Assessing adherence-based quality measures in epilepsy

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Abstract

Objective. To examine the relationship of three alternative measures of adherence with seven negative outcomes associated with epilepsy for development of a quality measure in epilepsy.

Design. Retrospective cohort analysis.

Setting. PharMetrics national claims database.

Participants. Patients in the PharMetrics database for the years 2004–08 taking antiepileptic drugs.

Intervention. None.

Main Outcome Measures. For each definition of adherence, the odds ratios (ORs) comparing non-adherent with adherent groups were assessed for consistency and direction for the number of hospital admissions, emergency room (ER) visits, head injuries including traumatic brain injuries, falls, motor vehicle accidents (MVAs), fractures and a ‘seizure’ outcome defined as hospital admissions or ER visits with a primary diagnosis of epilepsy or convulsions.

Results. The inclusion criteria were met by 31,635 individuals. In the multivariate analysis, the adherent group had lower odds of hospital admissions with ORs for the eight specifications ranging from 0.729 to 0.872 and ER visits where ORs for the eight specifications ranged from 0.750 to 0.893. The eight ORs for head injuries ranged from 0.647 to 0.888. For fractures, the ORs ranged from 0.407 to 0.841. Our proxy for seizure was inconsistently associated with adherence status.

Conclusions. All the adherence measures defined non-adherent groups that were associated with negative outcomes in epilepsy.

Keywords: quality management, quality indicators, measurement of quality, epilepsy, quality of care

Introduction

The Institute of Medicine has defined quality as ‘the degree to which health care services increase the likelihood of the desired health outcomes’ [1]. Health-care quality measures, consistent with the Institute of Medicine definition, can be defined to improve quality or performance. The purpose of this article is to define measures that could be used to improve the quality of care by measuring prescription drug utilization and possible undesirable outcomes in epilepsy.

Epilepsy is one of the most common neurologic disorders, affecting an estimated 2.1–2.7 million persons in the USA [2, 3], and costs approximately $15.5 billion in medical costs and lost or reduced earnings and productivity each year [3]. The majority of people with epilepsy are able to manage their condition by using one or more pharmacological therapies [4]. Previous studies have reported that ~30–60% of patients with epilepsy are non-adherent to their prescribed antiepileptic drug (AED) therapy [5, 6]. In a patient survey, more than 70% of respondents reported AED dose omission [7]. In addition, some results have suggested that poor adherence is associated with higher risk of seizures [8], increases in medical resource utilization and costs [5] and severe clinical consequences, including increased risk of death [9].

There are no widely adopted health-care quality measures for the management of a population with epilepsy. Organizations that endorse health-care quality measures may rely on researchers to generate and publish evidence on the performance of candidate metrics as quality measures. In a
population with epilepsy, the performance of an adherence-based quality measure could be assessed as its ability to define a non-adherent cohort with a greater likelihood of negative outcomes than the complementary adherent cohort. While adherence is only a proxy for actual patient outcomes, quality improvement efforts in epilepsy could be assessed by their effect in reducing the non-adherent population of patients with epilepsy.

A number of studies have documented an association between adherence and negative outcomes in epilepsy. Manjunath et al. [8] demonstrated that the hazard ratio for subsequent seizure with adherence measured using the medication possession ratio (MPR) was 0.83 (Manjunath's estimated hazard ratio has been inverted, since results are being reported relative to non-adherence throughout this article). A small study of 54 patients showed an association between seizure control and adherence measured on the Morisky scale [6]. In addition, a postal survey noted an 11% ($P = 0.10$) higher risk of seizure after a missed dose [7]. Davis et al. [10] demonstrated that non-adherence measured by the MPR was associated with approximately an 11% increased likelihood in hospitalizations, a 48% increased likelihood of admission to the emergency room (ER) and a 44% increased annual likelihood of injuries in motor vehicle accidents (MVAs). In an analysis of Medicaid data from three states, Faught et al. [9] demonstrated that poor adherence measured by the proportion of days with possession of at least one AED, typically referred to as proportion of days covered (PDC), resulted in a 50% increase in ER visits, an 86% increase in hospitalizations, a 108% increase in MVAs and a 21% increase in fractures.

Measurement of adherence to medication therapy is not standardized. In a 2006 review, Hess et al. [11] identified 11 different measures of medication adherence. The measures of adherence used in four separate articles specific to AED therapy are summarized in Table 1.

<table>
<thead>
<tr>
<th>Author</th>
<th>Numerator</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al. (2008) [10]</td>
<td>Sum of days supply</td>
<td>Days between the first AED prescription and expiration of the days’ supply of the last observed AED refill</td>
</tr>
<tr>
<td>Faught et al. (2008) [9]</td>
<td>Days in quarter with at least one AED in possession</td>
<td>Days in quarter</td>
</tr>
<tr>
<td>Ettinger et al. (2009) [13]</td>
<td>Sum of days supply</td>
<td>Days between the first AED prescription and expiration of the days’ supply of the last observed AED refill</td>
</tr>
<tr>
<td>Manjunath et al. (2009) [8]</td>
<td>Sum of days supply in cumulative period assessed every 30 days</td>
<td>Days in cumulative period assessed every 30 days</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug.

**Methods**

**Data source**

The data set for this retrospective analysis was the PharMetrics Patient-Centric Database (IMS Health, Norwalk, CT, USA) of claims from more than 90 different managed care organizations representing more than 55 million lives. The study data set encompassed claims with dates of service from 1 September 2003 through 30 September 2008.

**Patient identification**

Study patients were identified during the identification period, 1 March 2004 to 30 September 2007. The index date was defined as the date of the first AED pharmacy claim during the identification period with enrollment 6 months before and 12 months after the index date. The AED drugs were identified using the generic name field in the Pharmetrics data base. The definitions of study time periods are shown in Fig. 1. Patients were required to be at least 18 years old of age on the index date (no upper age limit) with at least one medical claim with any diagnosis of epilepsy (ICD-9 codes 345.xx) (in any of the four diagnosis fields) in the 6-month period prior to or on the index date. Patients had to have at least two AED pharmacy claims on separate dates and at least 60 days supply for products identified by the generic names for AED drugs (Table 2) during the study time frame. Only patients who were continuously enrolled for at least 6 months prior to the index date and continuously eligible for 12 months after the index date (follow-up period) were included in the study (Fig. 2).
Adherence measures

After reviewing the existing literature for epilepsy and adherence, three types of adherence measures were selected: PDC, MPR and gaps in therapy.

Proportion of days covered

The PDC was defined as the number of unique days with AED therapy in the 365 days after the index date divided by 365. Each day on which the patient had possession of an AED was counted as 1 day of possession, even for patients with multiple AED therapies.

\[
PDC = \frac{\text{Number of days with AED therapy}}{365}
\]

Medication possession ratio

The MPR has widely divergent meanings in the literature. We defined the MPR as the sum of the days supplied from all AED prescriptions within 365 days after the index date divided by 365. When the days supplied overlapped the 365th day, the days supplied were only counted until the 365th day. When patients were on more than one product in the studied category, the MPR could have exceeded 1.0 and was truncated at 100% [12].

\[
MPR = \frac{\sum \text{Days supplied}}{365}
\]

Gap in therapy

Gap in therapy was defined as a period without drug supply, measured as the days between a prescription fill date and the number of days supplied and the date of the next prescription fill. For example, if an individual received a 30-day supply on 15 March, but no further drug supplies until 1 May, the gap in therapy would be 17 days.

These three types of adherence measures can be used to assign adherence status to a given patient, given an adherence threshold. In this study, PDC and MPR were examined at thresholds of 70, 80 and 90%, while the gaps in therapy measure were examined for threshold gaps of 15 and 30 days. The associated population level measure for each of these definitions was the percentage of patients with adherence rates above the threshold percentage (MPR and PDC) or without gaps in therapy at or exceeding the gap threshold.

Outcome measures

In this article, the following seven negative outcomes associated with epilepsy were studied: hospital admissions; ER visits; head injuries, including traumatic brain injuries (TBIs); fractures, falls, MVAs and a proxy measure for seizure. Medical claims were analyzed for the presence of these outcomes. Hospital and ER visit outcomes were assessed independent of diagnosis [i.e. they were not limited to claims with a diagnosis of epilepsy (ICD-9 codes 345.xx) or seizure (ICD-9 codes 780.3x)]. All claims were searched for the following codes. Head injuries (including TBI) were defined as ICD-9 codes 800–804, 850–854, 873 and 959.01 [9]. MVAs were defined as ICD-9 code E810.0–E825 and fractures were defined as ICD-9 codes 800–829 [9]. Falls were defined as ICD-9 codes E880.0–E886.9 [10]. A proxy for
A difference of proportions test was used to compare the likelihood of each outcome based on adherence. This difference in proportions test was repeated for all eight definitions.
of adherence (MPR 70%, MPR 80%, MPR 90%, PDC 70%, PDC 80%, PDC 90%, gaps in therapy of 15 days and gaps in therapy of 30 days). Univariate odds ratios (ORs) and the 95% confidence intervals for each comparison of adherent to non-adherent patients were calculated.

To further examine how performance of the adherence measures was influenced by covariates, logistic regression models for four bivariate outcomes (hospital admissions, ER visits, proxy for seizure and accidents/injuries) were constructed, controlling for potentially influential covariates, such as age, gender, Deyo-adapted Charlson comorbidity index, comorbidities, including neurotic disorder, brain tumor, depression and dementia, type of insurance, defined as either commercial, Medicare, Medicaid or self-insured. Because the samples for head injuries, fractures, falls and MVAs were too small to construct separate models, they were collapsed into an outcome defined as accident/injury. ORs were once again generated for the eight definitions of adherence under consideration. No adjustments were made for multiple comparisons. We did not correct for multiple comparisons which, in this case, would simply expand the size of the confidence intervals of each point estimate.

Results

The application of study criteria to create the final study population is depicted in Fig. 2. After applying the criteria for eligibility, diagnosis and AED use, 31,635 patients were included in the study population.

The mean age of the population was 47.4 years, and 31.7% of the population was aged 18–39 years. Females comprised 56% of the population. The most commonly used AED was phenytoin, with 34.4% of the patients filling at least one prescription for that product, followed by carbamazepine (22.9%), and levetiracetam (20.5%). On average, patients filled prescriptions for 1.68 different AED products, with 63.7% exposed to only one product during the study period. The average number of prescriptions filled per patient in the 12-month follow-up period was 7.53. More than one-third (37.1%) of the population had a mental health diagnosis. Common mental health comorbidities included neurotic disorders (8.7%), depressive disorder (7.5%) and affective psychoses (7.1%). More than 17% of the population had scores ≥3 (range, 0–18) on the Deyo-adapted Charlson comorbidity index.

The mean adherence in terms of MPR was 84.3% across the study population. Using PDC, the mean adherence was 78.9%. Approximately half of the population (49.8%) had at least 1 gap of 15 days or more without AED therapy. Nearly, one-third (30.8%) had at least 1 gap of 30 days or more without AED therapy.

The univariate ORs for the seven outcome measures are shown in Table 3. ORs of <1.0 are consistent with the hypothesis that adherence is associated with a reduced likelihood of negative outcomes. The probability of admissions and ER visits was lower for all eight of the adherence measure definitions. The odds of head injuries and fractures were significantly lower for adherent patients defined by the two gaps in therapy measures and by all three PDC measures. For falls, MVAs and the proxy for seizure, no consistent pattern across the measures was observed.

Table 4 reports the adjusted ORs and 95% confidence intervals for negative outcomes between adherent and non-adherent patients using multivariate logistic regression.

For the outcomes of hospital admissions and ER visits, all ORs are <1.0, indicating reduced likelihood of the event for adherent patients. For accidents/injuries, adherence is again directionally associated with lower rates of accidents and injuries across all adherence measures. Some of the confidence intervals include one making it less certain that adherence is associated with a better outcome. For the seizure proxy outcome, directionally unexpected ORs were seen and the confidence intervals crossed 1.0 for all of the measures except the MPR measures.

Discussion

Previous work has found that poor adherence with AED therapy is associated with adverse clinical events [8–10, 13]. This article illustrates that the choice of adherence measures has implications for quality improvement purposes. These measures are consistent with those developed by the Pharmacy Quality Alliance (PQA) for β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, biguanide, sulfonylurea, thiazolidinedione and statins [14]. The PQA measures use the PDC and a single gap of ≥30 days.

Hundreds of articles in Pubmed have assessed adherence measures and many have examined single measures of adherence as predictors of adverse events. Only a few have compared measures within a single disease as predictors of adverse outcomes. Martin et al. [15] found that for evaluating medication class effects in schizophrenic patients, the PDC and the MPR were similar, with the biggest differences in patients who switched drugs within a class. Weiden et al. [16] in another study of schizophrenia found that all measures of non-adherence, including gaps in therapy of as little as 10 days and MPR were correlated with increased risk of hospitalization. In diabetics, Karve et al. [17] compared eight measures, including the MPR, gaps in therapy and PDC as predictors of hospitalization among diabetics and found that the MPR and PDC out-performed other measures in predicting the likelihood of hospitalization. Vink et al. [18] found little difference between gaps and therapy >30 days and MPR above 80% for diabetics.

This article compared the association of several adherence measures, using different thresholds, to examine possible outcomes. We find some differences in the associations across measures. Previous work has mainly focused on a single adherence measure, without consideration of different thresholds. The use of a standard 80% threshold, as is common in the literature, is often unsupported by evidence in a given therapeutic area. In this study, multiple thresholds were examined for each type of adherence measure. In the
### Table 3 Univariate ORs of the relationship between medication adherence and epilepsy-related outcomes (n = 31,635)

<table>
<thead>
<tr>
<th></th>
<th>15-day gap</th>
<th>30-day gap</th>
<th>MPR 70%</th>
<th>MPR 80%</th>
<th>MPR 90%</th>
<th>PDC 70%</th>
<th>PDC 80%</th>
<th>PDC 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission</strong></td>
<td>0.707 (0.665, 0.752)</td>
<td>0.746 (0.700, 0.795)</td>
<td>0.498 (0.466, 0.532)</td>
<td>0.747 (0.700, 0.797)</td>
<td>0.801 (0.753, 0.853)</td>
<td>0.650 (0.609, 0.694)</td>
<td>0.641 (0.603, 0.682)</td>
<td>0.648 (0.609, 0.690)</td>
</tr>
<tr>
<td><strong>ER visits</strong></td>
<td>0.683 (0.648, 0.719)</td>
<td>0.700 (0.662, 0.739)</td>
<td>0.465 (0.439, 0.493)</td>
<td>0.761 (0.720, 0.805)</td>
<td>0.811 (0.770, 0.855)</td>
<td>0.674 (0.638, 0.713)</td>
<td>0.684 (0.649, 0.721)</td>
<td>0.690 (0.655, 0.727)</td>
</tr>
<tr>
<td><strong>Head injuries, including TBIs</strong></td>
<td>0.719 (0.546, 0.946)</td>
<td>0.647 (0.490, 0.854)</td>
<td>0.744 (0.549, 1.008)</td>
<td>0.804 (0.603, 1.073)</td>
<td>0.888 (0.673, 1.171)</td>
<td>0.679 (0.510, 0.903)</td>
<td>0.688 (0.524, 0.904)</td>
<td>0.649 (0.489, 0.862)</td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td>0.594 (0.290, 1.215)</td>
<td>0.979 (0.463, 2.068)</td>
<td>1.022 (0.442, 2.365)</td>
<td>1.217 (0.547, 2.711)</td>
<td>1.015 (0.496, 2.077)</td>
<td>0.697 (0.336, 1.446)</td>
<td>0.575 (0.287, 1.149)</td>
<td>0.387 (0.174, 0.863)</td>
</tr>
<tr>
<td><strong>MVAs</strong></td>
<td>0.707 (0.224, 2.229)</td>
<td>1.335 (0.361, 4.932)</td>
<td>0.572 (0.172, 1.901)</td>
<td>0.568 (0.180, 1.790)</td>
<td>0.853 (0.271, 2.687)</td>
<td>0.511 (0.162, 1.611)</td>
<td>0.575 (0.185, 1.783)</td>
<td>0.388 (0.105, 1.432)</td>
</tr>
<tr>
<td><strong>Fractures</strong></td>
<td>0.466 (0.356, 0.669)</td>
<td>0.529 (0.411, 0.681)</td>
<td>0.796 (0.598, 1.058)</td>
<td>0.841 (0.643, 1.099)</td>
<td>0.777 (0.603, 1.000)</td>
<td>0.653 (0.503, 0.849)</td>
<td>0.591 (0.460, 0.760)</td>
<td>0.407 (0.305, 0.541)</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>0.844 (0.740, 0.962)</td>
<td>0.931 (0.810, 1.070)</td>
<td>1.283 (1.084, 1.517)</td>
<td>1.348 (1.156, 1.572)</td>
<td>1.502 (1.302, 1.734)</td>
<td>1.013 (0.874, 1.175)</td>
<td>0.924 (0.808, 1.056)</td>
<td>1.005 (0.882, 1.146)</td>
</tr>
</tbody>
</table>

ER, emergency room; MPR, medication possession ratio; MV A, motor vehicle accident; PDC, proportion of days covered; TBI, traumatic brain injury.

### Table 4 Multivariate associations between medication adherence and epilepsy-related outcomes (n = 31,634*)

<table>
<thead>
<tr>
<th></th>
<th>15-day gap</th>
<th>30-day gap</th>
<th>MPR 70%</th>
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<th>PDC 70%</th>
<th>PDC 80%</th>
<th>PDC 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admissions</strong></td>
<td>0.775 (0.725, 0.827)</td>
<td>0.808 (0.755, 0.866)</td>
<td>0.796 (0.739, 0.857)</td>
<td>0.822 (0.767, 0.882)</td>
<td>0.872 (0.816, 0.932)</td>
<td>0.739 (0.689, 0.793)</td>
<td>0.729 (0.682, 0.779)</td>
<td>0.741 (0.693, 0.792)</td>
</tr>
<tr>
<td><strong>ER visits</strong></td>
<td>0.750 (0.710, 0.793)</td>
<td>0.764 (0.721, 0.809)</td>
<td>0.831 (0.780, 0.866)</td>
<td>0.852 (0.803, 0.903)</td>
<td>0.893 (0.844, 0.944)</td>
<td>0.780 (0.735, 0.828)</td>
<td>0.789 (0.746, 0.835)</td>
<td>0.793 (0.750, 0.838)</td>
</tr>
<tr>
<td><strong>Accidents/ injuries</strong></td>
<td>0.639 (0.521, 0.785)</td>
<td>0.676 (0.553, 0.826)</td>
<td>0.897 (0.716, 1.123)</td>
<td>0.934 (0.756, 1.154)</td>
<td>0.928 (0.759, 1.134)</td>
<td>0.770 (0.625, 0.948)</td>
<td>0.757 (0.620, 0.924)</td>
<td>0.593 (0.478, 0.736)</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>0.917 (0.803, 1.046)</td>
<td>1.003 (0.871, 1.155)</td>
<td>1.431 (1.207, 1.697)</td>
<td>1.493 (1.278, 1.746)</td>
<td>1.640 (1.418, 1.895)</td>
<td>1.158 (0.997, 1.347)</td>
<td>1.051 (0.916, 1.205)</td>
<td>1.138 (0.996, 1.300)</td>
</tr>
</tbody>
</table>

ER, emergency room; MPR, medication possession ratio; PDC, proportion of days covered. Covariates: age, gender, Charlson comorbidity index, region (Northeast, South, Midwest, West), payment type (commercial, Medicare, Medicaid, self-insured, other), plan type (HMO, PPO, POS, other), number of concomitant drugs excluding anti-seizure medications (classes include antianxiety, antidepressants, antimania, antipsychotics, and mood stabilizers), number of comorbidities, provider speciality or primary care, time from diagnosis to index date.

*One patient with missing gender was excluded from the multivariate analysis.
univariate analysis of the two most tangible outcomes, hospital admissions and ER visits, varying the adherence threshold level for MPR resulted in significantly different likelihood of adverse clinical outcomes. As the MPR threshold defining the adherent population rose from 70 to 80% to 90%, the likelihood of adverse outcome of the adherent group, while still lower than its associated non-adherent group, increased relative to that non-adherent group. In other words, the difference in the likelihood of these negative events was more apparent when comparing populations with MPR < 70% with those with MPR ≥ 70% than it was when comparing populations with MPR < 90% with those with MPR ≥ 90%. The PDC and gaps in therapy measures did not have any pattern of statistically significant ORs in response to varying thresholds.

These results can be used by organizations seeking to track the quality of care in their populations with epilepsy or by agencies responsible for endorsing quality measures. Other considerations for optimal quality measures, such as complexity of calculation and ease of interpretation, were not addressed here.

All of the adherence measures at all levels are in the expected direction, but the measures vary in the strength of their association with less common events. Narrow confidence intervals, indicating stronger measures, were found for admissions, ER visits, head injuries and fractures. For the latter two outcomes, the confidence intervals were wider for the MPR, indicating that these are not as strongly associated with these outcomes. This is probably because of the small number of events in these outcomes. For seizures and falls, the MPR measures are not in the expected direction and the confidence intervals for all measures are large. In the case of falls, this is because of the small number of observed events. In the case of seizures, it is likely because diagnostic coding is insufficient to differentiate between new onset seizures and a history of seizures, making the outcome measure itself unreliable.

**Limitations**

There are a number of limitations that must be kept in mind when interpreting the results of this study. First, the associations between adherence and outcomes reported from this retrospective analysis cannot be assumed to be causal. Despite the incorporation of multivariate analysis, there may be other explanatory factors unobservable through claims data. Secondly, while claims data are a reliable measure of prescription refill behavior, they may not accurately reflect adherence in terms of actual medication-taking behavior. In particular, adherence will be overstated using MPR if patients are on multiple concomitant AEDs. Thirdly, the selected outcomes of interest in epilepsy could only be approximated using claims data, recognizing that actual clinical outcomes, such as the occurrence of seizures, are not reliably observable in these data. Until linkable electronic medical records containing full text from all payers—health insurance, automobile insurance and worker’s compensation—are developed, it will never be possible to fully ascertain seizure outcomes.

Using proxy measures means we assume that incorrect ascertainment of outcomes is not correlated with the types of measures. Finally, these adherence-based quality measures only report on an intermediate process outcome, not an actual clinically measured outcome. Until available databases and reporting systems allow more sophisticated measurement, proxy measures such as these are the only alternative. Fifthly, since we performed a cross-sectional analysis, we did not assess the timing of non-adherence relative to possible events. This would be very difficult to implement in a quality measure.

**Conclusion**

This article explores the performance of different population-level measures of adherence in epilepsy for use as quality measures. Both PDC and gaps in therapy produced significant adjusted ORs in the expected direction for the negative outcomes of admissions, ER visits, head injuries and fractures. More research needs to be conducted on the dynamics of MPR in epilepsy, given the results observed here and the recognized bias in MPR for cases of concomitant AED therapy.

**Conflict of interest**

M.D. and J.F. are employed by Ortho-McNeil Janssen Pharmaceuticals. M.J.G. and D.I.B. have conducted projects funded by the pharmaceutical industry.

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