# Medication Adherence, Utilisation of Healthcare Services and Mortality of Patients with Epilepsy on Opiate Replacement Therapy: A Retrospective Cohort Study

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## *Abstract*

**Introduction:** Substance misuse is not uncommonly recognized in people with epilepsy (PWE). Mortality is significantly greater in those with comorbid substance misuse but it remains unclear whether epilepsy care and management contribute to this. This cohort study aims to compare the rates of mortality in PWE receiving opiate replacement therapy (ORT) and PWE alone, as well as evaluate their medication adherence, levels of engagement with epilepsy services as currently delivered and utilisation of unscheduled hospital care.

**Material and Methods:** A 5-year historical cohort for PWE was identified and manually validated using electronic patient records registered with NHS Tayside. Overall incidence rates for mortality and contact with emergency health care services were calculated for PWE receiving ORT and PWE alone. Engagement with outpatient epilepsy services was also noted. Adherence to antiepileptic drugs (AEDs) was expressed in terms of medication possession ratio (MPR).

**Results:** Of the 1297 PWE attending a tertiary care epilepsy service, 68 (5.3%) PWE were receiving ORT. The mortality rate was significantly greater in PWE on ORT in comparison to PWE only (7.4% vs 1.7 %; $P<0.05$; relative risk of death: 4.34, 95% CI 1.19 to 15.7), as well as the incidence of emergency health care services contact being higher (24.5% vs 17.7%; $P<0.05$; incidence rate ratio: 1.39, 95% CI: 1.12-1.71). Poor adherence to AEDs was also more common in PWE on ORT (28.4% vs 23.5%; $P= 0.02$), as well as failure to engage with elective outpatient services (8.4% vs 3.0%; $P<0.05$; rate ratio 2.77, 95% CI: 1.86-4.1).

**Conclusion:** PWE on ORT are less likely to engage with elective epilepsy services as currently delivered or take AEDs as prescribed despite most of these patients having daily attendance at a community pharmacist. This may contribute to the significantly increased rates of mortality and unscheduled hospital care. Clinicians and policymakers should consider service redesign to meet the demands of this high-risk population in an attempt to reduce mortality and morbidity.

**Keywords:** epilepsy, opiate, methadone, mortality, adherence, antiepileptic drugs

## Introduction

Epilepsy is the most common chronic neurological disorder in the UK with approximately 400 000 affected[1]. Mortality has been shown to be consistently higher in people with epilepsy (PWE) compared to people without epilepsy and almost half of epilepsy-related deaths occur in those younger than 55 years old[2].

A number of physical and psychiatric comorbidities are more common in those with epilepsy in comparison to the general population[3-4]. Some individual comorbid conditions are associated with particularly poor outcomes, for example, comorbid substance misuse and dependency. In addition, the Scottish National Drug-Related Deaths database reported epilepsy as a documented comorbid medical condition in almost 12% of all drug-related deaths in 2012[5].

It is not clear why mortality rates in PWE and comorbid substance dependency are high and whether epilepsy care, engagement with epilepsy services or levels of adherence to antiepileptic drugs (AEDs) contribute. Poorer adherence to AEDs has consistently been shown to be associated with poorer outcomes in PWE[6] and it is conceivable that despite attending a community pharmacist regularly, PWE on opiate replacement therapy (ORT), in the form of Methadone, have lower rates of AED adherence. Demonstration of such would be an important finding allowing policymakers to consider novel methods of service delivery to reduce mortality and emergency healthcare use.

This study aimed to determine the frequency of ORT in a representative sample of PWE attending a tertiary care epilepsy service in the UK; describe the rates of mortality and contact with emergency health care services within this population in comparison to a matched population of PWE only; and evaluate medication adherence of these two groups, along with their levels of engagement with epilepsy services as currently delivered.

Abbreviations: people with epilepsy (PWE); antiepileptic drugs (AEDs); opiate replacement therapy (ORT); Community Health Index (CHI); medication possession ratio (MPR); Scottish Index of Multiple Deprivation (SIMD)

## Materials and Method

Each individual registered with a primary care practice in Scotland has a unique ten-digit community health index (CHI) number. This CHI number allows linkage of health-related datasets providing a unique electronic resource of information on aspects such as outpatient clinic attendances, hospital admissions, community dispensing drug data and mortality.

A 5-year historical cohort for PWE was identified and manually validated using electronic patient records registered with the regional health board area of NHS Tayside. Patients were included if they were over 16 years of age and attended an outpatient appointment with epilepsy services within the period of 1st January 2010 and 31st December 2015.

Overall incidence rates for mortality and contact with emergency health care services were calculated for PWE alone and for PWE in receipt of an ORT prescription for Methadone. Contact with emergency health care services included Emergency Department attendances, hospital admissions and out-of-hours contact.

Adherence status was evaluated using medication possession ratio and was considered in quarters (3 monthly). This allowed for adherence to change over time rather than applying the concept of fixed adherence during the entire study period. Poor adherence was defined as MPR of less than 80% to match previous large epidemiological studies[6]. Polytherapy was defined as more than one AED consistently prescribed for more than 180 days.

Engagement with epilepsy services was determined by attendance at outpatient clinics and information obtained from NHS Scotland outpatients datasets.

P-values were calculated using Chi-squared tests, for categorical data, and Student t-tests, for continuous data.

Socioeconomic status based on home postcode for each patient was also measured using Scottish Index of Multiple Deprivation (SIMD)[7]. PWE only and PWE on ORT were matched on the basis of age (+/- 5years), social class and gender. Each PWE on ORT was matched with 4 PWE only in the majority of cases.

## *Results*

*Basic demographics*

Between 1st January 2010 and 31st December 2015, 1297 PWE attended their regional centre for epilepsy. Of these, 68 (5.2%) PWE were receiving an ORT prescription for Methadone. Mean age at first clinic attendance was 36.4 years old for PWE only and 35.7 years old for PWE on ORT.

An unexposed (non-ORT) comparison group matched for age, gender and socioeconomic status was identified from the PWE only cohort (n=236). The baseline demographics features of the unexposed and exposed patients are summarised in Table 1.

| | | **Unexposed** PWE only | **Exposed** PWE on ORT |
|---|---|---|---|
| | | (n=236) | (n=68) |
| Gender | Male | 148 (62.7%) | 41 (60.3%) |
| | Female | 88 (37.3%) | 27 (39.7%) |
| Age range | 18 to 29 | 66 (28%) | 15 (22.1%) |
| | 30 to 39 | 78 (33.1%) | 32 (47.1%) |
| | >40 | 92 (39%) | 21 (30.9%) |
| SIMD | 1 | 130 (55.1%) | 40 (58.8%) |
| | 2 | 50 (21.2%) | 15 (22.1%) |
| | 3+ | 56 (23.7%) | 13 (19.1%) |

***Table 1. Demographic features: Unexposed (non-ORT) Vs Exposed (ORT) population.***

*Scottish Index of Multiple Deprivation (SIMD). Each decile contains 10% of Scotland's population. Decile 1: most deprived; decile 10: least deprived.*

*Follow-up*

The study cohort (n=304) generated 599 patient-years of follow up. Mean follow-up period for exposed (ORT) and unexposed (non-ORT) patients was similar (23.28 months for case vs 23.88 months for controls).

*Deaths*

The mortality rate of PWE on ORT was significantly greater than the PWE only group. During the follow-up period, there were 9 deaths. 5 of these deaths were identified in PWE on ORT (7.4%) and 4 in the PWE only group (1.7%); p-value<0.05; relative risk of death 4.34, 95% CI 1.19-15.7.

*Overall Adherence to AEDs*

2396 treatment quarters were included for analysis. PWE on ORT generated 522 treatment quarters during follow-up compared to 1874 for PWE only. Poor adherence (MPR<80%) was identified more commonly in PWE on ORT in comparison to the PWE only cohort: 148/522 (28.4%) vs 441/1874 (23.5%), respectively; p-value= 0.02.

At least one period of poor adherence was commonly identified in both groups: 41/68 (60.3%) in PWE on ORT vs 138/236 (58.5%) in PWE only.

*Contact with Emergency Health Care Services*

During the follow-up period, contact with emergency health care services was recorded in 461 treatment quarters. Of these, 128/522 (24.5%) were identified in PWE on ORT vs 331/1874 (17.7%) in the PWE only cohort**;** p-value<0.05; incidence rate ratio 1.39, 95% CI: 1.12-1.71.

*Engagement with Outpatient Epilepsy Services*

A failure to attend an elective outpatient appointment was identified in 101 treatment quarters. PWE on ORT failed to attend 44/522 (8.4%) vs 57/1874 (3.0%) for PWE only. Thus, the non-attendance rate within the exposed group was almost three times higher than the unexposed control group; p-value<0.05; rate ratio 2.77, 95% CI: 1.86-4.1.

*Polytherapy*

The majority of PWE received a single AED during the period of interest. The use of polytherapy was significantly lower in PWE on ORT compared to the PWE only group: 15/68 (22.1%) vs 107/236 (45.3%), respectively; p-value = 0.0006.

## Discussion

This study shows that PWE who are prescribed Methadone ORT are at significantly greater risk of death in comparison to PWE not on ORT. This higher risk cohort appears to engage less effectively with the current model of elective outpatient epilepsy services but utilise emergency health care services at a higher rate. Despite attending community pharmacist services regularly to collect their Methadone prescription (typically daily), PWE on ORT show lower rates of adherence to prescribed AEDs. This regular community contact may afford an opportunity for pharmacists, under the supervision of local clinicians, to consider co-dispensing AEDs to these patients when attending to collect their ORT. Such an initiative may improve AED adherence in this patient group and potentially reduce utilisation of emergency health care services and mortality.

This is the first study to use record linkage to explore AED adherence and clinical outcomes in this high-risk group. Despite selecting patients sequentially from a clinical service that covers a regional health board area, the prevalence of ORT reported here within a cohort of PWE is likely to represent an underestimate because clinic attendance was mandatory for inclusion. This method has almost certainly therefore, led to a selection bias with inclusion of a more stable population. Accordingly, this study is likely to have underestimated the adverse outcomes for PWE on ORT overall. We chose this approach however, for two reasons. First, we were keen to ensure diagnostic accuracy, including those with expert clinician-confirmed diagnoses of epilepsy. Second, we were keen to explore the outcomes in those who would be considered a relatively stable cohort having regular contact with healthcare professionals and thus, more

likely to be amenable to potential future interventions such as co-dispensing of prescribed Methadone and AEDs.

The high frequency of polytherapy within the PWE only cohort may suggest this unexposed population had a higher proportion of drug treatment refractory patients. If this explanation is correct, we may have expected to see a greater number of deaths and adverse events within this cohort and consequently, we may have also potentially underestimated the relative risk of adverse outcomes in the PWE on ORT cohort. In addition, it is unknown whether the lower rates of polytherapy seen in PWE on ORT reflect an active decision on the part of the responsible clinician or poor engagement with neurology services from this group in the form of irregular clinic attendance.

There are competing explanations to account for the increased mortality rate in the PWE on ORT cohort. The first is that a prescription of Methadone, in combination with AEDs, confers a greater risk of death. One could speculate that this may be the result of an increased QT interval, as many AEDS and Methadone can alter cardiac conduction, theoretically leading to a fatal arrhythmia[8, 9]; this requires further assessment. A further explanation could be that a "chaotic" lifestyle during periods of variable adherence to Methadone directly led to death. Finally, as we did not consider comorbidity, there remains a possibility that patients on Methadone have greater comorbidity, directly influencing mortality. Quantifying additional comorbidity and Methadone-related factors would have required an additional cohort consisting of Methadone only patients and much of the data required for this was not available.

## Conclusion

This study demonstrates that PWE on prescribed ORT have poor clinical outcomes, AED adherence and are less likely to engage with epilepsy services as currently configured and delivered. Clinicians and policymakers should

consider service redesign to meet the demands of this high-risk population in an attempt to reduce mortality and morbidity.

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