

TITLE: The causes of death in epilepsy: a systematic review

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Abstract

Background

Population-based studies have consistently found a two to three fold increase in mortality rates in patients with epilepsy (PWE) compared with the general population. The cause of this increase remains uncertain but several risk factors have been identified including non-adherence to medication, treatment for depression and alcohol abuse.

Aim

To describe mortality rates in individuals with epilepsy and examine amenable causes of death.

Method

A search of MEDLINE and PsycINFO lead to 14 papers being reviewed. The inclusion criteria stated that papers had to examine mortality rates in PWE and had to look at the role of psychological variables in the cause of death.

Results

Mortality and suicide rates were increased in PWE. PWE were at higher risk of being diagnosed with a psychiatric disorder than the general population. Being diagnosed with a comorbid psychiatric disorder was significantly associated with external cause of death (suicide and accidents) in PWE. Non-adherence to medication increased mortality rates by 50%.

Conclusion

Psychiatric disorders and drug and alcohol abuse disorders are treatable and non-adherence with medication can be reduced through improving patient education. This may reduce some causes of death in epilepsy.

Introduction

Epilepsy is the most common serious neurological condition worldwide(1). It is estimated that at any one time 50 million individuals in the world have epilepsy(2). Before the age of 75, epilepsy is the fifth and eighth highest amenable mortality condition in men and women respectively(3).

In the United Kingdom, all-cause mortality is declining, however there appears to be a trend suggesting that mortality from epilepsy is increasing; from 1997 to 2003 the relative increase in mortality in females was 28% and in males 17%(4).

Consistently, both retrospective and prospective population based studies have found a two to three fold increase in mortality rates in patients with epilepsy (PWE) compared with reference populations(5–8). This increased mortality rate is not uniform and varies according to the population studied, the age and gender of the patient and the aetiology and type of epilepsy(6).

The epilepsy population is studied using the standardized mortality ratio (SMR), defined as the ratio of the observed deaths in the population of interest compared to the expected deaths in age and sex matched individuals in the general population.

In the first year following the diagnosis of epilepsy, mortality rates are at their highest. These rates reflect the underlying causes of epilepsy for example degenerative conditions, tumours or cerebrovascular disease(6,9). The highest SMR in epilepsy is found in children; this mainly reflects the high death rates seen in children with neurodeficits and a low mortality rate in children in the general population. Highest excess mortality is found in the elderly(9).

The aetiology of epilepsy can be separated into three broad categories; idiopathic, cryptogenic and symptomatic. The highest SMR is seen in people with acute and remote symptomatic epilepsy; this is presumably due to the underlying lesion causing the seizure. The mortality rate is two to five times higher than that of the general population in remote symptomatic epilepsy(9). It remains controversial as to whether mortality rates are elevated in idiopathic epilepsy and a recent systematic review found that the majority of studies only find a borderline increase(10).

The leading causes of death in epilepsy are cerebrovascular disease, neoplastic disease (even after excluding primary brain tumours) and pneumonia(9). External causes of death (accidents such as, drowning, burns and accidental poisoning, and suicide) are also increased in epilepsy(9). Although not the focus of this review, it is important to mention sudden unexplained death in epilepsy (SUDEP), which is considered to be the most common cause of epilepsy-related death, being twenty fold higher than in the general population(11). The annual incidence of SUDEP increases further to one in 200 in people with intractable epilepsy(6). Suicide risk is also elevated in PWE, rates of suicide widely vary between zero to twenty-five per-cent(5).

The reasons behind the increased mortality rates in epilepsy are uncertain. Several risk factors have been identified including non compliance with medication, being treated for depression, recorded alcohol problems and previous injuries(4).

There is increasing literature describing the rates of psychiatric comorbidity in PWE. In a substantial proportion of PWE, psychiatric disorders are present. The incidence of depressive symptoms in PWE compared with the general population and patients with other chronic and neurological disorders is significantly higher(12,13). Additionally, PWE have an almost three fold increased risk of developing schizophrenia-like psychosis compared to the reference population(13).

It had been proposed that psychiatric disorders are more prevalent due to perceived loss of control in response to the diagnosis of epilepsy(12). A bidirectional link has been proposed between

epilepsy and psychiatric disorders; individuals with epilepsy have a lower seizure threshold and so are more susceptible to seizures and people with seizures are at increased risk of developing a psychiatric disorders(12).

Thapar et al have described a complex interaction between depression, anxiety and stress and their impact on seizure activity(14). Depression appears to mediate the relationship between patient perceived stress and anxiety on seizure frequency and recency(14). Additionally, there is a reciprocal relationship between seizure frequency and depressive symptom scores(15). The mechanisms behind this relationship maybe linked with neurobiological changes(14), but other mechanisms affecting behavior such as increased alcohol consumption or non-adherence with antiepileptic and antidepressant medication must not be overlooked.

Recognizing the link between psychiatric disorders and epilepsy is vital so preventative measures can be implemented; for example, early treatment of underlying psychiatric conditions and addressing underlying socio-economic stressors and the stigma associated with epilepsy.

Aim of review

The aim of this review is to describe mortality rates in individuals with a diagnosis of epilepsy and examine amenable causes of death. Mortality, suicide and accident rates will be examined, alongside risk factors for mortality; psychiatric disease, substance-related disorders, accidents and non-adherence to antiepileptic drugs (AED).

Method

Relevant papers were searched for in two databases:

1. Ovid MEDLINE (1946 to February week 1 2014)
2. PsycINFO (1806- February Week 2 2014)

Searches included using both MeSH headings and 'free-text searches'. All MeSH headings(*) were exploded and all sub-headings were used.

MeSH headings in MEDLINE and PsycINFO differed and so similar headings were used. If a MeSH heading was not available this was included as a 'free-text search' alongside the appropriate and available MeSH heading.

MEDLINE search:

1. Epilepsy*, epilepsy;
2. Mortality*, mortality, epilepsy mortality;
3. Mental disorders*, mental disorders, Substance-related disorders*, alcoholism, Patient compliance*, patient compliance, Suicide*, suicide, Self-injurious behaviour*, self harm.

PsycINFO search:

1. Epilepsy*, epilepsy
2. Death and dying*, mortality, epilepsy mortality
3. Mental disorders*, mental disorders, alcoholism*, alcohol abuse*, drug abuse*, drug dependency*, substance-related disorder, patient compliance, Treatment compliance*, Suicide*, suicide, Self-injurious behaviour*, self-harm.

Combination of these words (1∩2∩3) in these databases resulted in 684 papers (597 from MEDLINE and 87 from PsycINFO). These papers were selected if they fit with the inclusion and exclusion criteria. This provided 8 papers to be reviewed.

The reference lists of relevant articles were searched for additional relevant papers.

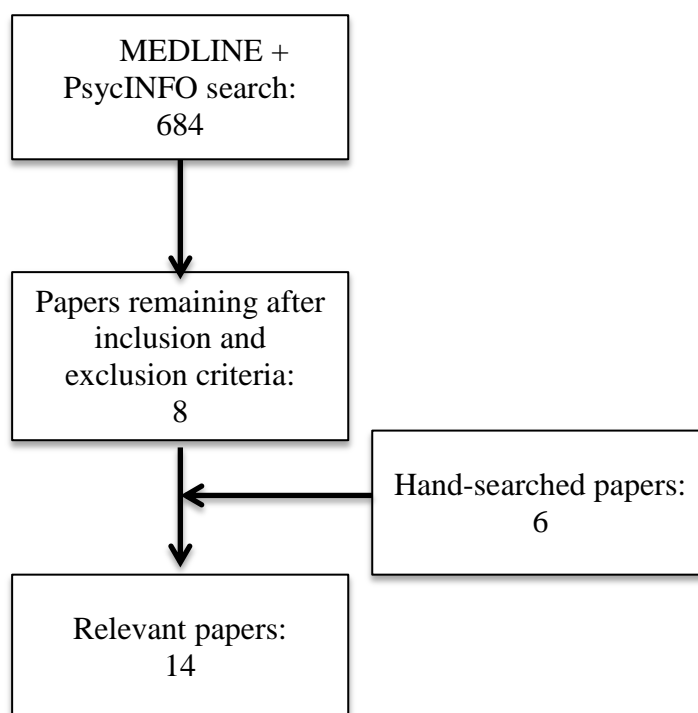
Inclusion criteria:

- Papers written in English
- Studies that investigated the cause of death in adults diagnosed with epilepsy
- Studies looked at the role of psychological variables in the mortality of patients with epilepsy
- No limit on publication date

Exclusion criteria:

- Studies investigating epilepsy in children
- Studies only investigating sudden unexpected death in epilepsy patients

Literature search tree:



Results

Fourteen papers were evaluated; a summary of these papers is shown in Table 1.

All papers were reviewed to look at overall mortality, suicide and accident rates. The prevalence and contribution of three psychological variables to mortality rates in PWE were investigated; psychiatric disorders, drug and alcohol misuse and non-adherence to AED.

Paper	Study Design	Participant recruitment	Primary Outcome	Overall mortality rates	Suicide rates	Accident rates	Psychiatric comorbidity	Substance-related disorders	Non-adherence
Fazel et al, Lancet (2013) (19)	Prospective, case-control	Patients identified through National Patient Register in Sweden – outpatient and hospitalized patients (n=69995).	Mortality rates and cause of death in patients with epilepsy and rates of psychiatric comorbidity (ICD-8,9,10).	☐	☐	☐	☐	☐	
Ridsdale et al, The British Journal of General Practice: The Journal of the Royal College of General Practitioners (2011) (4)	Nested Case-Control	United Kingdom General Practice Research Database. Patients selected if they had been diagnosed with epilepsy and received one or more anticonvulsant drugs.	Mortality rates in patients with epilepsy. To identify risk factors for mortality in epilepsy.	☐	☐	☐	☐	☐	☐
Mohanraj et al, Lancet Neurology (2006) (16)	Retrospective, comparative	Patients newly diagnosed with epilepsy between 1981 to 2001 from the Epilepsy Unit at the Western Infirmary Glasgow (N=890). Chronic epilepsy patients who had been referred (inadequately controlled seizures) and then treated at the Epilepsy unit (N=2689).	Mortality rates in patients with chronic and newly diagnosed epilepsy.	☐	☐	☐	☐		
Zieliński et al, Epilepsia (1974) (20)	Retrospective, population	All patients with epilepsy in Warsaw identified from records on psychiatric and neurological in and outpatients of the National Insurance Office, and of long-term institutions (1965-1969) (N=6710). Records of patients with epilepsy who died in a mental hospital from 1952-1971 (N=97).	Mortality rates and cause of death in patients with epilepsy.	☐	☐	☐		☐	
Nilsson et al, Epilepsia (1997) (17)	Cohort study	Epilepsy patients (>15 years) with epilepsy admitted to hospital between 1980-1989 registered in the Stockholm County In-Patient Register. (N=9061)	Mortality rates and causes of death (ICD-8, 9) in patients with epilepsy.	☐	☐	☐	☐	☐	

Paper	Study Design	Participant Recruitment	Primary Outcome	Overall mortality rates	Suicide rates	Accident rates	Psychiatric comorbidity	Substance-related disorders	Non-Adherence
Rafnsson et al, Neuroepidemiology (2001) (18)	Population-based incidence study	Patients first diagnosed with unprovoked seizures between 1960-1964. (N=224).	Cause-specific mortality rates in patients with epilepsy (ICD-7)	☐	☐	☐			
St Germaine-Smith et al, Epilepsia (2008) (26)	Cohort study	Patients with epilepsy (diagnosed using ICD-9-CM code 345 or ICD-10-CA codes G40-41) were identified using five linked administrative databases in Calgary, Canada (1996-2005). (N=7253)	To develop an epilepsy-specific comorbidity risk adjustment index.	☐			☐	☐	
Christensen et al, Lancet Neurology (2007) (22)	Population-based cohort-controlled study	Epilepsy patients identified using five nationwide longitudinal registries in Denmark. Suicide cases identified using the Cause of Death Register in Denmark (1981-1997).	Mortality rates and cause of death (ICD-8, ICD-10) in patients with epilepsy. Psychiatric comorbidity (ICD-8, ICD-10, psychiatrist diagnosis)		☐		☐	☐	
Fukuchi et al, Epilepsy Research (2002) (21)	Case-control study	Records of deceased patients (Outpatients of the Kansai Regional Epilepsy Center and National Neuropsychiatry Centre) with well-classified epilepsy. Patients excluded if they had unclassified epilepsy or had died due to the underlying disease (N=43). Matched with control patients with definite subtypes of epilepsy (exclusion: unclassified epilepsy) (N=1722). Epilepsy definition based on International League Against Epilepsy.	Causes of death in patients with epilepsy.		☐	☐	☐		
Mainio et al, Epilepsy & Behaviour (2007) (24)	Population-based study	All suicide victims (1988-2002) in Oulu, Northern Finland. Data from death certificates, forensic medico-legal investigation and hospital admissions from the Finnish Hospital Discharge Register (N=1887).	Suicide rates and psychiatric comorbidity (ICD-8,9,10) in patients with epilepsy		☐		☐	☐	

Paper	Study design	Participant recruitment	Primary Outcome	Overall mortality rates	Suicide rates	Accident rates	Psychiatric comorbidity	Substance-related disorders	Non-adherence
Hesdorffer et al, <i>Annals of Neurology</i> (2012) (12)	Matched, longitudinal cohort study	United Kingdom General Practice Research Database. Patients newly diagnosed with incident epilepsy aged between 10-60y who had at least one epilepsy GRPD coded recorded between 1993-2005) and at least two antiepileptic drug prescriptions one to six months after diagnosis (N=3773) were matched with controls (N=14,025)	Examine diagnosis of psychiatric disorders before and after onset of epilepsy. Suicide rates in patients with epilepsy.		☐		☐	☐	
Nilsson et al, <i>Epilepsia</i> (2002) (23)	Case-control study	Patients >15 years who were hospitalized and discharged with epilepsy between 1980-1989 identified on the Stockholm County Council In-Patient Register.	Suicide rates in patients with epilepsy. To identify risk factors for suicide.		☐		☐	☐	
Faught et al, <i>Neurology</i> (2008) (25)	Retrospective cohort study	Patients identified using health insurance claims data from Florida, New Jersey and Iowa. Patients >18 years, at least one neurologist visit with a diagnosis of epilepsy (ICD-9) or non-febrile convulsions (ICD-9 780.3 or 780.39) and two or more pharmacy dispensing of antiepileptic drugs following diagnosis and six months or longer of being enrolled on Medicaid before the first AED dispensing.	Non-compliance with anti-epileptic medication and mortality rates.	☐		☐			☐
Trans et al, <i>Epilepsia</i> (2008) (27)	Pilot Study	Patients with epilepsy identified by a previous prevalence survey (n=46)	Phenobarbital compliance and mortality rates						☐

Table 1: A table to show all the papers reviewed and to show whether they examined mortality rates, suicide rates, psychiatric comorbidity, substance-related disorders on non-compliance. (ICD: International Classification of Diseases).

Overall mortality:

Fazel et al, 2013 (19)	aOR: 11.1
Ridsdale et al, 2011 (4)	Appears to be a relative increase in mortality by 28% in females, 17% in males
Mohanraj et al, 2006 (16)	Newly diagnosed epilepsy SMR: 1.42 Chronic epilepsy SMR: 2.05
Zieliński, 1974 (20)	Mortality rate was 1.8 times higher in patients with epilepsy
Nilsson et al, 1997 (17)	SMR: 3.6
Rafnsson et al, 2001 (18)	SMR: 2.25 in male patients with epilepsy
St Germaine-Smith et al, 2011 (26)	Mortality rate in patients with epilepsy 7.9%

Table 2: A table to show the results looking at overall mortality in patients with epilepsy from the papers analyzed.

SMR (Standardized Mortality Ratio), aOR (Adjusted odds ratio).

The SMR ranged from 1.42 to 3.6(16–18). Fazel et al reported an increase in all-cause mortality with an odds ratio of 11.1, after adjustment for sociodemographic confounding factors(19). The SMR was higher in patients with chronic epilepsy (2.05) compared with patients with newly diagnosed epilepsy (1.42)(16). Ridsdale et al reported an apparent increase in mortality rates in PWE from 1997 to 2003.

In patients with newly diagnosed epilepsy, symptomatic epilepsy was associated with significantly increased mortality rates compared with idiopathic and cryptogenic epilepsy(16,18). In patients with chronic epilepsy, symptomatic, unclassified and cryptogenic epilepsy had significantly increased mortality rates but idiopathic epilepsy did not(16). Epilepsy due to other diseases, especially encephalopathy, had the worse prognosis(20).

It was found that the largest cause of death was due to conditions that caused the epilepsy(19). Leading causes were neoplasms, cerebrovascular disease, respiratory disease and SUDEP. In institutionalized patients, death from epilepsy (status epilepticus, SUDEP, fatal accidents due to seizures) accounted for 20% of deaths(20) and Fukuchi et al found that 23.3% of deaths in PWE were due to SUDEP(21). External causes of death were increased in all studies.

For external cause of death, odds ratios were highest for the first 6 months after diagnosis and in patients with special epilepsy syndromes (ICD-10 G40.5)(19).

Increasing age at the time of epilepsy diagnosis was associated with decreased survival(16). This compares with Nilsson et al and Mohanraj et al who found that mortality rates were higher in younger patients(16,17).

Rafnsson et al only found a significant increase in all cause mortality in male PWE (SMR 2.25), and Zieliński reported that mortality rates were over twice as high in men, when patients were over 30 years(20). Mohanraj found that survival rates were higher in females(16).

Suicide:

Fazel et al, 2013 (19)	aOR: 3.7
Mohanraj et al, 2006 (16)	More likely to occur in patients with chronic vs newly-diagnosed epilepsy
Zieliński et al, 1974 (20)	Suicide was the cause of death in 7.3% known epileptics
Christensen et al, 2007 (22)	RR: 3.17
Nilsson et al, 1997 (17)	SMR: 3.5
Rafnsson et al, 2001 (18)	SMR: 5.80 (males)
Nilsson et al, 2002 (23)	RR: 9.3
Fukuchi et al, 2002 (21)	SMR: 5.80 (Males, Temporal Lobe Epilepsy)
Mainio et al, 2007 (24)	1.3% of suicide victims had epilepsy
Hesdorffer et al, 2012 (12)	Increase in suicidality before and after onset of epilepsy

Table 3: The suicide rates seen in people with epilepsy compared with reference populations.
aOR (adjusted odds ratio) RR (Relative risk) SMR (Standardized mortality ratio)

PWE were over three times more likely to commit suicide(17,18,21,22). Suicide was more likely to occur in patients with chronic epilepsy whereas self harm was more likely to occur in newly diagnosed patients(16).

One study found that suicide rates were only increased in men and another found that rates were twice as high in men compared to women(18,21). Epilepsy suicide victims were older than those who did not have epilepsy (47.7 years vs 43.0 years)(24).

Nilsson et al found that the relative risk of suicide increased to 16.0 if onset was before the age of 18, however Christensen et al found no effect of age at diagnosis on suicide rates(22).

Being diagnosed with a psychiatric disorder was a strong risk factor for suicide; the risk of suicide in PWE without a psychiatric disease was 2.36 compared with 21.4 for PWE with a psychiatric disease(22). In PWE, the relative risk of suicide increased nine-fold with the presence of a psychiatric illness, and 10-fold if the patient was taking antipsychotic medication.

Nilsson et al did not find an association between the risk of suicide and a particular type of epilepsy(23), however Fukuchi et al only found an association between suicide and temporal lobe epilepsy (TLE)(21).

Successful suicides in epilepsy were more likely to follow previous suicide attempts compared with suicides in the general population; 15.2% suicides were recurrences in PWE compared with 4.2% in controls (12). This was found in another paper where 20% of suicide victims who had epilepsy had previously attempted suicide compared with 9.8% of victims without epilepsy(24).

Accidents:

Fazel et al, 2013 (19)	<ul style="list-style-type: none"> • Non-motor vehicle accidents <ul style="list-style-type: none"> ○ 37.5% accidental drug poisoning ○ 16.1% falls ○ 15.2% drowning ○ 30.9% unspecified accidental deaths 	<ul style="list-style-type: none"> • aOR: 5.5
Fukuchi et al, 2002 (21)	<ul style="list-style-type: none"> • Deaths due to accidents 	<ul style="list-style-type: none"> • 30.2%
Mohanraj, 2006 (16)	<ul style="list-style-type: none"> • Cause of death due to accidents were significantly increased in patients with chronic epilepsy 	<ul style="list-style-type: none"> • SMR: 2.60
Nilsson et al, 1997 (17)	External causes of death: <ul style="list-style-type: none"> • Undetermined injury • Accidents caused by fire or flames • Accidents caused by submersion, suffocations or foreign bodies • Accidental falls • Transport accidents 	<ul style="list-style-type: none"> • SMR: 11.1 • SMR: 10.3 • SMR: 8.2 • SMR: 4.6 • SMR: 1.8
Rafnsson, 2001 (18)	<ul style="list-style-type: none"> • Accidents, poisoning, violence in men with: <ul style="list-style-type: none"> ○ Unprovoked seizures ○ Remote symptomatic unprovoked seizures ○ Unprovoked seizures of unknown cause 	<ul style="list-style-type: none"> • SMR: 2.84 • SMR: 7.27 • SMR: 1.76
Ridsdale et al, 2011 (4)	<ul style="list-style-type: none"> • Mortality was associated with having an injury in the previous year 	<ul style="list-style-type: none"> • OR: 1.41
Zieliński, 1974 (20)	<ul style="list-style-type: none"> • In known epileptic patients, cause of death due to accidents (not due to seizure) 	<ul style="list-style-type: none"> • 4.1%
Faught et al, 2008 (25)	Non adherence associated with 50% increase in fractures and motor-vehicle accidents	

Table 6: A table showing the contribution of accidents to the mortality rate in epilepsy. aOR (adjusted relative risk), OR (odds ratio), (SMR (standardized mortality ratio), IRR (incidence rate ratio).

In male PWE with unprovoked seizures, the SMR for accidents, poisoning and violence was 2.84, however this increased to 7.7 when only looking at remote symptomatic seizures(18).

In patients with chronic epilepsy, accidents were the third cause of greatest excess mortality and accidents occurred significantly more in those with chronic epilepsy compared to those with newly diagnosed epilepsy(16). Nilsson et al found that the highest cause of external cause of death was accidental death due to fire or flames(17). In PWE with psychiatric comorbidity there was an association between epilepsy and mortality from an external cause(19). Non-adherence also increased the risk of accidents by 50%(25).

Psychiatric disorders:

Author	Psychiatric disorder investigated	Outcome
Christensen et al, 2007 (22)	<ul style="list-style-type: none"> • Affective disorders • Chronic alcohol abuse • Other • Schizophrenia • Anxiety 	<p>The adjusted relative risk of suicide in patients with epilepsy and a psychiatric disease</p> <ul style="list-style-type: none"> • aRR: 19.9 • aRR: 11.9 • aRR: 11.9 • aRR: 7.55 • aRR: 7.24
Nilsson et al, 2002 (23)	<ul style="list-style-type: none"> • Depression • Depression and abuse • Alcohol or drug abuse 	<p>% Present in epilepsy patients who committed suicide.</p> <ul style="list-style-type: none"> • 26.8% • 19.2% • 11.5%
Mainio et al, 2007 (24)	<ul style="list-style-type: none"> • Previous attempted suicide 	<ul style="list-style-type: none"> • 20% in people with epilepsy vs 9.8% without epilepsy
Ridsdale et al, 2011 (4)	<p>Mortality was associated with:</p> <ul style="list-style-type: none"> • Being currently treated with antidepressants • Alcohol abuse 	<ul style="list-style-type: none"> • OR 1.39 • OR 2.96
Nilsson et al, 1997 (17)	<ul style="list-style-type: none"> • Alcohol dependency syndrome • Alcoholic psychosis • Drug dependence • Mental disorders 	<p>Cause specific mortality (SMR)</p> <ul style="list-style-type: none"> • 24.6 • 22.5 • 13.3 • 10.8
Hesdorffer et al, 2012 (12)	<ul style="list-style-type: none"> • Depression • Anxiety • Bipolar • Psychosis • Substance misuse • Suicidality 	<ul style="list-style-type: none"> • IRR increased before and after onset of epilepsy
Fazel et al, 2013 (19)	<ul style="list-style-type: none"> • Depression • Alcohol abuse 	<p>Rates of psychiatric comorbidity after epilepsy diagnosis</p> <ul style="list-style-type: none"> • 5.5% • 3.6% <p>75% of those who died from external cause had a lifetime diagnosis of psych disease</p>
Mohanraj et al, 2006 (16)	<ul style="list-style-type: none"> • Self harm 	<ul style="list-style-type: none"> • Cause specific SMR of 2.62 for self harm in newly diagnosed epilepsy group
Fukuchi et al, 2002 (21)	<ul style="list-style-type: none"> • Post-ictal psychosis 	<ul style="list-style-type: none"> • Half of the suicide victims with epilepsy committed suicide during a period of post-ictal psychosis
St Germaine-Smith et al, 2011 (26)	<ul style="list-style-type: none"> • Depression • Alcohol abuse 	<p>Prevalence of comorbidities in epilepsy group</p> <ul style="list-style-type: none"> • 28.2% • 10.1% <p>No significant association with mortality.</p>

Table 5: A table showing which psychiatric disorders (including alcohol and drug abuse) were investigated and the contribution of these disorders in mortality in epilepsy and how prevalent they are in epilepsy patients. aRR (adjusted relative risk), OR (odds ratio), (SMR (standardized mortality ratio), IRR (incidence rate ratio).

The main psychiatric disorders investigated were depression, psychosis, anxiety, self-harm, drug and alcohol abuse, self-harm and suicidality (Table 4). There was an increased relative risk of psychiatric disorders in PWE; 4.33(22). St Germaine-smith et al found that in PWE, 28.2% had depression and 10.1% abused alcohol(26).

The most common psychiatric comorbidity found was depression(22,23,26). In PWE, a diagnosis of a psychiatric disorder was increased before and after the diagnosis of epilepsy compared with the general population - whether the psychiatric disorder was diagnosed before or after epilepsy onset did not impact significantly on mortality rates(19).

Special syndromes were found to have higher rates of comorbidities (81.3%) compared with unspecified, focal and generalized epilepsy (45.2%, 36% and 29.6% respectively)(19).

A comorbid psychiatric disorder in epilepsy was associated with external cause of mortality, suicide and non-vehicle accidents (aOR 3.5, 2.1 and 1.9 respectively)(19). There was no association between psychiatric comorbidity and death from neoplasm or neurological causes(19).

Those with a comorbid psychiatric disorder were shown to have a strong risk of committing suicide; the risk of suicide in PWE was 1.99 compared with 13.7 in PWE with a psychiatric disease(22). Additionally, analysis of patients with a psychiatric disease revealed that if patients also had epilepsy, the risk of suicide was increased (1.21)(22).

Mainio et al found that suicide victims with epilepsy were more likely to suffer from a psychiatric disease; 76% of PWE had a diagnosis of a psychiatric disorder compared with 43% of people without epilepsy(24). Nilsson et al found that in 27% of PWE whose cause of death was suicide had depression and 19% had depression and a history of abuse.

Fukuchi et al found that half of the epilepsy patients who committed suicide did so during a post-ictal psychotic episode(21).

One paper did not find a significant an association between psychiatric comorbidity and mortality(26).

Alcohol and drug disorders:

Fazel et al, 2013 (19)	56% of epilepsy patients who died from an external cause had a history of substance misuse
Ridsdale et al, 2011 (4)	Mortality in epilepsy associated with alcohol misuse OR 2.96
Christensen et al (22)	Risk of suicide in epilepsy patients who abuse alcohol RR 11.9
Nilsson et al, 1997 (17)	Cause of death: <ul style="list-style-type: none"> • Alcohol dependency syndrome SMR 24.6 • Alcohol psychosis SMR 22.5 • Drug dependency SMR 13.3
Nilsson et al, 2002 (23)	41% of male epilepsy patients who committed suicide were alcohol or drug abusers vs 60% in general population in Stockholm
Hesdorffer et al, 2012 (12)	Increase substance dependency and abuse before and after diagnosis of epilepsy
Mainio et al, 2007 (24)	NO contribution of alcohol to mortality
St Germaine- smith et al, 2011 (26)	Alcohol abuse not significantly associated with mortality.

Table 6: A table to show the contribution of alcohol and drug abuse disorders to mortality in epilepsy.
OR (odds ratio), RR (Relative Risk), SMR (Standardized Mortality Ratio).

Six papers reviewed found that alcohol or drug abuse was associated with mortality, especially suicide.

Nilsson et al found that the SMR was highest for patients with alcohol dependency syndrome and alcohol psychosis (24.6, 22.5 respectively)(17). Alcohol misuse was associated with nearly a three times increase in mortality rate(4) and Fazel et al found that alcohol abuse was associated with external cause of death; 56% of patients with epilepsy who died from an external cause abused alcohol(19).

St Germaine-Smith et al found that although 10.1% of PWE abused alcohol, this was not significantly associated with mortality(26). Nilsson et al 2002 found that in Stockholm individuals who commit suicide were more likely to abuse alcohol than PWE who commit suicide(23).

Non-adherence to medication:

Faught et al, 2008 (25)	Non-adherence with AED associated with a 3 fold increase in mortality
Tran et al, 2008 (27)	No fully compliant patients with epilepsy died during study vs 11% with low compliance.
Ridsdale et al, 2011 (4)	Not collecting medication for 91-182 days was associated with mortality OR 1.83

Table 7: A table to show the impact of non-adherence with anti-epileptic medication (AED) on mortality rates in epilepsy.

Of the 666,941 patient quarters investigated by Faught et al, 74% were associated with adherence and 26% with non-adherence. Non adherent quarters were associated with a three fold increase in mortality, even after controlling for adherence to other medication(25). Similarly, Ridsdale found

increased mortality rates in patients who did not collect their repeat prescription for anti-epileptic medication for 91-182 days (OR 1.83)(4). Tran et al found that there were no deaths in fully compliant patients, compared with one in the low complaint group (11%) and 19% of patients who dropped out of the program quickly(27).

Faught et al stated that if medication was not collected for over 180 days it was presumed that medication was no longer needed, possibly due to the patient achieving seizure freedom(25). They found that these patients had similar mortality rates to adherent patients(25).

Seizure control and the impact on mortality was investigated by Ridsdale et al who found that being seizure free (no seizures within the previous 12 months) was associated with a lower mortality rate (OR: 0.78)(4). Nilsson et al found that the relative risk of suicide was 4.3 when comparing patients who had >50 seizures a year versus being seizure free(23). Mohanraj et al showed that nearly all-excess mortality was found in patients who did not achieved seizure freedom; SMR 2.54 for patients not responding to treatment compared with 0.95 in those who had entered remission(16).

Discussion

In 2005, epilepsy and status epilepticus were considered the 6th cause of avoidable mortality in men when looking at standardized years of life lost(28). This study aimed to describe mortality rates in PWE and examine amenable causes of death.

In concordance with previous studies, overall mortality in PWE was increased compared with the reference population(16,17). It has previously been reported that patients with symptomatic epilepsy have the highest mortality rates and this was shown in four of the studies reviewed(16,18–20,23). The most common cause of death was due to the disease which caused the epilepsy(19). Major causes of death included neoplasm, cerebrovascular disease, SUDEP and external causes of death.

The SMR for suicide ranged from 3.17 to 5.80(17,21,22). This is consistent with a 2005 meta-analyses which found that suicide rates are increased in individuals with epilepsy, even though not all studies found an increase(29).

One study found that suicide rates were only increased in patients with TLE, and half of the suicides occurred during post-ictal psychosis(21). In TLE comorbid inter-ictal psychiatric symptoms are increased(30). When patients with TLE are administered the symptom checklist-90-revised questionnaire, they are shown to have significantly worse scores for phobic anxiety, anxiety, obsessive-compulsive and depression compared to controls, suggesting that patients with TLE may experience more emotional and behavioral distress(30). This may explain the increased suicide rate.

Two groups found that when psychiatric comorbidity and sociodemographic factors were adjusted for, the suicide rate remained elevated for PWE(22,23). In one study, epilepsy psychiatric outpatients from one of the five nationwide longitudinal registries, were only included in the last 2 years of the study(22). Psychiatric co-morbidity may therefore be under-represented in those who committed suicide. Also, patients with mild depression may not seek help and may treat their depression by non-conventional means. Both studies used large nationwide databases; therefore mild depression may not have been recorded, leading to under-representation of depression in those who committed suicide.

Alternatively, other psychological factors may be playing a role in suicide alongside psychiatric disorders including non-adherence and social factors such as lack of patient support or having

another chronic disease. Interestingly, Nilsson et al found that in PWE, having a concomitant medical disorder did not increase suicide risk(23).

Accidents were increased in PWE, particularly those with remote symptomatic epilepsy. In PWE who died due to an external cause of death, 75% had a comorbid psychiatric disease – 23% had depression and 56% had a substance-abuse disorder(19). Non-adherence also increased the risk of accidents(25).

PWE were found to have an increased lifetime risk of being diagnosed with a psychiatric disorder - depression being the most common disorder found. Newly diagnosed patients were more likely to self-harm compared with the general population - this may be due to the perceived loss of control after the diagnosis of epilepsy(16). Patients with chronic epilepsy were more likely to commit suicide(16). Suicidality was increased before and after the onset of epilepsy diagnosis and it was found that PWE were more likely to have previously attempted suicide compared with suicide victims in the general population(12).

Psychiatric disease increased the risk of external causes of death but it did not appear to be associated with other causes of death for example cerebrovascular disease and neoplasm(19), perhaps highlighting that deaths from suicide and accidents are the most preventable in epilepsy.

One study did not find a significant association between depression and mortality(26). This maybe because the follow-up time of this study was too short for depression to become severe enough, or that only a small number of depressed PWE in their study committed suicide.

The association between alcohol and mortality in epilepsy was controversial. There was evidence for alcohol and drug abuse being associated with increased mortality and suicide rates however St Germaine Smith et al did not find this.

Approximately 39% of PWE or non-febrile convulsions have been shown to be non-adherent to anti-epileptic medication and this rises to 43% in patients over the age of 65(31). This review found that non-adherence was associated with a three-fold increase in mortality rate in PWE, after adjustment for sex, age and medical comorbidities(25). Similarly, Ridsdale et al showed that not collecting a repeat prescription for 91-182 days was associated with increased mortality(4). Faught et al measured adherence by using the medication possession ration (MPR); an MPR 0.8 was the threshold for adherence(25). A systematic review found the MPR to be widely used in evaluating adherence and a MPR value of 0.8 is used to decided whether a patient is adherent or non-adherent(32).

African-American women over the age of 65 were associated with non-compliance compared with white, males aged 18-39(25). Patient factors generally involved in non-adherence appear to match these findings; non-white race, depression and having a chronic condition, however patients who are non-adherent are generally younger(33).

The patients involved in the study carried out in rural Laos experienced greater healthcare difficulties, however the effect of non-adherence on medication was still evident with those who were adherent having the greatest survival rate(27).

Seizure freedom was also shown to reduce mortality rates and having over 50 seizures per year was associated with an increased risk of suicide compared with those who had no seizures(4,23).

Although non-adherence was associated with mortality, papers did not explore if non-adherence increases a particular cause of death or if there is a connection between non-adherence and other psychological factors.

Some problems were noted with other studies reviewed. Nilsson et al(23) used a large epilepsy cohort, however all these patients had been hospitalized at least once because of epilepsy, which may mean that they had more severe or poorly controlled epilepsy compared with PWE in the general population.

The inclusion criteria for epilepsy in the study carried out by Nilsson et al(17) was only meant to include epilepsy patients with unprovoked seizures but a random survey of a group of these patients found that 21% of patients had symptomatic epilepsy, non-epileptogenic seizures or a single seizure (17). The results from Tran et al may not be able to be generalized to other populations, as the subjects in their trial experienced problems with access to health-care, which is not a major cause of non-adherence in western countries(27).

Additionally, it is difficult to compare the studies reviewed as it is unclear which screening tools for psychiatric disorders including alcohol and drug abuse were used.

After reviewing these papers it is still unclear whether a particular type of epilepsy is associated with mortality, or if certain types of epilepsy are more likely to be present alongside psychological factors. It is also unclear if there is a combined effect of different psychological factors on mortality rates in epilepsy. This needs further investigation in the future.

Due to the fact that different types of studies were reviewed, a screening tool could not be implemented to review these papers and determine their validity. This means that the strength of the evidence is unclear, so it is difficult to know whether the results obtained can be generalized to general populations.

Conclusion

In this study, increased rates of mortality have been described. Preventable causes of death appear to be those due to suicide and accidents. Psychological causes have been shown to contribute to increased rates of suicide and accidents. Psychiatric disorders and substance-abuse disorders are treatable disorders and treating these disorders should reduce suicide rates and accidental deaths. Non-compliance can be overcome through better patient education and reducing the stigma associated with epilepsy. Accidents can also be avoided through educating patients for example regarding safety measures and specialist epilepsy nurses have an important educational role.

Acknowledging the contribution of psychological causes to mortality in PWE may prevent some amenable causes of death.

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