A study on the epidemiology of incident seizures in patients with neuropsychiatric disorders

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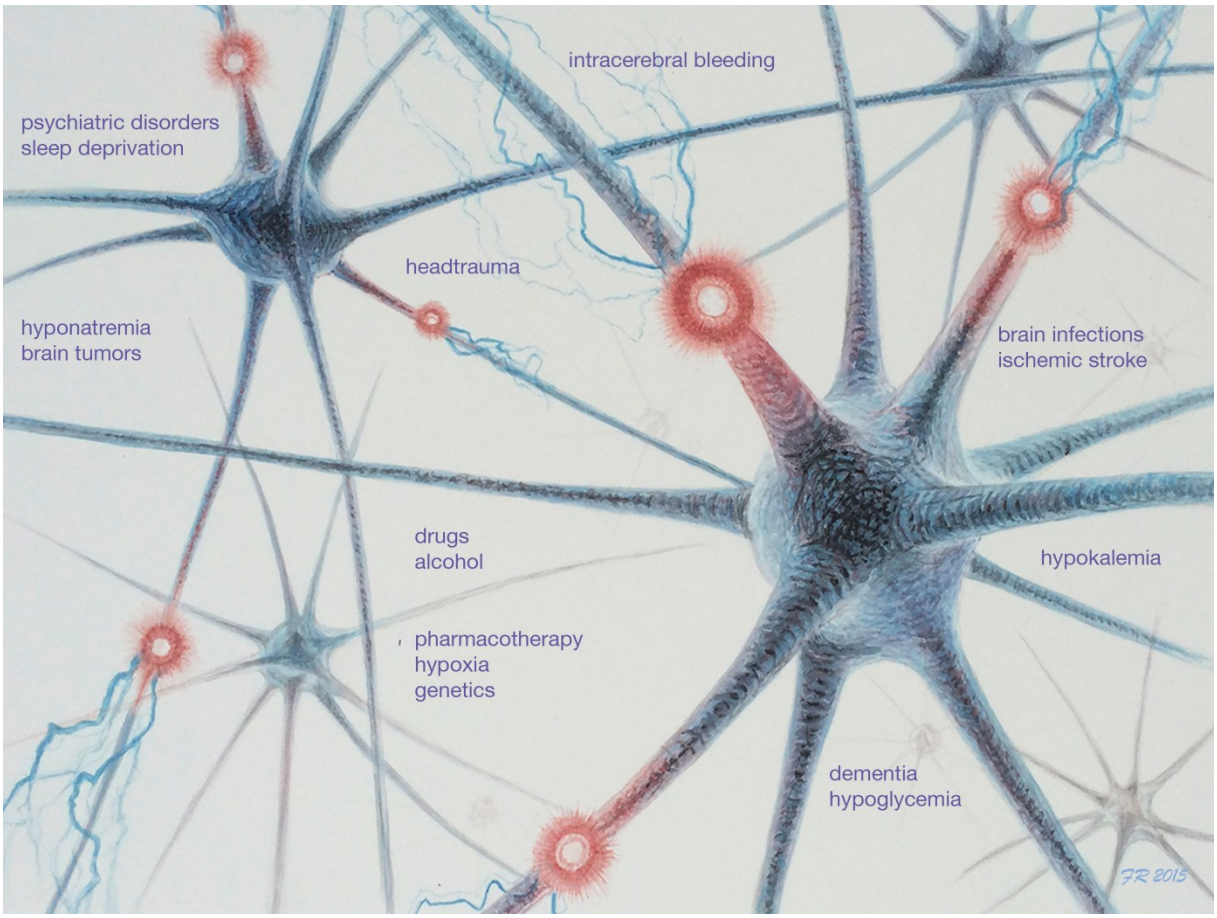

The various risk factors for seizures, a painting by Franziska Rauch (2015)

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I. Summary

Pharmacoepidemiology studies use and effects of drugs in large numbers of people. It allows the investigation and quantification of rare beneficial or adverse events of drugs used by the general population under “real-world” conditions. Pharmacoepidemiologic research strongly depends on and has been facilitated by the development of large scale health care databases. Among these the U.K. Clinical Practice Research Datalink (CPRD) stands as one of the largest and best validated medical records databases worldwide. The CPRD was initiated more than 25 years ago and contains records on diagnoses, drug prescriptions, demographics, lifestyle variables and medical procedures performed from over 12 million patients contributing 64 million person-years of prospectively recorded primary healthcare data.

CPRD data was employed in all studies carried out in this thesis. The goal was set to identify and analyze risk factors for new-onset seizures in patients with neuropsychiatric disorders. While it has long been suspected that patients suffering from neuropsychiatric disorders exhibit an increased risk of new-onset seizures no significant real-world evidence exists on risk factors associated with these seizures.

We first investigated risk factors for new-onset seizures in adult patients with depression. Our results suggest that patients suffering from depression were at an increased risk of seizures if they abused drugs, suffered from alcoholism, had a history of cerebrovascular disease or recent brain injury, comorbid dementia, or comorbid psychiatric disorders. Additionally we found current users of cephalosporins or antiarrhythmics to be at an increased risk of seizures compared with non-users of these drug classes.

In a follow-up study we assessed the association between antidepressant drug use and new-onset seizures in adult patients with depression. Our data suggest that the absolute risk of seizures in this population was rare, irrespective of whether patients used antidepressants or not. Additionally we found that the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) was associated with a twofold increased risk of seizures compared to non-use. However, tricyclic antidepressants (TCAs) at low doses, as prescribed in this primary care setting, were not associated with seizures. Among users of SSRIs and SNRIs, treatment initiation was associated with a higher risk of seizures compared to longer-term treatment. Finally, we could demonstrate that higher doses of antidepressants

prescribed were associated with an increased risk of seizures than lower doses, although small sample sizes limited conclusiveness.

In the final study of this thesis, the potential association between antipsychotic drug use and new-onset seizures among patients with different underlying neuropsychiatric disorders was investigated. The results obtained in this study demonstrate that the association between antipsychotic drug use and seizures was strongly modified by the underlying neuropsychiatric indication. Our data shows that patients with dementia exhibited a significantly higher risk of seizures than patients with affective disorders, irrespective of the use of antipsychotics. Additionally, in patients with affective disorders, current use of medium to high potency first-generation antipsychotics (haloperidol, prochlorperazine, or trifluoperazine) was associated with a more than twofold increased risk of seizures compared to non-use of antipsychotics. In all of these patients, use of all other antipsychotics was not associated with new-onset seizures. In patients with dementia, current use of the second-generation antipsychotics amisulpride, aripiprazole, risperidone, or sulpiride, was not associated with seizures, while current use of all other antipsychotics was associated with an increased risk of seizures.

We found that the inability to adjust for confounding by disease severity, the unproven validity of the diagnoses of affective disorders and seizures, and the limited sample sizes in sub-analyses posed a certain limit to our studies.

Nevertheless, all studies carried out in this thesis provide new insight into the poorly understood relationship between neuropsychiatric disorders and new-onset seizures. Formally quantifying the occurrence of seizures and assessing risk factors for seizures among this restricted study population was only feasible through access to the large existing data set comprising detailed patient information available from the CPRD.

II. Abbreviations

ADHD	Attention deficit hyperactivity disorder
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BCE	Before the Christian Era
BCDSP	Boston Collaborative Drug Surveillance Program
BMI	Body mass index
BPU	Basel Pharmacoepidemiology Unit
CI	Confidence interval
CNS	Central nervous system
CPRD	Clinical Practice Research Datalink
CT	Computed tomography
DDD	Defined daily dose
EEG	Electroencephalogram
FFDCA	Federal Food, Drug and Cosmetic Act
GP	General Practitioner
GABA	Gamma-aminobutyric acid
GPRD	General Practice Research Database
IR	Incidence rate
MRI	Magnet resonance imaging
NA	Not applicable
NMDA	N-Methyl-D-aspartic acid
OR	Odds ratio
PYs	Person-years
RCT	Randomized Controlled Trial
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TIA	Transient ischemic attack
U.S.	United States
U.K.	United Kingdom
VAMP	Value Added Medical Products

1. Introduction

1.1 Pharmacoepidemiology

1.1.1 Defining pharmacoepidemiology

Pharmacoepidemiology, a subdiscipline of epidemiology, investigates use and effects of drugs in large numbers of people.[1,2] Combining clinical pharmacology (i.e., the study of effects of drugs in humans) with epidemiology (i.e., the study of factors that influence or determine the occurrence and distribution of health-related states or events in populations),[2–4] pharmacoepidemiology is primarily used to study large populations of individuals, contrary to clinical pharmacology.[1]

1.1.2 Historical development of pharmacoepidemiologic studies

Before the 1950s, little proof was demanded in terms of safety and efficacy prior to introducing new drugs to the market.[1] Only upon occurrence of harmful events associated with drug use, regulatory actions were taken to ensure drug safety.

One of the most far-reaching drug scandals was the extensive prescription of thalidomide, a sedative drug, to pregnant women.[5] At the time thalidomide showed no toxic effects in animals and was thus assessed and advertised as safe for use in pregnancy.[5] Thalidomide was introduced to the European market in 1957, and withdrawn only four years later.[5] During this period of time, it caused birth defects in more than 10,000 children who were born with missing limbs or limb anomalies.[5]

In 1962, the U.S. government thus made amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), requiring formal proof of efficacy and relative safety in terms of risk-to-benefit ratio for any disease to be treated.[6] The 1962 amendments to the FFDCA enforced the process leading to the establishment of so-called clinical trials, which are nowadays standard procedure prior to placing a new drug on the market.[6]

1.1.3 Clinical trials and the role of pharmacoepidemiology

Clinical trials are used to investigate pharmacokinetic and pharmacodynamic properties of a drug, and to evaluate a drug's efficacy, safety, and tolerability.[6] They are carried out in a series of subsequent steps, so-called phases, where each phase is designed to investigate a specific aspect of the process of drug development (see **Figure 1** for details).

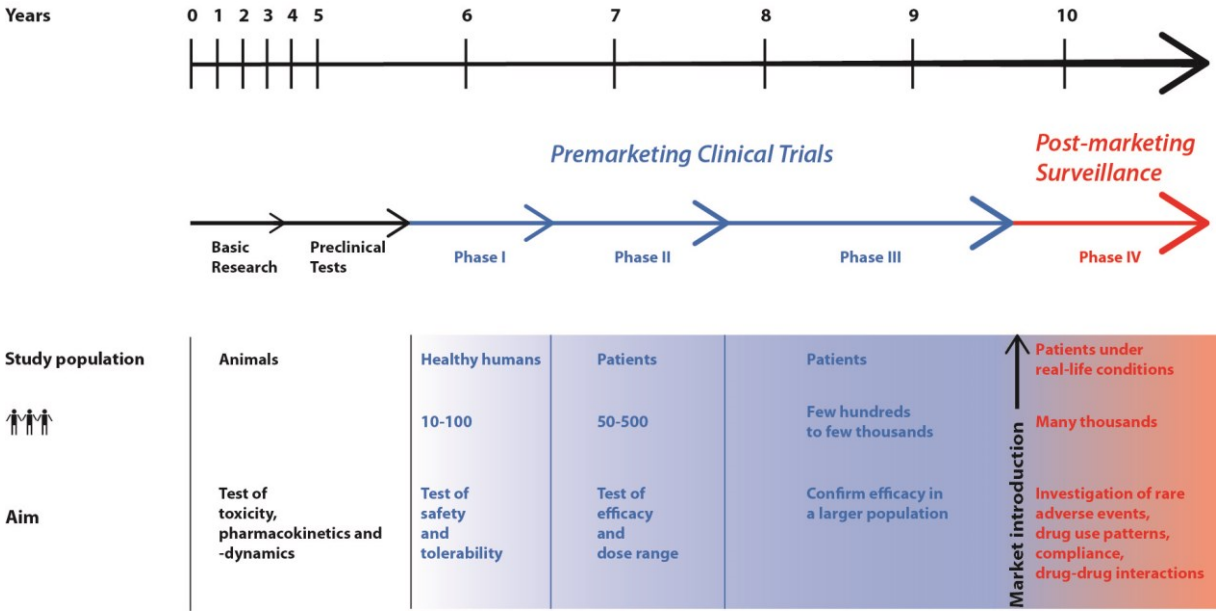

Figure 1: Clinical trials are carried out in a step-wise manner. Each phase of the trial aims to answer a specific question. Figure adapted from[6].

1.1.3.1 Clinical trials: phase I to III

Phases I to III of clinical trials are limited in sample size and observational duration (as shown in **Figure 1**).

These initial phases of clinical trials are conducted in a well-defined, yet artificial environment, where specific patient subgroups (e.g., elderly patients, polymorbid patients who use various drugs, women of childbearing age, and children) are excluded from the analysis.[6]

1.1.3.2 Clinical trials: phase IV

As the drug is placed on the marked and thus used by the general population, including all patient subgroups, phase IV of clinical trials is initiated. The so-called post-marketing surveillance phase studies beneficial and adverse effects of drugs in the general population.[3] Since drugs are often used over longer periods of time in "real life" than in phases I to III of clinical trials, phase IV investigates rare or delayed adverse or beneficial effects that were not noticed prior to market introduction.[1]

The post-marketing surveillance comprises pharmacovigilance and pharmacoepidemiology studies. Pharmacovigilance studies are based on spontaneous reporting systems of adverse drug events, and are important to detect signs of adverse events not seen in phases I-III of clinical trials.[7] Such reports are however difficult to interpret; only a small (unknown) proportion of suspected adverse events of drugs are reported spontaneously, and adverse events are more likely reported if they are serious, or if the drug has received a lot of media attention.[3,7,8]

Formal quantification and investigation of adverse drug events is done in pharmacoepidemiologic research.[1,8] Therefore, it is essential to know the number of people exposed and not exposed to the drug under investigation, as well as the number of people in each group who developed the outcome in question. In conclusion, the major goal of pharmacoepidemiologic research is to describe drug utilization patterns under "real life" conditions and to quantitatively investigate previously undetected beneficial or adverse drug effects.[1]

1.1.4 Association types in pharmacoepidemiology

Pharmacoepidemiology investigates potential associations between drug exposure and beneficial or adverse outcomes. An association is defined as two events (i.e., drug exposure and outcome under investigation) occurring together repeatedly, with this repeated occurrence taking place more often than a chance occurrence.[3] The following four scenarios can result from investigating such potential associations: No association, artifactual associations, indirect associations, or causal associations.[9]

1.1.4.1 No association

No association between exposure and outcome is observed when exposure and outcome are in fact independent of one another or when the power of the study was too low to detect an association.

The power of a study can be defined as the probability to detect an association between exposure and outcome if the association exists.[2] The power increases with the precision of the outcome variable, the strength of the association, the sample size, and increased α-level (refer to 1.1.4.2).[10]

1.1.4.2 Chance and bias – two types of artifactual associations

Chance (i.e., random error), is a *random* variation due to every study being performed on only a sample of the entire population while inferring from this subset to the whole population. Depending on the analyzed sample results will vary due to irregular variations. Random errors associated with the results obtained from analyzing such subsets will decrease with increasing sample size.[2,4,8]

Whether associations observed between exposures and outcomes are due to chance or not can be assessed by statistical testing. First, an (arbitrarily) selected level, the α-level, is set. The α-level specifies the probability P that an association is due to chance only when in reality no association exists.[4] As a standard, an α-level of 0.05 is chosen, referring to the P-level reported in most pharmacoepidemiologic studies.[4,10]A reported association between a specific exposure and outcome with a P-value smaller than 0.05 ($P<0.05$) is interpreted as a statistically significant association, thus ruling out the possibility of a chance finding with a confidence of greater or equal to 0.95 ($\geq$ 95%).[8,9] P-values do not convey a message on the strength or the relevance of an association; they simply convey a message on how unlikely an observed association would be if in reality there was no association.[10]

In contrast to chance, **bias** (i.e., systematic error), is a *systematic* variation due to treating or evaluating two study groups consistently differently. Unlike chance, bias is insensitive to sample size and cannot be ruled out by statistical testing.[8]

Bias can cause an apparent association between exposure and an outcome when in reality no association exists.[9] It is therefore important to prevent bias by selecting a proper study design since it cannot be controlled for after study completion. The literature distinguishes broadly between two types of bias: selection and information bias.

Selection bias refers to situations in which the estimated effect of an exposure on an outcome is distorted due to procedures used to select subjects for study participation.[2,8] For example, if study participation is voluntary, participators might differ systematically in exposure and outcome status from those declining participation; since the association between exposure and outcome among nonparticipants is unknown, so is the degree of the systematic error introduced.[8]

Information bias refers to situations in which the estimated effect of an exposure on an outcome is distorted because the information collected on exposure and/or outcome is erroneous.[8] Common types of information bias are measurement bias (i.e., measurement of exposure or outcome is not done in a comparable way in groups to be compared), recall bias (i.e., individuals affected by the outcome remember exposures differently than individuals not affected by the outcome), or interviewer bias (i.e., interviewers behave differently with the groups to be compared).[8]

1.1.4.3 Indirect associations

Indirect ("spurious") associations result from confounding. Confounding variables are variables other than the exposure or outcome under investigation. They are associated with the exposure (without being an effect of the exposure) and are risk factors for the outcome, creating an apparent association or masking a real association between exposure and outcome.[8,9]

An example of a confounder is the apparent association between wearing leather shoes in bed at night and suffering from a headache the morning after. One could claim that wearing leather shoes at night causes headaches, when in reality it is heavy drinking associated with forgetting to take off the shoes before going to bed.[11]

Confounding in pharmacoepidemiologic studies can be limited if the existence of a confounder is known and if the confounder can be measured.[8] This can be done by

restricting the study population (i.e., exclusion of individuals with potential confounders), matching cases and controls (in case-control analyses) or exposed and non-exposed individuals (in cohort studies) on potential confounders, stratifying the analyses by the potential confounder, or mathematical adjustments in the analysis.[8]

1.1.4.4 Causal associations

The primary aim of pharmacoepidemiologic research is to determine whether a certain exposure is causally associated with a specific outcome. However, statistical testing cannot assess causality and thus an observed association can, even when statistically significant, be simply due to bias or confounding (see previous chapters for a discussion of these factors).

Nevertheless, certain criteria that were developed in 1965 by Sir Austin Bradford Hill,[12] can be applied to assess the likelihood of a causal association. The most important of these criteria for pharmacoepidemiologic research, and their respective meanings, are summarized in **Table 1.**

Table 1: Bradford Hill criteria and their respective meanings used to assess causality in pharmacoepidemiologic studies (summarized from[12]).

Criterion	Meaning
Strength of the association	The stronger the association the more likely a causal link.
Consistency	The association has been observed by different investigators, in different places and times, and under different circumstances.
Temporality	The exposure must precede the outcome. A typical pitfall: a drug is taken for early signs of a disease which has not yet been diagnosed. The temporal sequence suggests that the drug causes the disease, when in reality the disease started before the drug exposure.
Dose-response relationship	The higher the exposure (e.g. an increase in drug dose) the greater the effect (e.g. adverse event).
Biological plausibility/Coherence with existing information	Good general theory to explain a causal link. The association makes sense taking into account the evidence from the literature; however this criterion strongly depends on the available literature. This criterion is never absolute, as knowledge changes over time, and so does plausibility that something is true.
Experimental evidence	Changing the exposure under controlled conditions causes a change in the outcome.
Reversibility	Removal of exposure leads to decline in outcome.

None of these "Bradford Hill criteria" are considered sufficient to prove causality.[12] However, the more criteria are met, the more likely an association is causal.[9] Thus, any observed association in pharmacoepidemiology has to be interpreted in the context of the best evidence available at the time the study is carried out.[9]

1.1.5 Study designs in pharmacoepidemiology

Pharmacoepidemiologic research is frequently categorized into observational studies (descriptive studies, analytical studies) and interventional studies (e.g. randomized controlled trials).[13] Depending on the purpose of the research, some study designs are better suited than others (refer to the subsequent chapters for discussion of the different study types).

1.1.5.1 Observational studies

Observational studies are categorized into descriptive or analytical studies and are used to investigate drug utilization patterns and drug safety.[13] A major advantage of observational studies is that they can be applied if interventional studies are unethical (e.g., if an exposure is known to be harmful), unnecessary (e.g., if an intervention is already proven to be efficient), or not feasible (e.g., if the outcome is rare or delayed).[14]

1.1.5.1.1 Descriptive studies

Descriptive studies are employed to characterize existing distributions of exposures or outcomes without investigating causal inferences.[2] Descriptive studies are useful for generating hypotheses, although they cannot be applied to determine whether exposure or outcome occurred first.[15] Additionally, due to the lack of comparison groups, no causal associations can be determined.[2,13,15] In the following, the different types of descriptive studies including case reports, case series, ecologic studies, and cross-sectional studies are discussed.

Case reports describe the experience of one patient while **case series** describe the experience of several patients when using a particular drug (e.g., what clinical features are observed after a drug overdose?). Case reports and case series do not provide sufficient evidence for making causal inferences, but they often give rise to hypotheses.[13] For

example, several authors reported seizures as an adverse event in patients using second-generation antipsychotics such as quetiapine, aripiprazole, or olanzapine, in therapeutic or in overdoses.[16–20]

Ecologic studies do not investigate data from individual patients, but from groups. These studies can be useful to describe differences in the prevalence of certain exposures and outcomes between groups or countries.[13] However, no conclusions can be drawn at the individual level, because confounding factors of the individuals are unknown.[13] In a recent study the correlation between antidepressant prescribing patterns in Organization for Economic Co-operation and development (OECD) countries and the rates of suicide was assessed.[21] While a weak positive correlation between antidepressant use and suicide was observed between countries, no inference could be made at a person's individual risk of suicide associated with the use of antidepressants.[21]

In **cross-sectional (prevalence) studies**, a certain exposure or outcome in a population is assessed at a specific point in time, or during a specific time span. The prevalence of an exposure or outcome is defined as the total number of individuals who have the exposure or outcome under investigation at a particular time (or over a particular time span), divided by the population at risk of having this exposure or outcome at that time (or over that particular time span).[2] The prevalence of an exposure or outcome in a population is often reported as a percentage. Examples of cross-sectional studies are investigations on lifetime prevalence estimates of major depression across different countries.[22,23]

1.1.5.1.2 Analytical studies

Analytical studies assess and quantify the association between exposures and outcomes.[2] Cohort and case-control studies are two main study types used to test hypotheses on the etiology or risk factors for an outcome.

Cohort studies identify the study population based on exposure status, as described in the following two paragraphs summarized from[24]. The population is followed over time to investigate differences in outcomes between the different exposure groups. In their simplest form, cohort studies compare exposed individuals (i.e., individuals with the alleged risk or protective factor) to unexposed individuals (i.e., individuals not having this

factor) with regard to subsequent outcome frequency. In more elaborate settings, different exposure groups can be studied simultaneously.

In cohort-studies, the study population is initially outcome-free and the occurrence of the outcome is measured over time. This type of study can be performed prospectively (i.e., data on exposure and outcomes is collected while the study is conducted) or retrospectively (i.e., data on exposure and outcomes is already available at the time the study is conducted) (see **Figure 2**, upper part).

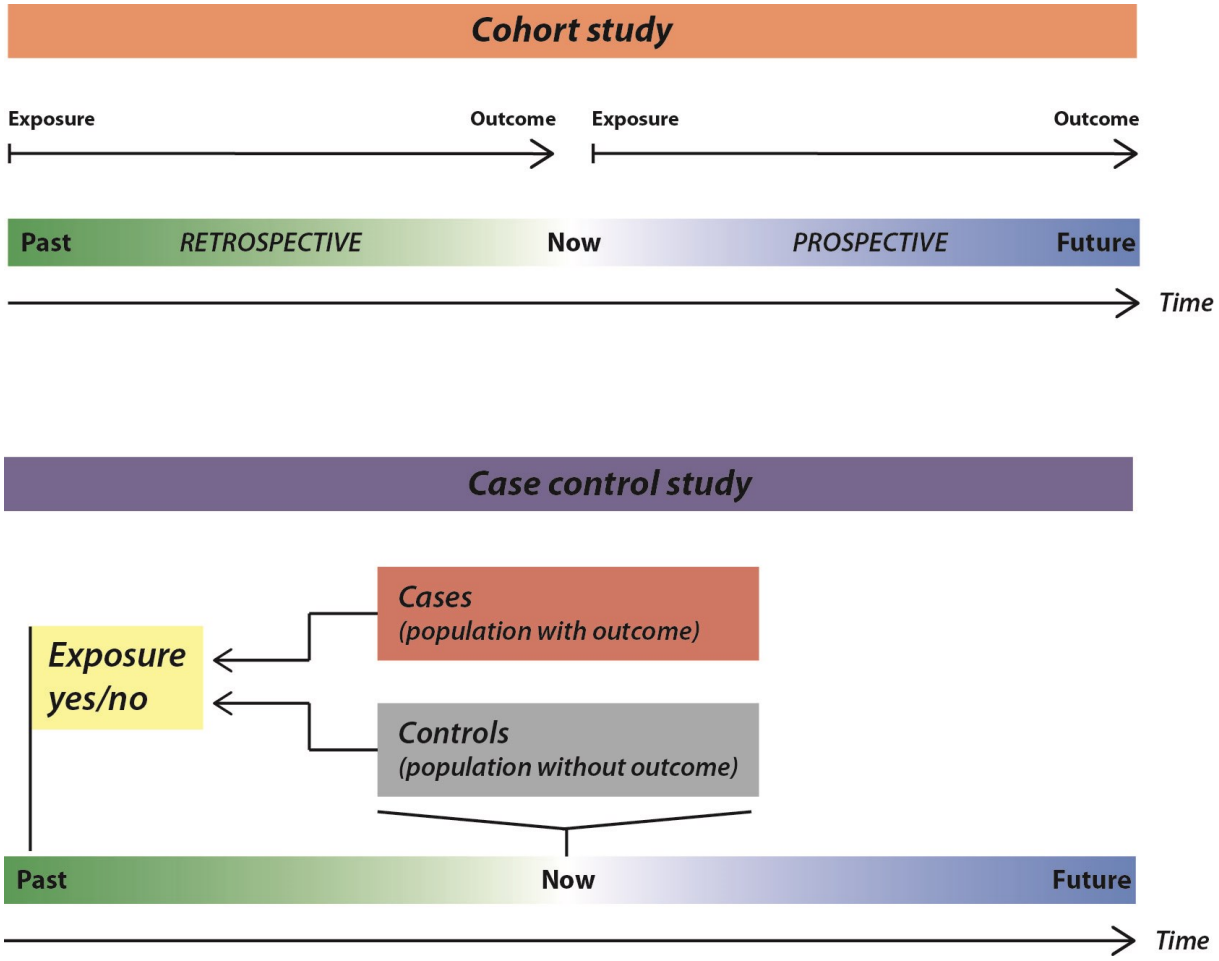

Figure 2: Settings of cohort and case-control studies (adapted from[24,25]).

For example, a British cohort study published in 2011 assessed the association between the use of tricyclic and related antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or other antidepressants, and severe adverse events, in depressed patients aged 65 or over.[26]

In a **case-control study**, the study population is identified based on outcome status. Cases with an outcome are compared with controls without the outcome, looking for differences in antecedent exposures (see **Figure 2**, lower part).[25]

In a case-control study conducted between 1995 and 1999, the cases were all Icelandic patients aged 10 years or over who had a first unprovoked seizure; for each case, a suitable age-matched control who did not have seizures up to the time the case had a seizure was identified.[27] The odds ratio of antecedent major depressive disorder was 1.7-fold increased among cases compared with controls, suggesting that major depressive disorder is a risk factor for first unprovoked seizures.[27]

Table 2 summarizes advantages and limitations of cohort studies and case-control studies.

Table 2: Differences between cohort- and case-control studies, and advantages and limitations of both study designs.[9,13,24,25,28]

	Cohort study	**Case-control study**	**Comments**
Sample size	Large	Usually smaller than cohort study	
Time	Slow	Rapid	Not an issue for retrospective database research using medical records
Cost	High	Usually smaller	Not an issue for retrospective database research using medical records
Analysis	Computationally more complex than case-control studies	Computationally easier than cohort studies	Especially if time-dependent exposures are analyzed
More suited for	Rare exposures: special groups with a high frequency of the exposure can be identified and included in the study population	Rare outcomes: a sufficiently large number of cases with the outcome can be included	
Outcomes to be studied	Multiple	Just one	In case-control studies, it is important to ensure that the exposure occurred prior to the outcome
Exposures to be studied	Just one	Multiple	
Measures	All measures, including incidence rates, attributable risks, and relative risks	Only odds ratio: incidence rates cannot be calculated as the size of the population at risk is unknown	The odds ratio is a valid estimate of the relative risk if: 1) the cases are representative of the population at risk, 2) the controls are randomly selected from the population giving rise to the cases, 3) the outcome is rare in the population at risk (<5%)
Validity of exposure data	Generally higher than in case-control studies (as participants are selected based on their exposure)	Generally lower than cohort studies: retrospective assessment of exposure limits its validity	Not an issue for retrospective database research using medical records

Table 2 (cont.)

	Cohort study	**Case-control study**	**Comments**
Comparison of exposed and unexposed groups/ cases and controls	Exposed and unexposed individuals must be as similar as possible at baseline in all aspects except the exposure under investigation	Controls should be selected from the same population that gave rise to the cases	
Causal relationships	More reliable: all subjects are outcome-free at the beginning (temporal relationship given), and exposure information can be more accurately assessed	Less reliable: temporal relationship not as easily identified, exposure information can be biased	Not an issue for retrospective database research using medical records

Generally one refers to a **nested case-control study** when the population within which a case-control study is conducted is well defined.[8] Nested-control studies rely on the advantages of both cohort and case-control studies.

The following paragraph represents a summary of[28]:

In a nested case-control study a cohort of individuals is followed until they develop the outcome under investigation or until their follow-up ends due to other reasons (e.g., death or loss to follow-up). The analysis is then conducted as a case-control analysis. The individuals who developed the outcome are defined as cases, and the date of their outcome is named index date. The individuals who did not develop the outcome up to the index date of the case are potential controls. Instead of analyzing the whole original cohort of individuals (as is done in cohort studies), only the cases and a defined number of all potential controls are analyzed. Thus, nested case-control studies are well suited to investigate time-dependent exposures (e.g., drugs in a large cohort of individuals followed over many years). In such cases, nested case-control analyses are computationally less complex than analyses of the entire cohort.

Additionally, nested case-control studies are advantageous if exposure information is costly (e.g., analyses of blood samples), and when seeking this information for everyone in the cohort is too expensive.[8]

1.1.5.2 Experimental (interventional) studies

The following paragraph represents a summary of[4]:

Experimental studies are cohort studies in which the exposure status is determined by the investigators. This study design allows testing the efficacy or risk of an intervention. In randomized control trials (RCTs), the intervention is allocated randomly (i.e. the assignment is unpredictable). The major strength of this design is that investigators cannot allocate the intervention, thus all patients are as likely to receive it. Thus, in large RCTs the groups with or without the intervention are likely to be similar with regard to potential confounding variables (e.g., age, sex, severity of disease).

As selection bias and confounding are avoided, associations demonstrated in RCTs are more likely to be causal than those demonstrated in observational studies.[9] However, RCTs lack

generalizability, since they cannot assess safety issues in large populations of individuals who use drugs under everyday conditions in clinical practice.[29]

1.1.6 Data sources in pharmacoepidemiology

The increased availability of large health care databases has facilitated pharmacoepidemiologic studies. Thus, drug utilization or safety studies can be conducted in subgroups of patients that were excluded from clinical trials. Additionally, if multiple years of patient follow-up data are available, assessment of long-term safety of drugs is possible.[3]

Available databases can be divided into the two main categories *medical records databases* (data is collected by physicians [usually primary care providers] who enter information on patients while providing medical care) and *administrative databases* (data is collected primarily for administrative purposes, such as reimbursement of health care services).[29,30]

One of the largest and best validated medical care databases worldwide is the U.K. Clinical Practice Research Datalink (CPRD).[31] This database was established in 1987 as 'Value Added Medical Products (VAMP)' database, and was long known as 'General Practice Research Database (GPRD)'.[32] In 2011, the CPRD contained records from more than 12 million patients contributing 64 million person-years of prospectively recorded primary healthcare data.[33]

The U.K. health care system is particularly suitable for establishing primary care research databases such as the CPRD, as almost every person in the U.K. is registered with a general practitioner (GP) who functions as a 'gate-keeper' in the healthcare system. Secondary care (specialist care, hospital care, etc.) is either provided at the request of the GP, or if directly assessed, full disclosure from secondary care is reported back to the GP.[33] Through this prospective recording by the GPs and the nearly complete medical histories of patients, this database is especially valuable for pharmacoepidemiology.

While prescription data is nearly completely documented as the GPs use the computer to generate prescriptions, diagnoses must be manually recorded and can therefore be incomplete or wrongly coded.[34] Although the validity of the diagnoses recorded in the CPRD is high (with an average positive predictive value of almost 90%), records of acute disorders may be less valid than records of chronic disorders.[34,35]

Today, researchers can access through a linkage system data from secondary care hospital episode statistics, death certification data, socioeconomic classification data, and disease registry data including the National Cancer Intelligence Network and the Myocardial Infarction National Audit Program register.[33]

Table 3 summarizes different data types available to researchers from the CPRD.

Table 3: Overview of the different data types available to researchers from the CPRD.[32]

Data	Details
Patient characteristics	Gender, birth year, weight, height, body mass index, occupation, ethnicity, marital status etc.
Patient demographics	Practice attended, U.K. region the patient lives in
Medical diagnoses	Recorded as "Read codes"
Drug prescriptions	Including quantity of the prescribed drug, and dose instructions
Lifestyle variables	Smoking status, alcohol consumption
Referrals to hospitals or specialists	With diagnoses, drug prescriptions
Laboratory tests	E.g. blood and urine tests

1.2 Seizures and Epilepsy

1.2.1 Defining seizures and epilepsy

Seizures are transient disruptions of brain function resulting from excessive neuronal activity.[36] Depending on location and extent of the affected brain regions, seizures result in alterations of muscle tone, sensations, consciousness, or behavior.[36] Seizures are clinical events that can occur in all people for example after sleep withdrawal, overdoses or withdrawal from certain drugs, or hypoxia.[37]

Epilepsy is a chronic condition of repeated spontaneous seizures.[36] Spontaneous seizures are defined as seizures without a direct precipitating cause. A diagnosis of epilepsy requires either at least two spontaneous seizures occurring more than 24h apart, one spontaneous seizure with a high risk of recurrence, or the diagnosis of an epilepsy syndrome (defined by a cluster of symptoms occurring together including seizure type, etiology, age of onset, and other factors).[38,39] Epilepsy is a disorder of the brain that is characterized by an enduring predisposition to generate seizures.[37]

1.2.2 History of seizures and epilepsy

Seizures and epilepsy have been studied by medical scholars throughout time. One of the earliest publication on epilepsy, "the Sacred Disease", part of the Hippocratic Collection, was written in 400 BCE, potentially by Hippocrates himself.[40] It was suggested that epilepsy is a hereditary disorder of the brain, and thus contemporary beliefs that seizures and epilepsy were a sign from the gods were refused[40]:

"*My own view is that those who first attributed a sacred character to this malady [i.e., epilepsy] were like the magicians, purifiers, charlatans and quacks of our own day, men who claim great piety and superior knowledge. Being at a loss, and having no treatment which would help, they concealed and sheltered themselves behind superstition, and called this illness sacred, in order that their utter ignorance might not be manifest."*

While this early report showed profound knowledge of the human body, it was not until very recently that the findings of Hippocrates were acknowledged. For example, throughout the Middle Ages and the Renaissance, patients with epilepsy were thought to be possessed by the devil and women with epilepsy were persecuted as witches.[41]

It was not until the mid-19th century, when John Hughlings Jackson recognized that seizures were caused by "occasional, sudden, excessive discharges of gray matter".[39] Jackson discovered that seizures could spread from a single focus with localized motor symptoms to generalized seizures accompanied by loss of consciousness.[36,39]

Following these findings, bromide, the first antiepileptic drug, became available, followed by phenobarbital (1912) and phenytoin (1937).[36,39] With the development of new techniques, such as the electroencephalogram (EEG) in 1929, neuroscientists were able to show that seizures are associated with neuronal hyperexcitability in the brain.[39]

1.2.3 Epidemiology of seizures and epilepsy

Worldwide, it has been estimated that up to 10% of people have at least one seizure at some point in their life, and 0.4 - 1% of people suffer from epilepsy.[42,43]

In developed countries the overall incidence rate of **spontaneous seizures** was estimated 55 per 100,000 person-years.[44,45] These data are not conclusive with regard to potential gender differences in seizure risk.[44–46] Spontaneous seizures occur most frequently in neonates and infants (incidence rate 100 to 130 per 100,000 person-years) and people aged 65 years or over (incidence rate 110 to 180 per 100,000 person-years).[44,46]

Focal seizures with or without generalization are assumed to be more common than generalized-onset seizures; however, in most studies misclassification of seizure types is difficult to estimate (*see chapter 1.2.6*).[44,45,47]

Estimates of the overall incidence rate of **epilepsy** range from 30 to 50 per 100,000 person-years in high income countries to 120 per 100,000 person-years in low-income countries.[42,43,47] The higher incidence of epilepsy in low-income countries compared to high-income countries is presumably caused by parasitic diseases associated with seizures, such as malaria or neurocysticercosis, as well as lower standards in medical infrastructure.[47] It was shown that incidence rates of epilepsy exhibit similar age-related trends as incidence rates of spontaneous seizures, with peaks in the first year of life and at ages 65 or over.[44,45]

Focal epilepsies, commonly caused by localized tumors, developmental malformations, or damages after head trauma or stroke, account for about 60% of all epilepsies. Generalized epilepsies, mostly based on genetic mutations, account for the remaining 40% of epilepsies.[39]

1.2.4 Risk factors for seizures and epilepsy

Risk factors for seizures and epilepsy vary by age groups, as **Table 4** displays. Across all age groups however, the causes of seizures remain unknown in most cases.

Table 4: Causes of seizures overall (%) and by age group (✓: frequent cause in this age group).

	Causes							
Age group	Unidentified cause [44]	Cerebrovascular disease [44]	Neoplasms [44]	Traumatic brain injury [46,48,49]	Cerebral palsy/intellectual disability [44]	Infection [46,48,49]	Neurodegenerative diseases [44,46]	Other [46,48,49]
All ages	68%	9%	6%	5%	4%	1%	7%	1%
Neonates and children	✓			✓	✓	✓		
Middle aged	✓	✓		✓		✓		
Adults aged 65	✓	✓					✓	

Numerous additional risk factors for seizures have been identified (see **Table 5**).

Table 5: Additional risk factors for seizures

Category	**Risk Factor**	**References**
Additional risk factors for seizures	Heavy alcohol consumption or alcohol withdrawal	[50–53]
	Illicit drug use	[54]
	Medication use or withdrawal	[55–60]
	Metabolic or electrolyte imbalances	[61]
	Fever	[61]
	Severe dehydration	[62]
	Sleep deprivation	[63,64]
	Anoxic encephalopathy	[60]
Additional disorders associated with an increased risk of seizures	Depression and suicidality	[27,65,66]
	Other psychiatric disorders	[66,67]
	Migraine with aura	[68,69]
	Severe hypertension	[70,71]
	Attention deficit (hyperactivity) disorder	[72]
	Multiple sclerosis	[73,74]
	Systemic lupus erythematosus	[74]
	Preeclampsia	[60]

1.2.5 Mechanism of seizures

Little is known about the physiological processes underlying seizures. The following paragraphs summarize the current knowledge about how seizures may be generated by the brain[36,39,75]:

Glutamate is the major excitatory transmitter while GABA (γ-Aminobutyric acid) is the main inhibitory transmitter in the brain. It is currently believed that excessive synaptic activity during seizure results from an imbalance between these two antagonistic neurotransmitters.

Depolarization and thus neural excitation is triggered by two types of glutamate regulated channels, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-Methyl-D-aspartic acid), in combination with voltage gated sodium and calcium channels. Hyperpolarization and therefore neural inhibition is caused by activation of GABA receptor-mediated chloride channels and different types of potassium channels.

Under normal conditions, post-hyperpolarization following an action potential prevents immediate generation of a new action potential and thus neuron hyperexcitation. However, during a seizure, neurons located in the seizure focus exhibit a prolonged depolarization phase (depolarization shift), which can be identified as a sharp waveform in the EEG of patients. The observed depolarization shift is followed by rapid firing of action potentials in affected neurons. During such an event GABAergic inhibition of regulatory signals appears to be suppressed, enabling the spread of neural hyperexcitability to surrounding areas in the brain.

1.2.6 Seizure types

Focal seizures start within networks of one brain hemisphere, and are classified based on whether they affect consciousness or awareness.[76] Focal seizures can evolve to generalized seizures affecting both hemispheres.[76]

Generalized seizures begin at some point within, and rapidly engage networks distributed in both brain hemispheres.[76]

Classification and features of focal and generalized seizures are summarized in **Table 6**.[43,76–78]

Table 6: Classification and key features of focal and generalized seizures. Summarized from[43,76–78].

		Typical manifestations	Consciousness	Duration
Focal seizures	*Without impairment of consciousness or awareness*	Motor symptoms: jerking, spasms, posturing, reversible weakness in one side of the body (Todd's paralysis) Sensory- or psychic symptoms (i.e. aura): tingling, numbness, pain, feeling of heat, hallucinations (flashing lights), sudden intense emotions (fear, depression, anger, irritability), dysphasia, disturbance of memory, sensations of unreality or depersonalization, hallucination of vision, taste, or smell	*Preserved*	Mostly only a few seconds
	With impairment of consciousness or awareness	Altered consciousness (confusion, unresponsiveness, motor arrest) Automatisms (repetitive movements such as chewing, lip smacking, fiddling, tapping, whistling, humming, uncoordinated violent behavior)	*Impaired or lost*	Few seconds to minutes
Generalized seizures	*Tonic*	Stiffening of muscles (e.g. contraction of facial or respiration muscles, rising up of arms) Falling over, usually backward	*Impaired or lost*	Less than 60 s, person recovers quickly
	Clonic	Jerking or twitching of limbs or body		About 2 min
	Myoclonic	Brief contraction of muscles, resulting in sudden irregular jerking or twitching of trunk or one or more limbs Sometimes caused by drugs (antidepressants, antipsychotics), drug toxicity or withdrawal, post-hypoxic brain damage Presentation varies from subtle jerk to violent jolt		Fraction of a second
	Atonic	Sudden relaxation of muscles Person often falls over, usually forward (also called "drop attacks")		Less than 60 s, person recovers quickly
	Tonic-clonic ("grand mal")	Loss of consciousness, tonic phase with flexion and rigidity Clonic phase with convulsions of usually all four limbs Stertorous breathing, froth of saliva from mouth, loss of bladder control, cyanosis		Tonic phase: 10-30 s Clonic phase: 30-60 s Confusion after: > 10 min
	Absence ("petit mal")	Abrupt loss of consciousness and cessation of motor activity, staring vacantly into space Mostly in children or adolescents, continue into adulthood in 7-80% of cases EEG diagnostic in more than 90% of cases		Mostly less than 10 s

1.2.7 Diagnosis of seizures

Diagnosis of an epileptic seizure mainly relies on the patient's clinical history, rendering eye witness reports of seizures crucial in establishing a correct diagnosis.[78]

Although no features exclusively correlated with epileptic seizures are known, a handful of strong seizure markers have been identified to this point: postictal confusion,[78,79] occurrence out of sleep,[79] cyanosis,[78,79] lateral tongue biting,[78,79] preceding "déjà vu" or "jamais vu",[78,79] confirmed unresponsiveness, head or eye turning to one side,[78,79] rhythmic limb shaking,[78] and unusual posturing.[78,79]

Following an initial seizure event, an EEG recording is done to detect potential abnormalities in electrical activity. However, less than half of patients undergoing epileptic seizures show detectable EEG abnormalities within 24h after seizure occurrence.[80] Additionally, magnet resonance imaging (MRI) or computed tomography (CT) are used to detect direct causes of seizures, such as brain injuries, brain tumors, or stroke.[61]

A variety of medical conditions imitate symptoms of epileptic seizures leading to one third of false epileptic seizure diagnoses.[78] For example, about 20% of patients referred to epilepsy centers have psychogenic nonepileptic seizures, by definition a psychiatric, not a neurologic disorder.[79] This type of seizures is characterized by a resistance to antiepileptic drugs, unusual triggers, a tendency to occur in the presence of an audience, a history of psychiatric diagnoses, and the presence of a normal EEG during video monitoring of the seizure.[79]

Differential diagnosis of epileptic seizures should therefore include the following seizure imitators[61,80,81]:

i. Neurological disorders such as transient ischemic attacks, transient global amnesia, migraine, restless legs syndrome.
ii. Cardiovascular disorders such as vasovagal syncopes, orthostatic hypotension, cardiac arrhythmias, or structural heart disease.
iii. Sleep disorders such as obstructive sleep apnea, hypnic jerks, or narcolepsy.
iv. Movement disorders such as paroxysmal dyskinesia.
v. Psychological disorders such as night terror, panic attacks, or psychogenic nonepileptic seizures.

From the seizure imitators listed above syncopes and psychogenic nonepileptic seizures are most frequently misdiagnosed as epileptic seizures.[79] It has been reported that the occurrence of syncopes is more likely compared to epileptic seizures when nausea, sweating, lightheadedness, or prolonged standing or sitting precede the event.[78,80] Motor symptoms associated with syncopes are clonic or myoclonic but stop once the patient lies horizontally.[79] Additionally, bradycardia and hypotension are more common in patients with syncopes, while tachycardia and hypertension are more common in patients with epileptic seizures.[61]

1.2.8 Therapy of seizures

Currently, no cure for epilepsy exists. However, available therapies reduce seizure occurrence in 70-80% of patients and thus strongly improve quality of life.[39,82]

While first-time seizures are treated pharmacologically only under certain circumstances, recurrent seizures in patients with epilepsy are treated with antiepileptic drugs to reduce morbidity and mortality associated with further seizures.[82]

Anti-seizure drugs can be categorized according to different types of mechanism:

1) **Sodium channel blockers** inhibit Na^+-channels to recover from inactivation und reduce the ability of neurons to fire action potentials at high frequency (e.g., carbamazepine, lamotrigine, phenytoin, topiramate, valproic acid, and zonisamide).
2) **$GABA_A$ receptor agonists** inhibit the postsynaptic cell by increasing the inflow of chloride ions into the cell, thus hyperpolarizing the neuron (e.g., benzodiazepines and barbiturates)
3) **Inhibitors of the presynaptic GABA transporter** promote GABA release into the synaptic cleft (e.g. tiagabine).
4) **Calcium channel blockers** inhibit opening of voltage-gated T-type Ca^{2+}-channels thus reducing Ca^{2+} ion inflow and postsynaptic neuron depolarization (e.g., ethosuximide, valproic acid).
5) **NMDA-type and AMPA-type glutamate receptor antagonists** reduce Na^+ ion inflow into the postsynaptic neuron, thus inhibiting postsynaptic depolarization (e.g. felbamate, topiramate, phenobarbital, tiagabine).

Chapter 2

Aims of the thesis

2. Aims of the thesis

Neuropsychiatric disorders have repeatedly been reported to increase the risk of seizures.[27,65–67,83–86] The overall aim of this thesis was to study the occurrence and the determinants of new-onset seizures among patients with neuropsychiatric disorders under real-world conditions.

An initial project aimed to explore risk factors for new-onset seizures among adult patients with depression. Although several observational studies have reported a correlation between depression and seizures,[27,65–67] risk factors for new-onset seizures in patients with depression have not been investigated. Thus, this project assessed the association between lifestyle factors (e.g., drug abuse, alcoholism, and smoking), neurologic or psychiatric comorbidities, and concomitantly used drugs, and new-onset seizures in adult patients with depression.

Two subsequent studies aimed at investigating the association between psychotropic drug use and seizures, thereby discriminating between potential drug effects and effects of the underlying neuropsychiatric disorders.

The purpose of the second project was to explore the association between antidepressant drug use and new-onset seizures among adult patients with depression. Since antidepressants are used for numerous disorders (i.e., depression, anxiety disorders, bipolar disorder, obsessive-compulsive disorders, post-traumatic stress disorder, and chronic pain),[87] and since seizure risk might be affected differently by these disorders, the study population was set to users of antidepressants for unipolar depression. As seizure risk is increased when applying antidepressants in overdose,[57,88–90] this study aimed to explore dose-dependent effects within therapeutic dose ranges of antidepressants.

The third project studied the association between antipsychotic drug use in adults with neuropsychiatric disorders and new-onset seizures. Little evidence on antipsychotic-induced seizures can be found and to this day the role of the underlying indication has not been investigated.[91–94] This project thus aimed to explore the risk of seizures associated with antipsychotic drug use for patients with underlying schizophrenia, affective disorders, or dementia.

Chapter 3

Seizure projects

3. Seizure projects

3.1 Project 1: Risk factors for seizures in adult patients with depression

Unabbreviated title: Lifestyle factors, psychiatric and neurologic comorbidities, and drug use associated with incident seizures among adult patients with depression: a population-based nested case-control study

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Project 1: Risk factors for seizures in adult patients with depression

3.1.1 Abstract

Objective

To investigate risk factors for incident seizures among adult patients with depression.

Methods

We conducted a nested case-control analysis in adult patients with newly diagnosed depression, using data from the U.K.-based Clinical Practice Research Datalink (CPRD). Among cases with incident seizures and matched controls, we estimated odds ratios (ORs) with 95% confidence intervals (CIs) of potential risk factors for seizures as reported from data of the general population: underweight (body mass index <18.5 kg/m^2), smoking, alcoholism, drug abuse, psychiatric or neurologic comorbidities, and concomitant use of drugs.

Results

Of 186,540 patients with depression, 1,489 developed a seizure during follow-up. Being underweight (OR, 1.67 [95% CI, 1.23-2.26]), a current smoker (OR, 1.45 [95% CI, 1.26-1.67]), having alcoholism (OR, 2.98 [95% CI, 2.56-3.47]), and drug abuse (OR, 2.51 [95% CI, 1.94-3.24]), were associated with increased risks of seizures compared to normal weight, non-smoking, no alcoholism, and no drug abuse, respectively. Previous stroke/transient ischemic attack (OR 6.07 [95% CI, 4.71-7.83]) or intracerebral bleeding (OR 8.19 [95% CI, 4.80-13.96]), and comorbid dementia (OR 6.83 [95% CI, 4.81-9.69]), were strongly associated with seizures. Current use of cephalosporins (OR, 2.47 [95% CI, 1.61-3.78]) and antiarrhythmics (OR, 1.59 [95% CI, 1.26-2.01]) was associated with an increased risk of seizures compared to non-use.

Conclusion

Among adult patients with depression, being underweight, smoking, alcoholism, and drug abuse, were associated with seizures. Remote stroke and comorbid dementia were strong risk factors for seizures. Current use of cephalosporins or antiarrhytmics was associated with an increased risk of seizures compared to non-use.

3.1.2 Introduction

Depression is a common and disabling disorder. Lifetime prevalence estimates of major depression range between about 7% in some Asian countries to about 20% in certain European countries and the United States.[22] Patients with depression develop seizures more frequently than individuals without depression,[27,65,67] and it has been suggested that common neurobiological abnormalities increase the risk for both disorders.[84] Apart from depression, suicidal ideation/attempt, psychiatric disorders including schizophrenia, bipolar disorder, and obsessive-compulsive disorders, and neurologic disorders including dementia, Parkinson's disease, multiple sclerosis, ischemic or hemorrhagic stroke, transient ischemic attack (TIA), brain infections, brain tumors, severe brain trauma, or migraine with aura, have been associated with seizures.[27,61,62,66,69,78] Use of antidepressants, antipsychotics, antimalarials, antibiotics, antivirals, immunosuppressants, stimulants, sedatives, or opioids, has also been associated with the occurrence of seizures.[55,56,58,95] Alcohol intoxication, withdrawal or dependence, or abuse of recreational drugs, are recognized risk factors for seizures.[50,54,78]

No observational study has yet explored risk factors for new-onset seizures among patients with depression. This study aimed to investigate in detail which lifestyle factors, comorbidities, and co-medications are associated with seizures among adult patients with depression.

3.1.3 Methods

Study design and data source

We conducted a retrospective population-based nested case-control study using data from the U.K.-based Clinical Practice Research Datalink (CPRD). The CPRD encompasses approximately 10,000,000 patient records provided by general practitioners (GPs) throughout England, Wales, Scotland and Northern Ireland.[31] The patients enrolled in participating practices are representative of the U.K. with regard to age, sex, and geographic distribution. Researchers have access to anonymized data of patients which encompass demographics, lifestyle factors, medical diagnoses (recorded as 'Read codes'), and drug prescriptions. The recording of diagnoses and drug prescriptions has been validated and proven to be of high quality.[34,35] Data from the CPRD have repeatedly been used to conduct observational studies on depression [96–98] and seizures.[86,99,100] This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency research.

Project 1: Risk factors for seizures in adult patients with depression

Study population

We identified all patients aged 18 to 89 years with an incident depression diagnosis followed by an antidepressant drug treatment, or a first prescription for an antidepressant drug followed by an incident depression diagnosis within one year thereafter, between January 1998 and December 2012. Incident depression was defined by Read codes corresponding to the International Classification of Diseases version 10 (ICD-10) codes for depression. The date of the incident depression diagnosis or the first prescription for an antidepressant drug, whichever came first, will subsequently be called 'start date'. We excluded patients with a recorded history of epilepsy or seizures, any antiepileptic drug therapy, HIV, non-cerebral malignancy, or benign or malignant brain tumors prior to the start date. Patients had to have had at least three years of active history in the database prior to the start date to minimize inclusion of patients with prevalent rather than incident depression.

Definition of cases

Cases were patients in the study population who had at some point after the start date (1) an incident diagnosis of seizures or epilepsy defined by recorded Read codes corresponding to ICD-10 codes for seizures or epilepsy, (2) a first prescription for an antiepileptic drug followed by an incident diagnosis of seizures or epilepsy (as defined under [1]) within three months thereafter, or (3) a first prescription for an antiepileptic drug preceded or followed by a Read code record of a suspected seizure within three months before or after, provided that an incident diagnosis of seizures or epilepsy (as defined under [1]) followed at any time thereafter. The date of (1), (2), or (3), whichever came first, will be referred to as 'index date'. Cases older than 90 years were excluded as were those with a record of HIV, non-cerebral malignancy, or benign or malignant brain tumors diagnosed between the start date and the index date, or within one month after the index date.

Control selection

For each case we identified up to four controls from the study population who had no diagnoses for seizures during the study period. We matched controls to cases on index date, age (+/- 2 years), sex, GP practice, number of years of history in the CPRD prior to the index date (+/- 2 years), and - to match on a proxy for depression severity - antidepressant exposure at the index date, defined by the quantity and type of antidepressant prescribed by the GP at

the closest visit prior to the index date and the daily dose instructions recorded. If no dose instruction was available, we used default values in the following order: (1) the dose instruction given for the same drug at any time prior to the index date, (2) the defined daily dose if no dose instruction was recorded at any time prior to the index date, or (3) the dose of one unit (i.e. tablet or capsule) of sustained release forms. We matched cases and controls on the following types of antidepressant exposure at the index date: (1) 'No antidepressant treatment': the patient had been diagnosed with depression, but had not yet received a prescription for an antidepressant; (2) 'Mono use' of antidepressants: the patient was prescribed only one of the following antidepressants at the index date: (a) selective serotonin reuptake inhibitors (SSRIs) [citalopram, escitalopram, fluoxetine, paroxetine, sertraline, or fluvoxamine], (b) serotonin norepinephrine reuptake inhibitors (SNRIs) [venlafaxine and duloxetine], (c) tricyclic antidepressants (TCAs) [amitriptyline, clomipramine, doxepin, imipramine, trimipramine, nortriptyline, lofepramine, and dosulepin], or (d) 'other antidepressants' (reboxetin, mirtazapine, bupropion, trazodone, viloxazine, nefazodone, St. John's wort, tryptophan, or agomelatine); (3) 'Mixed use' of antidepressants: the patient was prescribed concomitantly at least two of the antidepressants listed above at the index date; (4) 'Past use' of antidepressants: the patient had been prescribed antidepressants in the past, but the treatment had elapsed. We applied the same exclusion criteria to controls as to cases.

Exposure variables

We assessed information on body mass index (BMI) [<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, or unknown], lifestyle factors including smoking status (non, current, former, or unknown), alcohol consumption (none, 1-14, 15-28, 29-42, >42 units/week, or unknown), alcoholism (based on Read codes), and drug abuse (based on Read codes) recorded at any time prior to the index date.[51,54,101,102]

We assessed the prevalence of any of the following comorbidities based on Read codes recorded at any time prior to until three months after the index date: schizophrenia, manic episodes/bipolar disorder, obsessive-compulsive disorder, anxiety disorders, suicidal ideation/suicide attempt, dementia, Parkinson's disease, multiple sclerosis, intracerebral bleeding, ischemic stroke/TIA, major head trauma (head trauma with intracranial injury), meningitis or encephalitis, brain abscess, migraine, attention deficit hyperactivity disorder (ADHD), and sinus vein thrombosis.[27,61,62,67,69,72,78]

Lastly, we assessed the use of drugs that have been reported to alter the risk of seizures: atypical or typical antipsychotics, benzodiazepines or non-benzodiazepine hypnotics, barbiturates, penicillins, cephalosporins, fluoroquinolones, carbapenems, antimalarials, antivirals, immunosuppressants, opioids, anticonvulsants, antiarrhythmics, and stimulants.[55–58] 'Non-users' of such drugs were those with no prescriptions prior to the index date, 'current users' and 'past users' received the last prescription ≤90 days or >90 days prior to the index date, respectively.

Data analysis

Analyses were conducted with SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA), using conditional logistic regression methods for matched case-controls studies.

We calculated crude odds ratios (ORs) with 95% confidence intervals (CIs) for each exposure variable and exposure level for which numbers of observations were sufficient to conduct meaningful analyses. All estimated odds ratios were conditional on the matching factors. We calculated odds ratios for all comorbidities (yes/no). Additionally, for psychiatric comorbidities and acute neurologic comorbidities (intracerebral bleeding, ischemic stroke/TIA, major head trauma, meningitis or encephalitis, and brain abscess), we categorized diagnoses by the timing (within 12 months prior to until 3 months after the index date, >12 months prior to the index date). We calculated odds ratios for drugs categorized by timing of use (current, past use), and for current use by the number of recorded prescriptions prior to the index date (1-3, ≥3).

3.1.4 Results

Of 186,540 patients with depression, there were 1,489 cases with a diagnosis of an incident seizure or epilepsy. The mean age of cases (+/- standard deviation) was 47.2 (+/- 18.9) years and 51.2% of patients were female.

Approximately 40% of cases were aged 18-39 years, 30% 40-59 years, and 30% 60-90 years at the index date (**Table 7**). More than 50% were past users of antidepressants while almost 30% were current mono users of an SSRI. Being underweight (BMI <18.5 kg/m^2) was associated with an increased risk of seizures compared to normal weight (BMI between 18.5 and 25.0 kg/m^2). Current smoking, drinking more than 42 units of alcohol per week, alcoholism, and drug abuse (mainly unspecified drug abuse, abuse of opioids, cannabis, or

anxiolytics/hypnotics) were associated with increased risks of seizures compared to non-smoking, non-drinking, no alcoholism, and no drug abuse, respectively (**Table 7**).

Anxiety disorders and suicidal ideation/suicide attempt were most frequently observed among cases and controls (**Table 8**). People with depression and one of the following comorbidities, schizophrenia, manic episodes or bipolar disorder, anxiety disorders, and suicidal ideation/suicide attempt, were at increased risk of seizures compared to people with depression alone (**Table 8**).

Psychiatric comorbidities diagnosed within 12 months prior to until 3 months after the index date were associated with higher risks of seizures than psychiatric comorbidities diagnosed >12 months prior to the index date, although most differences were not significant (**Table 9**).

Having comorbid dementia (OR 6.83 [95% CI, 4.81-9.69]), previous intracerebral bleeding (OR 8.19 [95% CI, 4.80-13.96]) or ischemic stroke/TIA (OR 6.07 [95% CI, 4.71-7.83] was strongly associated with the risk of seizures (**Table 10**). The associations with intracerebral bleeding, ischemic stroke/TIA, and major head trauma, were stronger when the diagnosis was recorded within 12 months prior to until 3 months after the index date compared to those with a diagnosis recorded >12 months prior to the index date (**Table 11**). Overall, prevalent migraine was not associated with seizures (OR 1.13 [95% CI, 0.94-1.36]) [**Table 10**], while migraine with aura tended to be associated with an increased risk of seizures (OR 2.00 [95% CI, 0.81-4.96]) [data not shown].

Current use of antiarrhythmics (mainly propranolol) or cephalosporins was associated with 1.6- and 2.5-fold increased risks of seizures compared to non-use, respectively (**Table 12**). Past use of these drug classes was not associated with seizures. Treatment initiation was more strongly associated with seizures in users of antiarrhythmics and cephalosporins than longer-term treatment.

Table 7: Characteristics and lifestyle factors of cases with seizures and matched controls[a]

Characteristics	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n=5,932)	Crude OR	95% CI
Sex				
Male	726 (48.8)	2,886 (48.7)	NA	NA
Female	763 (51.2)	3,046 (51.4)	NA	NA
Age, years				
18-29	310 (20.8)	1,230 (20.7)	NA	NA
30-39	295 (19.8)	1,167 (19.7)	NA	NA
40-49	292 (19.6)	1,188 (20.0)	NA	NA
50-59	193 (13.0)	775 (13.1)	NA	NA
60-69	150 (10.1)	587 (9.9)	NA	NA
70-79	132 (8.9)	515 (8.7)	NA	NA
80-90	117 (7.9)	470 (7.9)	NA	NA
Exposure to antidepressants				
No use	79 (5.3)	313 (5.3)	NA	NA
Past use	776 (52.1)	3,104 (52.3)	NA	NA
Mono use of SSRIs	399 (26.8)	1,596 (26.9)	NA	NA
Mono use of SNRIs	49 (3.3)	186 (3.1)	NA	NA
Mono use of TCAs	62 (4.2)	244 (4.1)	NA	NA
Mono use of other antidepressants	48 (3.2)	189 (3.2)	NA	NA
Mixed use of antidepressants	76 (5.1)	300 (5.1)	NA	NA
Body mass index, kg/m^2				
<18.5	68 (4.6)	145 (2.4)	1.67	1.23-2.26
18.5-24.9	571 (38.4)	1,989 (33.5)	1	reference
25.0-29.9	339 (22.8)	1,602 (27.0)	0.73	0.63-0.85
≥30.0	256 (17.2)	1,199 (20.2)	0.73	0.62-0.87
Unknown	255 (17.1)	997 (16.8)	0.91	0.76-1.09
Smoking status				
Nonsmoker	511 (34.3)	2,320 (39.1)	1	reference
Current smoker	584 (39.2)	1,887 (31.8)	1.45	1.26-1.67
Former smoker	325 (21.8)	1,476 (24.9)	0.98	0.84-1.15
Unknown	69 (4.6)	249 (4.2)	1.33	0.98-1.80
Alcohol consumption[c] (in units/week)				
Nondrinker	652 (43.8)	2,499 (42.1)	1	reference
1-14	439 (29.5)	1,954 (32.9)	0.86	0.75-0.99
15-28	89 (6.0)	405 (6.8)	0.86	0.67-1.11
29-42	49 (3.3)	172 (2.9)	1.12	0.80-1.56
>42	102 (6.9)	136 (2.3)	2.97	2.25-3.93
Unknown	158 (10.6)	766 (12.9)	0.78	0.64-0.96

Table 7 (cont.)

Characteristics	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n=5,932)	Crude OR	95% CI
Alcoholism[d]				
No	1,121 (75.3)	5,295 (89.3)	1	reference
yes	368 (24.7)	637 (10.7)	2.98	2.56-3.47
Drug abuse[d]				
no	1,383 (92.9)	5,748 (96.9)	1	reference
yes[e]	106 (7.1)	184 (3.1)	2.51	1.94-3.24

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods section). All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] Based on Read code records at any time prior to the index date.

[d] Based on Read code records at any time prior to the index date until 3 months after the index date.

[e] Read code records mainly corresponding to unspecified drug abuse (50.3%), abuse of opioids (14.1%) , cannabis (12.4%), anxiolytics/hypnotics (12.4%), and psychostimulants (4.8%).

Table 8: Odds ratios of psychiatric comorbidities among cases with seizures and matched controls[a]

Psychiatric comorbidity	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n= n=5,932)	Crude OR	95% CI
Schizophrenia				
No[c]	1,457 (97.9)	5,865 (98.9)	1	reference
Yes[d]	32 (2.2)	67 (1.1)	1.93	1.25-2.98
Manic episodes/bipolar disorder				
No[c]	1,474 (99.0)	5,905 (99.5)	1	reference
Yes[d]	15 (1.0)	27 (0.5)	2.25	1.19-4.26
Obsessive-compulsive disorder				
No[c]	1,473 (98.9)	5,874 (99.0)	1	reference
Yes[d]	16 (1.1)	58 (1.0)	1.09	0.63-1.90
Anxiety disorders				
No[c]	1,087 (73.0)	4,526 (76.3)	1	reference
Yes[d]	402 (27.0)	1,406 (23.7)	1.20	1.05-1.37
Suicidal ideation/suicide attempt				
No[c]	1,231 (82.7)	5,376 (90.6)	1	reference
Yes[d]	258 (17.3)	556 (9.4)	2.13	1.80-2.52

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods). All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] Defined as no Read code record of the respective disorder at any time prior to until 3 months after the index date.

[d] Defined as a Read code record of the respective disorder at any time prior to until 3 months after the index date.

Table 9: Odds ratios of psychiatric comorbidities among cases with seizures and matched controls[a], by timing of the diagnosis

Psychiatric comorbidity	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n= n=5,932)	Crude OR	95% CI
Schizophrenia				
No diagnosis[c]	1,457 (97.9)	5,865 (98.9)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	12 (0.8)	19 (0.3)	2.50	1.20-5.24
>12 months prior to the ID	20 (1.3)	48 (0.8)	1.71	1.01-2.90
Manic episodes/bipolar disorder				
No diagnosis[c]	1,474 (99.0)	5,905 (99.5)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	9 (0.6)	10 (0.2)	3.80	1.50-9.63
>12 months prior to the ID	6 (0.4)	17 (0.3)	1.41	0.56-3.58
Obsessive-compulsive disorder				
No diagnosis[c]	1,473 (98.9)	5,874 (99.0)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	5 (0.3)	12 (0.2)	1.67	0.59-4.74
>12 months prior to the ID	11 (0.7)	46 (0.8)	0.94	0.49-1.83
Anxiety disorders				
No diagnosis[c]	1,087 (73.0)	4,526 (76.3)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	112 (7.5)	295 (5.0)	1.60	1.27-2.02
>12 months prior to the ID	290 (19.5)	1,111 (18.7)	1.09	0.94-1.27
Suicidal ideation/suicide attempt				
No diagnosis[c]	1,231 (82.7)	5,376 (90.6)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	64 (4.3)	86 (1.5)	3.48	2.48-4.88
>12 months prior to the ID	194 (13.0)	470 (7.9)	1.89	1.57-2.27

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable; ID, index date.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods section). All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] Defined as no Read code record at any time prior to until 3 months after the index date.

Table 10: Odds ratios of neurologic comorbidities among cases with seizures and matched controls[a]

Neurologic comorbidity	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n=5,932)	Crude OR	95% CI
Dementia				
No[c]	1,389 (93.3)	5,845 (98.5)	1	reference
Yes[d]	100 (6.7)	87 (1.5)	6.83	4.81-9.69
Parkinson's disease				
No[c]	1,470 (98.7)	5,901 (99.5)	1	reference
Yes[d]	19 (1.3)	31 (0.5)	2.43	1.35-4.39
Multiple sclerosis				
No[c]	1,479 (99.3)	5,910 (99.6)	1	reference
Yes[d]	10 (0.7)	22 (0.4)	1.82	0.86-3.84
Intracerebral bleeding				
No[c]	1,447 (97.2)	5,910 (99.6)	1	reference
Yes[d]	42 (2.8)	22 (0.4)	8.19	4.80-13.96
Ischemic stroke/ Transient ischemic attack				
No[c]	1,306 (87.7)	5,753 (97.0)	1	reference
Yes[d]	183 (12.3)	179 (3.0)	6.07	4.71-7.83
Major head trauma[e]				
No[c]	1,260 (84.6)	5,484 (92.5)	1	reference
Yes[d]	229 (15.4)	448 (7.6)	2.36	1.97-2.82
Meningitis or encephalitis				
No[c]	1,469 (98.7)	5,889 (99.3)	1	reference
Yes[d]	20 (1.3)	43 (0.7)	1.86	1.10-3.16
Migraine				
No[c]	1,320 (88.7)	5,322 (89.7)	1	reference
Yes[d]	169 (11.4)	610 (10.3)	1.13	0.94-1.36

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods section). All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] Defined as no Read code record of the respective disorder at any time prior to until 3 months after the index date.

[d] Defined as a Read code record of the respective disorder at any time prior to until 3 months after the index date.

[e] Defined as head trauma with intracranial injury.

Table 11: Odds ratios of neurological comorbidities among cases with seizures and matched controls[a], by timing of the diagnosis

Neurological comorbidity	No. Cases (%)[b] (n=1,489)	No. Controls (%)[b] (n= n=5,932)	Crude OR	95% CI
Intracerebral bleeding				
No diagnosis[c]	1,447 (97.7)	5,910 (99.6)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	18 (1.2)	5 (0.1)	15.03	5.56-40.63
>12 months prior to the ID	24 (1.6)	17 (0.3)	6.10	3.22-11.54
Ischemic stroke/ Transient ischemic attack				
No diagnosis[c]	1,306 (87.7)	5,753 (97.0)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	90 (6.0)	24 (0.4)	20.27	12.40-33.13
>12 months prior to the ID	93 (6.3)	155 (2.6)	3.53	2.61-4.77
Major head trauma				
No diagnosis[c]	1,260 (84.6)	5,484 (92.5)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	61 (4.1)	30 (0.5)	9.14	5.82-14.34
>12 months prior to the ID	168 (11.3)	418 (7.1)	1.85	1.52-2.25
Meningitis or encephalitis				
No diagnosis[c]	1,469 (98.7)	5,889 (99.3)	1	reference
Diagnosis by timing				
Within 12 months prior to until 3 months after the ID	X	X	NA	NA
>12 months prior to the ID	19 (1.3)	42 (0.7)	1.81	1.05-3.11

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable: numbers in the contingency table were not adequate to calculate odds ratios; X, cell contains <5 observations (due to ethics regulations to preserve confidentiality, the exact count is not displayed); ID, index date.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods section). All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] Defined as no Read code record of the respective disorder at any time prior to until 3 months after the index date.

Table 12: Odds ratios of selected drug groups among cases with seizures and matched controls[a], by current[b] or past[c] use, and by current use and number of prescriptions

Drug group	No. Cases (%)[d] (n=1,489)	No. Controls (%)[d] (n= n=5,932)	Crude OR	95% CI
Atypical antipsychotics[e]				
No use	1,380 (92.7)	5,695 (96.0)	1	reference
Current use	63 (4.2)	130 (2.2)	2.11	1.53-2.92
Current use by nr. of presc.				
1-3	11 (0.7)	20 (0.3)	2.42	1.15-5.09
>3	52 (3.5)	110 (1.9)	2.06	1.45-2.92
Past use	46 (3.1)	107 (1.8)	1.85	1.30-2.65
Typical antipsychotics[f]				
No use	1,011 (67.9)	4,497 (75.8)	1	reference
Current use	70 (4.7)	121 (2.0)	2.71	1.99-3.70
Current use by nr. of presc.				
1-3	38 (2.6)	52 (0.9)	3.35	2.18-5.14
>3	32 (2.2)	69 (1.2)	2.20	1.42-3.40
Past use	408 (27.4)	1,314 (22.2)	1.43	1.25-1.64
Benzodiazepines or non-benzodiazepine hypnotics[g]				
No use	687 (46.1)	3,260 (55.0)	1	reference
Current use	254 (17.1)	482 (8.1)	2.76	2.29-3.32
Current use by nr. of presc.				
1-3	50 (3.4)	97 (1.6)	2.60	1.81-3.74
>3	204 (13.7)	385 (6.5)	2.80	2.29-3.43
Past use	548 (36.8)	2,190 (36.9)	1.22	1.07-1.39
Penicillins[h]				
No use	249 (16.7)	1,024 (17.3)	1	reference
Current use	150 (10.1)	510 (8.6)	1.23	0.97-1.55
Current use by nr. of presc.				
1-3	25 (1.7)	114 (1.9)	0.91	0.58-1.44
>3	125 (8.4)	396 (6.7)	1.32	1.03-1.70
Past use	1,090 (73.2)	4,398 (74.1)	1.03	0.88-1.21
Cephalosporins[i]				
No use	1,013 (68.0)	4,223 (71.2)	1	reference
Current use	34 (2.3)	58 (1.0)	2.47	1.61-3.78
Current use by nr. of presc.				
1-3	24 (1.6)	33 (0.6)	3.05	1.80-5.17
>3	10 (0.7)	25 (0.4)	1.69	0.81-3.54
Past use	442 (29.7)	1,651 (27.8)	1.14	1.00-1.30

Table 12 (cont.)

Drug group	No. Cases (%)[d] (n=1,489)	No. Controls (%)[d] (n= n=5,932)	Crude OR	95% CI
Fluoroquinolones[j]				
No use	1,262 (84.8)	5,102 (86.0)	1	reference
Current use	11 (0.7)	36 (0.6)	1.20	0.61-2.37
Current use by nr. of presc.				
1-3	9 (0.6)	25 (0.4)	1.40	0.65-3.02
>3	X	11 (0.2)	NA	NA
Past use	216 (14.5)	794 (13.4)	1.11	0.94-1.31
Antimalarials[k]				
No use	1,398 (93.9)	5,490 (92.6)	1	reference
Current use	23 (1.5)	86 (1.5)	1.04	0.65-1.65
Current use by nr. of presc.				
1-3	X	16 (0.3)	NA	NA
>3	21 (1.4)	70 (1.2)	1.16	0.71-1.90
Past use	68 (4.6)	356 (6.0)	0.75	0.57-0.98
Immunosuppressants[l]				
No use	1,471 (98.8)	5,867 (98.9)	1	reference
Current use	10 (0.7)	39 (0.7)	1.03	0.51-2.06
Current use by nr. of presc.				
1-3	X	X	NA	NA
>3	9 (0.6)	39 (0.7)	0.93	0.45-1.91
Past use	8 (0.5)	26 (0.4)	1.22	0.55-2.70
Opioids[m]				
No use	457 (30.7)	2,165 (36.5)	1	reference
Current use	301 (20.2)	812 (13.7)	1.89	1.59-2.26
Current use by nr. of presc.				
1-3	46 (3.1)	102 (1.7)	2.15	1.50-3.09
>3	255 (17.1)	710 (12.0)	1.84	1.53-2.23
Past use	731 (49.1)	2,955 (49.8)	1.22	1.06-1.40
Anticonvulsants[n]				
No use	1,371 (92.1)	5,695 (96.0)	1	reference
Current use	68 (4.6)	103 (1.7)	2.85	2.07-3.92
Current use by nr. of presc.				
1-3	20 (1.3)	27 (0.5)	3.11	1.74-5.54
>3	48 (3.2)	76 (1.3)	2.75	1.89-4.01
Past use	50 (3.4)	134 (2.3)	1.59	1.14-2.21
Antiarrhythmics[o]				
No use	1,134 (76.2)	4,745 (80.0)	1	reference
Current use	114 (7.7)	309 (5.2)	1.59	1.26-2.01
Current use by nr. of presc.				
1-3	25 (1.7)	32 (0.5)	3.27	1.93-5.52
>3	89 (6.0)	277 (4.7)	1.38	1.06-1.78
Past use	241 (16.2)	878 (14.8)	1.16	0.99-1.37

Table 12 (cont.)

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable; nr., number; presc., prescriptions; X, cell contains <5 observations (due to ethics regulations to preserve confidentiality, the exact count is not displayed).

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and exposure to antidepressants at the index date (as described in the methods section). All ORs presented are conditional on the matching factors.

[b] Defined as last prescription ≤90 days ago

[c] Defined as last prescription >90 days ago

[d] Due to rounding, percentages may not total 100.

[e] Mainly consisting of olanzapine (35.5%), risperidone (30.1%), quetiapine (21.4%), and amisulpride (6.1%).

[f] Mainly consisting of prochlorperazine (76.2%), flupentixol (5.3%), chlorpromazine (4.5%), and thioridazine (4.3%)

[g] Mainly consisting of diazepam (39.0%), zopiclone (26.0%), temazepam (19.1%), and chlordiazepoxide (4.4%)

[h] Mainly consisting of amoxicillin (64.2%), flucloxacillin (19.2%), penicillin (12.5%), and phenoxymethylpenicillin (2.1%).

[i] Mainly consisting of cefalexin (67.7%), cefaclor (18.5%), and cefradine (8.5%).

[j] Mainly consisting of ciprofloxacin (85.5%), ofloxacin (9.6%)

[k] Mainly consisting of quinine (62.9%), atovaquone and proguanil (13.1%), mefloquine (11.1%), and chloroquine (9.4%).

[l] Mainly consisting of methotrexate (44.6%), and azathioprine (38.6%).

[m] Mainly consisting of codeine (56.0%), dihydrocodeine (19.6%), dextropropoxyphene (12.0%), and tramadol (9.1%).

[n] Mainly consisting of gabapentin (38.6%), pregabalin (18.0%), carbamazepine (14.1%), and sodium valproate (10.4%)

[o] Mainly consisting of propranolol (68.2%), diltiazem (10.5%), and digoxin (8.0%).

3.1.5 Discussion

This large population-based nested case-control study revealed that underweight, current smoking, high alcohol consumption, alcoholism, and drug abuse were associated with increased risks of seizures in adult patients with depression. Patients with comorbid dementia or a history of intracerebral bleeding, ischemic stroke/TIA, or major head trauma, had considerably higher risks of seizures than patients without these comorbidities. Current use of cephalosporins or antiarrhythmics was also associated with an increased risk of seizures compared to non-use of these drug groups.

These results on the association between BMI and lifestyle factors and the risk of seizures among patients with depression are consistent with reports from the general population.[51,101,102] Being an underweight (BMI≤18.5kg/m^2) adult was associated with a non-significantly increased risk of seizures (adjusted relative risk 1.6 [95% CI, 0.7 to 3.8]) in a study using a different U.K. population-based database.[102] Additionally, while we observed a crude 1.5-fold (95% CI, 1.3- to 1.7-fold) increased risk of seizures with current smoking compared to non-smoking, a study based on data from the Nurses' Health Study II reported an adjusted 2.6-fold (95% CI, 1.5- to 4.4-fold) increased risk of seizures among women who currently smoked compared to women who did not smoke.[101] In accordance with our results, ex-smoking was not associated with seizures in that study.[101] Our results concur with a meta-analysis reporting a dose-dependent association between alcohol consumption and the risk of seizures, with a risk curve rising steeply after a threshold of approximately 28 units of alcohol consumption per week.[51] Lastly, drug abuse has repeatedly been associated with increased risk of seizures in the general population, either through direct toxicity or withdrawal.[54]

Our results further suggest that depressed patients with comorbid schizophrenia, manic episodes or bipolar disorder, or suicidal ideation/suicide attempt were approximately twice as likely to experience an incident seizure as depressed patients without these psychiatric comorbidities. While depression, schizophrenia, bipolar disorder, and suicidal ideation/suicide attempt have been reported to be individual risk factors for seizures,[27,65–67,85] our study suggests that schizophrenia, bipolar disorder, and suicidal ideation/suicide attempt represent additional risk factors for seizures among patients with depression. Psychiatric comorbidities diagnosed close to the index date tended to be associated with increased risks of seizures compared to psychiatric comorbidities diagnosed further in the past, a finding which is

supported by a Swedish observational study on the association between psychiatric disorders and seizures.[67]

Depressed patients with comorbid dementia or a history of intracerebral bleeding, ischemic stroke/TIA, or recent major head trauma, were at a substantially increased risk of developing seizures compared to depressed patients without these comorbidities. The risk increases ranged from approximately 7-fold for comorbid dementia to approximately 20-fold for recently diagnosed ischemic stroke/TIA. These results are consistent with the epidemiologic literature on these neurologic disorders and their strong individual association with acute symptomatic or progressive seizures in the general population. In an observational study among patients aged 65 or over, a diagnosis of dementia was associated with a 7- to 11-fold increased risk of incident seizures compared with no such diagnosis.[86] Additionally, several population-based studies reported a 23- to 35-fold increased risk of seizures in patients with stroke in the first year after their stroke diagnosis, compared to the general population.[103–105] In our study, depression with comorbid migraine was overall not associated with an increased risk of seizures compared with depression alone, but depression with comorbid migraine with aura was. These results are in line with the results of an observational study by Hesdorffer et al. (2007) among an Icelandic population aged 10 years or over.[69]

We observed increased risks of seizures associated with current, but not past use of cephalosporins and antiarrhythmics (mainly propranolol). As these effects were not adjusted for confounding factors other than the matching variables, these associations might either represent true adverse drug effects, or they could alternatively be related to underlying disorders for which the drugs were prescribed. The finding that current and past users of antipsychotics, benzodiazepines, opioids, and anticonvulsants, had increased odds ratios of seizures compared to non-users, might suggest that underlying disease or disease severity leading to these drug prescriptions - rather than the drug itself - was associated with the occurrence of seizures.

We investigated the association between lifestyle factors, comorbidities, and co-medication and the risk of incident seizures among a large population of patients with incident depression who were followed for up to 16 years. The study was based on one of the largest and best validated medical records databases worldwide. However, it is a limitation that depression and seizure diagnoses were not formally validated in the CPRD. Thus, to ascertain the validity of the depression diagnosis, we only included patients in our base population if they received at

least one antidepressant prescription within a year prior to or at any time after the depression diagnosis. As only selected patients receive antiepileptic therapy after the first seizure,[82] we decided to include patients with recorded seizure codes even if they did not receive any antiepileptic therapy afterwards. However, we developed the algorithm used to define a first-time seizure by reviewing a random sample of 150 profiles of patients with a record of seizure/epilepsy at some time after the depression diagnosis to assess the likelihood of the seizure diagnosis.

Through matching, our analyses were adjusted for sex, age, calendar time, number of years of history in the database, GP practice, and antidepressant exposure status at the index date (a potential proxy for depression severity). As this study aimed to crudely describe the features that distinguish depressed patients who develop seizures from depressed patients who do not develop seizures rather than test formal hypotheses, we did not adjust our multivariate analyses for other potential confounders. Our estimated odds ratios should therefore be interpreted as crude descriptive associations rather than unbiased risk estimates.

In conclusion, our study suggests that among adult patients with depression, current smoking, drinking of more than five to six units of alcohol a day, alcoholism, and drug abuse were potential risk factors for seizures. Patients with psychiatric comorbidities, dementia, or recorded histories of ischemic stroke and/or TIA, intracerebral bleeding, or major head trauma, had substantially higher risks of seizures compared to patients without these comorbidities. Lastly, current use of cephalosporins or antiarrhythmics was associated with an increased risk of seizures compared to non-use in patients with depression.

3.2 Project 2: Antidepressant drug use and the risk of seizures

Unabbreviated title: Risk of seizures associated with antidepressant use in patients with depressive disorder: nested case-control analysis

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Under Review at *Drug Safety*

Project 2: Antidepressant drug use and the risk of seizures

3.2.1 Abstract

Objective

To assess the risk of first-time seizures in association with exposure to antidepressants in patients with depressive disorders.

Methods

We conducted a retrospective follow-up study with a nested case-control analysis using data from the U.K.-based Clinical Practice Research Datalink (CPRD). We estimated crude incidence rates with 95% confidence intervals (CIs) of seizures in depressed patients who used selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), 'other antidepressants', no antidepressants, or who had used antidepressants in the past. To adjust for potential confounding, we estimated odds ratios of antidepressant drug use among cases with seizures and matched controls in a nested case-control analysis.

Results

Of 151,005 depressed patients, 619 had an incident seizure during follow-up. Incidence rates per 10,000 person-years were 12.44 (95% CI, 10.67-14.21) in SSRI users, 15.44 (95% CI, 8.99-21.89) in SNRI users, 8.33 (95% CI, 4.68-11.98) in TCA users, 9.33 (95% CI, 6.19-12.46) in non-users of antidepressants, and 5.05 (95% CI, 4.49-5.62) in past users of antidepressants. In the case-control analysis, relative risk estimates for seizures were increased in current users of SSRIs (adjusted odds ratio 1.98, 95% CI 1.48-2.66) and SNRIs (adjusted odds ratio 1.99, 95% CI 1.20-3.29), but not TCAs (adjusted odds ratio 1.36, 95% CI 0.86-2.14), compared with non-use.

Conclusion

Current use of SSRIs or SNRIs was associated with a twofold increased risk of first-time seizures compared to non-use, while current use of TCAs (mostly low dose) was not associated with seizures. Treatment initiation in SSRI and SNRI users was associated with the highest risk of seizures.

3.2.2 Introduction

Depression is among the top three leading causes of disease burden in terms of disability-adjusted life years in high-income countries.[106] In the U.K. about 25% of adults suffer from an episode of major depression at least once in their lifetime.[23] Patients with moderate to severe depression should receive treatment including pharmacotherapy.[107] Second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or 'other antidepressants' (such as trazodone, reboxetine, bupropion or mirtazapine), are preferred to older tri- or tetracyclic antidepressants as first-line antidepressants.[108]

Most antidepressants induce seizures in overdose,[57,88,89] but the seizure risk at therapeutic dose ranges remains unclear. Clinical trials suggested higher seizure incidence in patients assigned to placebo than to most second-generation antidepressants.[93] Therapeutic use of tricyclic antidepressants (TCAs) has been associated with an increased risk of seizures, a risk reported to be higher than the risk for therapeutic use of SSRIs.[55,57,58,109,110] Conversely, a recent British observational study found that use of SSRIs, venlafaxine, or mirtazapine, was associated with an increased risk of seizures compared to use of TCAs in depressed patients aged 65 or older.[26]

Evidence to date mainly comes from trials that were limited to few patients and focused on efficacy and short-term safety.[57,58,93,109,111] To analyze seizure risk in a large 'real life setting' we estimated absolute and relative risk estimates of seizures in 151,005 adult patients with depression who used various types of antidepressants and were followed over a period of up to 14 years.

3.2.3 Methods

Study design and data source

We conducted a retrospective population-based follow-up study with a nested case-control analysis, using data from the U.K.-based Clinical Practice Research Datalink (CPRD). The CPRD encompasses some 10,000,000 patient records provided by some 600 participating general practitioner (GP) practices.[31] Patients are representative of the U.K. with regard to age, sex, and geographic distribution. GPs provide data on patient characteristics, medical diagnoses (recorded as 'Read codes'), and drug prescriptions in a standardized and

anonymous form. The records of diagnoses and drug prescriptions have been validated and proven to be of high quality.[34,35] Data from the CPRD have been used to conduct observational studies on depression or antidepressant use[98,112–115] and on seizures.[86,99,100,115] This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency research.

Study population

Between 1998 and 2010, we identified all patients aged 18 to 89 years with an incident depression diagnosis followed by an antidepressant drug treatment or a first prescription for an antidepressant followed by an incident depression diagnosis within one year thereafter. Depression was defined by Read codes corresponding to the International Classification of Diseases version 10 (ICD-10) codes. The date of the incident depression diagnosis or the first prescription for an antidepressant, whichever came first, will subsequently be called 'start date'. We excluded patients with a diagnosis of epilepsy or any antiepileptic therapy prior to the start date, and patients with important risk factors for seizures such as a recorded history of alcoholism, drug abuse, head trauma, intracerebral bleeding, brain tumor, brain abscess, sinus vein thrombosis, meningitis, encephalitis, HIV, or cancer prior to the start date. We did not exclude patients with dementia or a history of stroke and/or TIA even though they are risk factors for seizures[86,105] because we aimed to investigate the potential effect modification by these comorbidities on our results. Patients had to have had at least three years of active history in the database prior to the start date to avoid inclusion of patients with prevalent depression.

Follow-up and definition of seizure cases

We followed all patients from the start date until they had (1) an incident record of seizure or epilepsy (corresponding to ICD-10 codes; as shown in, (2) a first prescription of antiepileptic therapy for reasons other than epilepsy, (3) until they turned 90 years old, (4) died, (5) left the database, (6) reached the end of data drawdown (December 2012), or (7) until one month prior to a first record of an important risk factor for seizures (as described under 'study population'), whichever came first. Patients whose follow-up ended due to (1) will subsequently be called 'cases', and the date of the seizure will be referred to as 'index date'.

Person-time analysis

We assessed person-time for four antidepressant classes and corresponding single drugs between the start date and the end of follow-up: (1) SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine), (2) SNRIs (venlafaxine and duloxetine), (3) TCAs (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, nortriptyline, lofepramine, and dosulepin), or (4) other antidepressants (mirtazapine, bupropion, reboxetine, and trazodone).

We included patients who used solely one antidepressant, who switched antidepressants, or who concomitantly used different antidepressants during follow-up, and accumulated person-time as follows: (1) no exposure to antidepressants ('no antidepressant treatment'), defined as the period between the first diagnosis of depression and the first prescription for an antidepressant, provided that the diagnosis occurred prior to the prescription; (2) current exposure to solely one antidepressant ('mono use'), defined as use from the day of the prescription through the expected end of treatment plus 7 days, provided that no other antidepressant was prescribed in this period. Patients who switched between different antidepressants but had no period of overlapping treatment contributed person-time to mono use of these different antidepressants; (3) current exposure to more than one antidepressant drug concomitantly ('mixed use'), defined as use from the day when at least two antidepressants were prescribed concomitantly through the expected end of treatment of all or all but one antidepressant plus 90 days (to ascertain that if a person switched from mixed use to mono use and developed a subsequent seizure, the discontinued drug was most likely not associated with the seizure). Patients who remained treated with one antidepressant after the period of mixed use plus 90 days contributed person-time to mono use for the remaining drug thereafter; and (4) past exposure after the stop of antidepressant treatment ('past use'), defined as the time after 7 or 90 days (depending on whether use was mono or mixed) after treatment had elapsed. The duration of treatment was derived from the recorded number of tablets or volume of liquids and the daily dose instructions.

Nested case-control analysis

For each case we identified four controls from the study population who did not develop seizures during follow-up. Controls were matched to cases on age (±2 years), sex, GP, index date, duration of history in the database prior to the index date (±2 years), and duration of

depression (±1 year). Case and control exposure was classified according to the timing of antidepressant use prior to the index date; 'non-users' were those who had no antidepressant prescriptions prior to the index date; 'current users' and 'past users' were those who had received the last prescription ≤90 days or >90 days prior to the index date, respectively. We further classified current users by number of prescriptions prior to the index date (1, 2-3, 4-5, >5 for SSRIs; 1-3, >3 for SNRIs, TCAs, and other antidepressants). We additionally stratified current users by sex. We evaluated antidepressant single drugs if they were used by at least 30 patients at the index date. Users of antidepressant single drugs were classified by daily dose intake (≤1 defined daily dose (DDD)[116], >1 defined daily dose) if the expected observations per cell of the contingency table were larger than 5. We assessed daily dose intake at the index date based on the quantity of drug prescribed by the GP at the previous visit and the daily dose instructions. If no dose instruction was available, we used default values in following order: (1) the dose instruction given for the same drug at the closest visit prior to the previous visit, (2) the defined daily dose if no dose instruction was recorded at any time prior, or (3) the dose of one unit (i.e. tablet or capsule) of sustained release forms.

Statistical analysis

We conducted a crude person-time analysis to estimate incidence rates with 95% confidence intervals (95% CIs) of seizures in patients with no antidepressant treatment, with any mono use, with mono use of different antidepressant classes and corresponding single drugs, and with past use of antidepressants. We stratified incidence rates by sex and age (18-49 vs. 50-89 years).

In the nested case-control analysis, we used SAS statistical software (version 9.3; SAS Institute, Cary, NC, USA) to conduct conditional logistic regression analyses. Relative risk estimates of antidepressant use among cases and controls were calculated as odds ratios with 95% CIs. Odds ratios in this study were a valid relative risk estimate because the incidence rates of seizures were low (< 5%) in patients with no antidepressant treatment and in patients using antidepressants.[25] We defined the reference group as patients who never used the respective antidepressant class in a given analysis (for analyses of drug classes) or antidepressant single drug (for analyses of single drugs) prior to the index date, and adjusted multivariate models for all other antidepressants used. We calculated odds ratios for antidepressant classes categorized by timing of antidepressant use (current/past use), and for current use by sex and number of prescriptions prior. In addition, we calculated odds ratios of

antidepressant single drug use, and where appropriate, categorized by dose used at the index date. Based on preexisting literature, we *a priori* adjusted our main multivariate models for alcohol consumption (none, 1-14 units/week, >14 units/week, unknown), history of other psychiatric disorders (schizophrenia, compulsive disorders, or affective disorders other than depression), dementia, Parkinson's disease, transient ischemic attack [TIA], stroke, suicidal ideation, and current or past use of antipsychotics, opioids, benzodiazepines, or other antidepressants than those studied.[27,55,62] We tested additional potential confounders (cardiovascular diseases, diabetes, hypertension, hyperlipidemia, hypothyroidism, sleep disorders, migraine, or multiple sclerosis; use of lithium, monoamine oxidase inhibitors, antibiotics, antimalarials, or antiarrhythmic drugs) but did not include them in the final model as they did not alter the risk estimates by >5%.

To assess potential effect modification, we conducted additional analyses comparing risk estimates between patients with depression with or without comorbid dementia, and patients with depression with or without a history of stroke and/or TIA.

In sensitivity analyses, we explored whether risk estimates differed if we defined the reference group as patients with no antidepressant treatment prior to the index date, and if we distinguished between patients who used solely one antidepressant vs. those who switched antidepressants during follow-up, as switching of antidepressants has been associated with more severe depression.[117]

3.2.4 Results

We identified 151,005 patients with incident depression who met our inclusion criteria. Among those, we identified 619 seizure cases and 2,476 controls in the nested case-control analysis. Mean age (± standard deviation) at the index date was 48.6 (± 20.6) years and 57.2% of patients were female.

Incidence rates

The estimated incidence rates of seizures per 10,000 person-years (PYs) were 12.58 (95% CI, 11.03-14.13), 9.33 (95% CI, 6.19-12.46), and 5.05 (95% CI, 4.49-5.62) in patients with current mono use, no antidepressant treatment, and past use of antidepressants, respectively (**Table 13**). Estimated incidence rates per 10,000 PYs for current mono use of SSRIs, SNRIs, and TCAs were 12.44 (95% CI, 10.67-14.21), 15.44 (95% CI, 8.99-21.89), and 8.33 (95% CI,

4.68-11.98), respectively. Among patients treated with SSRIs or SNRIs, incidence rates tended to be higher in older (50-89 years) than in younger patients (18-49 years).

Current users of escitalopram and paroxetine were as likely to develop seizures as non-users of antidepressants. Current users of sertraline, venlafaxine, or mirtazapine developed seizures almost twice as likely as non-users of antidepressants, although these differences were not statistically significant (**Table 14**).

Nested case-control analysis

Prevalent diagnoses of TIA, stroke, dementia, Parkinson's disease, schizophrenia and concurrent use of antipsychotic drugs or cephalosporin antibiotics were associated with increased odds of seizures (**Table 15**).

Current use of SSRIs (adjusted odds ratio 1.98 [95% CI, 1.48-2.66]) and SNRIs (adjusted odds ratio 1.99 [95% CI, 1.20-3.29]) was associated with increased odds of seizures in both sexes compared to non-use of the respective drug classes, while current use of TCAs was associated with slightly increased odds of seizures in men, but not in women (**Table 16**). The odds of seizures were highest at treatment initiation with SSRIs and SNRIs.

Among single antidepressants, use of citalopram (adjusted odds ratio 1.69 [95% CI, 1.25-2.28]), sertraline (adjusted odds ratio 2.53 [95% CI, 1.49-4.30]), fluoxetine (adjusted odds ratio 1.51 [95% CI, 1.06-2.16]), and venlafaxine (adjusted odds ratio 2.52 [95% CI, 1.44-4.42]), was associated with significantly increased odds of seizures compared to non-use (**Table 17**). We observed trends toward higher odds of seizures with increasing dose for fluoxetine, venlafaxine, and mirtazapine.

Due to low numbers of patients with dementia or stroke/TIA, we could not explore effect modification by these disorders in users of all antidepressant drug classes. Current use of SSRIs tended to be more strongly associated with seizures in patients with dementia (adjusted odds ratio 6.74 [95% CI, 1.53-29.62]) than those without dementia (adjusted odds ratio 1.90 [95% CI, 1.41-2.55]) (as shown in **Table 18**). We observed no effect modification by history of stroke/TIA in users of SSRIs or TCAs (as shown in **Table 19**).

Odds ratios did not change considerably when we compared antidepressant users to patients with depression who did not yet take any antidepressant medication (as shown in **Table 20**).

Additionally, switching antidepressants was not associated with substantially different odds ratios of seizures compared to using the same antidepressant during follow-up (as shown in **Table 21**).

Table 13: Incidence rates of seizures in patients with depression with no antidepressant treatment, with current and past use of antidepressants, and with current use of different antidepressant drug classes, by age or sex

Antidepressant drug class	Person-years	No. of cases with outcome	IR per 10,000 person-years	95% CI
No antidepressant treatment				
Overall	36,457	34	9.33	6.19-12.46
Stratified by age				
18-49 years	25,885	29	11.20	7.13-15.28
50-90 years	10,573	5	4.73	0.58-8.87
Stratified by sex				
men	10,400	12	11.54	5.01-18.07
women	26,057	22	8.44	4.91-11.97
Antidepressant treatment (overall)				
Overall	200,331	252	12.58	11.03-14.13
Stratified by age				
18-49 years	113,055	126	11.15	9.20-13.09
50-90 years	87,276	126	14.44	11.92-16.96
Stratified by sex				
men	62,805	107	17.04	13.81-20.27
women	137,526	145	10.54	8.83-12.26
Past use of antidepressants				
Overall	609,764	308	5.05	4.49-5.62
Stratified by age				
18-49 years	391,520	183	4.67	4.00-5.35
50-90 years	218,244	125	5.73	4.72-6.73
Stratified by sex				
men	199,125	133	6.68	5.54-7.81
women	410,639	175	4.26	3.63-4.89
SSRIs				
Overall	152,758	190	12.44	10.67-14.21
Stratified by age				
18-49 years	91,036	97	10.66	8.53-12.78
50-90 years	61,722	93	15.07	12.01-18.13
Stratified by sex				
men	46,664	76	16.29	12.63-19.95
women	106,094	114	10.75	8.77-12.72

Table 13 (cont.)

Antidepressant drug class	Person-years	No. of cases with outcome	IR per 10,000 person-years	95% CI
SNRIs				
Overall	14,253	22	15.44	8.99-21.89
Stratification by age				
18-49 years	8,025	10	12.46	4.74-20.18
50-90 years	6,228	12	19.27	8.37-30.17
Stratification by sex				
men	5,343	10	18.72	7.12-30.32
women	8,910	12	13.47	5.85-21.09
TCAs				
Overall	24,004	20	8.33	4.68-11.98
Stratified by age				
18-49 years	9,983	11	11.02	4.51-17.53
50-90 years	14,021	9	6.42	2.23-10.61
Stratified by sex				
men	6,918	12	17.35	7.53-27.16
women	17,086	8	4.68	1.44-7.93
Other Antidepressants[a]				
Overall	9,316	20	21.47	12.06-30.88
Stratified by age				
18-49 years	4,010	8	19.95	6.13-33.78
50-90 years	5,306	12	22.62	9.82-35.42
Stratified by sex				
men	3,880	9	23.20	8.04-38.36
women	5,436	11	20.24	8.28-32.19

Abbreviations: IR, incidence rate; CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] This group consisted of the drugs mirtazapine, bupropion, reboxetine, and trazodone

Table 14: Incidence rates of seizures in current users of most frequently used single antidepressants, by age or sex

Antidepressant drug	Person-years	No. of cases with outcome	IR per 10,000 person-years	95% CI
Citalopram				
Overall	61,677	87	14.11	11.14-17.07
Stratified by age				
18-49 years	35,286	44	12.47	8.78-16.15
50-90 years	26,391	43	16.29	11.42-21.16
Stratified by sex				
men	18,551	36	19.41	13.07-25.75
women	43,127	51	11.83	8.58-15.07
Escitalopram				
Overall	8,080	8	9.90	3.04-16.76
Stratified by age				
18-49 years	4,940	4	8.10	0.16-16.03
50-90 years	3,139	4	12.74	0.25-25.23
Stratified by sex				
men	2,545	2	7.86	NA
women	5,535	6	10.84	2.17-19.51
Fluoxetine				
Overall	49,488	52	10.51	7.65-13.36
Stratified by age				
18-49 years	31,847	31	9.73	6.31-13.16
50-90 years	17,640	21	11.90	6.81-17.00
Stratified by sex				
men	14,434	23	15.93	9.42-22.45
women	35,054	29	8.27	5.26-11.28
Paroxetine				
Overall	17,537	16	9.12	4.65-13.59
Stratified by age				
18-49 years	9,807	8	8.16	2.50-13.81
50-90 years	7,730	8	10.35	3.18-17.52
Stratified by sex				
men	5,955	4	6.72	0.13-13.30
women	11,582	12	10.36	4.50-16.22
Sertraline				
Overall	15,912	27	16.97	10.57-23.37
Stratified by age				
18-49 years	9,119	10	10.97	4.17-17.76
50-90 years	6,793	17	25.03	13.13-36.92
Stratified by sex				
men	5,155	11	21.34	8.73-33.95
women	10,758	16	14.87	7.59-22.16

Table 14 (cont.)

Antidepressant drug	Person-years	No. of cases with outcome	IR per 10,000 person-years	95% CI
Venlafaxine				
Overall	13,153	22	16.73	9.74-23.71
Stratified by age				
18-49 years	7,444	10	13.43	5.11-21.76
50-90 years	5,709	12	21.02	9.13-32.91
Stratified by sex				
men	4,993	10	20.03	7.61-32.44
women	8,160	12	14.71	6.39-23.03
Amitriptyline				
Overall	9,854	12	12.18	5.29-19.07
Stratified by age				
18-49 years	3,845	8	20.81	6.39-35.23
50-90 years	6,010	4	6.66	0.13-13.18
Stratified by sex				
men	2,723	8	29.38	9.02-49.74
women	7,131	4	5.61	0.11-11.11
Mirtazapine				
Overall	7,032	12	17.06	7.41-26.72
Stratified by age				
18-49 years	2,971	5	16.83	2.08-31.58
50-90 years	4,061	7	17.24	4.47-30.00
Stratified by sex				
men	3,061	7	22.87	5.93-39.81
women	3,971	5	12.59	1.55-23.63

Abbreviations: IRs, incidence rates; CI, confidence interval; NA, not applicable.

Table 15: Characteristics of cases with seizures and matched controls[a]

Characteristics	No. Cases (n=619) (%)[b]	No. Controls (n=2,476) (%)[b]	OR[c]	95% CI
Sex				
Male	265 (42.8)	1,060 (42.8)	NA	NA
Female	354 (57.2)	1,416 (57.2)	NA	NA
Age, years				
18-29	153 (24.7)	604 (24.4)	NA	NA
30-39	101 (16.3)	400 (16.2)	NA	NA
40-49	95 (15.4)	383 (15.5)	NA	NA
50-59	70 (11.3)	293 (11.8)	NA	NA
60-69	66 (10.7)	279 (11.3)	NA	NA
70-79	66 (10.7)	246 (9.9)	NA	NA
80-90	68 (11.0)	271 (11.0)	NA	NA
Body mass index, kg/m^2				
<18.5	18 (2.9)	54 (2.2)	1.32	0.75-2.32
18.5-24.9	221 (35.7)	868 (35.1)	1	reference
25.0-29.9	137 (22.1)	641 (25.9)	0.82	0.65-1.05
≥30.0	112 (18.1)	452 (18.3)	0.95	0.73-1.23
Unknown	131 (21.2)	461 (18.6)	1.15	0.86-1.53
Smoking status				
Nonsmoker	251 (40.6)	1,027 (41.5)	1	reference
Current smoker	175 (28.3)	687 (27.8)	1.05	0.84-1.32
Former smoker	147 (23.8)	597 (24.1)	1.02	0.80-1.29
Unknown	46 (7.4)	165 (6.7)	1.07	0.70-1.65
Alcohol consumption (in units/week, any time prior to the index date)				
Nondrinker	257 (41.5)	946 (38.2)	1	reference
1-14	211 (34.1)	900 (36.4)	0.85	0.69-1.05
>14	52 (8.4)	247 (10.0)	0.75	0.53-1.06
Unknown	99 (16.0)	383 (15.5)	0.85	0.63-1.17
Comorbidities at any time prior to the index date				
Transient ischemic attack	40 (6.5)	51 (2.1)	3.76	2.37-5.96
Ischemic stroke	72 (11.6)	71 (2.9)	5.36	3.67-7.84
Dementia	51 (8.2)	38 (1.5)	6.72	4.20-10.77
Parkinson's disease	10 (1.6)	14 (0.6)	3.05	1.31-7.13
Compulsive disorders and/or affective disorders[d]	31 (5.0)	101 (4.1)	1.25	0.82-1.91
Schizophrenia	16 (2.6)	15 (0.6)	4.27	2.11-8.63
Suicide attempt and/or suicidal ideation	65 (10.5)	125 (5.1)	2.28	1.65-3.15

Table 15 (cont.)

Characteristics	No. Cases (n=619) (%)[b]	No. Controls (n=2,476) (%)[b]	OR[c]	95% CI
Migraine	70 (11.3)	251 (10.1)	1.14	0.85-1.51
Concurrent drug use[e]				
Antipsychotic drugs[f]	54 (8.7)	64 (2.6)	4.07	2.74-6.05
Benzodiazepines	79 (12.8)	167 (6.7)	2.05	1.52-2.77
Penicillins	48 (7.8)	204 (8.2)	0.92	0.63-1.35
Cephalosporins[g]	17 (2.8)	30 (1.2)	2.42	1.32-4.43
Antimalarials	9 (1.5)	32 (1.3)	1.12	0.52-2.38
Opioids[h]	97 (15.7)	290 (11.7)	1.50	1.14-1.99

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable.

[a] Controls were matched to cases on age, sex, index date, GP practice, duration of history in the CPRD, and duration of depression. All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] ORs for different categories of body mass index, smoking status, and alcohol consumption were adjusted for each other. ORs for comorbidities and concomitant drug use were not adjusted.

[d] Affective disorders excluding depression.

[e] Last prescription within 90 days prior to index date.

[f] This group consisted mainly of phenothiazines such as prochlorperazine (76.4%) or chlorpromazine/promazine (3.8%).

[g] This group consisted mainly of first-generation cephalosporins such as cephalexin (66.3%) or cefadrine (9.0%).

[h] This group consisted mainly of codeine/dihydrocodeine (74.8%), dextropropoxyphene (17.7%), and tramadol (6.5%).

Table 16: Odds ratios for seizures in users of different antidepressant drug classes, by current or past use, by current use and sex, or by current use and number of prescriptions prior to the index date

Antidepressant drug class	**No. Cases (n=619) (%)[a]**	**No. Controls (n=2,476) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
SSRIs						
No use	105 (17.0)	557 (22.5)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	243 (39.3)	629 (25.4)	2.03	1.57-2.63	1.98	1.48-2.66
Current use stratified by sex[c]						
men	100 (16.2)	286 (11.6)	1.62	1.12-2.36	1.84	1.19-2.85
women	143 (23.1)	343 (13.8)	2.46	1.72-3.52	2.22	1.47-3.37
Current use by number of prescriptions						
1	27 (4.4)	48 (1.9)	2.99	1.79-5.02	3.35	1.89-5.92
2-3	37 (6.0)	105 (4.2)	1.97	1.25-3.09	2.37	1.46-3.87
4-5	28 (4.5)	89 (3.6)	1.70	1.06-2.72	1.51	0.90-2.52
>5	151 (24.4)	387 (15.6)	1.97	1.46-2.65	1.77	1.26-2.48
Past use (last presc. >90 days ago)	271 (43.8)	1,290 (52.1)	1.07	0.82-1.39	1.16	0.87-1.56
SNRIs						
No use	551 (89.0)	2,290 (92.5)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	31 (5.0)	64 (2.6)	2.07	1.32-3.24	1.99	1.20-3.29
Current use stratified by sex[c]						
men	14 (2.3)	33 (1.3)	1.77	0.92-3.42	1.86	0.87-3.97
women	17 (2.7)	31 (1.3)	2.38	1.29-4.41	2.15	1.06-4.37
Current use by number of prescriptions						
1-3	12 (1.9)	12 (0.5)	4.27	1.88-9.72	4.03	1.70-9.56
>3	19 (3.1)	52 (2.1)	1.56	0.91-2.69	1.24	0.67-2.29
Past use (last presc. >90 days ago)	37 (6.0)	122 (4.9)	1.29	0.87-1.89	1.17	0.76-1.79

Table 16 (cont.)

Antidepressant drug class	No. Cases (n=619) (%)[a]	No. Controls (n=2,476) (%)[a]	OR crude	95% CI	OR adj.[b]	95% CI
TCAs						
No use	475 (76.7)	1,896 (76.6)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	35 (5.7)	147 (5.9)	0.95	0.64-1.40	0.99	0.63-1.53
Current use stratified by sex[c]						
men	20 (3.3)	66 (2.6)	1.25	0.73-2.14	1.58	0.85-2.96
women	15 (2.4)	81 (3.3)	0.72	0.41-1.28	0.58	0.30-1.13
Current use by number of prescriptions						
1-3	11 (1.8)	48 (1.9)	0.91	0.45-1.82	0.80	0.36-1.77
>3	24 (3.9)	99 (4.0)	0.97	0.61-1.54	0.86	0.52-1.43
Past use (last presc. >90 days ago)	109 (17.6)	433 (17.5)	1.01	0.79-1.29	1.09	0.82-1.43
Other antidepressants[d]						
No use	552 (89.2)	2,299 (92.9)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	34 (5.5)	51 (2.1)	2.88	1.83-4.54	2.30	1.34-3.96
Current use stratified by sex[c]						
men	20 (3.2)	25 (1.0)	3.46	1.86-6.42	3.78	1.87-7.61
women	14 (2.3)	26 (1.1)	2.31	1.17-4.56	0.97	0.38-2.50
Current use by number of prescriptions						
1-3	10 (1.6)	13 (0.5)	3.21	1.41-7.34	3.28	1.31-8.20
>3	24 (3.9)	38 (1.5)	2.76	1.61-4.71	1.63	0.84-3.16
Past use (last presc. >90 days ago)	33 (5.3)	126 (5.1)	1.08	0.73-1.61	0.92	0.59-1.43

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] Due to rounding, percentages may not total 100.

[b] Adjusted for alcohol consumption, other antidepressant drugs, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicidal ideation, dementia, Parkinson's disease, TIA, and stroke.

[c] Reference groups: Male non-users (for men), female non-users (for women).

[d] This group consisted of the drugs mirtazapine, bupropion, reboxetine, and trazodone.

Table 17: Odds ratios for seizures in users of different antidepressant single drugs, by use and by dose used at the index date[a]

Antidepressant drug	No. Cases (n=619) (%)[b]	No. Controls (n=2,476) (%)[b]	OR crude	95% CI	OR adj.[c]	95% CI
Citalopram						
No use at the ID	527 (85.1)	2,267 (91.6)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	92 (14.9)	209 (8.4)	1.94	1.48-2.54	1.69	1.25-2.28
Use at the ID by dose						
≤20mg (≤DDD)	65 (10.5)	155 (6.3)	1.84	1.35-2.51	1.68	1.19-2.37
>20mg (>DDD)	27 (4.4)	54 (2.2)	2.22	1.37-3.59	1.72	1.01-2.93
Escitalopram						
No use at the ID	611 (98.7)	2,455 (99.2)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	8 (1.3)	21 (0.9)	1.54	0.68-3.50	1.28	0.48-3.40
Fluoxetine						
No use at the ID	569 (91.9)	2,336 (94.4)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	50 (8.1)	140 (5.7)	1.47	1.05-2.06	1.51	1.06-2.16
Use at the ID by dose						
≤20mg (≤DDD)	38 (6.1)	120 (4.9)	1.30	0.89-1.90	1.41	0.94-2.10
>20mg (>DDD)	12 (1.9)	20 (0.8)	2.42	1.18-4.94	1.99	0.92-4.29
Paroxetine						
No use at the ID	602 (97.3)	2,422 (97.8)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	17 (2.8)	54 (2.2)	1.27	0.73-2.21	1.04	0.56-1.92
Sertraline						
No use at the ID	589 (95.2)	2,434 (98.3)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	30 (4.9)	42 (1.7)	2.92	1.81-4.69	2.53	1.49-4.30
Use at the ID by dose						
≤50mg (≤DDD)	14 (2.3)	21 (0.9)	2.75	1.39-5.46	2.42	1.15-5.11
>50mg (>DDD)	16 (2.6)	21 (0.9)	3.08	1.61-5.90	2.64	1.26-5.54

Table 17 (cont.)

Antidepressant drug	No. Cases (n=619) (%)[b]	No. Controls (n=2,476) (%)[b]	OR crude	95% CI	OR adj.[c]	95% CI
Venlafaxine						
No use at the ID	592 (95.6)	2,429 (98.1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	27 (4.4)	47 (1.9)	2.49	1.51-4.10	2.52	1.44-4.42
Use at the ID by dose						
≤100mg (≤DDD)	13 (2.1)	32 (1.3)	1.76	0.89-3.50	1.86	0.88-3.95
>100mg (>DDD)	14 (2.3)	15 (0.6)	3.78	1.82-7.83	3.73	1.63-8.55
Amitriptyline[d]						
No use at the ID	603 (97.4)	2,435 (98.3)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	16 (2.6)	41 (1.7)	1.60	0.88-2.90	1.48	0.75-2.92
Mirtazapine						
No use at the ID	604 (97.6)	2,443 (98.7)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Use at the ID	15 (2.4)	33 (1.3)	1.86	1.00-3.48	1.53	0.73-3.20
Use at the ID by dose						
≤30mg (≤DDD)	10 (1.6)	26 (1.1)	1.58	0.75-3.32	1.19	0.50-2.84
>30mg (>DDD)	5 (0.8)	7 (0.3)	2.89	0.92-9.11	3.16	0.79-12.69

Abbreviations: ID, index date; OR, odds ratio; CI, confidence interval; adj., adjusted; DDD, defined daily dose (as described in the methods section).

[a] We assessed use and dose used at the index date from the quantity of drug prescribed at the previous visit and the daily dose instruction given. If no information on daily dose instruction was available, we used default values as described in the methods section. These default values were used in 27 (9.0%), 5 (17.2%), 25 (13.2%), 10 (14.1%), 11 (15.3%), 25 (33.8%), 25 (43.9%), or 8 (16.7%) patients who at the index date used citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, amitriptyline, or mirtazapine, respectively.

[b] Due to rounding, percentages may not total 100.

[c] Adjusted for alcohol consumption, other antidepressant drugs, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicidal ideation, dementia, Parkinson's disease, TIA, and stroke.

[d] Of 57 users, only 10 (17.5%) used doses >75mg (>DDD) at the ID

Table 18: Odds ratios for seizures in users of different antidepressant drug classes compared to non-users of antidepressants, by current or past use, and by dementia

Analysis restricted to patients with dementia						
Antidepressant drug class	**No. Cases (n=51) (%)[a]**	**No. Controls (n=38) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
SSRIs						
No use	7 (1.1)	9 (0.4)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	29 (4.7)	11 (0.4)	4.48	1.26-15.87	6.74	1.53-29.62
Past use (last presc. >90 days ago)	15 (2.4)	18 (0.7)	1.20	0.35-4.13	1.44	0.33-6.27
SNRIs						
No use	44 (7.1)	34 (1.4)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	X	X	NA	NA	NA	NA
Past use (last presc. >90 days ago)	5 (0.8)	X	NA	NA	NA	NA
TCAs						
No use	43 (7.0)	29 (1.2)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	X	X	NA	NA	NA	NA
Past use (last presc. >90 days ago)	8 (1.3)	5 (0.2)	0.97	0.28-3.33	0.64	0.14-2.96
Other antidepressants[c]						
No use	39 (6.3)	31 (1.3)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	9 (1.5)	6 (0.2)	2.64	1.59-4.38	1.41	0.37-5.36
Past use (last presc. >90 days ago)	X	X	NA	NA	NA	NA

Table 18 (cont.)

Analysis restricted to patients without dementia						
Antidepressant drug class	**No. Cases (n=568) (%)[a]**	**No. Controls (n=2,438) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
SSRIs						
No use	98 (15.8)	548 (22.1)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	214 (34.6)	618 (25.0)	1.95	1.49-2.55	1.90	1.41-2.55
Past use (last presc. >90 days ago)	256 (41.4)	1,272 (51.4)	1.07	0.82-1.41	1.15	0.86-1.55
SNRIs						
No use	507 (81.9)	2,256 (91.1)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	29 (4.7)	61 (2.5)	2.16	1.36-3.43	2.11	1.27-3.52
Past use (last presc. >90 days ago)	32 (5.2)	121 (4.9)	1.19	0.79-1.80	1.11	0.72-1.73
TCAs						
No use	432 (69.8)	1,867 (75.4)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	35 (5.7)	143 (5.8)	1.10	0.74-1.63	1.06	0.68-1.64
Past use (last presc. >90 days ago)	101 (16.3)	428 (17.3)	1.05	0.82-1.36	1.10	0.83-1.46
Other antidepressants[c]						
No use	513 (82.9)	2,268 (91.6)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	25 (4.0)	45 (1.8)	2.64	1.59-4.38	2.50	1.41-4.42
Past use (last presc. >90 days ago)	30 (4.9)	125 (5.1)	1.11	0.74-1.68	0.88	0.56-1.39

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; NA, not applicable; X, cell contains <5 observations (due to ethics regulations to preserve confidentiality, the exact count is not displayed).

Table 19: Odds ratios for seizures in users of different antidepressant drug classes compared to non-users of antidepressants, by current or past use, and by a history of stroke/TIA

Analysis restricted to patients with a history of stroke/TIA						
Antidepressant drug class	**No. Cases (n=90) (%)[a]**	**No. Controls (n=103) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
SSRIs						
No use	15 (2.4)	24 (1.0)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	50 (8.1)	31 (1.3)	1.93	0.87-4.27	2.35	0.98-5.61
Past use (last presc. >90 days ago)	25 (4.0)	48 (1.9)	0.71	0.31-1.67	0.85	0.34-2.14
SNRIs						
No use	85 (13.7)	96 (3.9)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	X	5 (0.2)	NA	NA	NA	NA
Past use (last presc. >90 days ago)	X	X	NA	NA	NA	NA
TCAs						
No use	65 (10.5)	70 (2.8)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	8 (1.3)	16 (0.7)	0.58	0.22-1.52	0.82	0.27-2.45
Past use (last presc. >90 days ago)	17 (2.8)	17 (0.7)	1.17	0.53-2.57	1.01	0.42-2.42
Other antidepressants[c]						
No use	77 (12.4)	98 (4.0)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	6 (1.0)	X	NA	NA	NA	NA
Past use (last presc. >90 days ago)	7 (1.1)	X	NA	NA	NA	NA

Table 19 (cont.)

Analysis restricted to patients without a history of stroke/TIA						
Antidepressant drug class	**No. Cases (n=90) (%)[a]**	**No. Controls (n=103) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
SSRIs						
No use	90 (14.5)	533 (21.5)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	193 (31.2)	598 (24.2)	1.88	1.42-2.48	1.94	1.42-2.63
Past use (last presc. >90 days ago)	246 (39.7)	1,242 (50.2)	1.09	0.82-1.44	1.18	0.87-1.60
SNRIs						
No use	466 (75.3)	2,194 (88.6)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	27 (4.4)	59 (2.4)	2.36	1.46-3.80	2.08	1.24-3.51
Past use (last presc. >90 days ago)	36 (5.8)	120 (4.9)	1.44	0.97-2.14	1.20	0.78-1.84
TCAs						
No use	410 (66.2)	1,826 (73.8)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	27 (4.4)	131 (5.3)	0.97	0.63-1.50	1.03	0.65-1.65
Past use (last presc. >90 days ago)	92 (14.9)	416 (16.8)	0.97	0.77-1.30	1.08	0.80-1.44
Other antidepressants[c]						
No use	475 (76.7)	2,201 (88.9)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	28 (4.5)	49 (2.0)	3.10	1.89-5.10	2.03	1.12-3.68
Past use (last presc. >90 days ago)	26 (4.2)	123 (5.0)	1.01	0.65-1.56	0.82	0.51-1.31

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; NA, not applicable; X, cell contains <5 observations (due to ethics regulations to preserve confidentiality, the exact count is not displayed).

Table 20: Odds ratios for seizures in users of different antidepressant drug classes compared to non-users of antidepressants, by current or past use

Antidepressant drug class	No. Cases (n=619) (%)[a]	No. Controls (n=2,476) (%)[a]	OR crude	95% CI	OR adj.[b]	95% CI
No use of antidepressants	34 (5.5)	228 (9.2)	1	reference	1	reference
SSRIs						
Current use (last presc. ≤ 90 days ago)	243 (39.3)	629 (25.4)	2.56	1.70-3.86	2.06	1.35-3.16
Past use (last presc. >90 days ago)	271 (43.8)	1,290 (52.1)	1.37	0.89-2.09	1.21	0.78-1.89
SNRIs						
Current use (last presc. ≤ 90 days ago)	31 (5.0)	64 (2.6)	3.71	2.06-6.67	2.11	1.06-4.20
Past use (last presc. >90 days ago)	37 (6.0)	122 (4.9)	2.39	1.37-4.17	1.25	0.64-2.45
TCAs						
Current use (last presc. ≤ 90 days ago)	35 (5.7)	147 (5.9)	1.75	1.02-3.01	1.04	0.56-1.92
Past use (last presc. >90 days ago)	109 (17.6)	433 (17.5)	1.91	1.21-3.03	1.15	0.68-1.94
Other antidepressants[c]						
Current use (last presc. ≤ 90 days ago)	34 (5.5)	51 (2.1)	5.22	2.87-9.48	2.44	1.19-4.98
Past use (last presc. >90 days ago)	33 (5.3)	126 (5.1)	2.00	1.14-3.49	0.99	0.50-1.96

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; NA, not applicable; presc., prescription; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] Cases and controls could be users of more than one antidepressant group and thus be listed more than once in the table (thus percentages do not total 100%).

[b] Adjusted for alcohol consumption, other antidepressant drug classes, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicide attempt or suicidal ideation, dementia, Parkinson's disease, TIA, and stroke.

[c] This group consisted of the drugs mirtazapine, bupropion, reboxetine, and trazodone.

Table 21: Odds ratios for seizures in users of different antidepressant drug classes compared to non-users of antidepressants, by current or past use, and by switching of antidepressants during follow-up, compared to non-users of antidepressants

Antidepressant drug class	**No. Cases (n=619) (%)[a]**	**No. Controls (n=2,476) (%)[a]**	**OR crude**	**95% CI**	**OR adj.[b]**	**95% CI**
No use	34 (5.5)	228 (9.2)	1	reference	1	reference
Analyses restricted to patients who did not switch antidepressants						
SSRIs						
Current use (last presc. ≤ 90 days ago)	150 (24.2)	396 (16.0)	2.56	1.68-3.91	2.13	1.37-3.30
Past use (last presc. >90 days ago)	148 (23.9)	800 (32.3)	1.22	0.78-1.90	1.19	0.75-1.88
SNRIs						
Current use (last presc. ≤ 90 days ago)	6 (1.0)	16 (0.7)	2.79	0.99-7.88	2.21	0.74-6.57
Past use (last presc. >90 days ago)	X	26 (1.1)	NA	NA	NA	NA
TCAs						
Current use (last presc. ≤ 90 days ago)	15 (2.4)	63 (2.5)	1.70	0.85-3.37	1.51	0.74-3.11
Past use (last presc. >90 days ago)	27 (4.4)	157 (6.3)	1.30	0.73-2.31	1.07	0.59-1.95
Other antidepressants[c]						
Current use (last presc. ≤ 90 days ago)	9 (1.5)	13 (0.5)	5.19	2.02-13.33	2.17	0.72-6.48
Past use (last presc. >90 days ago)	X	18 (0.7)	NA	NA	NA	NA

Table 21 (cont.)

Antidepressant drug class	No. Cases (n=619) (%)[a]	No. Controls (n=2,476) (%)[a]	OR crude	95% CI	OR adj.[b]	95% CI
No use	34 (5.5)	228 (9.2)	1	reference	1	reference
Analyses restricted to patients who switched antidepressants						
SSRIs						
Current use (last presc. ≤ 90 days ago)	93 (15.0)	233 (9.4)	2.59	1.63-1.14	1.87	1.11-3.15
Past use (last presc. >90 days ago)	123 (19.9)	490 (19.8)	1.65	1.04-2.61	1.15	0.68-1.96
SNRIs						
Current use (last presc. ≤ 90 days ago)	25 (4.0)	48 (1.9)	4.04	2.15-7.59	2.31	1.05-5.08
Past use (last presc. >90 days ago)	34 (5.5)	96 (3.9)	2.84	1.60-5.05	1.58	0.75-3.37
TCAs						
Current use (last presc. ≤ 90 days ago)	20 (3.2)	84 (3.4)	1.77	0.94-3.34	0.66	0.28-1.57
Past use (last presc. >90 days ago)	82 (13.3)	276 (11.2)	2.29	1.42-3.70	0.96	0.47-2.00
Other antidepressants[c]						
Current use (last presc. ≤ 90 days ago)	25 (4.0)	38 (1.5)	5.23	2.72-10.08	2.57	1.13-5.88
Past use (last presc. >90 days ago)	31 (5.0)	108 (4.4)	2.20	1.24-3.90	0.99	0.48-2.06

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; NA, not applicable; presc., prescription; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; X, cell contains <5 observations (due to ethics regulations to preserve confidentiality, the exact count is not displayed).

[a] Cases and controls could be users of more than one antidepressant group and thus be listed more than once in the table (thus percentages do not total 100%).

[b] Adjusted for alcohol consumption, other antidepressant drug classes, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicide attempt or suicidal ideation, dementia, Parkinson's disease, TIA, and stroke.

[c] This group consisted of the drugs mirtazapine, bupropion, reboxetine, and trazodone.

3.2.5 Discussion

The findings of this observational study suggest that patients with depressive disorder who are treated with SSRIs and SNRIs are at a higher risk of developing seizures than untreated patients or patients who received antidepressant drug treatment in the past. Our estimated incidence rates tended to be higher in SSRI and SNRI users and lower in TCA users than in non-users of antidepressants, especially in patients aged 50 or over. Estimated incidence rates of seizures were low irrespective of any antidepressant treatment. Adjusted relative risk estimates suggested that SSRI and SNRI users were at a twofold increased risk of developing seizures than non-users, and that the period of treatment initiation was associated with the highest risk of seizures. In addition, effect modification by underlying dementia, but not stroke/TIA, may be important in users of SSRIs.

Alper et al. found significantly lower incidence rates of seizures among depressed patients who used second-generation antidepressants than those who used placebo.[93] However, these findings were based on a very limited number of patients with seizures in the placebo groups, and this missing information about seizure occurrence in the placebo groups questions the validity of their findings.[93] Conversely, our incidence rate estimates which were based on 4.5 times as many cases with seizures observed and a considerably longer follow-up period were higher in users of second-generation antidepressants than in patients with no antidepressant treatment. Our incidence rate estimate in past users was closely similar to incidence rates of unprovoked seizures in the non-depressed European populations.[44,45] Of interest, this incidence rate in past users was significantly lower than the incidence rate in depressed patients who did not yet use antidepressants. This finding supports the theory that untreated depression is a risk factor for seizures.[27,65,66,84]

Our results of the nested case-control analysis are in line with a recent British observational study on severe adverse events related to antidepressants in depressed patients aged over 65 years, which reported increased hazard ratios of seizures among SSRI users (adjusted hazard ratio 1.83, 95% CI 1.49-2.26) and users of other antidepressants (adjusted hazard ratio 2.24, 95% CI 1.60-3.15), but not TCA users (adjusted hazard ratio 1.02, 95% CI 0.76-1.38), compared to non-users.[26] Our results in patients aged between 18 and 90 suggested that current use of SSRIs or SNRIs was associated with an increased risk of seizures compared to non-use, in particular at treatment initiation. Overall, current use of TCAs was not associated with seizures compared to non-use, although we observed a potential slight risk difference

between men and women. TCAs were generally prescribed at low doses among our study population: the most frequently used TCA amitriptyline was rarely prescribed at doses higher than 75-100 mg, the minimum daily dose considered by some authors to be effective compared to placebo for treatment of depression.[118]

In this study we provide absolute and relative risk estimates of developing seizures in a large population of adult depressed patients who were followed over a long period of time and under 'real-life' conditions. To our knowledge, no other study thus far has provided detailed information on the role of timing, duration, and dose of antidepressant use on the risk of seizures. Our results suggest that treatment initiation and for some substances increasing dose are important risk factors for developing seizures among users of SSRIs and SNRIs. We addressed potential confounding by excluding patients with major risk factors for seizures, matching controls to cases on age, gender, GP practice, and duration of depression, and adjusting multivariate models for other potential confounders reported in the literature.

There are limitations to this study. First of all, the ascertainment of a first epileptic seizure is not guaranteed through the Read code record; other medical conditions could wrongly have been classified as seizures. As antiepileptic drugs are usually only prescribed to selected patients after the first seizure,[82] we did not want to consider patients with subsequent antiepileptic treatment only. Also, potential misclassification of seizures was likely to be similarly distributed across users of different antidepressants. Second, the limited number of cases with seizures (especially in the analyses of single drugs) resulted in imprecise risk estimates. Although point estimates revealed trends toward higher or lower risk associated with different antidepressants and doses prescribed, the differences were not statistically significant. Third, we could not adjust our analyses for depression severity based on rating scales, as this information is not available in the CPRD. Depression has been associated with an increased risk of seizures in a review of clinical trials,[93] in epidemiological studies,[27,65,66] and in reviews of neurobiological studies,[84,119] and depression severity may be associated with the choice of antidepressant drug and dose prescribed. However, we aimed to minimize confounding by depression severity on our results by including patients with an ICD-10 coded depression diagnosis only if they received an antidepressant treatment at some point after the diagnosis to exclude patients with mild and transient depression. To avoid comparing patients with more severe depression to patients with less severe depression, we matched controls to cases on duration of depression and included users of other antidepressants than the ones studied in the reference group of the nested case-control analysis. A sensitivity analysis in

which we compared patients with antidepressant treatment to patients with no treatment yielded closely similar relative risk estimates and thus argued against substantial confounding by indication. Last, to further assess the influence of depression severity on the relative risk estimates, we explored the association of interest in patients who did or did not switch between drug treatments,[117] and observed no substantial differences in relative risk estimates.

In conclusion, our study suggested that depressed patients who currently used SSRIs and SNRIs were at a higher risk of developing incident seizures than untreated patients. Current use of TCAs was not associated with the occurrence of seizures, a finding that may be explained by low dosages of TCAs prescribed. Treatment initiation rather than longer-term treatment was an important risk factor for the development of seizures. Our findings on the risk of seizures associated with single antidepressants were based on a limited number of cases and controls; further studies, preferably taking into account underlying depression severity and drug doses taken, are needed to confirm them. Also, further research is required on the association between antidepressant use and seizure frequency in patients with diagnosed epilepsy and comorbid depression.

3.3 Project 3: Antipsychotic drug use and the risk of seizures

Unabbreviated title: Antipsychotic Drug Use and the Risk of Seizures: Follow-up Study with a Nested Case-Control Analysis

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Project 3: Antipsychotic drug use and the risk of seizures

3.3.1 Abstract

Objective

To investigate the association between antipsychotic drug use and the development of first-time seizures in patients with schizophrenia, affective disorders, or dementia.

Methods

We used data from the U.K.-based Clinical Practice Research Datalink database to conduct a follow-up study with a nested case-control analysis between 1998 and 2013. We identified patients with schizophrenia, affective disorders, or dementia, and estimated incidence rates of seizures among users of four antipsychotic subclasses, defined according to existing hypotheses on their seizure-inducing potential (1. olanzapine or quetiapine; 2. amisulpride, aripiprazole, risperidone, or sulpiride; 3. low to medium potency first-generation antipsychotics [chlorpromazine, zuclopenthixol, flupenthixol, pericyazine, promazine, thioridazine]; 4. medium to high potency first-generation antipsychotics [haloperidol, prochlorperazine, trifluoperazine]), and among those who did not use antipsychotics. To adjust for confounding, we estimated odds ratios for seizures separately among patients with affective disorders or dementia, stratified by antipsychotic use and timing of use.

Results

In the total cohort of 60,121 patients (who had schizophrenia, affective disorders, or dementia), the incidence rate of seizures per 10,000 person-years was 32.6 (95% confidence interval [CI] 22.6-42.6) in users of olanzapine or quetiapine, 24.1 (95% CI 13.2-34.9) in users of amisulpride, aripiprazole, risperidone, or sulpiride, 49.4 (95% CI 27.7-71.0) in users of low to medium potency antipsychotics, 59.1 (95% CI 40.1-78.2) in users of medium to high potency antipsychotics, and 11.7 (95% CI 10.0-13.4) in non-users of antipsychotics. Patients with dementia had significantly higher incidence rates of first-time seizures compared with patients with affective disorders, irrespective of antipsychotic drug use. In patients with affective disorders, current use of medium to high potency first-generation antipsychotics was associated with an increased risk of seizures (adjusted odds ratio 2.51 [95% CI 1.51-4.18]) compared with non-use, while use of other antipsychotics was not associated with seizures. In patients with dementia, current use of olanzapine or quetiapine (adjusted odds ratio 2.37 [95% CI 1.35-4.15]), low to medium potency first-generation antipsychotics (adjusted odds ratio

3.08 [95% CI 1.34-7.08]), and medium to high potency first-generation antipsychotics (adjusted odds ratio 2.24 [95% CI 1.05-4.81]) was associated with an increased risk of seizures compared with non-use, but current use of amisulpride, aripiprazole, risperidone, or sulpiride (adjusted odds ratio 0.92 [95% CI 0.48-1.75]) was not. Use of antipsychotics in patients with schizophrenia could not be investigated due to small numbers.

Conclusions

Current use of medium to high potency first-generation antipsychotics was associated with a 2.5-fold increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders. In these patients, current use of all other antipsychotic subclasses was not associated with seizures. In patients with dementia, current and past use of all antipsychotic subclasses, except amisulpride, aripiprazole, risperidone or sulpiride, was associated with an increased risk of seizures.

3.3.2 Introduction

Antipsychotics are commonly used in patients with schizophrenia, affective disorders, or dementia.[120] These drugs have been associated with seizures, especially if high doses are applied, if a rapid dose increase occurs, or if other risk factors for seizures are present.[55,57]

Across first-generation antipsychotics, low potency drugs with strong sedation (particularly aliphatic phenothiazines) have been associated with a higher risk of seizures than high potency drugs.[3–6] The evidence on this association is scarce and is mainly based on one observational study in hospitalized psychiatric patients published almost 50 years ago.[91] In this study, the overall incidence of seizures over 4.5 years was 1.2% among 859 phenothiazine users, while no seizures occurred among 669 non-users of phenothiazines.[91]

Among second-generation antipsychotics clozapine has repeatedly been associated with the highest risk of seizures.[93,122–124] In a meta-analysis of clinical trials including a limited number of patients observed over a short time period, the incidence rate of seizures was higher in users of clozapine, olanzapine, and quetiapine compared to placebo, but not in users of risperidone or ziprasidone.[93] Also, users of clozapine, olanzapine, and quetiapine more frequently reported seizures than users of other second-generation antipsychotics (such as risperidone, amisulpride, or aripiprazole) in two studies based on pharmacovigilance data susceptible to reporting bias and confounding.[92,94]

Using primary care observational data collected in the U.K. over a time span of 15 years, we aimed to explore the association between antipsychotic drug use and the development of first-time seizures in a large population of adult patients with schizophrenia, affective disorders, or dementia. We further aimed to investigate the role of the underlying indication on the risk of seizures in antipsychotic drug users.

3.3.3 Methods

Study design and data source

We used data from the U.K.-based Clinical Practice Research Datalink (CPRD) database to conduct a retrospective population-based follow-up study with a nested case-control analysis. The CPRD was established more than 25 years ago and encompasses data on some eight million people who are registered with approximately 700 general practitioners (GPs), as

described in detail elsewhere.[31,32,125,126] The GPs record information on demographics, lifestyle variables, medical diagnoses (recorded as 'Read codes'), hospitalizations, and drug prescriptions in a standardized anonymous form. The records on drug exposure and diagnoses have repeatedly been validated and proven to be of high quality [34,35]. The CPRD has been the data source for several observational studies on antipsychotic drug use [127–129] and on seizures.[86,99,100,115] This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency research (London, U.K.).

Study population

We identified all patients aged 18 to 89 years between January 1998 and December 2011, who (1) had a first-time diagnosis of schizophrenia, affective disorders, or dementia, followed by an antipsychotic prescription at any time thereafter, or (2) a first-time prescription for an antipsychotic drug, provided that a first-time diagnosis of schizophrenia, affective disorders, or dementia followed within one year. Schizophrenia, affective disorders, and dementia were defined by codes corresponding to the International Classification of Diseases version 10 (ICD-10) codes F20-29 'Schizophrenia, schizotypal and delusional disorders', F30-39 'Mood [affective] disorders', and F00-F03 'Dementia in Alzheimer's disease', 'Vascular dementia', 'Dementia in other diseases classified elsewhere', and 'Unspecified dementia'. The date of (1) or (2), whichever came first, will subsequently be called the 'start date'. We excluded patients with a diagnosis of seizures or epilepsy, or any records of antiepileptic prescriptions, prior to the start date. Additionally, we excluded patients with recorded major risk factors for seizures such as a history of alcoholism, drug abuse, head trauma, intracerebral bleeding, brain tumor, brain abscess, sinus vein thrombosis, meningitis, encephalitis, HIV, or cancer prior to the start date. Patients were required to have had at least one year of active history in the database prior to the start date and those with codes suggesting a history of schizophrenia, affective disorders, or dementia prior to the start date were excluded.

Follow-up and definition of seizure cases

We followed all patients from the start date until they had (1) a first-time diagnosis of seizure or epilepsy (corresponding to ICD-10 codes G40 'Epilepsy', G41 'Status epilepticus', or R56.8 'Other and unspecified convulsions'), (2) a first-time prescription for an antiepileptic drug followed by a first-time diagnosis of seizure or epilepsy (as defined under [1]) within

three months thereafter, (3) a first-time prescription for an antiepileptic drug preceded or followed by a code of a suspected seizure within three months before or after, provided that a first-time diagnosis of seizure of epilepsy (as defined under [1]) followed at any time thereafter, (4) until they turned 90 years old, (5) died, (6) left the database, (7) reached the end of last data collection (December 2013), or (8) until one month prior to a first-time record of a major risk factor for seizures (as described under 'study population'), whichever came first. Patients whose follow-up ended due to (1), (2), or (3) will subsequently be called 'cases', and their date of follow-up end will be referred to as 'index date'.

Person-time analysis

We assessed person-time for four antipsychotic subclasses according to existing hypotheses on their seizure-inducing potential (as described in the 'Introduction'). We included individual drugs in these subclasses if they encompassed at least 100 person-years of accumulated use. Subclasses included: (1) second-generation drugs associated with a high risk of seizures (olanzapine or quetiapine), (2) other second-generation drugs (amisulpride, aripiprazole, risperidone, and sulpiride), (3) low to medium potency first-generation drugs (chlorpromazine, zuclopenthixol, flupenthixol, pericyazine, promazine, thioridazine), and (4) medium to high potency first-generation drugs (haloperidol, prochlorperazine, trifluoperazine). We classified first-generation drugs into low to medium or medium to high potency according to 'The American Psychiatric Publishing Textbook of Psychopharmacology'.[130]

Person time was accumulated as follows: (1) no exposure to antipsychotics ('no antipsychotic treatment') was defined as the period between the first diagnosis of affective disorders, schizophrenia, or dementia, and the first prescription for an antipsychotic, provided that the diagnosis occurred prior to the prescription; (2) current exposure to only one antipsychotic ('mono use') was defined as use from the day of the prescription through the expected end of treatment plus 7 days, provided that no other antipsychotic was prescribed in this period. Patients who switched between different antipsychotics but had no period of overlapping treatment contributed person-time to mono use of these different antipsychotics; (3) current exposure to more than one antipsychotic concomitantly ('mixed use') was defined as use from the day when at least two antipsychotics were prescribed concomitantly through the expected end of treatment of all or all but one antipsychotic plus 90 days. Patients who remained treated with one antipsychotic after the period of mixed use contributed person-time to mono

use for the remaining drug thereafter; and (4) past exposure after stopping antipsychotic treatment ('past use') was defined as the time after mono- or mixed use had elapsed. The duration of treatment was derived from the recorded quantity of tablets, injections, or oral liquids, and the dose instructions. If no quantity or dose instruction was recorded, we used default values in the following order: (1) the quantity and/or dose instruction recorded for the same drug at the closest visit prior to the previous visit, or, if no information was available at any time before, (2) the quantity and/or dose instruction most frequently recorded among our study population for the same drug.

Nested case-control analysis

For each case we identified up to four controls from the study population with no seizures during the study period. Controls were matched to cases on age (year of birth ± 2 years), sex, index date, and duration of history in the database prior to the index date (± 2 years). Additionally, controls were matched to cases on underlying schizophrenia, affective disorders, or dementia. If patients had diagnoses for more than one of these disorders prior to the index date, they were matched according to the following order based on smallest chance of remission/recovery and strongest association with seizures: (1) dementia, (2) schizophrenia, and (3) affective disorders.[66,85,86]

Case and control exposure to antipsychotics was classified according to the timing of antipsychotic use prior to the index date; 'non-users' were those who had no antipsychotic prescriptions prior to the index date; 'current users' and 'past users' were those who had received the last prescription ≤90 days or >90 days prior to the index date, respectively. Additionally, current users were stratified by exposure duration ('short-term users' and 'long-term users' were those who had received the first prescription ≤90 days or >90 days prior to the index date, respectively). Because incidence rates of seizures differed significantly between patients with affective disorders and patients with dementia in the follow-up part of the study, we conducted the nested case-control analysis among cases and controls with underlying affective disorders or dementia separately (number of patients with schizophrenia was too low for a separate analysis). We evaluated individual antipsychotic drugs if there were at least 5 exposed subjects in each exposure level. Where possible we classified each antipsychotic drug by the dose prescribed at the index date (≤1 defined daily dose, > 1 defined daily dose).[116]

Statistical analysis

We conducted a crude person-time analysis to estimate incidence rates of seizures, with 95% confidence intervals (95% CIs), for the following exposures: any mono use, mono use of different antipsychotic subclasses, mono use of individual drugs, past use of antipsychotics, and no use of antipsychotics. Incidence rates were estimated among the whole cohort of patients with schizophrenia, affective disorders, or dementia, and separately among patients who had diagnoses of affective disorders or dementia only.

In the nested case-control analysis, we used SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) to conduct conditional logistic regression analyses. Relative risk estimates of antipsychotic use among cases and controls were calculated as odds ratios with 95% CIs. Our reference group comprised patients with no antipsychotic treatment prior to the index date. Based on preexisting literature, we a priori adjusted multivariate models for alcohol consumption (none, 1-14 units/week, >14 units/week, unknown), compulsive disorders, Parkinson's disease, stroke and/or transient ischemic attack (TIA), suicidal ideation/attempts, and current or past use of antidepressants, anticonvulsants, opioids, benzodiazepines, or antipsychotics other than those studied.[55,62,66,131] We tested as additional potential confounders a history of cardiovascular diseases, diabetes, hypertension, hyperlipidemia, hypothyroidism, sleep disorders, renal diseases, or migraine, and concurrent use of antibiotics, anti-malarial drugs, stimulants, and immunosuppressant or antiarrhythmic drugs, but we did not include them in the final model as they did not alter the risk estimates by more than 5%.

To assess potential effect modification we stratified cases and controls by history of stroke and/or TIA, or of underlying disorders (affective disorders, dementia) and age (18-59 years, 60-90 years).

In sensitivity analyses we explored whether risk estimates of seizures associated with the use of antipsychotic subclasses differed if the reference group included non-users of the respective antipsychotic subclass (who potentially used other subclasses) prior to the index date. Additionally, we excluded users of prochlorperazine from the exposed group, to explore whether the risk of seizures associated with the use of medium to high potency first-generation antipsychotics changed since this drug is often used to treat nausea rather than psychotic symptoms.

3.3.4 Results

We identified 60,121 patients who met our inclusion criteria, of whom 79.6% were diagnosed with affective disorders, 11.2% with dementia, 3.0% with schizophrenia, and 6.2% with more than one disorder. Of these patients, 583 had a first-time diagnosis of seizure during follow-up. We also conducted a nested case-control analysis of 334 cases and 1,336 controls all of whom had an affective disorder, and 202 cases and 773 controls all of whom had dementia. Mean age (± standard deviation) at the index date of patients with affective disorders or dementia was 47.7 (±18.5) years and 76.7 (±8.1) years, respectively.

Incidence rates

Among the entire study population, the estimated incidence rates of seizures per 10,000 person-years (PYs) were 38.0 (95% CI, 31.1-44.9), 11.7 (95% CI, 10.0-13.4), and 12.4 (95% CI, 10.9-13.8) in current mono users, non-users, or past users of antipsychotics, respectively (**Table 22**). The highest incidence rate of seizures was among users of medium to high potency first-generation drugs (59.1 per 10,000 person-years [95% CI, 40.1-78.2]), and lowest for users of the second-generation drugs amisulpride, aripiprazole, risperidone, or sulpiride (24.1 per 10,000 person-years [95% CI, 13.2-34.9]). Among individual drugs, use of haloperidol was associated with the highest incidence rate of seizures (115.4 per 10,000 person-years [95% CI, 50.1-180.7]). Incidence rates of seizures were significantly higher in patients with dementia than in patients with affective disorders, irrespective of antipsychotic treatment (**Table 22**). Incidence rates of seizure were similar in non-use and past use of antipsychotics among patients with affective disorders, while in patients with dementia, past use of antipsychotics was associated with significantly higher incidence rate of seizures than non-use.

Nested case-control analysis

In the nested case-control analysis history of suicide attempt and/or suicidal ideation, migraine, or stroke/TIA, and concurrent use of opioids, benzodiazepines, anticonvulsants, or antidepressants were associated with an increased risk of seizures in patients with affective disorders (**Table 23**). History of stroke/TIA and concurrent use of benzodiazepines, were associated with an increased risk of seizures in patients with dementia.

Current use of first-generation medium to high potency antipsychotics (adjusted odds ratio 2.51 [95% CI, 1.51-4.18]) was associated with an increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders (**Table 24**). In these patients, current use of all other antipsychotic subclasses was not associated with seizures. In patients with dementia, current and past use of all first-generation antipsychotics and olanzapine and quetiapine, was associated with an increased risk of seizures compared to non-use of antipsychotics, while use of amisulpride, aripiprazole, risperidone, or sulpiride was not associated with seizures (**Table 24**). Due do small numbers of patients with current antipsychotic use, we could not calculate meaningful odds ratios for current use stratified by exposure duration.

Table 25 displays odds ratios of seizures associated with the most frequently prescribed antipsychotic individual drugs in patients with affective disorders or dementia, respectively. Current use of prochlorperazine was associated with an increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders (**Table 25**). Current use of all antipsychotic individual drugs except risperidone and past use of all antipsychotic individual drugs were associated with increased risks of seizures compared to non-use of antipsychotics in patients with dementia (**Table 25**). Most users of antipsychotic drugs were prescribed doses that were lower than or equal to the defined daily dose at the index date (88.0% of olanzapine or quetiapine users, 92.4% of amisulpride, aripiprazole, risperidone, or sulpiride users, 97.8% of low to medium potency first-generation antipsychotic users, and 100% of medium to high potency first-generation antipsychotic users). Thus, we were unable to assess a potential dose-effect relationship of antipsychotic drug use in relation to the risk of seizures.

Due to low numbers of patients with a history of stroke/TIA, potential effect modification by indication (affective disorders or dementia) could not be assessed in this subgroup. However, in the whole study population, the effects of antipsychotic use on the risk of seizures did not differ materially between those with and without a history of stroke/TIA (**Table 26**).

Current use of medium to high potency first-generation antipsychotics was associated with increased risks of seizures in all age groups (adjusted odds ratios 2.20 [95% CI, 1.18-4.09] and 4.97 [95% CI, 1.68-14.67] in patients less than 60 years or 60 years or over, respectively) [data not shown]. Most patients with dementia (94.6%) were aged 60 years or over while 1,233 (73.2%) patients with affective disorders were aged less than 60 years, and 447 (26.8%) were aged 60 years or over at the index date.

When the reference group was defined as non-use of the respective subclass of antipsychotics the results were closely similar (**Table 27**) to those of the main analysis (**Table 24**). Excluding prochlorperazine from the subclass of first-generation medium to high potency antipsychotics yielded a higher odds ratio of seizures in patients with affective disorders (adjusted odds ratio 12.56 [95% CI, 3.31-47.67]) compared to the estimate from the main analysis (**Table 24**), although the difference was not statistically significant.

Table 22: Incidence rates of seizures in patients with no antipsychotic treatment, with current and past use of antipsychotics, and with current use of different antipsychotic subclasses or single drugs, by underlying disorder

	PYs	No. of patients with seizures	IR [per 10,000 PYs]	95% CI
Whole study population				
No antipsychotic treatment	156,386	183	11.7	10.0-13.4
Past use	218,623	270	12.4	10.9-13.8
Any mono use	30,779	117	38.0	31.1-44.9
Olanzapine or quetiapine	12,577	41	32.6	22.6-42.6
Olanzapine	*6,839*	*13*	*19.0*	*8.7-29.3*
Quetiapine	*5,738*	*28*	*48.8*	*30.7-66.9*
Amisulpride, aripiprazole, risperidone, or sulpiride	7,895	19	24.1	13.2-34.9
Amisulpride	*1,256*	*5*	*39.8*	*4.9-74.7*
Risperidone	*5,012*	*13*	*25.9*	*11.8-40.0*
Low to medium potency antipsychotics[a]	4,051	20	49.4	27.7-71.0
Promazine	*839*	*8*	*95.4*	*29.3-161.4*
Medium to high potency antipsychotics[b]	6,256	37	59.1	40.1-78.2
Haloperidol	*1,040*	*12*	*115.4*	*50.1-180.7*
Prochlorperazine	*4,404*	*19*	*43.1*	*23.7-62.5*
Trifluoperazine	*812*	*6*	*73.9*	*14.8-133.0*
Analysis restricted to patients with affective disorders				
No antipsychotic treatment	139,686	117	8.4	6.9-9.9
Past use	199,303	164	8.2	7.0-9.5
Any mono use	16,718	35	20.9	14.0-27.9
Olanzapine or quetiapine	6,427	7	10.9	2.8-19.0
Amisulpride, aripiprazole, risperidone, or sulpiride	2,832	X	NA	NA
Low to medium potency antipsychotics[a]	2,627	6	22.8	4.6-41.1
Medium to high potency antipsychotics[b]	4,831	21	43.5	24.9-62.1
Prochlorperazine	*4,093*	*17*	*41.5*	*21.8-61.3*
Analysis restricted to patients with dementia				
No antipsychotic treatment	7,864	38	48.3	33.0-63.7
Past use	6,326	67	105.9	80.6-131.3
Any mono use	4,956	50	100.9	72.9-128.8
Olanzapine or quetiapine	1,826	20	109.5	61.5-157.5
Quetiapine	*1,523*	*18*	*118.2*	*63.6-172.7*
Amisulpride, aripiprazole, risperidone, or sulpiride	1,594	11	69.0	28.2-109.8
Risperidone	*1,063*	*6*	*56.4*	*11.3-101.6*
Low to medium potency antipsychotics[a]	794	7	88.1	22.8-153.4
Medium to high potency antipsychotics[b]	742	12	161.6	70.2-253.1
Haloperidol	*488*	*10*	*205.0*	*77.9-332.0*

Table 22 (cont.)

Abbreviations: PYs, person-years; IR, incidence rate; CI, confidence interval; NA, not applicable; X, Cell contains <5 patients (due to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).

[a] This group consisted of chlorpromazine, zuclopenthixol, flupentixol, pericyazine, promazine, and thioridazine.

[b] This group consisted of haloperidol, prochlorperazine, and trifluoperazine.

Table 23: Characteristics of cases with seizures and matched controls[a], by underlying disorder

Analysis restricted to patients with affective disorders				
Characteristics	**No. Cases (%)[b] (n=334)**	**No. Controls (%)[b] (n=1,336)**	**OR crude**	**95% CI**
Sex				
Male	113 (33.8)	452 (33.8)	NA	NA
Female	221 (66.2)	884 (66.2)	NA	NA
Age, years				
18-39	134 (40.2)	536 (40.1)	NA	NA
40-59	111 (33.3)	442 (33.1)	NA	NA
60-90	89 (26.7)	358 (26.8)	NA	NA
Smoking status				
Nonsmoker	132 (39.5)	570 (42.7)	1	reference
Current smoker	111 (33.2)	396 (29.6)	1.22	0.91-1.63
Former smoker	76 (22.8)	305 (22.8)	1.08	0.78-1.49
Unknown	15 (4.5)	65 (4.9)	0.99	0.53-1.87
Alcohol consumption (units/week, any time prior to the index date)				
Nondrinker	156 (46.7)	620 (46.4)	1	reference
1-14	119 (35.6)	453 (33.9)	1.04	0.80-1.36
>14	25 (7.5)	101 (7.6)	0.98	0.60-1.59
Unknown	34 (10.2)	162 (12.1)	0.82	0.54-1.26
Comorbidities any time prior to the index date[c]				
Suicide attempt and/or suicidal ideation	49 (14.7)	129 (9.7)	1.63	1.14-2.33
Parkinson's disease	X	11 (0.8)	NA	NA
Migraine	55 (16.5)	152 (11.4)	1.58	1.12-2.24
Transient ischemic attack/ischemic stroke	45 (13.5)	44 (3.3)	7.45	4.25-13.04
Compulsive disorders	11 (3.3)	28 (2.1)	1.59	0.78-3.24
Concurrent[d] drug use				
Opioids	82 (24.6)	210 (15.7)	1.93	1.35-2.76
Benzodiazepines	52 (15.6)	136 (10.2)	1.83	1.26-2.66
Betalactam-Antibiotics	50 (15.0)	138 (10.3)	1.50	0.95-2.35
Anticonvulsants[e]	19 (5.7)	37 (2.8)	2.30	1.26-4.18
Any antidepressants	185 (55.4)	528 (39.5)	1.46	0.89-2.39
Selective serotonin reuptake inhibitors	124 (37.1)	331 (24.8)	1.83	1.27-2.64
Tricyclic antidepressants	43 (12.9)	124 (9.3)	1.45	0.98-2.15
Other antidepressants[f]	39 (11.7)	106 (7.9)	1.57	1.06-2.35

Table 23 (cont.)

Analysis restricted to patients with dementia				
Characteristics	**No. Cases (%)[b] (n=202)**	**No. Controls (%)[b] (n=773)**	**OR crude**	**95% CI**
Sex				
Male	73 (36.1)	286 (37.0)	NA	NA
Female	129 (63.9)	487 (63.0)	NA	NA
Age, years				
18-39	X	X	NA	NA
40-59	11 (5.5)	19 (2.5)	NA	NA
60-90	191 (94.5)	754 (97.5)	NA	NA
Smoking status				
Nonsmoker	102 (50.5)	388 (50.2)	1	reference
Current smoker	17 (8.4)	67 (8.7)	0.92	0.51-1.67
Former smoker	72 (35.6)	278 (36.0)	1.01	0.71-1.45
Unknown	11 (5.5)	40 (5.2)	1.05	0.49-2.28
Alcohol consumption (units/week, any time prior to the index date)				
Nondrinker	110 (54.5)	433 (56.0)	1	reference
1-14	64 (31.7)	222 (28.7)	1.13	0.79-1.60
>14	X	33 (4.3)	NA	NA
Unknown	24 (11.9)	85 (11.0)	1.12	0.66-1.91
Comorbidities any time prior to the index date[c]				
Suicide attempt and/or suicidal ideation	X	18 (2.3)	NA	NA
Parkinson's disease	10 (5.0)	39 (5.1)	1.00	0.49-2.05
Migraine	X	29 (3.8)	NA	NA
Transient ischemic attack/ischemic stroke	59 (29.2)	122 (15.8)	2.45	1.68-3.58
Compulsive disorders	X	X	NA	NA
Concurrent[d] drug use				
Opioids	28 (13.9)	113 (14.6)	0.89	0.55-1.45
Benzodiazepines	57 (28.2)	139 (18.0)	1.80	1.22-2.66
Betalactam-Antibiotics	28 (13.9)	101 (13.1)	1.12	0.64-1.96
Anticonvulsants[e]	11 (5.5)	25 (3.2)	1.62	0.78-3.38
Any antidepressants	67 (33.2)	250 (32.3)	1.11	0.77-1.61
Selective serotonin reuptake inhibitors	47 (23.3)	147 (19.0)	1.30	0.87-1.93
Tricyclic antidepressants	X	28 (3.6)	NA	NA
Other antidepressants[f]	26 (12.9)	89 (11.5)	1.21	0.74-1.96

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not applicable; X, Cell contains <5 patients (due to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).

[a] Controls were matched to cases on age, sex, index date, duration of history in the CPRD, and underlying disorder (schizophrenia, affective disorders, or dementia) diagnosed prior to the index date. All ORs presented are conditional on the matching factors.

[b] Due to rounding, percentages may not total 100.

[c] The reference group for the calculation of the ORs comprised patients who never had a record of the respective disorder at any time prior to the index date.

[d] Last prescription within 90 days prior to index date; the reference group for the calculation of the ORs comprised patients who had no records of the respective drug at any time prior to the index date.

[e] This drug group mainly consisted of the drugs sodium valproate (38.3%), gabapentin (24.5%), carbamazepine (12.8%), and pregabalin (10.6%).

[f] This drug group mainly consisted of the drugs venlafaxine (38.0%), mirtazapine (36.5%), and trazodone (20.4%).

Table 24: Odds ratios for seizures in users of different antipsychotic subclasses, by current or past use, and by underlying psychiatric disorder

Analysis restricted to patients with affective disorders						
Antipsychotic drug group	**No. Cases (%)[a] (n=334)[b]**	**No. Controls (%)[a] (n=1,336)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotics	128 (38.3)	542 (40.6)	1	reference	1	reference
Olanzapine or quetiapine						
Current use (last presc. ≤ 90 days ago)	10 (3.0)	38 (2.8)	1.14	0.55-2.36	0.61	0.27-1.38
Past use (last presc. >90 days ago)	12 (3.6)	39 (2.9)	1.33	0.67-2.67	0.83	0.37-1.87
Amisulpride, aripiprazole, risperidone, or sulpiride						
Current use (last presc. ≤ 90 days ago)	5 (1.5)	27 (2.0)	0.78	0.29-2.08	0.43	0.14-1.32
Past use (last presc. >90 days ago)	12 (3.6)	37 (2.8)	1.41	0.71-2.81	1.10	0.48-2.49
Low to medium potency antipsychotics[d]						
Current use (last presc. ≤ 90 days ago)	6 (1.8)	21 (1.6)	1.22	0.48-3.09	1.11	0.41-2.98
Past use (last presc. >90 days ago)	32 (9.6)	114 (8.5)	1.20	0.77-1.87	0.88	0.52-1.48
Medium to high potency antipsychotics[e]						
Current use (last presc. ≤ 90 days ago)	36 (10.8)	56 (4.2)	2.76	1.72-4.43	2.51	1.51-4.18
Past use (last presc. >90 days ago)	120 (35.9)	546 (40.9)	0.93	0.69-1.26	0.86	0.63-1.19

Table 24 (cont.)

Analysis restricted to patients with dementia						
Antipsychotic drug group	**No. Cases (%)[a] (n=202)[b]**	**No. Controls (%)[a] (n=773)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotics	46 (22.8)	290 (37.5)	1	reference	1	reference
Olanzapine or quetiapine						
Current use (last presc. ≤ 90 days ago)	36 (17.8)	101 (13.1)	2.33	1.43-3.80	2.37	1.35-4.15
Past use (last presc. >90 days ago)	22 (10.9)	57 (7.4)	2.66	1.47-4.80	2.66	1.33-5.30
Amisulpride, aripiprazole, risperidone, or sulpiride						
Current use (last presc. ≤ 90 days ago)	18 (8.9)	106 (13.7)	1.08	0.60-1.94	0.92	0.48-1.75
Past use (last presc. >90 days ago)	30 (14.9)	86 (11.1)	2.32	1.37-3.94	1.87	1.00-3.50
Low to medium potency antipsychotics[d]						
Current use (last presc. ≤ 90 days ago)	14 (6.9)	27 (3.5)	3.82	1.79-8.16	3.08	1.34-7.08
Past use (last presc. >90 days ago)	31 (15.4)	71 (9.2)	2.99	1.75-5.12	2.97	1.55-5.69
Medium to high potency antipsychotics[e]						
Current use (last presc. ≤ 90 days ago)	14 (6.9)	37 (4.8)	2.57	1.28-5.19	2.24	1.05-4.81
Past use (last presc. >90 days ago)	50 (24.8)	154 (19.9)	2.14	1.35-3.39	2.09	1.22-3.59

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; presc., prescription.

[a] Due to rounding, percentages may not total 100.

[b] Cases and controls could be users of more than one antipsychotic drug group and thus be listed more than once in the table.

[c] Adjusted for all other antipsychotics, alcohol status, antidepressants, anticonvulsants, benzodiazepines, opioids, compulsive disorders, Parkinson's disease, suicidal ideation/attempts, and stroke and/or transient ischemic attack.

[d] This group consisted of chlorpromazine, zuclopenthixol, flupentixol, pericyacine, promazine, and thioridazine.

[e] This group consisted of haloperidol, prochlorperazine, and trifluoperazine.

Table 25: Odds ratios for seizures in users of different antipsychotic single substances, by current or past use, and by underlying disorder

Analysis restricted to patients with affective disorders						
Antipsychotic drug group	**No. Cases (%)[a] (n=334)[b]**	**No. Controls (%)[a] (n=1,336)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotics	128 (38.3)	542 (40.6)	1	reference	1	reference
Quetiapine						
Current use (last presc. ≤ 90 days ago)	6 (1.8)	15 (1.1)	1.74	0.66-4.56	1.17	0.40-3.45
Past use (last presc. >90 days ago)	9 (2.7)	18 (1.4)	2.15	0.95-4.91	1.36	0.52-3.54
Risperidone						
Current use (last presc. ≤ 90 days ago)	5 (1.5)	18 (1.4)	1.18	0.43-3.24	0.63	0.20-1.97
Past use (last presc. >90 days ago)	11 (3.3)	31 (2.3)	1.53	0.74-3.14	1.04	0.45-2.42
Prochlorperazine						
Current use (last presc. ≤ 90 days ago)	28 (8.4)	52 (3.9)	2.26	1.35-3.79	1.95	1.11-3.41
Past use (last presc. >90 days ago)	107 (32.0)	520 (38.9)	0.87	0.64-1.18	0.79	0.57-1.10
Analysis restricted to patients with dementia						
Antipsychotic drug group	**No. Cases (%)[a] (n=202)[b]**	**No. Controls (%)[a] (n=773)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotics	46 (22.8)	290 (37.5)	1	reference	1	reference
Olanzapine						
Current use (last presc. ≤ 90 days ago)	5 (2.5)	16 (2.1)	1.92	0.67-5.47	1.77	0.56-5.62
Past use (last presc. >90 days ago)	9 (4.5)	24 (3.1)	2.48	1.07-5.72	1.70	0.60-4.83
Quetiapine						
Current use (last presc. ≤ 90 days ago)	31 (15.4)	85 (11.0)	2.41	1.43-4.05	2.52	1.40-4.55
Past use (last presc. >90 days ago)	16 (7.9)	47 (6.1)	2.39	1.23-4.63	2.75	1.29-5.85

Table 25 (cont.)

Antipsychotic drug group	No. Cases (%)[a] (n=202)[b]	No. Controls (%)[a] (n=773)[b]	OR crude	95% CI	OR adj.[c]	95% CI
Risperidone						
Current use (last presc. ≤ 90 days ago)	11 (5.5)	61 (7.9)	1.13	0.55-2.31	1.11	0.52-2.40
Past use (last presc. >90 days ago)	23 (11.4)	65 (8.4)	2.21	1.24-3.91	2.05	1.02-4.10
Promazine						
Current use (last presc. ≤ 90 days ago)	9 (4.5)	16 (2.1)	4.04	1.66-9.81	2.58	0.91-7.26
Past use (last presc. >90 days ago)	13 (6.4)	25 (3.2)	3.58	1.69-7.58	3.99	1.64-9.71
Haloperidol						
Current use (last presc. ≤ 90 days ago)	10 (5.0)	23 (3.0)	2.96	1.30-6.71	2.83	1.14-7.00
Past use (last presc. >90 days ago)	26 (12.9)	44 (5.7)	3.80	2.15-6.73	3.82	1.91-7.65

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; presc., prescription.

[a] Due to rounding, percentages may not total 100.

[b] Cases and controls could be users of more than one antipsychotic drug group and thus be listed more than once in the table.

[c] Adjusted for all other antipsychotics, alcohol status, antidepressants, anticonvulsants, benzodiazepines, opioids, compulsive disorders, Parkinson's disease, suicidal ideation/attempts, and stroke and/or transient ischemic attack.

Table 26: Odds ratios for seizures in users of different antipsychotic drug groups, by current or past use, and by history of stroke or TIA prior to the index date

Analysis restricted to patients without stroke/TIA prior						
Antipsychotic drug group	**No. Cases (%)[a] (n=465)[b]**	**No. Controls (%)[a] (n=2,056)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotic drugs	156 (27.3)	783 (35.2)	1	reference	1	reference
Olanzapine or quetiapine						
Current use (last presc. ≤ 90 days ago)	43 (7.5)	150 (6.7)	1.67	1.11-2.49	1.30	0.83-2.01
Past use (last presc. >90 days ago)	31 (5.4)	113 (5.1)	1.56	0.99-2.46	1.32	0.79-2.20
Amisulpride, aripiprazole, risperidone, or sulpiride						
Current use (last presc. ≤ 90 days ago)	21 (3.7)	145 (6.5)	0.75	0.45-1.25	0.55	0.32-0.95
Past use (last presc. >90 days ago)	40 (7.0)	128 (5.8)	1.76	1.15-2.68	1.42	0.88-2.29
Low to medium potency antipsychotics[d]						
Current use (last presc. ≤ 90 days ago)	18 (3.2)	47 (2.1)	1.99	1.10-3.60	1.69	0.91-3.14
Past use (last presc. >90 days ago)	50 (8.8)	179 (8.0)	1.52	1.05-2.19	1.25	0.83-1.88
Medium to high potency antipsychotics[e]						
Current use (last presc. ≤ 90 days ago)	43 (7.5)	94 (4.2)	2.43	1.60-3.69	2.22	1.44-3.41
Past use (last presc. >90 days ago)	144 (25.2)	681 (30.6)	1.09	0.84-1.42	1.05	0.79-1.39

Table 26 (cont.)

Analysis restricted to patients with stroke/TIA prior						
Antipsychotic drug group	**No. Cases (%)[a] (n=106)[b]**	**No. Controls (%)[a] (n=170)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
No use of antipsychotic drugs	24 (4.2)	58 (2.6)	1	reference	1	reference
Olanzapine or quetiapine						
Current use (last presc. ≤ 90 days ago)	11 (1.9)	19 (0.9)	1.48	0.61-3.57	1.24	0.50-3.08
Past use (last presc. >90 days ago)	8 (1.4)	10 (0.5)	1.81	0.63-5.21	1.74	0.58-5.25
Amisulpride, aripiprazole, risperidone, or sulpiride						
Current use (last presc. ≤ 90 days ago)	6 (1.1)	11 (0.5)	1.35	0.43-4.25	1.18	0.36-3.88
Past use (last presc. >90 days ago)	8 (1.4)	21 (0.9)	0.94	0.36-2.43	0.77	0.28-2.09
Low to medium potency antipsychotics[d]						
Current use (last presc. ≤ 90 days ago)	X	5 (0.2)	NA	NA	NA	NA
Past use (last presc. >90 days ago)	16 (2.8)	17 (0.8)	2.45	1.06-5.66	2.30	0.96-5.53
Medium to high potency antipsychotics[e]						
Current use (last presc. ≤ 90 days ago)	13 (2.3)	9 (0.4)	3.46	1.27-9.45	3.38	1.21-9.44
Past use (last presc. >90 days ago)	34 (6.0)	48 (2.2)	1.58	0.81-3.11	1.55	0.77-3.14

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; presc., prescription; X, Cell contains <5 patients (due to ethics regulations to preserve confidentiality, we are not allowed to display cells with a count of <5 patients).

[a] Due to rounding, percentages may not total 100.

[b] Cases and controls could be users of more than one antipsychotic drug group and thus be listed more than once in the table.

[c] Adjusted for all other groups of antipsychotics, alcohol status, antidepressants, anticonvulsants, benzodiazepines, opioids, compulsive disorders, Parkinson's disease, suicidal ideation/attempts, and stroke and/or transient ischemic attack.

[d] This group consisted of chlorpromazine, zuclopenthixol, flupentixol, pericyacine, promazine, and thioridazine.

[e] This group consisted haloperidol, prochlorperazine, and trifluoperazine.

Table 27: Odds ratios for seizures in users of different antipsychotic drug groups, by current or past use and age, and by current use and number of prescriptions prior to the index date, and by underlying disorder; reference group non-users of the respective drug group

Analysis restricted to patients with affective disorders						
Antipsychotic drug group	**No. Cases (%)[a] (n=334)[b]**	**No. Controls (%)[a] (n=1,336)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
Olanzapine or quetiapine						
No use	312 (93.4)	1,259 (94.2)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	10 (3.0)	38 (2.8)	1.07	0.52-2.18	0.66	0.31-1.43
Past use (last presc. >90 days ago)	12 (3.6)	39 (2.9)	1.25	0.64-2.45	0.92	0.43-1.93
Amisulpride, aripiprazole, risperidone, or sulpiride						
No use	317 (94.9)	1,272 (95.2)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	5 (1.5)	27 (2.0)	0.73	0.28-1.94	0.49	0.18-1.37
Past use (last presc. >90 days ago)	12 (3.6)	37 (2.8)	1.31	0.67-2.54	1.24	0.61-2.54
Low to medium potency antipsychotics[d]						
No use	296 (88.6)	1,201 (89.9)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	6 (1.8)	21 (1.6)	1.17	0.47-2.92	1.17	0.44-3.09
Past use (last presc. >90 days ago)	32 (9.6)	114 (8.5)	1.14	0.75-1.73	0.95	0.61-1.50
Medium to high potency antipsychotics[e]						
No use	178 (53.3)	734 (54.9)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	36 (10.8)	56 (4.2)	2.71	1.70-4.30	2.60	1.58-4.28
Past use (last presc. >90 days ago)	120 (35.9)	546 (40.9)	0.91	0.70-1.20	0.89	0.66-1.21

Table 27 (cont.)

Analysis restricted to patients with dementia						
Antipsychotic drug group	**No. Cases (%)[a] (n=202)[b]**	**No. Controls (%)[a] (n=773)[b]**	**OR crude**	**95% CI**	**OR adj.[c]**	**95% CI**
Olanzapine or quetiapine						
No use	144 (71.3)	615 (79.6)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	36 (17.8)	101 (13.1)	1.57	1.03-2.39	1.61	1.02-2.52
Past use (last presc. >90 days ago)	22 (10.9)	57 (7.4)	1.74	1.02-2.96	1.68	0.96-2.97
Amisulpride, aripiprazole, risperidone, or sulpiride						
No use	154 (76.2)	581 (75.2)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	18 (8.9)	106 (13.7)	0.63	0.37-1.06	0.63	0.36-1.12
Past use (last presc. >90 days ago)	30 (14.9)	86 (11.1)	1.35	0.85-2.14	1.20	0.73-1.96
Low to medium potency antipsychotics[d]						
No use	157 (77.7)	675 (87.3)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	14 (6.9)	27 (3.5)	2.55	1.26-5.16	2.15	0.99-4.66
Past use (last presc. >90 days ago)	31 (15.4)	71 (9.2)	2.01	1.25-3.21	1.86	1.12-3.08
Medium to high potency antipsychotics[e]						
No use	138 (68.3)	582 (75.3)	1	reference	1	reference
Current use (last presc. ≤ 90 days ago)	14 (6.9)	37 (4.8)	1.68	0.88-3.21	1.57	0.78-3.16
Past use (last presc. >90 days ago)	50 (24.8)	154 (19.9)	1.40	0.95-2.04	1.41	0.93-2.13

Abbreviations: OR, odds ratio; CI, confidence interval; adj., adjusted; presc., prescription.

[a] Due to rounding, percentages may not total 100.

[b] Cases and controls could be users of more than one antipsychotic drug group and thus be listed more than once in the table.

[c] Adjusted for all other antipsychotics, alcohol status, antidepressants, anticonvulsants, benzodiazepines, opioids, compulsive disorders, Parkinson's disease, suicidal ideation/attempts, and stroke and/or transient ischemic attack.

[d] This group consisted of chlorpromazine, zuclopenthixol, flupentixol pericyacine, promazine, and thioridazine.

[e] This group consisted of haloperidol, prochlorperazine, and trifluoperazine.

3.3.5 Discussion

In this observational study using data from a U.K. based primary care database, we observed that current mono users of antipsychotics had two- to threefold higher risks of seizures compared to non-users of antipsychotics. Current users of medium to high potency first-generation antipsychotics had significantly higher risks of seizures than current users of the second-generation antipsychotics amisulpride, aripiprazole, risperidone, or sulpiride. Irrespective of antipsychotic drug use, patients with dementia experienced seizures more frequently than patients with affective disorders. The number of patients with schizophrenia was too limited to estimate separate incidence rates for these patients.

After adjusting for potential confounding and stratifying by underlying affective disorders or dementia, we observed that current use of medium to high potency first-generation antipsychotics was associated with a more than twofold increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders. In these patients, current use of all other antipsychotics was not associated with seizures. In patients with dementia, current use of all first-generation antipsychotics and the second generation antipsychotics olanzapine and quetiapine, was associated with an increased risk of seizures compared to non-use of antipsychotics. This effect was also seen in past users of antipsychotics in those with dementia, suggesting that the association may be due to dementia progression or severity, leading to antipsychotic drug use, rather than a causal effect of antipsychotics. Notably, current use of amisulpride, aripiprazole, risperidone, or sulpiride, was not associated with the occurrence of seizures in patients with dementia.

Our results do not corroborate existing evidence for a higher seizure risk in association with strongly sedating low-potency first-generation drugs (especially aliphatic phenothiazines) compared with less sedating high-potency first-generation drugs.[55,57,121,123,132] However, this evidence is based mainly on one observational study conducted between 1960 and 1965, which reported a higher seizure incidence among phenothiazine (especially chlorpromazine) users compared to non-users.[91] As the group of non-users in that study comprised patients who used other first-generation antipsychotics as well as those who did not use any antipsychotics, a comparison of seizure risk associated with different first-generation antipsychotics was not possible.[91] Additionally, in contrast to our study, patients with major direct risk factors for seizures were not excluded from this study.[91] We observed slightly higher incidence rates of seizures in users of medium to high potency first-generation

antipsychotics (mainly haloperidol and prochlorperazine) than in users of low to medium potency first-generation antipsychotics (mainly flupenthixol, chlorpromazine, and promazine), although differences did not reach statistical significance. After adjusting for potential confounding, current use of medium to high potency, but not low to medium potency first-generation antipsychotics, was associated with an increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders.

In contrast to the available literature that describes a higher risk of seizures associated with clozapine, olanzapine, and quetiapine (three structurally related antipsychotics) compared to other second-generation antipsychotics,[92–94] our rates of seizures were not significantly different between users of olanzapine or quetiapine and users of other second-generation antipsychotics. However, we could not investigate the risk of seizures associated with clozapine use, the second-generation antipsychotic reported to be most strongly associated with seizures,[93,122,124] because treatment with clozapine in the U.K. takes place almost exclusively in secondary care and there was little use captured in the CPRD. Yet, among patients with dementia, we did observe an increased risk of seizure with current use of olanzapine or quetiapine compared to non-use. This effect was not present for current use of other second-generation antipsychotics.

To our knowledge, no other study to date has investigated the risk of first-time seizures associated with use of antipsychotics in such a large population of patients over such a long observation period. The available studies on the risk of seizures in association with antipsychotics had no control group and were prone to bias and confounding,[91,92,94] or had only a very small control group.[93] Moreover, these studies did not assess the risk of seizures in association with antipsychotics separately for each underlying disorder.

In this study, we observed that patients with dementia were at a significantly increased risk of seizures compared to patients with affective disorders, irrespective of whether they used antipsychotics or not. This finding is consistent with the results of another observational study from our group based on data from the CPRD that reported that dementia is a major risk factor for developing seizures.[86] Notably, current use of drugs of the subclass amisulpride, aripiprazole, risperidone, and sulpiride (especially the single drug risperidone), was not associated with the development of seizures in patients with dementia. Thus, with regard to seizure risk, our results support that risperidone has so far been the only antipsychotic in the U.K. licensed for short-term use in patients with dementia.[133]

In this study, we aimed to minimize confounding by excluding patients with major risk factors for seizures. Additionally, we controlled for further confounding by matching controls to cases on age, gender, calendar time, and underlying disorder which presumably led to the prescription of antipsychotics. Lastly, we adjusted our analyses for additional potential confounders such as alcohol consumption, relevant comorbidities or concomitantly used drugs. However, there may still be some residual confounding by unmeasured risk factors for seizures such as disease severity. Non-users of antipsychotics could potentially have been at a less severe disease stage than current users of antipsychotics. However, the sensitivity analysis in which we redefined the reference group as non-users of the respective drug subclass did not yield considerably different results than the main analysis.

We were not able to investigate a potential relationship between antipsychotic dose and the development of seizures, although the risk of seizures in association with antipsychotic drugs has been reported to be dose dependent.[91,124,134] However, antipsychotics were prescribed almost exclusively in doses equal to or lower than the defined daily dose, irrespective of the drug subclass. Therefore, the increased risk of seizures associated with current use of medium to high potency antipsychotics in patients with affective disorders could not be due to higher doses prescribed in this subclass compared to other subclasses. Due to limited numbers of current users of antipsychotics, we could not assess whether seizure risk was dependent on exposure duration. Additionally, some antipsychotic drugs, especially prochlorperazine, could have been prescribed for nausea rather than psychosis. However, excluding prochlorperazine users from the group of medium to high potency antipsychotic users led to an even higher risk estimate of seizures than the main analysis.

There may have been some outcome misclassification in this study, either if the seizure was missed by the GP or by the patient, or if a patient had a medical condition other than a seizure that was misreported as a seizure. However, potential misclassification of seizures was most likely not related to the antipsychotic drug used. Also, our algorithm to define a first-time seizure was developed by reviewing a random sample of 120 patient profiles, in which we assessed the likelihood of a seizure taking into account codes of antiepileptic drug prescriptions or codes of suspected seizures preceding the actual seizure code. Thus any misclassification was unlikely to materially affect our results. In addition, the validity of affective disorders diagnoses has not formally been investigated in the CPRD, but the database has proven to be of high validity with regard to many acute or chronic diseases in numerous previous studies.[34,35]

Conclusion

In conclusion, we observed that the risk of seizures associated with use of antipsychotics strongly differed according to the underlying disorder of the patient: It was considerably higher in patients with dementia than in patients with affective disorders, irrespective of antipsychotic drug use. In patients with affective disorders, current use of medium to high potency first-generation antipsychotics was associated with a more than twofold increased risk of seizures compared to non-use of antipsychotics, while current use of other antipsychotics was not associated with seizures. In patients with dementia, current use of amisulpride, aripiprazole, risperidone, and sulpiride, was not associated with an altered risk of seizures, while current use of all other antipsychotics was associated with an increased risk of seizures, compared to non-use of antipsychotics.

Chapter 4

Discussion

4. Discussion

It has long been suspected that patients suffering from neuropsychiatric disorders exhibit an increased risk of developing new-onset seizures. However, to this date, little real-world evidence on specific risk factors provoking new-onset seizures in patients with neuropsychiatric disorders exists. The primary aim of this thesis was set to identify and analyze such risk factors for new-onset seizures in patients with affective disorders, schizophrenia, or dementia, thereby focusing on antidepressant and antipsychotic drug use.

The first project suggested that patients with depression exhibit similar risk factors for new-onset seizures as those reported from the general population.[27,51,54,67,86,103–105] Patients with depression who abused drugs, had alcoholism, a history of cerebrovascular disease or recent head trauma, comorbid dementia, and psychiatric comorbidities such as schizophrenia or bipolar disorder, were at an increased risk of seizures compared to patients with depression without these features. Patients who currently used cephalosporin antibiotics or antiarrhythmics were at an increased risk of seizures than non-users of these drug classes.

The subsequent project was able to demonstrate that new-onset seizures among adult patients with depression were rare. We found that for patients treated with certain antidepressants (i.e., SSRIs, SNRIs, or mirtazapine, bupropion, reboxetine and trazodone), the incidence rate of seizures was higher than for non-users of antidepressants. However, absolute risk differences between exposed and non-exposed study groups were small.

Different types of antidepressants exhibited different relative risk estimates of seizures compared to non-use. Use of SSRIs and SNRIs was found to be associated with a twofold increased risk of seizures compared to non-use, while use of TCAs at low doses (as prescribed in this primary care setting) was not associated with seizures. It is important to note that these results do not challenge the evidence on the epileptogenic potential of TCAs in high doses.[57,88–90] Nevertheless, the results obtained support the current evidence that antidepressant-induced seizures are dose-dependent rather than just class-specific.[26,55,135]

The final project could demonstrate that the association between antipsychotic drugs and new-onset seizures is strongly modified by the underlying neuropsychiatric indication.

First of all, patients with dementia were at a considerably higher risk of seizures than those with affective disorders, irrespective of the use of antipsychotics. Secondly, we found that use of haloperidol, prochlorperazine, or trifluoperazine, was associated with a more than twofold increased risk of seizures compared to non-use of antipsychotics in patients with affective disorders. Finally we could show that in patients with dementia, use of all antipsychotic subclasses, except amisulpride, aripiprazole, risperidone or sulpiride, was associated with an increased risk of seizures. However, antipsychotic drug use could not be studied separately among patients with schizophrenia. Additionally, we were not able to further explore any potential dose-effect relationship of antipsychotics and seizures because in the care setting analyzed, antipsychotics were used at low doses only.

The subsequent paragraphs will discuss the following two factors that I found to have a major impact on the results: i) the data source and ii) the observational approach used to address the research questions.

4.1 Strengths and limitations of the data source

4.1.1 Sample size limitations

All studies carried out were based on primary care observational data provided by the U.K. CPRD, one of the world's largest and best validated medial record databases.[31,35,136] The CPRD currently encompasses anonymized data of roughly 12 million patients (about 6% of the U.K. population) and 64 million person-years of prospective follow-up.[33,34] Due to its size and long history this database is suitable for studying rare outcomes and outcomes with long-term latency periods.[136]

The main topic of this thesis was the study of the occurrence of new-onset seizures, a rare outcome with an incidence of 0.06% per year.[44,45] All studies were carried out based on a strongly restricted study population. Thus, despite the vast amount of data available in the CPRD, our analyses were limited by low sample sizes of patients who fulfilled the inclusion criteria.

The primary aim of the initial study was to describe risk factors for new-onset seizures rather than generate or test specific hypotheses. Including the entire population of adult patients with depression, the sample size for this study was not as limited as the sample sizes of the follow-up investigations. The negative impact of small sample sizes was found to be significant in the second and third project, thus limiting the precision of the results.

In the second project, the cohort of patients with depression who met the inclusion criteria comprised about 150,000 patients, however only 619 patients had a new-onset seizure during follow-up. We were only able to formally assess effect modification by a history of stroke/TIA, or prevalent dementia for SSRIs users. The low sample sizes in sub-analyses of single antidepressant drugs and potential dose-effect relationships led to low precision of the results.

In the final project the cohort of patients with neuropsychiatric disorders included about 60,000 patients, of whom as little as 583 patients experienced a new-onset seizure during follow-up.

Initially we wanted to study the risk of seizures associated with antipsychotics separately for patients with affective disorders, schizophrenia, or dementia. The limited number of cases with schizophrenia however prevented the separate study of patients suffering from this disorder.

Finally, most single antipsychotic drugs were too infrequently used in order for them to be analyzed individually and additionally, potential effects associated with the duration of treatment were not possible.

4.1.2 Validity of drug exposures and medical diagnoses

4.1.2.1 Validity of drug exposures

Validity and completeness of recorded drug prescriptions in the CPRD is reported to be high, as GPs issue prescriptions directly with the computer.[34,137]

However, several caveats need to be kept in mind when working with data of any medical records database. Firstly, prescription data are only a proxy for drug exposure, as drugs prescribed are not always used by the patients. Secondly, whether patients took their

prescribed medication as prescribed is unknown. Thirdly, although regular prescriptions at appropriate time intervals indicate adherence to drugs, accidental or intentional use of drugs in overdose cannot be ruled out.

Medication adherence has been reported to be a problem in patients with neuropsychiatric disorders.[138,139] However, multiple interacting factors appear to be associated with adherence to antidepressants and antipsychotics, reaching beyond drug tolerability.[139,140] Factors reported to affect drug adherence include patient education, positive attitude to medication, illness insight, collaborative management by GPs and psychiatrists and perceived risk of adverse events.[108,139,141]

In light of these earlier reports, non-differential non-adherence of patients prescribed different neuropsychiatric drug classes in the second and third project cannot be ruled out. For example, second-generation antidepressants have been found to be generally better tolerated than TCAs.[142] It is thus possible that patients using second generation antidepressants exhibit a higher drug adherence than patients with prescribed TCAs, and thus are at a higher risk of adverse events such as seizures. However, no significant difference in prescription patterns of patients using either type of antidepressant was found. Additionally, in the study population analyzed, most antidepressants were prescribed on a medium to long-term basis, reducing potential problems with medication adherence even further. Finally, a review of randomly selected patient profiles revealed that for those patients who received several prescriptions, prescriptions were regularly noted at the appropriate times, suggesting proper use of medication.

The chance that the results of the final study were altered due to differences in medication adherence between patients using different antipsychotic subclasses is small, as antipsychotic drug type does not seem to affect drug adherence.[139] Additionally, while it cannot be ruled out, it is highly unlikely that patients suffering from dementia were adherent to every antipsychotic drug subclass analyzed except amisulpride, aripiprazole, risperidone, or sulpiride (the only drug subclass not associated with increased seizure risk in patients with dementia), and that patients with affective disorders were only adherent to medium to high potency antipsychotics (the only drug class associated with an increased seizure risk in patients with affective disorders).

Thus, it can be said that prescription data does not prove drug exposure. However, for any of the projects carried out during this thesis, we assumed non-adherence to drugs to be randomly distributed between different groups of drug users. Therefore, while randomly distributed non- adherence may have introduced a small bias towards the null hypothesis (i.e., no association between psychotropic drugs and seizures), the overall interpretation of the results would remain unaffected.[3]

4.1.2.2 General validity of medical diagnoses

Especially for chronic diseases, the validity of medical diagnoses recorded in the CPRD is regarded to be high.[34,35] For example for diagnoses of schizophrenia or dementia, the positive predictive value (i.e., the proportion of diagnoses recorded that are confirmed by the GP to be correctly recorded) was estimated at 80%.[86,143,144]

However, to this day, validity of diagnoses of depression, other affective disorders, and seizures, has not been estimated.

For example, the positive predictive value of a depression diagnosis in primary care in general has reported to be only 42%.[145] Moreover, only 50% of patients suffering from depression are identified in general practice and only about 15% of these patients receive proper antidepressant treatment.[145] While no formal validation study of depression has been carried out so far with data of the CPRD, integration between primary and secondary care (a key feature of this database), has been shown to improve diagnostic validity of depression.[141]

In our second study, we resorted to a narrow definition of depression in order to avoid inclusion of non-depressed persons or depressed patients with various depression severities (*see 4.2.3*). Patients with codes related to dysthymia or bipolar disorders were thus excluded from our analysis. These measures increased homogeneity of the study population with respect to the underlying disease and its degree of severity. However, since dysthymia or bipolar disorder can exhibit similar features as unipolar depression,[146] and might not always be correctly distinguished from unipolar depression, a proper separation of these different disorders cannot be assured in this project.

Alternatively, to increase statistical power, one could have included patients with dysthymia and bipolar disorder, and perform sensitivity analyses to explore whether associations between antidepressants and seizures changed with different definitions of depression.[34]

4.1.2.3 Validity of seizure diagnosis

Based on the definition of epilepsy by the International League Against Epilepsy, antiepileptic treatment after a first seizure is justified only if the risk of seizure occurrence is ≥60% within the next 10 years.[38,82]

Throughout this thesis new-onset seizures were defined by first-ever recorded codes of seizure or epilepsy in a patient's profile, regardless of any subsequent antiepileptic treatment. The approach that one seizure code was sufficient for a patient to be classified as having experienced a seizure could have produced false positive cases.

However, in our studies we wanted to investigate the occurrence of first ever seizures in association with drugs. Thus, although the requirement of a formal epilepsy diagnosis (i.e., at least two seizures occurring more than 24 hours apart, or at least one seizure followed by antiepileptic drug therapy[38]) could have increased the positive predictive value of seizure diagnoses, we would have missed persons with only one acute symptomatic seizure.

It is well known that not all seizure types are equally well identified by patients and observers (*see 1.2.6*). Thus, although individuals who presented to secondary care or the emergency department after a seizure should be linked back to the CPRD, we expect not all seizures were captured in the patient records. Additionally, it is likely that not all seizures classified as newly onset were in fact first-ever seizures.

However, we found the validity of seizure diagnosis in our studies supported by the finding that the incidence rate of seizure among patients with depression in remission was comparable with the reported incidence rate of unprovoked seizures in the general population.[44,45]

Finally, any potential misclassification of seizures was likely to be distributed randomly across users of antidepressants or antipsychotics under investigation, introducing a bias towards the null hypothesis (i.e., no difference in seizure risk associated with different drugs).[3]

4.2 Strengths and limitations of the observational approach

4.2.1 Chance

All studies carried out during this thesis are based on a CPRD dataset comprising 6% of the U.K. population (i.e., >10 million individuals).[34] Due to its large size statistically significant associations can be observed frequently.[2,4,8]

The likelihood of false positive associations (i.e., type I error) increases however when multiple sub-analyses are performed on the same dataset.[147,148] Adjustments can be performed for multiple comparisons to reduce the type I error in statistical analyses. However, conventional methods appear to be a poor choice since they only decrease the α-level and thereby the power of the study.[149,150] Thus, rather than merely manipulating the cut-off that decides whether a finding is statistically significant or not it is considered better practice to disclose which analyses were carried out and discuss the reasoning underlying this choice.[149,150]

In line with these arguments all analyses carried out throughout this thesis were of type hypothesis generating rather than testing. All sub-analyses (e.g., stratified analyses by age, sex, comorbidities) were disclosed and limitations associated with the analysis of small subgroups discussed. Finally, no statistical adjustment for multiple comparisons was applied.

4.2.2 Bias

Collected CPRD patient data are representative of the U.K. population with regard to age, sex, and geographical distribution.[136]

Selection bias due to non-representative sampling is limited as no segment of the U.K. population is excluded from being enrolled with GPs contributing data to the CPRD. Also, cases and controls analyzed in our studies originated from the same well-defined cohort and thus were comparable in many important aspects associated with underlying seizure risk.

It is unlikely that upon usage of CPRD data **information bias** (e.g., measurement bias, recall bias, or interviewer bias) would have negatively impacted on our results, as the records were computerized prospectively in the context of daily clinical practice without any ulterior motive of answering specific research questions.

4.2.3 Confounding

Unlike bias we found confounding by indication to be a limiting factor in the interpretation of our studies.

In our first study we provided a coarse description of factors associated with new-onset seizures among patients suffering from depression. However, we did not adjust for confounding factors other than age, gender, calendar time, duration of history on the database and a proxy for depression severity. It is thus possible that associations between drug use and seizures were confounded by underlying indication (e.g., use of antibiotics by underlying infection/fever).

Similarly, in our second project, severity of depression might have been a predictor of seizure risk as well as antidepressant prescription. Direct adjustment for diseases severity was not possible as depression severity and quantity of depression symptoms are not recorded in the CPRD.

A means to validate our findings would have been to investigate association between antidepressants and seizures in patients with other underlying disorders (e.g., chronic pain disorders, obsessive compulsive disorder, anxiety disorders). This would have allowed us to ascertain that association patterns observed for different antidepressant classes remained stable across the different indications studied. However, depression is often a comorbidity of patients with named disorders.[146] Thus it is unlikely that a sufficient number of individuals with records of just one of these disorders would have been available for statistical analyses.

In our final study we assessed seizure risk associated with antipsychotics separately among patients with affective disorders or dementia to account for different underlying seizure risks correlated with these disorders.

Our findings indicate that in patients with dementia seizure risk was similarly increased for patients currently using antipsychotics as for those who had used antipsychotics in the past compared to patients diagnosed with dementia but not yet using antipsychotics.

It is thus possible that not actual use of antipsychotics but dementia severity leading to antipsychotics prescription predicted seizure occurrence.

4.2.4 Causality

Causality cannot be proven based solely on observational studies. There exists however a series of criteria that allow assessing the likelihood of causality in studies investigating the association between drug use and seizures.[12,56] In **Table 28** these criteria are discussed with regard to the studies carried out in this thesis.

Table 28: Discussion of the criteria used to assess the likelihood of causality [12,56] with regard to the associations observed in projects 3.1-3.3 of the thesis

	Project		
Criterion	*Project 3.1*	*Project 3.2*	*Project 3.3*
Strength	Absolute risk differences: not available Crude odds ratios: Strongly increased for: • intracerebral bleeding (OR 8.2) • ischemic stroke/TIA (OR 6.1) • dementia (OR 6.8) Moderately increased for: • alcoholism (OR 3.0) • drug abuse (OR 2.5) • schizophrenia/bipolar disorder (ORs around 2.0) • current use of antiarrhythmics (OR 1.6) • current use of cephalosporins (OR 2.5)	Absolute risk differences: small Adjusted odds ratios: Moderately increased for: • current use of SSRIs/SNRIs (ORs 2.0) • current use of mirtazapine, bupropion, reboxetine, or trazodone (OR 2.3) Not increased for: • current use of TCAs (OR 1.0)	Absolute risk differences: moderate Adjusted odds ratios: Moderately increased for: • current use of high potency first generation antipsychotics in patients with affective disorders (OR 2.5) • current use of all first-generation antipsychotics (ORs 2.2 to 3.1) and olanzapine or quetiapine (OR 2.4) in patients with dementia Not increased for: • current use of amisulpride, aripiprazole, risperidone, or sulpiride in patients with affective disorders (OR 0.4) or dementia (OR 0.9)

Table 28 (cont.)

Criterion	*Project 3.1*	*Project 3.2*	*Project 3.3*
Consistency	Similar associations reported in studies among the general population [51,54,56,67,85,86,103–105]	• Similar associations reported in an observational study among depressed patients aged 65 or over, using a different database and study design.[26] • Different associations reported in a meta-analysis of clinical trials (decreased risk of seizures associated with SSRIs or SNRIs compared to placebo).[93] • Studies among patients with epilepsy mostly reported a decrease in seizure frequency associated with use of SSRIs or SNRIs. [151]	• Very little post-marketing evidence exists on seizure risk associated with antipsychotics, results are not comparable with ours.[91,92,94] • Meta-analysis of clinical trials reported supported some findings (increased risk of seizures in users of second generation drugs olanzapine or quetiapine, but not risperidone, compared to placebo).[93]
Temporality	• Reverse causality not an issue as data collection occurred prospectively and as seizures have a clearly determinable onset • By study design it was ascertained that exposure happened prior to the seizure Temporal relationship between certain comorbidities and seizures was evident. Temporal relationship between drugs and seizures not assessed (no study aim).	Temporal relationship between antidepressant use and seizures suggested that seizures happened at treatment initiation.	Temporal relationship between antipsychotic use and seizures could not be investigated because of low statistical power.
Dose-effect relationship	Not investigated in this study.	Tendency for increased seizure risk with increasing doses of antidepressants, but low statistical power yielded imprecise results.	Could not be investigated because drugs were generally used at low doses.
Plausibility	Most associations observed make sense, taking into account the evidence from the literature on risk factors for seizures in the general population.	Difficult to assess: • Scarce evidence exists on the association between therapeutic dose ranges of psychotropic drugs as used in general practice settings and new-onset seizures. • The epileptogenic potential of psychotropic drugs is likely dose-dependent,[55,56] thus studies reporting a high seizure risk associated with certain drug classes in overdoses are not comparable to our study. • The mechanisms by which drugs change excitability of neurons remain largely unknown[56,57,59,135]	

Abbreviations: OR, odds ratio; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; PYs, person-years.

Many questions remain regarding a potential causal association between use of psychotropic drugs and seizures (see **Table 28** for details).

Well-conducted RCTs provide the strongest evidence for cause-effect relationships.[8] However, data on adverse events collected in this type of analysis is often incomplete since randomized control trials mostly study efficacy of drugs rather than adverse events.[152]

The sole available meta-analysis of clinical trials studying the association between psychotropic drugs and seizures confirmed this limitation.[93] In this study data on occurrence of seizures were not as rigorously recorded among patients assigned to placebo as patients assigned to active drugs rendering the results of the study questionable.

In summary, despite its inherent limitations, observational studies can provide new insight when studying adverse effects of drugs as demonstrated in the different studies carried out in this thesis which assessed in-depth the occurrence and determinants of new-onset seizures in a population of patients with neuropsychiatric disorders.

Studying this rare event as well as adjusting for important confounders was only possible since we were able to make use of the existing large data set, detailed patient information, and long follow-up data available from the CPRD.

However, additional large pharmacoepidemiologic studies conducted by different investigators, using different data and study designs, assessing temporal and dose-response relationships in more detail are warranted to corroborate our findings. Finally, in light of the results obtained it would be interesting to understand in more detail the molecular mechanism of how psychotropic drugs alter neuron excitability.

Chapter 5

Outlook

5. Outlook

The work of this thesis provides important insight on the epidemiology of incident seizures in patients with neuropsychiatric disorders. Based on the results obtained in the different studies important follow-up questions arise.

A key criterion of cause-effect relationships is a decline in outcome frequency once exposure stops.[12] Results of the two follow-up studies of my thesis suggest an association between use of different psychotropic drug classes and an increased risk of incident seizures. In light of these findings it would be important to analyze the number of cases in projects 3.2 and 3.3 who experienced recurrent seizures and/or were diagnosed with epilepsy after the incident seizure. Additionally, it would be important to investigate a potential association between recurrent seizures and/or epilepsy diagnosis and the continuation of psychotropic drug use.

If incident seizures observed in projects 3.2 and 3.3 were causally associated with the use of psychotropic drugs, one would expect to observe a lower seizure recurrence rate in patients who stopped the drug after the first seizure compared to those who continued with it. As GPs participating in the CPRD are encouraged to record each event causing significant morbidity and each significant diagnosis,[34] recurrent seizure leading to an epilepsy diagnosis or antiepileptic drug prescription should be recorded in the database.

Further, it is unclear to which extend antidepressants and antipsychotics are safe with respect to seizure exacerbation in patients with epilepsy and psychiatric disorders.[153,154] Several small prospective open-label trials reported no increase or even a decrease in seizure frequency among patients with epilepsy and comorbid depression after treatment start with SSRIs (mainly citalopram or sertraline) compared to prior treatment start.[155–158] However, no large cohort studies on this topic have been conducted so far. Furthermore, no significant evidence on safety of antipsychotics with regard to seizure exacerbation in patients with epilepsy is available.[154]

Thus it would be very important to assess the safety of an antidepressants and antipsychotics in patients with epilepsy and comorbid neuropsychiatric disorders with regard to seizure exacerbation. A potential challenge is that any cohort study investigating psychotropic drug safety in association with seizure frequency in patients with epilepsy would require a large number of patients with epilepsy and comorbid depression or indications requiring

antipsychotics therapy (e.g., schizophrenia, bipolar disorder, or dementia). Moreover, seizure frequency at baseline as well as each seizure frequency after drug initiation would have to be recorded rigorously. GPs participating in the CPRD are not required to computerize each recurrent event associated with a diagnosis, such as each recurrent seizure in a patient with diagnosed epilepsy, which makes this database unsuitable for a study like this.

Additional drugs or drug classes acting on the CNS have been reported to have epileptogenic potential, such as opioids and drugs used to treat ADHD.[55,56] Both drug classes have not yet been studied with regard to seizure risk in large population-based observational studies, but it would be important to know how safe they are with regard to seizure risk.

Drugs used to treat ADHD have for example been associated with seizures when ingested in overdose.[159] Moreover, ADHD patients have been reported to exhibit a higher risk of undergoing seizures compared to age-matched controls without ADHD.[160] To my knowledge however, no evidence exists on a potential association between therapeutic use of methylphenidate or atomoxetine and a further increased risk of seizures in patients with ADHD.[161,162] A study like this could potentially be conducted using CPRD data since this database at this moment comprises information on almost 25,000 patients with diagnosed ADHD, 3,600 atomoxetine users, and 22,300 methylphenidate users.

Unlike ADHD-related drugs, an association with seizures has been reported for therapeutic use of different opioids, including meperidine (buprenorphine), morphine, fentanyl, and tramadol.[55,56] An observational study published 15 years ago used CPRD data to investigate the association between use of tramadol, other opioids, or non-opioid analgesics, and incident idiopathic seizures.[100] While use of all analgesic drug classes was associated with an increased risk of seizures compared to non-use, numbers of seizure cases analyzed were small rendering relative risk estimates imprecise.[100] Larger study groups as provided by the CPRD today would facilitate to study the association between opioids and incident seizures.

Finally, the relationship between use of antiepileptic drugs and depression in patients with epilepsy remains unclear. It has been reported that depressed patients develop seizures more frequently compared to the general population.[66,67] However, patients with epilepsy also more often develop depression than the general population.[27,66,67] This bidirectional relationship suggests common neurobiological features of epilepsy and depression that reach beyond the idea that depression merely represents a stress reaction associated with epilepsy.[84,163–165]

In line of this argument a number of risk factors for developing depression in patients with epilepsy have been suggested, including use of antiepileptic drugs with negative effects on mood.[166–170] However most data on risk of depression associated with antiepileptic drugs come from clinical trials,[82,166–168,170–172] in which mood disorders were not the primary outcome measured and might not have been reported systematically. CPRD based data are well suited to study the relationship between antiepileptic drug use in patients with epilepsy and new-onset depression. In a further project we will thus study this potential relationship.

Chapter 6

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6. References

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“Our greatest weakness lies in giving up.

The most certain way to succeed is always to try just one more time”

Thomas A. Edison