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Bidirectionality of antiseizure and antipsychotic treatment: A population-based study

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ABSTRACT

Purpose: To study the prevalence and directionality of comorbid epilepsy and psychosis in Norway.
Methods: The Norwegian Prescription Database (NorPD) provided individual-based information on all antiseizure medications (ASMs) and antipsychotic drugs (APDs) dispensed during 2004–2017. Subjects were ≥18 years of age at the end of the study period. Diagnosis-specific reimbursement codes from the 10th revision of the International Classification of Diseases/2nd edition of the International Classification of Primary Care (ICD-10/ICPC-2) combined with ATC codes were used as indicators of diagnosis. Subjects had collected ASMs for epilepsy or APDs for psychosis at least four times, at least once issued with an ICD-10 code from the specialist healthcare service. Directionality was analyzed in subjects receiving both treatments. To reduce prevalent comorbidity bias, we employed a four-year comorbidity-free period (2004–2007). The use of specific ASMs and APDs was analyzed.
Results: A total of 31,289 subjects had collected an ASM for epilepsy at least four times, 28,889 an APD for psychosis. Both the prevalence of treatment for epilepsy and of treatment for psychosis was 0.8%. Further, 891 subjects had been treated for both conditions; 2.8% with epilepsy had been treated for psychosis, and 3.1% with psychosis had been treated for epilepsy. Among 558 subjects included in the analyses of directionality, 56% had collected the first APD before an ASM, whereas 41% had collected an ASM first. During the last year prior to comorbidity onset, levetiracetam, topiramate, or zonisamide had been used for epilepsy by approximately 40%, whereas olanzapine and quetiapine were most used in patients with psychosis, and clozapine in 13%.
Conclusion: The proportion of patients with prior antipsychotic treatment at onset of epilepsy is higher than previously acknowledged, as demonstrated in this nation-wide study. Apart from a shared neurobiological susceptibility, the bidirectionality of epilepsy and psychosis may be influenced by various environmental factors, including the interaction of pharmacodynamic effects. APDs may facilitate seizures; ASMs may induce psychiatric symptoms. In patients with combined treatment, these potential drug effects should receive ample attention, along with the psychosocial consequences of the disorders. A prudent multi-professional approach is required.

Abbreviations: NorPD, The Norwegian Prescription Database; ASMs, antiseizure medications; APDs, antipsychotic drugs; ICD-10, The 10th revision of the International Classification of Diseases; ICPC-2, The 2nd edition of the International Classification of Primary Care; DDD, Defined Daily Doses; ATC code, Anatomical Therapeutic Chemical code.

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1. Introduction

During recent years, there has been much focus on the comorbidity of psychiatric disorders in people with epilepsy. Psychosocial and neurobiological factors are at play. Virtually all psychiatric disorders seem to occur in a higher proportion of subjects with epilepsy than in those without, and observational studies have indicated a bidirectional relationship [1]. However, estimates have varied considerably across studies dependent on settings, sources of ascertainment, and diagnostic criteria. In a recent survey of patients acutely submitted to a psychiatric hospital, the life-time prevalence of epilepsy was 3.9% [2]. An extensive meta-analysis of 58 studies of psychosis in epilepsy showed a pooled prevalence of 5.6% (range 0.02–27%). There was substantial heterogeneity across individual studies, and further population-based research was requested [3].

Historically, psychosis in epilepsy has been attributed to the consequences of having seizures and the psychosocial burden of the diagnosis [4]. Less attention was given to the onset of epilepsy in people with prior psychosis [5]. In roughly the last 10 years, growing evidence of a reciprocal relationship also for psychosis has been found in selected populations, but few studies have had the data to substantiate this bidirectionality.

Some evidence has been documented in selected samples from various countries: A Japanese study from tertiary centers of 312 patients fulfilling the diagnostic criteria for both disorders identified 23 patients diagnosed with a psychotic disorder predating the diagnosis of epilepsy, whereas the majority developed interictal psychosis in the course of confirmed epilepsy [6]. In a Swedish case–control study of 1,885 subjects from the Stockholm Epilepsy Register, the risk for developing epilepsy after hospitalization for psychosis was increased by 2.3 compared to controls [7]. A similar retrospective cohort study of hospital admissions in the UK found an elevated risk of epilepsy of 2.1 and 3.0 in two different study materials including one covering the whole of England [8]. Another study from the UK using data from a general practice research database also demonstrated an increased rate of prior psychiatric disorders, including psychosis, in people with newly diagnosed epilepsy [9]. Likewise, two US studies of elderly subjects (>65 years), suggested that premorbid psychosis was an independent risk factor for late-onset epilepsy [10,11]. A recent literature review suggests that the incidence of epilepsy in patients with schizophrenia is 4–5 times higher than that of the general population [5]. Notwithstanding, scarce scientific attention has been given to the group of subjects with established psychosis at epilepsy onset, and the extent of this group is still not determined [3].

Hence, we set out to investigate the prevalence and directionality of comorbid epilepsy and psychosis in a population-based study of subjects receiving combined antipsychotic and antiseizure treatments using The Norwegian Prescription Database (NorPD) covering all Norwegian pharmacies. We wanted to assess the proportions of subjects first starting with either antipsychotic drugs (APDs) prescribed for psychosis or antiseizure medications (ASMs) prescribed for epilepsy.

2. Material and methods

This was a retrospective population-based observational study using pharmacoepidemiologic data from the NorPD.

2.1. Data material

The NorPD contains individual-based information on all drugs dispensed from Norwegian pharmacies from 2004. Diagnosis-specific codes reflect reimbursable indications, such as epilepsy and psychiatric disease. The 10th revision of the International Classification of Diseases (ICD-10) and the 2nd edition of the International Classification of Primary Care (ICPC-2) were implemented from 2008.

We obtained NorPD-data with information on all ASMs defined by the Anatomical Therapeutic Chemical code (ATC code) N03A and APDs defined by ATC code N05A collected from 2004 through 2017 in subjects ≥18 years of age at the end of the study period. The dataset included pseudonymous patient identification numbers, information on sex and year of birth, ATC code (version 2018), date of dispensation, number of defined daily doses (DDDs) per prescription, and reimbursement codes.

The adult population of Norway in the years 2004–2017 was collected from Statistics Norway [12].

2.2. Identification of diagnostic groups

Subjects were categorized into two diagnostic groups based on reimbursement codes: (1) epilepsy and (2) psychosis, limited to schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (Table 1). Four unique prescriptions of ASMs for epilepsy or APDs for psychosis were required for inclusion, of which at least one had been issued with an ICD-10 reimbursement code from the specialist healthcare service.

2.3. Directionality

In subjects with prescriptions of both ASMs and APDs (epilepsy and psychosis comorbidity), we analyzed the directionality of treatments according to the first date of dispensation of each drug. To reduce prevalent comorbidity bias, we employed a four-year comorbidity-free period for those included in the analysis of directionality, meaning that no subjects had collected treatment for both disorders during these years.

2.4. Antiseizure and antipsychotic treatment

For each subject in the comorbidity groups, we identified unique ASMs and APDs prescribed during the last twelve months before onset of treatment for each condition. We also analyzed the number of ASMs used for epilepsy and APDs for psychosis during these twelve months. Finally, we analyzed the distribution of ASMs and APDs used both by subjects with and without comorbidity during the entire study period. We calculated mean DDD/patient/day for both ASMs and APDs prescribed for epilepsy and psychosis, respectively, according to subjects with or without comorbidity. The total DDDs per year of each drug was divided by total number of users, and further divided by 365 days.

Table 1
Diagnostic group based on ATC code and reimbursement codes according to ICD-10 and ICPC-2.

Diagnostic group	ATC code	Reimbursement codes	
		ICD-10	ICPC-2
1 Epilepsy	N03A[a]	G40	N88
2 Psychosis	N05A[b]	F20-F29, -F2[c]	P72, P98, -72[c]

ATC code, Anatomical Therapeutic Chemical code; ICD-10, International Classification of Diseases; ICPC-2, International Classification of Primary Care.
[a] ATC code N03A: Antiseizure medication.
[b] ATC code N05A: Antipsychotics.
[c] Reimbursement codes defined by The Norwegian Medicines Agency 1.9.2008: -F2/-72 "Psychosis and psychotic symptoms in psychiatric disorders".

2.5. Statistical analysis

Stata software package, Version 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for the data analysis. Chi Squared (χ^2) test was used to test for significant association between groups of comorbidity or non-comorbidity and prescribed medication. The continuous data of the variable DDD/patient/day deviated from a normal distribution, hence the non-parametric two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare means. A p-value $\leq$0.05 was considered significant.

2.6. Ethics

The use of registry data for this study was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (2016/56 and 2018/629).

3. Results

3.1. Epilepsy

A total of 31,289 subjects had collected an ASM with a reimbursement code for epilepsy four times or more: 15,430 (49%) women and 15,859 (51%) men. The prevalence of treatment for epilepsy in the adult population of Norway was 0.8% (Table 2). By the end of the study period 4209 (13%) of the subjects had been without epilepsy treatment for more than 5 years, suggesting epilepsy in remission.

3.2. Psychosis

An APD for psychosis had been prescribed at least four times to 28,889 subjects: 13,863 (48%) women and 15,026 (52%) men. The prevalence of treatment for psychosis was also 0.8% (Table 2). By the end of the study period 4335 (15%) had not collected APDs for psychosis for at least 5 years.

3.3. Comorbid conditions

A total of 891 subjects were treated for both epilepsy and psychosis, 0.02% of the adult population. This gives a prevalence of APD treatment for the defined psychotic disorders in people also treated for epilepsy of 2.8%, and a prevalence of ASM treatment for epilepsy in people with psychosis of 3.1% (Table 2). There were 426 (48%) women and 465 (52%) men among the subjects with comorbid epilepsy and psychosis.

3.4. Directionality

The order of ASM and APD treatment in people with both epilepsy and psychosis is shown in Table 3. There were 558 subjects included in the analysis of directionality after the clean period 2004–2007. In 56% of the cases, the first APD was collected prior to the first ASM, whereas an ASM was collected first in 41%.

Table 2
Distribution and prevalence of epilepsy and psychosis in the adult population of Norway as defined by diagnostic reimbursement codes.

Diagnostic group	Subjects (n)	Prevalence (%)
Epilepsy	31,289	0.8[a]
Psychosis	28,889	0.8[a]
Comorbid epilepsy and psychosis	891	0.02[a]
Psychosis in epilepsy		2.8
Epilepsy in psychosis		3.1

[a] Prevalence in the adult population of Norway (average population 2004–2017; 3,790,620).

Table 3
Directionality of epilepsy and psychosis as assessed by diagnostic reimbursement codes in 558 comorbid patients.

	Subjects		Mean age at onset of comorbid condition
	N	%	
APD first	310	55.6	42 (SD 16.9)
ASM first	231	41.4	39 (SD 19.4)
APD ASM same date	17	3.1	
Total	558	100	

APD, Antipsychotic drug; ASM, Antiseizure medication.

3.5. Antiseizure and antipsychotic drugs

Fig. 1A and B provides an overview of the distribution of ASMs and APDs collected twelve months prior to onset of comorbidity. Out of the 231 subjects collecting ASMs first, 41 (18%) had not

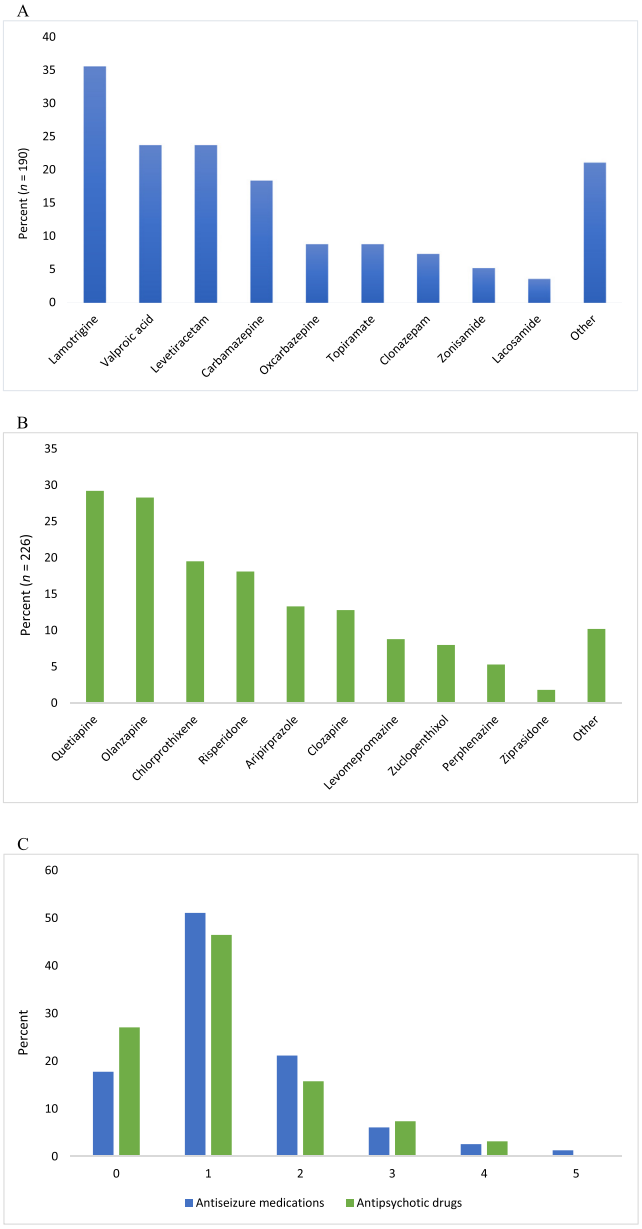


Fig. 1. Medications collected during the last year prior to onset of comorbidity; (A) antiseizure medications, (B) antipsychotic drugs, (C) numbers of used antiseizure medications and antipsychotic drugs.

Table 4
DDD/patient/day of ASMs and APDs according to groups of comorbidity and non-comorbidity.

	ASM		APD	
Year	Epilepsy w/psychosis[a]	Epilepsy w/o psychosis[a]	Psychosis w/epilepsy[b]	Psychosis w/o epilepsy[b]
2004	1.04	1.06	0.95	0.98
2005	1.02	1.09	1.01	1.02
2006	1.02	1.09	1.03	1.05
2007	1.04	1.10	1.12	1.05
2008	1.07	1.07	1.03	0.96
2009	1.09	1.05	1.01	0.90
2010	1.00	1.07	0.99	0.87
2011	1.02	1.06	1.05	0.89
2012	1.02	1.05	0.94	0.89
2013	0.98	1.04	0.90	0.88
2014	1.00	1.06	0.93	0.88
2015	1.03	1.08	0.92	0.88
2016	0.99	1.08	0.97	0.86
2017	1.07	1.12	0.96	0.89
Mean	1.03	1.07	0.99	0.93
SD	0.032	0.023	0.060	0.067

ASM, Antiseizure medication; APD, Antipsychotic drug.
[a] $p < 0.001$.
[b] $p = 0.021$.

collected an ASM during the last 12 months before starting an APD for psychosis (Fig. 1C). Ten patients in this group (24%) were ≤18 years of age when first collecting an APD, and 15 had been without ASM treatment for more than 5 years at the end of the study period, suggesting epilepsy in remission. Among the 190 subjects on epilepsy treatment at onset of psychosis, 72 (38%) had used two or more ASMs for epilepsy during the last year.

Olanzapine and quetiapine were the most frequent APDs used during the last twelve months before epilepsy onset. Eighty-four subjects (27%) had not collected an APD for psychosis during this year (Fig. 1C). Among the 226 subjects treated for psychosis the final year before epilepsy onset, 36% had used two or more APDs.

The average DDD/patient/day of ASMs for epilepsy was 1.0 in the epilepsy with psychosis group, compared to 1.1 in the group without comorbid psychosis (SD = 0.032 and 0.023 respectively), $p < 0.001$ (Table 4). For APDs the average DDD/patient/day was 1.0 (SD = 0.060) in the comorbidity group compared to 0.9 (SD = 0.067) in the non-comorbid psychosis group, $p = 0.021$.

During the entire study period, carbamazepine and levetiracetam were both used by a larger proportion of subjects in the non-comorbid epilepsy group, whereas topiramate, clonazepam, and valproic acid were used by more comorbid subjects (Fig. 2A). For APDs levomepromazine, chlorprothixene, risperidone, and clozapine were used by more subjects with comorbidity (Fig. 2B).

4. Discussion

To our knowledge this is the first population-based study examining the directionality of ASM and APD treatment in subjects with comorbid epilepsy and psychosis. Based on first time prescriptions among comorbid subjects, the present study suggests that the proportion of people with established psychosis at epilepsy onset is higher than previously recognized [6]. More than half of the patients with comorbid epilepsy and psychosis were already treated with APDs when they started treatment for epilepsy (56%). The findings corroborate the assumption of shared neurobiological mechanisms for these two brain disorders, conceivably due to both structural and genetic traits [13–15]. However, individuals harboring this inherent predisposition may not develop either definite psychosis or manifest epileptic seizures without further exposure to provocative environmental and acquired factors [16]. These factors should receive ample attention in the comprehensive management of people with comorbid epilepsy and psychosis.

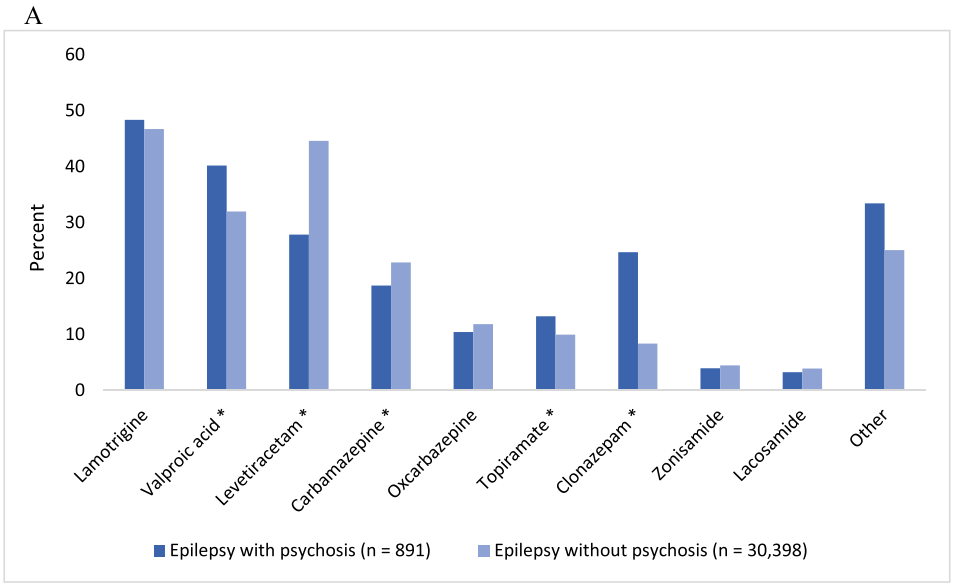
The bidirectionality of the two disorders forms two different clinical scenarios.

4.1. Psychosis following epilepsy

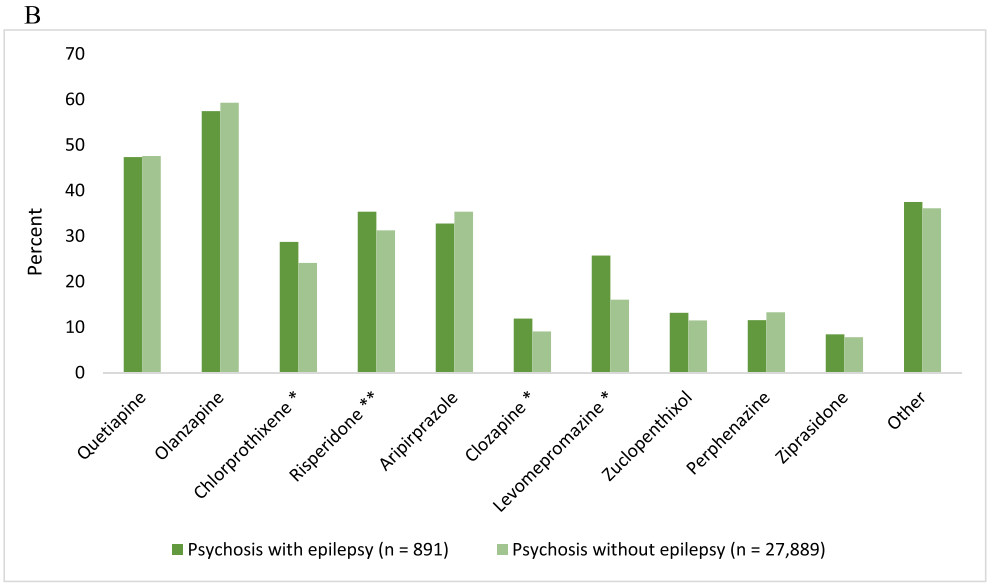
In the current definition of epilepsy by the International League Against Epilepsy, the principal elements of the diagnosis were extended beyond recurrent seizures to also include "the neurobiological, cognitive, psychological, and social consequences of the condition" [17]. This definition highlights the perceived stigma and the restrictions associated with the disease and encompasses a vulnerability to develop psychiatric disorders in people with epilepsy. Apart from the psychosocial impact of the disorder, various disease consequences with potential to induce psychosis have been addressed in the literature.

Postictal and interictal psychosis usually follow long-standing severe and uncontrolled epilepsy [18–20]. Postictal psychosis is a temporary event developing within hours to days after a seizure or a cluster of seizures, particularly in temporal lobe epilepsy, often with conspicuous violent and religious elements [21–23]. The primary treatment is optimization of ASMs rather than long-term APDs [24–26]. Interictal psychosis is usually a chronic disorder resembling nuclear schizophrenia, but negative symptoms are less prominent and emotional responsiveness often preserved [16]. The sum of seizures over time appears to contribute to the vulnerability for this most common form of psychosis in epilepsy [19]. Interictal psychosis usually presents later in life compared to schizophrenia [27]. Consistent with this, in the present study the mean age at first collected APD for psychosis was 39 years in subjects with epilepsy first. It has been suggested that psychotic symptoms may be facilitated by harmful ictal effects on brain function by so-called "kindling" or by vascular factors [14,20,28], or even by subclinical activity in the limbic system undetectable by scalp EEG [29]. Alternative psychosis, or so-called "forced normalization" as reflected in the EEG, may be brought on by abrupt seizure control and could indicate a biological antagonism between psychosis and seizures [18,30]. Accordingly, by this mechanism any successful ASM or other intervention might have the potential to induce psychosis in vulnerable patients [31].

Moreover, several ASMs may cause psychiatric and behavioral pharmacodynamic adverse effects, affecting between 15–20% of



*p < 0.005



*p < 0.005; **p = 0.01

Fig. 2. Medications used by subjects with or without comorbidity during the entire study period; (A) antiseizure medications, (B) antipsychotic drugs.

adult patients, of which psychosis was specifically reported in 0.5% in one study [32]. Psychosis has been reported as an adverse effect from various ASMs. The ASMs most commonly involved include ethosuximide, levetiracetam, topiramate, zonisamide, and vigabatrin [31–34]. In the present study, levetiracetam, topiramate, or zonisamide were used by approximately 40% of the patients with epilepsy during the last year prior to APD onset. However, drug effects may be difficult to sort out in people predisposed to psychosis by other factors. Noteworthy, levetiracetam was less used during the entire study period among patients with psychosis compared to those without, probably reflecting avoidance of this drug in patients with psychiatric problems, whereas topiramate was more used. Kanemoto et al. found that 45 among 132 patients with epilepsy and interictal psychosis had added ASMs or increased the dose before psychosis onset, half of these were related to zonisamide [35]. It has been suggested that any ASM may contribute to the development of psychosis in predisposed individuals [36]; however, the daily dose of ASMs has not been significantly associated with psychosis [37]. We did not identify an increased load of ASMs as expressed by mean DDDs in the group of subjects with epilepsy and psychosis.

Interestingly, 18% of the subjects with epilepsy first had not collected any ASM during the last 12 months prior to the first APD for psychosis. A large portion of these subjects were of young age, some possibly with childhood epilepsy in remission. An association even between uncomplicated or self-limited epilepsies and psychiatric disorders has been suggested [2,38,39].

4.2. Epilepsy following psychosis

A range of seizure precipitating factors may occur in psychiatric disease, either by endogenous mechanisms in the form of severe emotional stress and lack of sleep, or by exogenous influences due to the exposure to compounds which may lower the seizure

threshold. The pharmacological mechanisms comprise withdrawal effects from alcohol and benzodiazepines and direct neurotoxic effects from various drugs. A high load of APDs may induce seizures and increase the susceptibility to recurrent seizures in predisposed individuals [40]. Moreover, population-based data have shown that people with epilepsy are more often registered with substance use disorders than people without epilepsy, a comorbidity sometimes complicated by psychosis [41,42]. Abuse of various illicit drugs, such as cocaine and psychostimulants frequently precipitate seizures [43,44]. The association of substance use disorders and seizure disorders is a substantial clinical problem, as the borders between epilepsy and acute symptomatic seizures may be blurred [41]. Likewise, people with psychotic disorders may have an increased risk of developing focal epilepsy from various acquired causes, including head traumas associated with violent behavior and self-harm, as well as alcohol and drug intoxications [5,45].

Nearly all patients with long-lasting psychosis are treated with APDs. The impact of the seizure-inducing effects of these drugs in clinical practice has repeatedly been debated. Clozapine stands out as the drug with the most pronounced seizure-triggering effect. Clinical trial data in patients without epilepsy have also shown a higher risk of seizures for olanzapine and quetiapine than for ziprasidone, aripiprazole, and risperidone [26,46]. However, APD treatment, particularly clozapine, may also induce EEG slowing and epileptiform activity [47], leading to an unwarranted suspicion of epilepsy in some patients. Clozapine was used by nearly 15% of the subjects on APD treatment at onset of epilepsy. It had been used by a significantly larger proportion of subjects with epilepsy comorbidity during the entire study period. Clozapine should predominantly be prescribed when other APDs have failed, signifying difficult-to-treat psychosis [48]. Olanzapine and quetiapine were both used by almost 30%, whereas ziprasidone, risperidone, and aripiprazole were less used prior to epilepsy onset. Noteworthy, approximately one quarter of subjects with psychosis antedating epilepsy had not collected any APDs during the last year prior to onset of ASM treatment for epilepsy.

It has been emphasized that appropriate treatment of psychiatric disorders in people with epilepsy has been neglected due to an overestimated risk of seizures associated with APD treatment [1,26]. Some studies have even shown an improved seizure outcome in comorbid patients treated with careful APD regimens, possibly related to achieved control of psychiatric symptoms lessening seizure precipitants, including poor adherence to ASMs [5,40,49]. Nonetheless, data suggest that seizure induction is a dose-dependent class effect of APDs, which varies considerably among the numerous compounds [31,40,46]. A subset of people may be particularly vulnerable to this effect [40], and it is difficult to assess the real magnitude of this phenomenon in clinical practice. This study shows that the overall DDD burden of APDs for psychosis was significantly higher among subjects with epilepsy comorbidity compared to non-comorbid subjects. In some cases, an enzyme-inducing effect on APD serum concentrations from ASMs, such as carbamazepine, may underlie a need for higher doses [1]. The APD-treatment-response of people with epilepsy and psychosis compared to people with schizophrenia is still unknown [26], and psychosis in people with epilepsy might be more difficult to treat. The aim should be to treat people with epilepsy using the minimum effective doses of appropriate drugs [31], carefully considering seizure frequency as well as the total burden of adverse effects in subjects using various CNS-active drugs.

Any of the above discussed factors may worsen seizure control or even directly cause seizures and have to be considered in patients with comorbid seizures and psychiatric disease [28]. Such factors may frequently occur in concert and could conceivably have the potential to unveil a predisposition to developing epilepsy, sometimes with subthreshold effects adding to each other. These factors could explain why psychiatric disorders may lead to a worse response to the treatment of epilepsy [1,50].

4.3. Methodological issues

Antiseizure and antipsychotic drugs are used for a wide range of symptoms. The manifestations of epilepsy and its related psychopathology can be atypical and diverse, and most prescriptions in our study were issued in primary care. We acknowledge that the diagnosis of epilepsy is sometimes demanding in people with psychosis due to occasional episodic nonspecific behaviors and intermittent extrapyramidal adverse reactions from APDs. Unfortunately, no information on the classification of epilepsy could be retrieved from the present dataset. Noteworthy, about one quarter of people with epilepsy also have intellectual disability [51]. In these patients, specific psychiatric diagnoses are difficult to identify. In a recent British study addressing polypharmacy in a selected cohort of people with intellectual disability and epilepsy, 27% used APDs, but only 7% had a comorbid diagnosis of psychosis. This suggests not only a higher prevalence of psychosis in people with intellectual disability and epilepsy, but also a higher proportion of APD treatment for non-psychotic conditions, such as unspecific challenging behaviors [52]. However, patients in the present population-based study were strictly selected by reimbursement codes for epilepsy and psychosis, aiming to minimize this potential confounder.

The main strength of this study is the inclusion of the entire adult Norwegian population over a 14-year period, using data from the NorPD, which is a validated source of pharmacoepidemiological studies [53,54]. To ensure long-term treatment, only subjects with ASMs or APDs collected at least four times for the respective diagnoses were included. To further enhance diagnostic validity, the ICD-10 coding system employed by the specialist healthcare services, had been used at least once. By this procedure, the prevalence of patients using ASMs for epilepsy and APDs for psychosis (0.8% for both groups) met fairly well with recent Norwegian population-based prevalence studies both for epilepsy (0.65%) [55], and for psychosis (0.6% for schizophrenia-spectrum disorders) [41]. Prescriptions for affective psychoses were not included. We acknowledge that collected treatment does not necessarily reflect used medication. Also, drugs administered in hospitals or institutions are not included in the NorPD.

An obvious limitation of the study is that we could hardly determine the true onset of treatment in all patients. Selecting a long clean period increases internal validity as pointed out by Roberts et al. [56], but we could not exclude intermittent treatments prior to this period. Nevertheless, this was considered less likely for ASMs than for APDs, as treatment for epilepsy is usually more stable and long-term than for psychosis. Hence, we consider that this possible bias might have influenced the results toward an even higher proportion of onset of treatment for psychosis first.

We also acknowledge that the clinical onset of epilepsy and psychosis may differ from both the time of diagnosis and treatment onset of these disorders. A single seizure may be left untreated until another occurs [57], and the onset of psychosis requiring treatment may obviously be difficult to define [58]. However, the general principles of early symptomatic treatment of psychotic symptoms also apply in epilepsy-related interictal psychoses [31].

5. Conclusion

The present study suggests that the proportion of patients with prior antipsychotic treatment at onset of epilepsy is higher than

previously acknowledged. This particular group of patients should receive more clinical and scientific attention. The bidirectional comorbidity of epilepsy and psychosis indicates a shared neurobiological susceptibility, but various environmental factors may also be at play, including the interaction of pharmacodynamic effects. APDs may facilitate seizures, and ASMs may induce psychiatric symptoms. In patients with combined treatment, these potential drug effects should be carefully explored and monitored, along with the psychosocial and life-style consequences of the disorders. A comprehensive multi-professional approach is required. To broaden the understanding of the challenging association between psychosis and epilepsy, joint scientific and educational efforts between the fields of neurology and psychiatry should be reinforced.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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