Appendix e-1: Search Strategy, Quality Assessment, and Statistical Analysis

The search strategy was designed by a PhD-trained clinical investigator with relevant domain expertise (DNT) and the co-director of the Johns Hopkins Evidence-based Practice Center with extensive experience in systematic reviews (KAR). We searched MEDLINE via PubMed for English-language articles, using the following strategy:

((vertigo[mh] OR vertig*[tiab] OR dizziness[mh] OR dizz*[tiab]) AND (epilepsy[mh] OR epileps*[tiab] OR epilept*[tiab] OR seizure*[tiab] OR convuls*[tiab]) AND eng[la])

Our search was up to date through April 1, 2014. We also performed a manual search of reference lists from eligible articles. Due to resource constraints, we did not seek to identify research abstracts from meeting proceedings or unpublished studies, nor non-English language studies. Where appropriate, we attempted to contact authors regarding study details.

All identified articles were subject to title and abstract screening by two independent reviewers (AAT, SL). Articles were selected using pre-determined criteria. These criteria *excluded* papers that lacked original patient data, did not indicate any symptom data about dizziness or vertigo had been recorded, did not indicate any symptom data about seizures or epilepsy had been recorded, reported on dizziness or vertigo as side-effects of drug treatment trials in patients with seizures or epilepsy or were considered inappropriate for other (various) reasons. Note that studies reporting on dizziness or epilepsy in children (i.e., patients aged less than 18 years) and single case reports or case series with less than 5 patients were also potentially eligible.

Full-text screening was applied to all abstracts considered eligible or possibly eligible by at least one reviewer (i.e., labeled “yes” or “maybe” in the abstract review). Two independent reviewers (AAT, SL) identified whether full-text manuscripts were eligible and

provided a reason for exclusion. A third reviewer (DNT) verified the eligibility of selected articles and settled any discrepancies in selection status and reasons for exclusion. One unmasked rater (AAT) assessed the strength of the association between dizziness / vertigo and seizures / epilepsy (see Table 1 in the main manuscript) to identify cases with epileptic vertigo or dizziness in the included studies; a second unmasked rater (DNT) verified the strength of the reference standard.

Information abstracted from each article included study type, number of vertiginous / dizzy subjects, number of subjects with seizures / epilepsy, inclusion criteria, and study site. For each study, we extracted which diagnostic tests were used in the evaluation of the dizzy patient and in the patient with seizures and in what fraction of patients this test was positive and negative. If a study used data from a diagnostic test as an inclusion criterion or as part of the reference standard for diagnosis, that study was excluded from the analysis for that variable so as to avoid selection or diagnostic inclusion bias. For example, if a study included only patients with EEG-confirmed seizures that had seizure-related dizzy spells, then EEG results from this study were not considered when determining the fraction of EEG-confirmed epileptic vertigo or seizures.

Data were handled in EndNote X (Thomson Reuters, NY) and Microsoft Excel 2010 (Redmond, WA).

Search Results

Our search identified 1137 unique citations, of which 1004 were excluded at the abstract level (see flow diagram below for details in the search strategy). We did not require concordance on reason for abstract exclusion, but, of concordant codings (66.8%, n=671), exclusions were for the following reasons: 32% lacked original patient data; 1% did not indicate any symptom data about dizziness / vertigo had been recorded; 8% did not indicate

any symptom data about seizures / epilepsy had been recorded; 43% reported on dizziness or vertigo as side-effects of drug treatment trials in patients with seizures or epilepsy; and 17% were considered inappropriate for other reasons.

We sought to examine 133 full articles. At this step, the exclusion criterion "other" was replaced by the cause "no link between seizures and dizziness". This takes into account that in a given study both seizures and dizziness / vertigo may be reported, however, these symptoms may either not occur in the same patient or may have occurred at different times. After initial screening, there were 7 disagreements about study inclusion (kappa 0.89), and 2 disagreements on the reason for exclusion (kappa 0.96). These were settled by adjudication and discussion with the third reviewer. After final full-text review, 69 articles were excluded. The most common reason for exclusion was failure to provide a link between seizures and dizziness (70%, n=48), but other reasons for exclusion were as follows: lacked original patient data (17%, n=12); no symptom data about dizziness / vertigo provided (1%, n=1); no symptom data about seizures / epilepsy provided (9%, n=6); dizziness or vertigo reported as side-effects of drug treatment trials in patients with seizures or epilepsy (3%, n=2). A review of the bibliography of the selected 64 articles identified another 19 articles that met the inclusion criteria. Note that for clarity one article was disaggregated (increasing the number of selected articles to 65) as it reported on two independent study groups with different inclusion criteria (being seizures in the first and dizziness / vertigo in the second).[1] In total 83 articles reporting data from 84 studies were eligible. Eligible articles represented 7.2% of the total (n=1137) articles. These 83 articles reporting on data from 84 studies involved 11354 patients and described diagnoses in unselected dizzy patients or patients with seizures / epilepsy. In these 84 studies, the strength of association between the dizzy spells and seizures / epilepsy was determined (see Table 1 in the main manuscript).

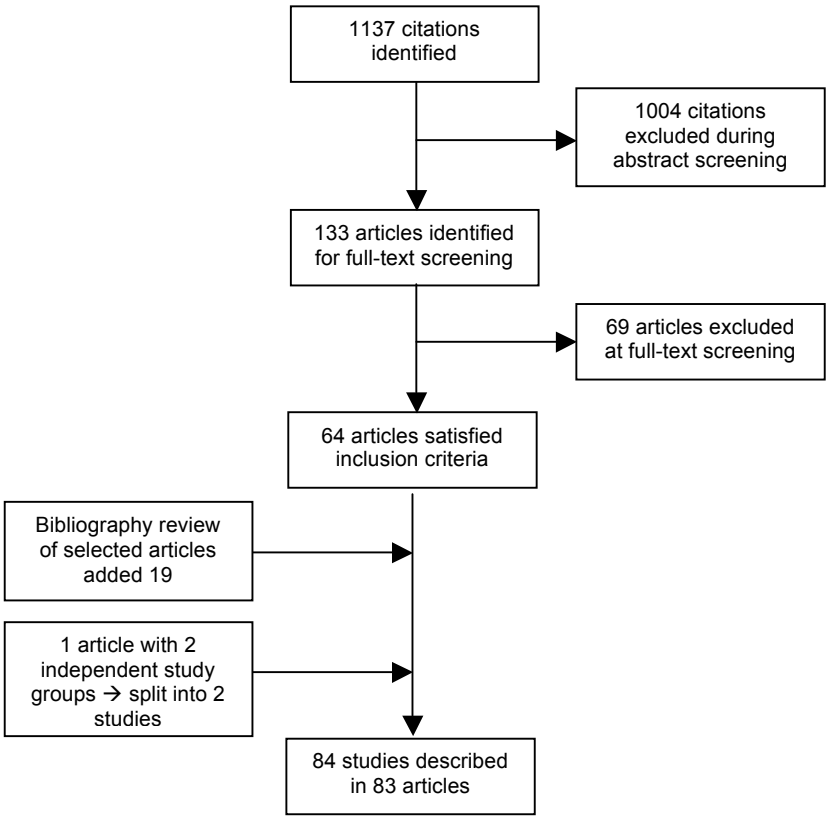
Comparison of studies with high or medium EEG quality vs. studies with low EEG quality

All studies were rated regarding their quality of EEG recordings, defining four groups: a) ictal EEG in all study participants, b) ictal or interictal EEG in all study participants, c) any EEG in some study participants, d) no EEG at all. Studies were assigned to one of two subgroups according to the quality of EEG recordings: in case all participants of a study received an EEG recording (a), the study was rated as high (ictal EEG in all participants) or medium (ictal or interictal EEG in all participants (b)). If EEG was available only in some (c) or none (d) of the study participants, the study was rated as low. To assess for a bias based on low study quality key factors such as the fraction of EVD patients and the seizure location were compared. We found the fraction of patients with ni-EVD (8.0% vs. 9.0%; high/medium EEG quality vs. low EEG quality) and i-EVD (1.5% vs. 0.1%) to be comparable in both groups. Similarly, a temporal lobe seizure focus was found at similar rates in both groups (81.7% vs. 87.5%, high/medium EEG quality vs. low EEG quality). These results suggest that including the group with low quality EEG testing is probably not biasing our results appreciably.

Definitions of "vertigo" and "dizziness" provided in the selected studies

Definitions for *vertigo* could be retrieved from 7 studies with a total of 304 patients (2.7%). Compared to the most recently published consensus definitions for vertigo and dizziness[2], these studies provided brief definitions only, referring to a false sense of *rotational* self-motion[3-7] or a *spinning*[8] or turning[9] sensation. Definitions for *dizziness* were provided in 2 studies (2 patients [0.2%])[5, 10] and, again, compared to current consensus definitions by Bisdorff and colleagues[2] remained vague, referring either to absence of *rotational vertigo*[5]

Flow diagram indicating selection of articles



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