statistical methods (e.g. cluster analysis, link analysis, deviation detection) proposed for quantitative signal detection of drug related adverse events in PV databases. The objective of disproportionality studies is prompt signal generation for unknown or underestimated ADRs in relation to a specific drug. Signal is defined as a higher than expected (disproportionate) number of AR reports in relation to a specific drug compared to other ARs reported in the database. These studies are used for automatic signal detection in the database, testing a working hypothesis before designing a larger pharmacoepidemiological study, validation of a pharmacological hypothesis about the mechanism of occurrence of ADRs and studying rare, nonspecific or delayed onset ADRs.[36]

The different methods for studying the disproportionality of ADR reports include frequentist methods (e.g. case/non-case studies or the proportional reporting ratio (PRR) studies) and Bayesian methods (e.g. multi-item gamma Poisson Shrinker (MGPS) method or the Bayesian confidence propagation neural network (BCPNN) method).[11]

The case/non-case design and reporting odds ratio (ROR) will be further explained for the purposes of this master thesis. Compared to the methods previously mentioned, this measure allows exploration of possible confounding via multivariate logistic regression[37] and has shown a greater sensitivity and early signal detection which is essential when investigating possible ADRs.[38]

4.2. Case/non-case studies

Case/non-case studies are one of the methods used to assess drug safety by analysing the disproportionality of adverse drug reaction reports in pharmacovigilance databases.[11]

Case/non-case studies use a 2x2 contingency table of the two categorical variables Drug Exposure (D) and Event Occurrence (E). Example is presented in tables 4-1 and 4-3.

Drug / Event	Drug	Other drugs	Sums (events)
Events	DE	dE	E
Other events	De	de	e
Sums (drugs)	D	d	N (Total reports)

Table 4—1: A 2x2 contingency table. Intersections of the datasets can be made by combining letters (e.g. DE is the subpopulation where the drug exposure as well as the event occurred).[23] For further details see text and table 4-2.

The letter D (capital) denotes exposure to a specific drug while a d (lowercase) denotes no exposure to said drug. An E (capital) denotes occurrence of an adverse event while an e (lowercase) denotes no occurrence of the event. A combination of these letters (D, d, E, e) can be used to create subpopulation of the data set. Reports containing the adverse reactions of interest (DE + dE = E) are defined as cases and all other reports are defined as non-cases (De + de = e) (that is patients who have been exposed to at least on drug and have experienced at least one AR that is not the AR under investigation).

D	Exposure to certain drug
d	No exposure to certain drug
E	Occurrence of certain AE
e	No occurrence of certain AE

DE	Drug exposure & event occurrence
De	Drug exposure & no event occurrence
dE	No drug exposure & event occurrence
de	No drug exposure & no event occurrence

Table 4—2: 2x2 contingency table cell naming

	Drug(s) of interest	All other drugs	∑
Adverse event(s) of interest	381	7267	7648
All other adverse events	55258	7303958	7359216
∑	55639	7311225	7366864

Table 4—3: A 2x2 contingency table, example. Drug of interest: Clozapine, Event of interest: Pneumonia aspiration. Source: OpenVigil 2.1. - MedDRA interface. Date accessed: 27/12/2019

The measure of disproportionality used in a case/non-case study is the reporting odds ratio (ROR) and it corresponds to the ratio of reporting odds between groups exposed and not exposed to the investigated drug.

The ROR is in fact an adapted Odds Ratio (OR) and is calculated using:

$$\mathrm{ROR} = \frac{\frac{\mathrm{DE}}{\mathrm{De}}}{\frac{\mathrm{dE}}{\mathrm{de}}} = \frac{\mathrm{DE} \times \mathrm{de}}{\mathrm{De} \times \mathrm{dE}}$$

This addition of “reporting” compensates for the fact that absolute rates as known from clinical studies can never be calculated due to lack of a correct denominator that is the number of the whole population, including non-users of the drug of interest.[39] (Figure 4-1)

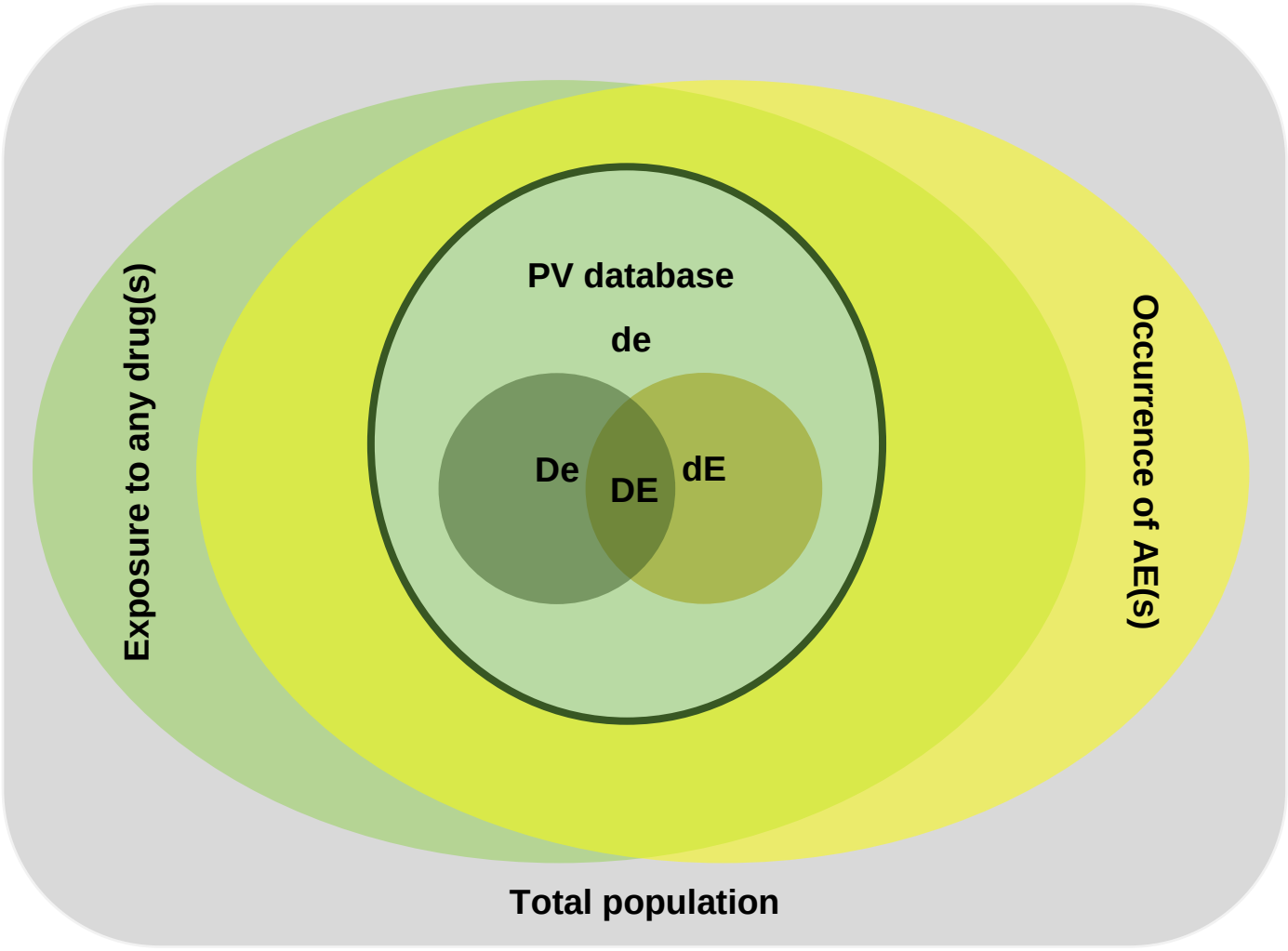

Figure 4—1: Any AE database contains a small subset of data from the total population. Individuals not taking any medication are excluded while not all drug users or patients that experience AEs report them to the authorities.[39]

The ROR can take several values. A disproportionality signal is only generated when ROR is greater than one meaning that the AR is more frequently reported with the investigated drug rather than other drugs. If a ROR is one or less, no signal is generated because the AR of interest is reported equally in cases and non-cases or is less reported with the investigated drug than with other drugs, respectively. Being a statistical measure, the ROR should also be presented with a 95% Confidence Interval (CI) and thus a statistically significant positive disproportionality signal is detected when the lower limit of the 95% two sided confident interval of the ROR is greater that one.[11]

4.3. Strengths of DPA

There are multiple advantages for DPA. All strengths mentioned in the paragraph 1.5 apply for DPA since it is a tool used in PV studies. DPA is a systematic way for regulatory agencies as well as manufacturers to flag potential issues of a drug from a database containing a constantly growing number of AE and drugs reports. It is a relatively inexpensive method compared to RCTs and it allows for faster implementation and thus identification of potential safety signals in relation to specific drug use. These signals generated from DPA might guide manufacturers to ameliorate their product and regulatory authorities to focus on specific drug related hypothesis that need further investigation to ensure public safety. A DPA study also allows for the incorporation of pharmacodynamic data in order to explore and suggest possible ADR-related mechanism.[2,11]

4.4. Limitations of DPA

Disproportionality analysis is an analysis of data extracted from pharmacovigilance databases and consequently all limitations mentioned in paragraph 1.6. should be considered when interpreting results from DPA. As mentioned above, temporal bias may be present when working with PV data and this may impact ROR estimates. One such phenomenon is the 'Weber effect' defined as a fluctuation in reporting patterns over time. Particularly, it is an increase in the number of reports witnessed mainly in the first two years of a drug's circulation or when an older drug is approved for a different indication or dosage followed by a decline in reporting rates mostly due to decreased interest from reporters for the drug and the ARs becoming better known. During this period, a high proportion of non-serious ARs reports is submitted creating 'noise' in the signal. This may result in an underestimation of the ROR (masking effect) since the number of De reports (denominator) will increased and the ROR will decrease and a variation of ROR over time. On the other hand, an overestimation of the ROR might come as a result of the 'notoriety effect' which is defined as an increase in the number of reports for a specific drug-AR combination following media coverage. Finally, media coverage of a specific drug- AR combination might lead to an increase in reporting of said AR with other drugs belonging to the same pharmacological or therapeutic class as the drug initially suspected in the alert (ripple effect). In any case, DPAs are less effective in recognising long-term ARs since the drug-AE association is

frequently overlooked.[11,40] Furthermore, a DPA is a statistical method meaning that signals produced from such an analysis are mostly exploratory rather than confirmatory of a causal relationship between a drug and an AE. Further investigation and data are need to prove causality and quantify the true risk ADRs occuring.[4,36] Lastly, residual and unmeasured confounders should always be considered as an inherited limitation of disproportionality analysis as a method.

5. FAERS DATABASE

5.1. What is FAERS?

United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is one of many post-marketing spontaneous reporting surveillance systems. It is a database that contains reports submitted to FDA concerning adverse events (AEs), medication errors and product quality complains resulting in AE. Report in the system might be submitted directly from medical professionals and the public and indirectly from the pharmaceutical industry. AEs and medical errors are coded using the preferred terms (PT) in MedDRA terminology. A complete data set consists of demographic, drug, reaction, outcome, report source, and drug therapy date information. FDA grants public access to its data offering external investigators the possibility to use this data source and conduct pharmacoepidemiological and/or pharmacovigilance analyses.[7,41]

5.2. Data mining of the FAERS

Data mining algorithms are an indispensable part of PV data analysis. Due to the constantly growing volume of PV databases and the need for a greater number of investigators from different backgrounds to access the data simple, easy to use, tools are needed to facilitate data processing. One such tool is OpenVigilFDA, a powerful way to access data without the need for a deep knowledge of programming. The data available via this interface date back to mid-2003.

OpenVigilFDA is a web-based pharmacovigilance analysis tool that uses the official openFDA Application Programming Interface to access FAERS. It provides user friendly interfaces that facilitates data extraction, reports analysis and working with specific clinical scenarios, powerful algorithms and highly configurable outputs in multiple formats. Other versions currently available with configurable search filters and output filters are OpenVigil1 and OpenVigil2. OpenVIgil1 operates on raw data while OpenVigil2 uses cleaned data and is designed for complete case analyses. OpenVigil2 is reported to be more stable and superior for analyses of disproportionality. It is worth noting that this does not imply that the reports are completely cleaned but rather that they contain at least one cleaned drug name.

Specifically, according to FDA approximately 86% of all records have at least one cleaned drug name but only a minor fraction of those reports contained an entirely cleaned medication list. [39,42] The latest version available is OpenVigil2.1-MedDRA that used the MedDRA ontology.

5.3. Medical Dictionary for Regulatory Activities (MedDRA)

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology is an international medical terminology developed in the late 1990s in order to facilitate international communication and sharing regulatory information for medical products (pharmaceuticals, biologicals, vaccines, drug-device combination products) used by humans. It is a multilingual terminology available in 13 languages.

MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle, excluding animal toxicology.

The MedDRA terminology has a specific structure. Relationships between terms can be classified in two categories, equivalence and hierarchical. The equivalence relationship represents a horizontal link and groups synonymous terms, or equivalent terms, under Preferred Terms (PT). The hierarchical relationship represents vertical links in the terminology creating degrees or levels. In a hierarchy, a superordinate term is a broad grouping term and it contains subordinate descriptors linked to it. There are five level from very specific to very general which provide options for data retrieval according to the level of specificity needed. [43]

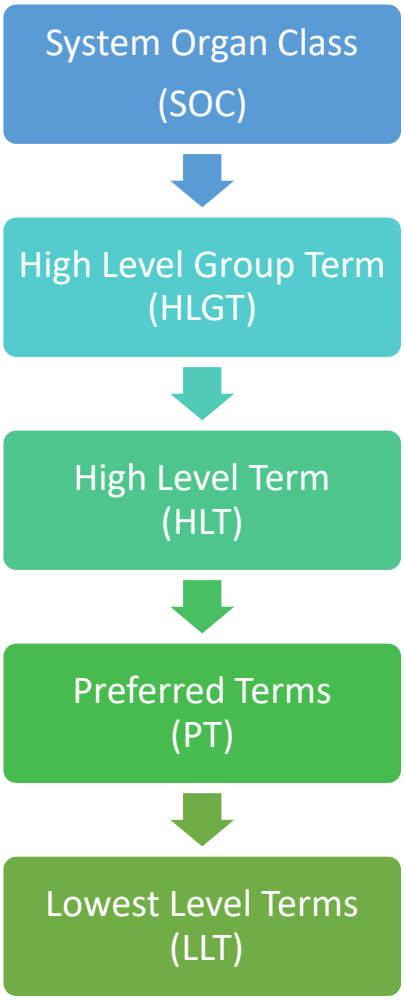

Figure 5—1: Structural Hierarchy of the MedDRA Terminology.

Beginning from the bottom, LLTs provide maximal specificity. PTs are distinct descriptors for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. Every LLT is linked to a unique PT and each PT has at least one LLT (itself) as well as synonyms and lexical variants. Related PTs are grouped together into HLTs based upon anatomy, pathology, physiology, aetiology or function while HLTs related to each other by anatomy, pathology, physiology, aetiology or function are linked to HLGTs that are grouped in SOCs which are groupings by aetiology, manifestation site or purpose. In addition, there is a SOC to contain issues pertaining to products and one to contain social circumstances.[43]

Further information on the MedDRA initiative and structure can be found at the MedDRA website[43] and the 'Introductory Guide MedDRA Version 22.0'. [44]

6. RECEPTOR OCCUPANCY THEORY

6.1. Definition

The term ‘drug-receptor theory’ is used for the total of equations and models that describe the interaction between chemical substances (ligands) and receptors. These ligands interact with the receptor to produce a change in its state that is then transmitted to the cell to which the receptor is connected. The first mathematical formulations to describe this biochemical phenomenon were created by A.J Clark (equation 6-1) and was referred to as the ‘occupancy theory’. According to Clark, the effect is directly proportional to the number of receptors occupied and the effect is terminated when the drug-receptor complex dissociates. [45]

$$response = \frac{[A]}{K_A + [A]} \qquad \text{(Equation 6-1)}$$

Equation 6-1: Clark’s formula. [A] is the concentration of a drug and K_A the equilibrium dissociation constant. The K_A for each ligand-receptor pair is unique.

6.2. Assumptions

Clark’s occupation theory is based on two major assumptions. Firstly, it implies that the maximal drug response equals maximal tissue response which is known not to be true for partial agonists. The second one suggests that the relationship between occupancy and response is linear and direct however there are data suggesting that nonlinear hyperbolic relationships between occupancy and response exists.

Through the years, the classic occupancy theory has been modified to tackle above mentioned limitations with Ariens modelling the effect of weak agonist and Stephenson presenting an equation that allowed for nonlinear relationships between receptor occupancy and tissue response.[45]

7. STUDY GOALS

As mentioned in chapter 2, an association between the classes of antipsychotic drugs and pneumonia has been suggested by several studies, however, the risk for pneumonia caused by specific antipsychotics has not been widely investigated.

The present study is a combined pharmacovigilance-pharmacodynamic approach based on data collected from FDA adverse events spontaneous reporting system (FAERS) database designed to detect:

i) A potential safety signal for specific individual antipsychotics and reporting pneumonia
ii) The association between the risk for reporting pneumonia and occupancy on neurotransmitter receptors and transporters.

8. METHODS

8.1. Cases/non case design

This study is a disproportionality analysis using case-non case design on pharmacovigilance data submitted in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database between the first quarter of 2004 and July 2019. Reports incorporating the narrow scope of the standardized MedDRA query (SMQ) 'infective pneumonia' were defined as cases. All other events were defined as non-cases. MedDRA preferred term (PT) 'pneumonia aspiration', a term not included in the previous SMQ, was selected as a secondary outcome since aspiration is an important cause of pneumonia especially in the elderly.[46] The OpenVigil2.1.-MedDRA interface was used to access the data, a tool that operates on cleaned FDA data (verified and normalised drug names).[39] To ensure further data quality, additional data cleaning was performed removing reports with errors, duplicates or missing data concerning the age, gender, reporting year, reporting country or drug name. Only reports including adults were included.

8.2. Drug exposure and potential confounding factors

Reports associated with twenty-one FDA approved antipsychotics (ATC N05A* excluding Lithium) were retrieved. Reports containing only non-FDA approved antipsychotics were excluded due to possible under-reporting while droperidol (N05AD08), prochlorperazine (N05AB04) and pimavanserin (N05AX17) were not included to avoid indication bias. To be include in the analysis, an antipsychotic had to have at least 100 unique reports in FAERS with at least one 'infective pneumonia' related report. As a result, molindone (N05AE02) was excluded. The final simple consisted of reports of twenty antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, thiothixene, trifluoperazine and ziprasidone). Reports with both single and multiple antipsychotic use were included with the latter being used in an analysis to identify a risk of reporting pneumonia and multiple antipsychotic use compared to

single antipsychotic use. Additional extracted data were identity numbers of the reports (ISR), case ID, gender, age, reporting year, reporting country and associated drugs.

Concomitant use of antibiotics, immunosuppressants, benzodiazepines and benzodiazepine-related drugs, acid-suppressive drugs, drugs with potential extrapyramidal symptoms and corticosteroids were considered as potential confounders (table 8-1). [47–50] The risk for reporting pneumonia was adjusted for further possible confounders: age, gender, years between drug approval date and the year of the report (for multiple vs single antipsychotic use this chronological confounder was expressed simply as the year of the report submission), reporting country and use of pneumonia associated drugs.

Acid suppressive drugs: cimetidine, dexlansoprazole, dexrabeprazole, esomeprazole, famotidine, lafutidine, lansoprazole, niperotidine, nizatidine, omeprazole, pantoprazole, rabeprazole, ranitidine, ranitidine bismuth citrate, roxatidine
Antiobiotics: amikacin, amoxicillin, ampicillin, arbekacin, aspoxicillin, azidocillin, azithromycin, azlocillin, aztreonam, bacampicillin, bacitracin, bekanamycin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, biapenem, brodimoprim, capreomycin, carbenicillin, carindacillin, carumonam, cefacetrile, cefaclor, cefadroxil, cefalexin, cefaloridine, cefalotin, cefamandole, cefapirin, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefradine, cefroxadine, cefsulodin, ceftaroline fosamil, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftobiprole, ceftolozane, ceftriaxone, cefuroxime, chloramphenicol, chlortetracycline, cilastatin, cinoxacin, ciprofloxacin, clarithromycin, clindamycin, clofoctol, clometocillin, clomocycline, cloxacillin, colistin, cycloserine, dalbavancin, dalfopristin, daptomycin, delafloxacin, demeclocycline, dibekacin, dicloxacillin, dirithromycin, doripenem, doxycycline, enoxacin, epicillin, eravacycline, ertapenem, erythromycin, faropenem, fleroxacin, flomoxef, flucloxacillin, flumequine, flurithromycin, fosfomycin, furazidin, fusidic acid, garenoxacin, gatifloxacin,

gemifloxacin, gentamicin, grepafloxacin, iclaprim, imipenem, isepamicin, josamycin, kanamycin, latamoxef, levofloxacin, lincomycin, linezolid, lomefloxacin, loracarbef, lymecycline, mandelic acid, mecillinam, meropenem, metacycline, metampicillin, methenamine, meticillin, metronidazole, mezlocillin, midecamycin, minocycline, miocamycin, moxifloxacin, nafcillin, nalidixic acid, nemonoxacin, neomycin, netilmicin, nifurtoinol, nitrofurantoin, nitroxoline, norfloxacin, ofloxacin, oleandomycin, oritavancin, ornidazole, oxacillin, oxolinic acid, oxytetracycline, panipenem, pazufloxacin, pefloxacin, penamecillin, penimepicycline, pheneticillin, phenoxymethylpenicillin, pipemidic acid, piperacillin, piromidic acid, pivampicillin, pivmecillinam, polymyxin B, pristinamycin, procaine benzylpenicillin, propicillin, prulifloxacin, quinupristin, ribostamycin, rifabutin, rifampicin, rifamycin, rifapentine, rokitamycin, rolitetracycline, rosoxacin, roxithromycin, rufloxacin, sisomicin, sitafloxacin, sparfloxacin, spectinomycin, spiramycin, streptoduocin, streptomycin, sulbactam, sulbenicillin, sulfadiazine, sulfadimethoxine, sulfadimidine, sulfafurazole, sulfaisodimidine, sulfalene, sulfamazone, sulfamerazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine, sulfametomidine, sulfametoxydiazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfapyridine, sulfathiazole, sulfathiourea, sultamicillin, talampicillin, tazobactam, tebipenem pivoxil, tedizolid, teicoplanin, telavancin, telithromycin, temafloxacin, temocillin, tetracycline, thiamphenicol, ticarcillin, tigecycline, tinidazole, tobramycin, tosufloxacin, trimethoprim, troleandomycin, trovafloxacin, vancomycin, xibornol
Benzodiazepines and benzodiazepine-related drugs: adinazolam, alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clotiazepam, cloxazolam, diazepam, doxefazepam, estazolam, eszopiclone, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, pinazepam, potassium clorazepate, prazepam, quazepam, temazepam, tofisopam, triazolam, zaleplon, zolpidem, zopiclone
Corticosteroids: aldosterone, beclometasone, beclomethasone, betamethasone,budesonide, ciclesonide, cloprednol, cortisone, cortivazol, deflazacort, desoxycortone, dexamethasone, fludrocortisone, flunisolide, fluocortolone, fluticasone, hydrocortisone, meprednisone, methylprednisolone,

mometasone, paramethasone, prednisolone, prednisone, prednylidene, rimexolone, triamcinolone
Drugs with potential extrapyramidal symptoms: abacavirtenofovir, acyclovir, adrenaline, alafenamide, alfametildopa, amiodarone, amphotericin B, arunavir, atazanavir, bictegravir, cinnarizine, clebopride, cobicistat, darunavir, diltiazem, disoproxil, dolutegravir, doravirine, efavirenz, elvitegravir, emtricitabine, epinephrine, flunarizine, fluoxetine, lamivudine, levetiracetam, levosulpiride, levothyroxine, lithium, lopinavir, lovastatin, medroxyprogesterone, methyldopa, metoclopramide, moclobemide, nevirapine, phenelzine, phenytoin, procaine, raltegravir, reserpine, rilpivirine, ritonavir, sertraline, stavudine, tetrabenazine, valproate, verapamil, vidarabine, zidovudine
Immunosuppressants: abatacept, abetimus, adalimumab, afelimomab, alefacept, alemtuzumab, anakinra, antilymphocyte immunoglobulin, antithymocyte immunoglobulin, apremilast, azathioprine, baricitinib, basiliximab, belatacept, belimumab, briakinumab, brodalumab, canacinumab, certolizumab pegol, cladribine, cyclosporine, daclizumab, dimethyl fumarate, eculizumab, efalizumab, emapalumab, etanercept, everolimus, fingolimod, golimumab, guselkumab, gusperimus, infliximab, ixekizumab, leflunomide, lenalidomide, mepolizumab, methotrexate, muromonab, mycophenolic acid, natalizumab, ocrelizumab, ozanimod, pirfenidone, pomalidomide, rilonacept, sarilumab, secukinumab, siltuximab, sirolimus, sirukumab, tacrolimus, teriflunomide, thalidomide, tildrakizumab, tocilizumab, tofacitinib, ustekinumab, vedolizumab, voclosporin

Table 8—1: Confounding medication

8.3. Pharmacodynamic data

Drug – receptor interaction was quantified using receptor occupancy theory. Mean receptor occupancy (Φ, %) was expressed as:

$$\Phi(\%) = 100 \times \frac{C_U}{K_i + C_U}$$

where C_U(nM) is the unbound drug concentration in blood and K_i(nM) is the inhibitory constant for each drug.[45]

On November 2019, the inhibitory constants (K_i) for three human transporters (SERT, NET, DAT) and twenty-three human receptors (serotonin receptors: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_5, 5-HT_6, 5-HT_7, adrenergic receptor alpha1/2 (regardless of subtype), muscarinic receptors: M_1, M_2, M_3, M_4, M_5, dopamine receptors D_1, D_2, D_3, D_4, D_5 and histamine receptor H_1) were retrieved from PDSP database[51]. When unavailable, IUPHAR/BPS database was used.[52] When more than one values were available the mean was calculated. The C_U was calculated using the equation

$$C_U = 1000 \times \frac{F_U \times C_T}{MW}$$

where F_U is the unbound drug fraction, C_T is the total drug concentration in blood and MW is the molecular weight of drug. To estimate the total drug concentration in blood C_T(ng/ml) the upper limit of the therapeutic reference range of each antipsychotic reported in The Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology [53] was used. Due to data unavailability, different sources were used for thiothixene[54]. The molecular weight (MW) of antipsychotics was extracted from IUPHAR database and the unbound drug fraction (F_U) from Drugbank[55] (when unavailable the work of Lombardo et al. was used [56]).

8.4. Statistics Analysis

Study population characteristics between cases and non-cases were compared. A Mann-Whitney U test was used for not normally distributed continuous variables (age, reporting year or years since approval date) and a chi-square test for categorical variables (gender, use of corticosteroids, immunosuppressants, acid-suppressive

drugs, benzodiazepine-related drugs, drugs with potential extrapyramidal symptoms, antibiotics and reporter country). A disproportionality analysis was performed to detect a possible signal for reporting 'infective pneumonia' and single antipsychotic use compared with all other reports with single antipsychotic use in the sample. An additional analysis was performed comparing multiple antipsychotic use to single antipsychotic use. Disproportionality was estimated using the adjusted reporting odds ratio (aROR) and its 95% confidence interval (CIs) in a multivariable logistic regression. For each antipsychotic drug, the aROR was defined as the odds of pneumonia-associated adverse drug reaction reports for the single antipsychotic divided by the odds for the other drugs in the sample adjusted for predefined confounders.[39] A positive disproportionality signal was reported when more than three reports were detected and the lower limit of the 95% two sided confident interval of the aROR was greater that one.[40] A secondary disproportionality analysis for the outcome of 'pneumonia aspiration' was performed.

Several sensitivity analyses were performed. Apart from aROR, an unadjusted ROR (uROR) was also calculated for each antipsychotic. It is generally considered that a minimum of 10 events should correspond to every independent variable included in a multivariant regression model (rule of thumb) and thus uROR might be a better measure for antipsychotics with a small number of pneumonia-associated reports.[57] To control for possible indication bias reports with clozapine were excluded as it is selectively prescribed for treatment-resistant schizophrenia.[58] Furthermore, antipsychotics with a strong association for reporting pneumonia were excluded to account for possible competition bias (suppression of a statistically significant disproportionality signal for a drug-event pair due to increased background reporting).[59,60] Lastly, to demonstrate adequate control of confounding a sensitivity analysis was performed excluding each group of possibly confounding medications (antibiotics, immunosuppressants, benzodiazepines and benzodiazepine-related drugs, acid-suppressive drugs, drugs with potential extrapyramidal symptoms and corticosteroids).

To identify molecular pathways possibly involved in antipsychotics-associated pneumonia we conducted Pearson's correlations coefficients (r) between the disproportionality signal (expressed as aROR) for reporting 'infective pneumonia' and receptor/transporter occupancy. A secondary analysis was performed for the outcome

‘pneumonia aspiration’. Occupancy degrees below 0.1%[61] as well as antipsychotics with less than three cases of pneumonia were excluded. For this analysis, alpha was adjusted with Bonferroni correction for multiple comparisons to minimise the risk for type I error, p = 0.05/26 = 0.00192 (twenty-six receptor/transporters examined). All analyses were performed using R version 3.6.1 (2019-07-05)[62].

9. RESULTS

9.1. Pharmacovigilance data

On July 2019, from the 6932328 FAERS reports available via OpenVigil2.1. and after further data cleaning a total of 119049 unique reports of twenty FDA approved antipsychotics were collected forming the final sample (Figure 9-1).

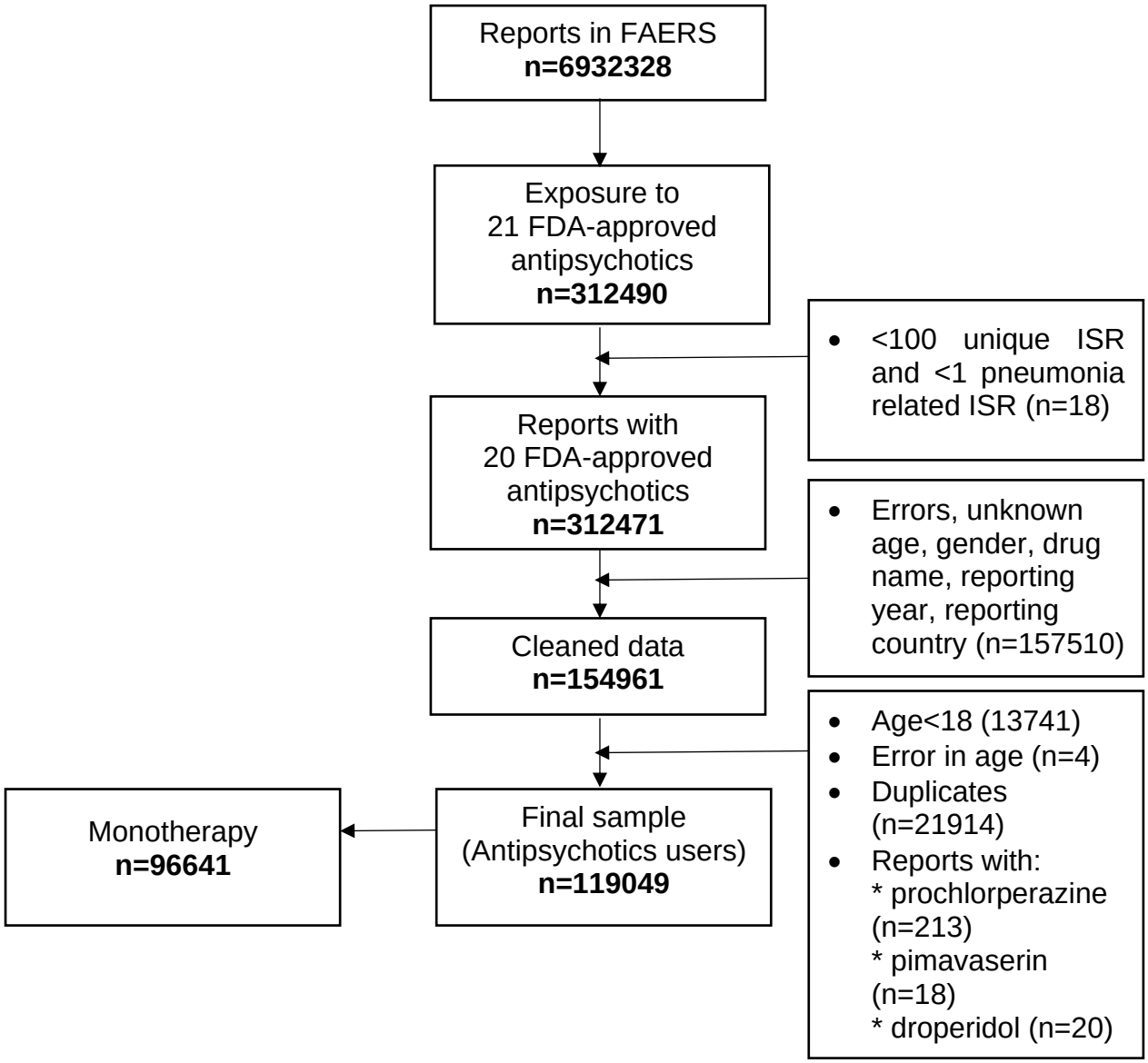

Figure 9—1: Flow diagram of reports. The total number of reports in the database of FAERS (extracted from OpenVigil2.1-MedDRA) was 6932328 of which 312471 included one or more of the 20 studied antipsychotics. Further data cleaning resulted in the final sample of 119049 reports. Among those, 96641 included use of a single antipsychotic.

The most strongly represented antipsychotics were single use of quetiapine (26%), clozapine (12.1%), aripiprazole (11.4%), olanzapine (10.5%) and risperidone (8.8%). Multiple antipsychotic use accounted for 18.9% of the final sample.

'Infective pneumonia' was identified in 1888 reports. Descriptive characteristics are presented in table 9-1. There were several statistically significant differences between cases and non-cases. Reports with cases included older patients, more frequently males, were submitted later in relation to reported antipsychotic approval date and originated more frequently outside the United States. Regarding concomitant drug use, cases were more frequently users of concomitant medications (corticosteroids, immunosuppressants, acid-suppressive drugs, antibiotics and drugs with potential extrapyramidal symptoms) except benzodiazepines and benzodiazepine-related drugs (p=0.6861).

	Infective pneumonia		
	Cases	**Non-cases**	**p-value**
Age			
Mean (SD)	54.2 (17.1)	46.4 (16.8)	<0.001
Median	54	45	
Gender			
Female (%)	909 (48)	62516 (53)	<0.001
Reporting Country			
United States (%)	849 (45)	66663 (57)	<0.001
Reporting year			
Mean (SD)	2012.1 (3.98)	2012.46 (3.92)	<0.001
Median	2012	2012	
*** Reporting years since approval**			
Mean (SD)	19.3 (8.2)	17.3 (9.5)	<0.001
Median	18	15	
Concomitant use			
Corticosteroids (%)	133 (7)	2772 (2)	<0.001
Immunosuppressants (%)	56 (3)	1405 (1)	<0.001
Acid-suppressive drugs (%)	220 (12)	7621 (7)	<0.001
Bdrd (%)	335 (18)	20341 (17)	0.6861
Parkinsonism (%)	434 (23)	17890 (15)	<0.001
Antibiotics (%)	86 (5)	2296 (2)	<0.001

Table 9—1: Population characteristics of cases of infective pneumonia and non-cases.

For the secondary outcome of aspiration pneumonia, a total of 624 reports including the preferred term ‘pneumonia aspiration’ were identified. Demographic and medical characteristics are included in table 9-2. In general, reports with ‘pneumonia aspiration’ similarly included older patients, more frequently males, were submitted later in relation to reported antipsychotic approval date and originated more frequently outside the United States. There was no difference in concomitant drug exposure except for bdrd (p<0.001) being more frequently co-reported with ‘pneumonia aspiration’.

	Pneumonia Aspiration		
	Cases	**Non-cases**	**p-value**
Age			
Mean (SD)	54.4 (19.1)	46.5 (16.9)	<0.001
Median	54	45	
Gender			
Female (%)	216 (35)	67303 (53)	<0.001
Reporting Country			
United States (%)	209 (33)	70203 (57)	<0.001
Reporting year			
Mean (SD)	2013.46 (4.23)	2012.45 (3.92)	<0.001
Median	2013	2012	
*** Reporting years since approval**			
Mean (SD)	20.7 (10.4)	17.3 (9.5)	<0.001
Median	19	15	
Concomitant use			
Corticosteroids (%)	13 (2)	2892 (2)	0.6533
Immunosuppressants (%)	4 (1)	1557 (1)	0.2496
Acid-suppressive drugs (%)	34 (5)	7807 (7)	0.2856
Bdrd (%)	207 (33)	20469 (17)	<0.001
Parkinsonism (%)	97 (16)	18227 (15)	0.9597
Antibiotics	15 (2)	2367 (2)	0.5636

Table 9—2: Comparison of population characteristics for the outcome of pneumonia aspiration.

9.2. Disproportionality analysis

Among reports with single antipsychotic use, positive disproportionality signal for reporting ‘infective pneumonia’ was identified for clozapine [aROR 3.7 (95% CI: 3.27 – 4.18)] and olanzapine [aROR 1.33 (95% CI: 1.16 – 1.53)]. (Figure 9-2 and table 9-1)

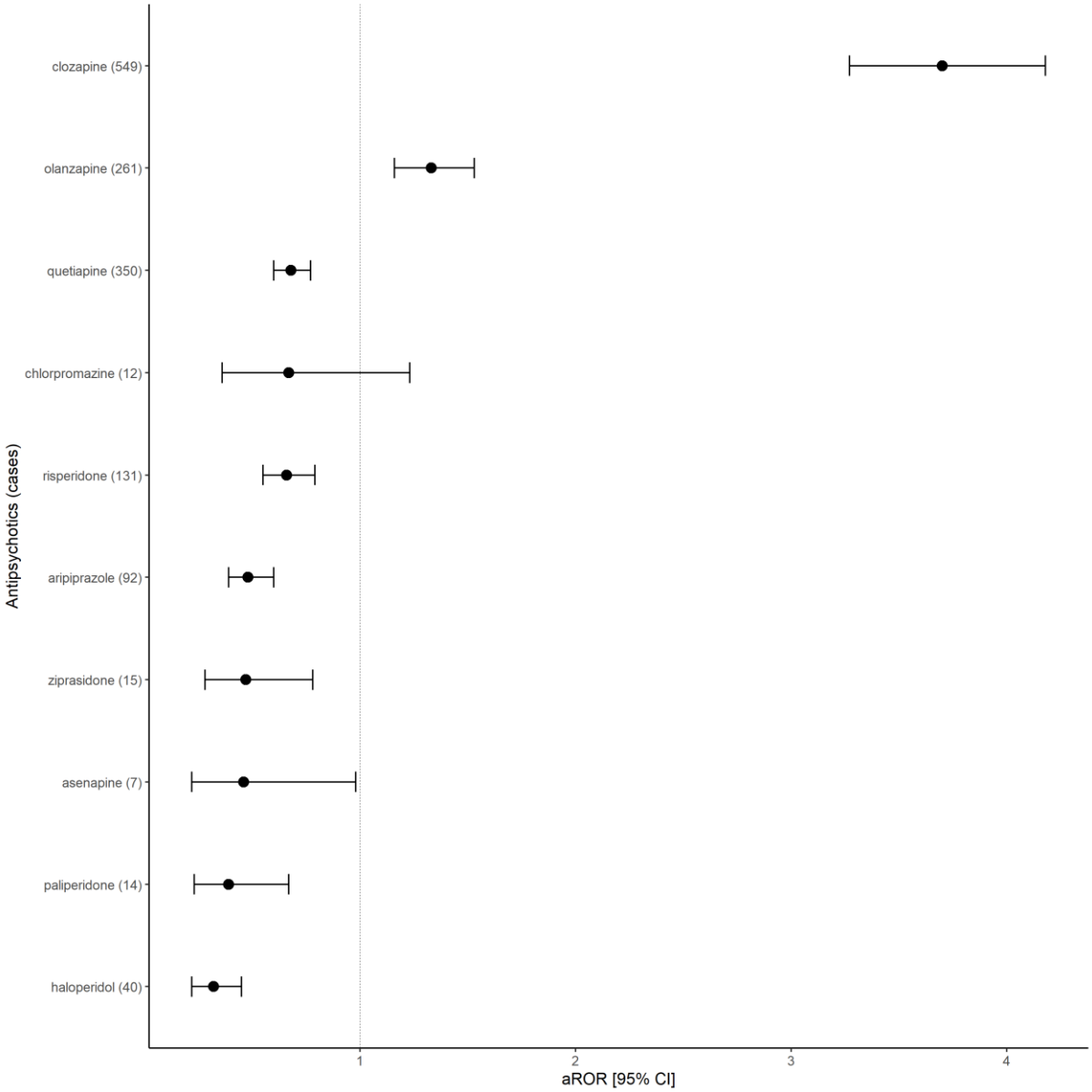

Figure 9—2: Disproportionality analysis in FAERS for the association between infective pneumonia and individual antipsychotics. The differential risk for reporting infective pneumonia of single antipsychotics compared to other single antipsychotics was quantified as adjusted reporting odds ratio (aROR) adjusted for predefined confounders (see text).

For the secondary outcome of pneumonia aspiration, a signal was identified for clozapine and olanzapine as well with an aROR of 1.42 (95% CI: 1.12 – 1.81) and 1.39 (95% CI: 1.08 – 1.79), respectively (Figure 9-3 and table 9-4).

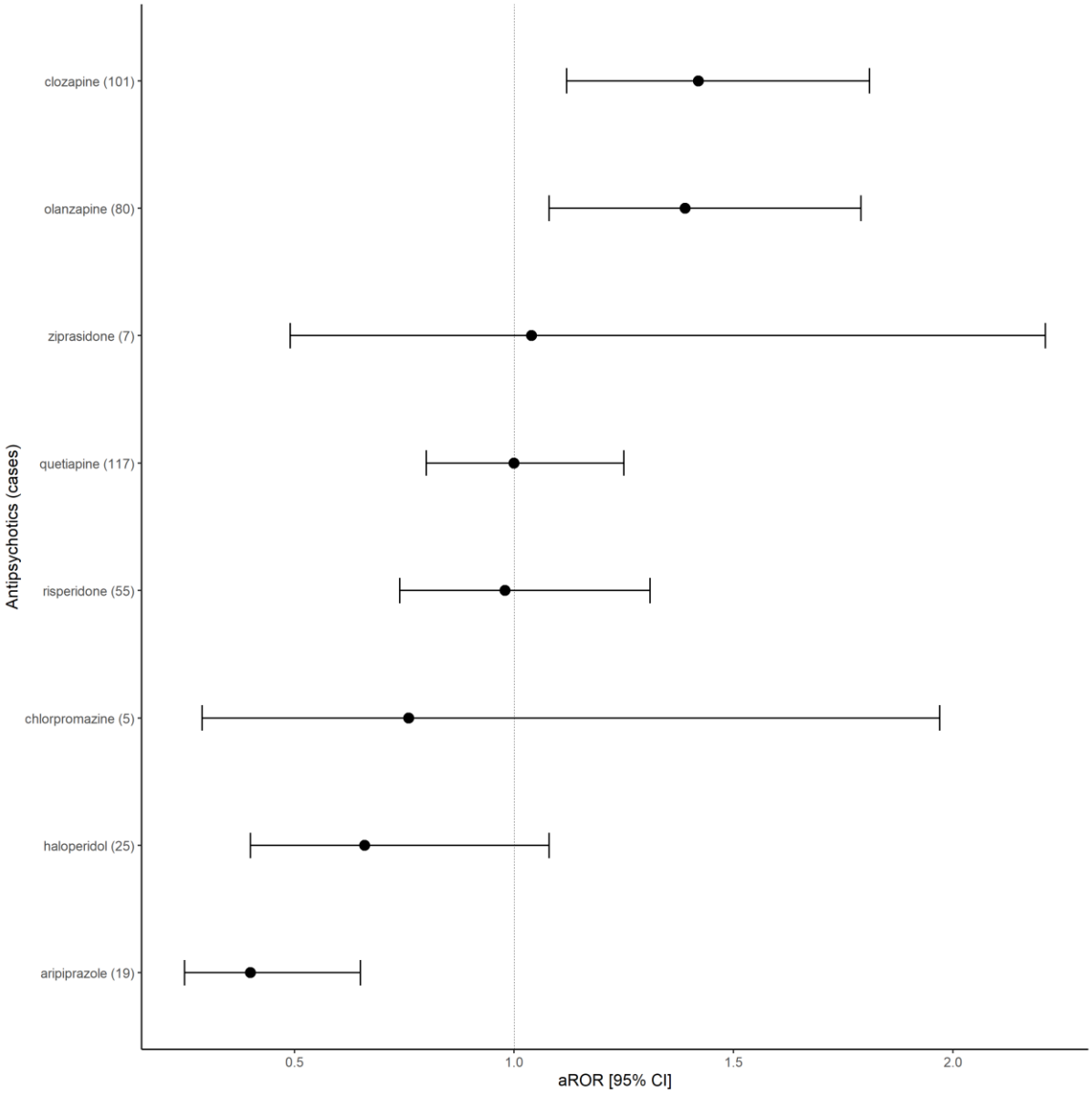

Figure 9—3: Disproportionality analysis in FAERS for the association between pneumonia aspiration and individual antipsychotics. The differential risk for reporting pneumonia aspiration of single antipsychotics compared to other single antipsychotics was quantified as adjusted reporting odds ratio (aROR) adjusted for predefined confounders (see text).

When multiple antipsychotic use was compared to single antipsychotic use an increased risk for reporting ‘infective pneumonia’ (aROR 1.22 [95% CI: 1.09 – 1.37]) and ‘pneumonia aspiration’ (aROR 1.92 [95% CI: 1.61 – 2.28]) was identified.

9.3. Sensitivity analyses

The uRORs were calculated for both outcomes and are presented in tables 9-3 and 9-4. A disproportionality signal was generated for haloperidol and reporting ‘pneumonia aspiration’ when unadjusted ROR were considered (uROR 1.63 [95% CI: 1.09 – 2.45). All other results remained unmodified with no additional signals being generated including APs with a low number of pneumonia-associated reports.

drug	DE	aROR	95% CIs	uROR	95% CIs
clozapine	549	3.7	3.27 - 4.18	3.45	3.1 - 3.84
olanzapine	261	1.33	1.16 - 1.53	1.44	1.26 - 1.65
quetiapine	350	0.68	0.6 - 0.77	0.65	0.58 - 0.73
chlorpromazine	12	0.67	0.36 - 1.23	1.15	0.65 - 2.03
risperidone	131	0.66	0.55 - 0.79	0.79	0.66 - 0.95
aripiprazole	92	0.48	0.39 - 0.6	0.4	0.32 - 0.5
ziprasidone	15	0.47	0.28 - 0.78	0.33	0.2 - 0.55
asenapine	7	0.46	0.22 - 0.98	0.27	0.13 - 0.57
paliperidone	14	0.39	0.23 - 0.67	0.26	0.15- 0.44
haloperidol	40	0.32	0.22 - 0.45	0.71	0.52 - 0.98

Table 9—3: aROR and uROR alongside their 95% two-sided confidence intervals are presented for single antipsychotics and the outcome 'infective pneumonia'.
DE: Drug exposure (single antipsychotic) – Event Occurrence (infective pneumonia).

drug	DE	aROR	95% CIs	uROR	95% CIs
clozapine	101	1.42	1.12 - 1.81	1.81	1.44 - 2.26
olanzapine	80	1.39	1.08 - 1.79	1.58	1.24 - 2.01
ziprasidone	7	1.04	0.49 - 2.21	0.55	0.26 - 1.16
quetiapine	117	1	0.8 - 1.25	0.81	0.66 - 1.01
risperidone	55	0.98	0.74 - 1.31	1.23	0.92 - 1.63
chlorpromazine	5	0.76	0.29 - 1.97	1.69	0.7 - 4.09
haloperidol	25	0.66	0.4 - 1.08	1.63	1.09 - 2.45
aripiprazole	19	0.4	0.25 - 0.65	0.29	0.18 - 0.46

Figure 9—4: aROR and uROR alongside their 95% two-sided confidence intervals are presented for single antipsychotics and the outcome ‘pneumonia aspiration’. DE: Drug exposure (single antipsychotic) and Event Occurrence (aspiration pneumonia).

When clozapine and olanzapine were excluded from the analysis (controlling for possible competition bias) a signal for quetiapine and reporting both outcomes was generated [infective pneumonia: aROR 1.33 (95% CI: 1.14 – 1.56), pneumonia aspiration: aROR 1.49 (95% CI: 1.13– 1.96)]. The rest of the results remained unmodified and exclusion of clozapine and other potential confounders (corticosteroids, immunosuppressants, acid-suppressive drugs, benzodiazepines and benzodiazepine related drugs, antibiotics and drugs with potential extrapyramidal symptoms) did not materially change the results.

9.4. Relationship between disproportionality for reporting infective/ aspiration pneumonia and receptor/transporter occupancy.

Due to limited data, occupancy was calculated for 18 out of 20 investigated antipsychotics (thiothixene and trifluoperazine were not included in Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology[53] and no reliable sources were identified) (Figure 9-1).

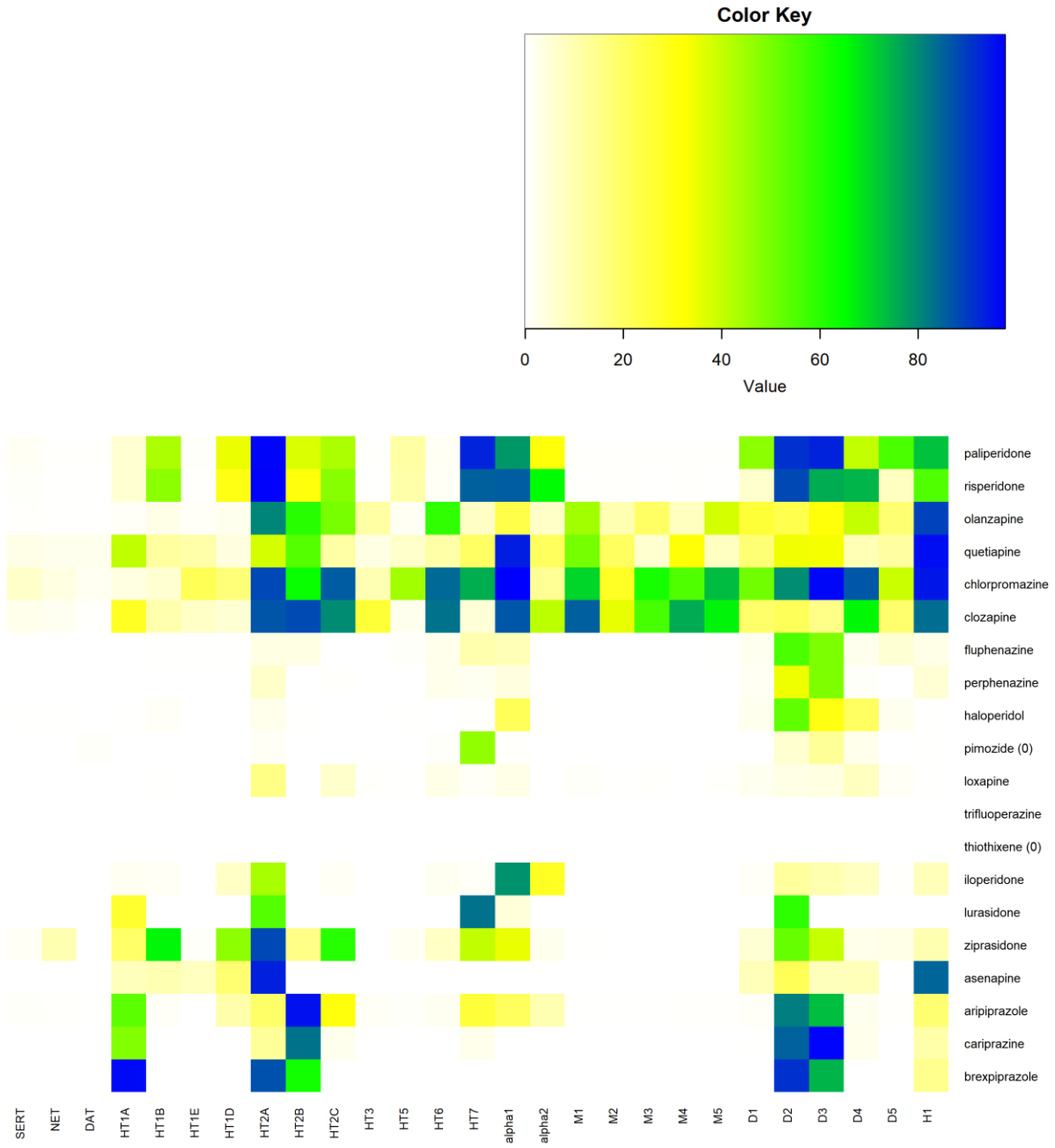

Figure 9—5: Receptor occupancy heatmap

Pearson's correlation coefficient (r) for receptor/transporter occupancy and aROR of reporting infective and aspiration pneumonia was calculated for 11 and 9 antipsychotics, respectively. Pearson's r between aROR for 'infective pneumonia' and 'pneumonia aspiration' and occupancy along with their p-values are displayed in Figures 9-6, 9-7.

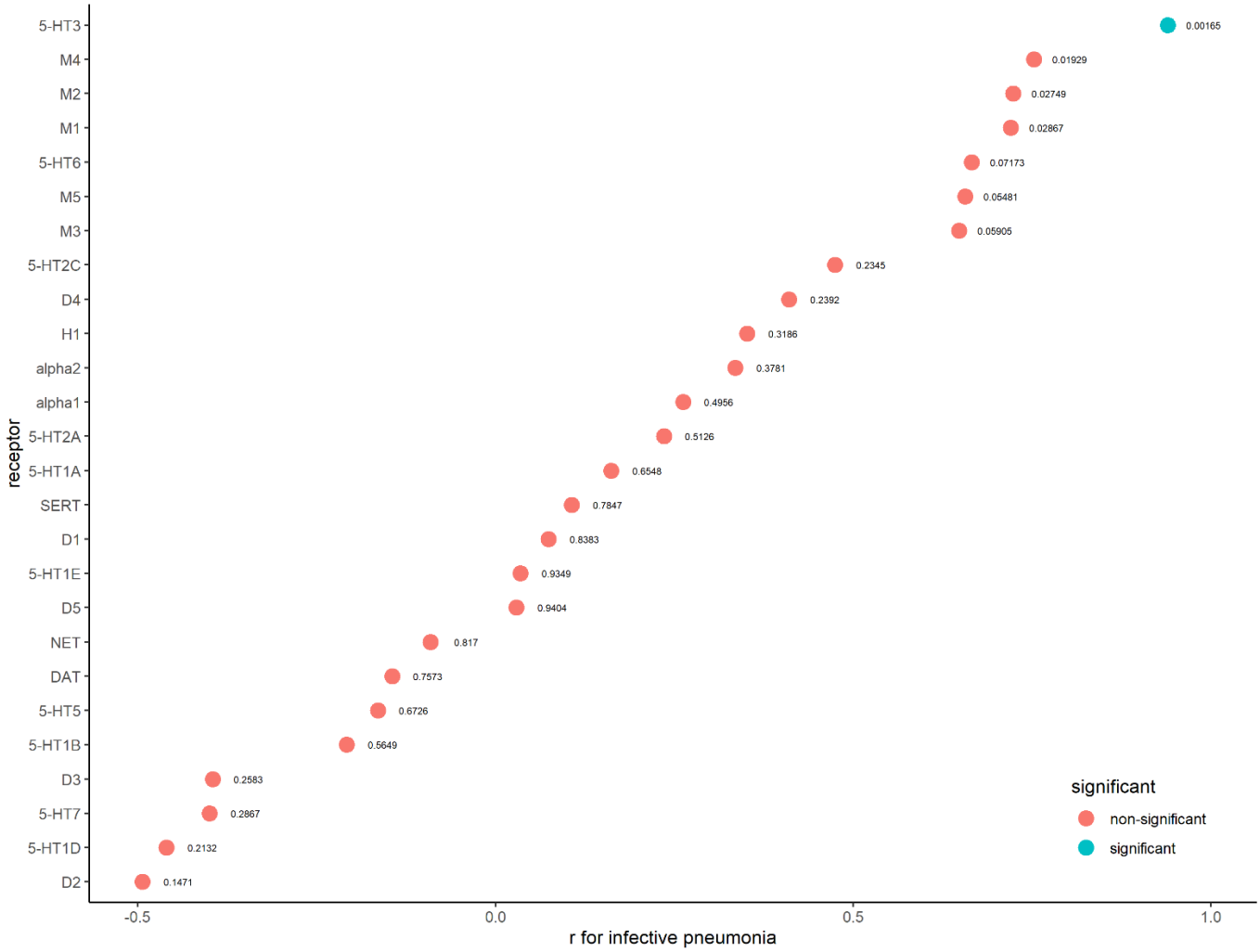

Figure 9—6: Pearson's correlation coefficients (r) and their p-values of the relationship between aROR for infective pneumonia and the occupancy on each receptor/transporter.

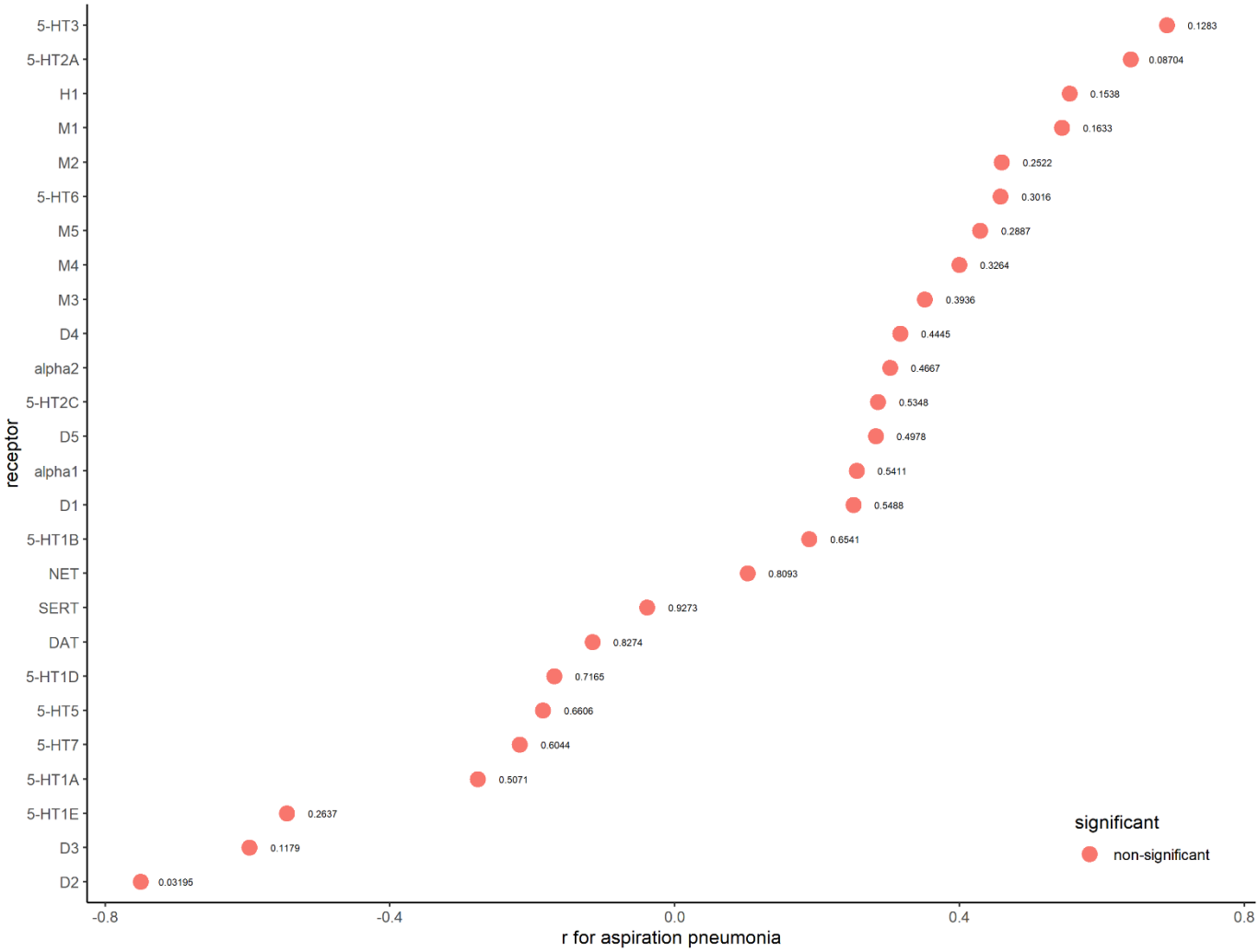

Figure 9—7: Pearson's correlation coefficients (r) and their p-values of the relationship between aROR for pneumonia aspiration and the occupancy on each receptor/transporter.

A significant correlation coefficient was identified only for the 5-HT3 receptor and the risk for reporting 'infective pneumonia', r = 0.98 [95% CI: 0.64 – 0.99], p = 0.001651. The muscarinic receptors M4 (r=0.75, p=0.019), M2 (r=0.73, p=0.027), M1 (r=0.72, p=0.029) demonstrated strong but not significant correlations after adjustments to Bonferroni correction. No statistically significant association were identified for the outcome of 'pneumonia aspiration'.

10. DISCUSSION

10.1. Summary

The present study investigates the risk for reporting pneumonia for 20 individual antipsychotics as well as for the use of multiple antipsychotics through a combined pharmacovigilance-pharmacodynamic approach. Our results suggest that there is an inter-drug variation of the risk for reporting 'infective pneumonia' and 'pneumonia aspiration' among antipsychotics. Clozapine, olanzapine and also the use of multiple antipsychotics were associated with reporting both infective and aspiration pneumonia after adjusting for predefined confounders.

10.2. Current knowledge

There are accumulating data showing the association between pneumonia and antipsychotic use. Recently, a meta-analysis of randomised-controlled trials of second generation antipsychotics with placebo suggested that pneumonia and pneumonia aspiration were among the reasons of death with the highest absolute difference between drug and placebo[29]. Additionally, a recently published umbrella review quantified the risk for six life-threatening medical events associated with antipsychotics with one of them being pneumonia. Observational data were used and a strong association between antipsychotics and pneumonia was identified (OR 1.84, 95% CI 1.62-2.09).[63] However, only few studies provide data on individual antipsychotics. Our results agree with a meta-analysis that calculated the risk of pneumonia for eleven antipsychotics with only six of these drugs having data from more than one study. Clozapine[64,65], olanzapine[64–66], haloperidol[64,66], quetiapine[64,65], risperidone[64,65,67] and zotepine[64,65] showed a significantly increased risk of pneumonia when all available data were considered.[68] For clozapine in particular, Rohde et al. using a self-controlled design reported that the largest increase in the number of schizophrenia patients who developed pneumonia was witnessed after clozapine initiation compared to other second generation antipsychotics, with an increase of 0.64% (1.22% to 1.87%). However, they failed to reach statistical significance (p=0.10) possibly due to the small number of clozapine users included in the study.[69] Another study using data from WHO's VigiBase found that the number of pneumonia reports in clozapine patients were higher than anticipated (p<0,001).[70] Several mechanisms have been suggested

to explain this association of clozapine, an antipsychotic selectively prescribed for treatment-resistant schizophrenia, and pneumonia including aspiration, sialorrhea, swallowing impairment, oesophageal dilatation and hypomotility with molecular pathways yet to be proven. Clozapine, olanzapine, as well as quetiapine, due to its similar structure, seems to interact stronger with muscarinic receptors compared to other antipsychotic drugs. Our results on M_1, M_2 and M_4 receptors agree with this finding even though no statistically significant association was identified. Histaminergic H_1 receptor blockage has been also associated with aspiration and pneumonia aspiration not only with clozapine but also olanzapine and quetiapine. On the other hand, most antipsychotics interact strongly with serotonin 5-HT_{2A} and 5-HT_{2C} receptors however the study design used in our study is unable to identify any possible involvement of these receptors as other antipsychotics are used as comparator.[71] Another possible mechanism of clozapine-associated pneumonia is the well-established clozapine-induced adverse drug reaction of agranulocytosis and also a recently suggested possible link between antibody deficiency and clozapine use leading to possible infections vulnerability.[72] The potential mechanism of olanzapine-associated pneumonia has not been widely investigated in the literature. A possible suggestion is that olanzapine and clozapine share a similar chemical structures and thus a similar pharmacodynamic profile.[73] Regarding the use of multiple antipsychotics, our results coincide with the finding of Kuo et al. who showed that antipsychotic polypharmacy was associated with an increased risk of developing pneumonia. Further investigation is needed to identify the mechanism behind this synergic effect.[65]

10.3. Limitations

There are several inherited limitations of studies relying on pharmacovigilance databases that were extensively discussed in chapter 1. Those include, under-reporting, selective reporting and information bias which are common and impede complementary analysis and confounding assessment.[4,11–15] To control for potential competition bias clozapine and olanzapine were excluded in a sensitivity analysis however further unaccounted competition bias is possible.[11,74] Moreover, changes in the database structure and organisation as well as in reporting requirements through years must also be considered.[15] A disproportionality analysis is a statistical method thus any signal is hypothesis generating and further investigation is need to prove

causality between the drug-event pair.[4] Residual and unmeasured confounders remain an inherited limitation of disproportionality analysis. For several antipsychotics, the small number of cases in the collected data did not allow for a robust multivariable logistic analysis and exploring the influence of confounding safely. That is particularly relevant for the outcome of aspiration pneumonia with small numbers of pneumonia associated-events per antipsychotic thus uROR should also be considered when interpreting the result.[75] An additional disproportionality signal was generated for haloperidol and reporting 'pneumonia aspiration' when uRORs were examined. Our pharmacodynamic approach bears also several limitations. Receptor theory is formulated based on several assumptions. It implies that maximal response to a drug is equal to maximal tissue response and that the relationship between occupancy and response is linear and direct.[45] Additionally, total drug concentrations in blood were used to estimate C_U since data on unbound cerebrospinal fluid concentrations of antipsychotics are generally unavailable.[76] Lastly, the mechanism of antipsychotic-associated pneumonia could not be adequately investigated, since correlations were underpowered based on maximum of ten drugs.

Despite their limitations, the spontaneous reporting system and disproportionality analysis are extremely valuable tools for safety monitoring. The strength of this study is the numerous reports of real-world antipsychotic drug use, the examination of data not limited to hospitalized patients, the attempt to work with individual antipsychotics rather than by class but also the investigation of possible increased risk when multiple antipsychotics are used.

10.4. Conclusion

In conclusion, our results suggest a disproportionality signal of clozapine and olanzapine risk for pneumonia, infective and aspiration. Multiple antipsychotic use was also associated with an increased risk for reporting both outcomes. Even though our study design does not allow any causality proof and an appropriate causality assessment is needed to validate our results, it is a step towards understanding the safety profile of antipsychotic drugs and optimising their use among individual patients.

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