Using common genetic variants to find drugs for common epilepsies

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Better drugs are needed for common epilepsies. Drug repurposing offers the potential of significant savings in the time and cost of developing new treatments. In order to select the best candidate drug(s) to repurpose for a disease, it is desirable to predict the relative clinical efficacy that drugs will have against the disease. Common epilepsy can be divided into different types and syndromes. Different antiseizure medications are most effective for different types and syndromes of common epilepsy. For predictions of antiepileptic efficacy to be clinically translatable, it is essential that the predictions are specific to each form of common epilepsy, and reflect the patterns of drug efficacy observed in clinical studies and practice. These requirements are not fulfilled by previously published drug predictions for epilepsy. We developed a novel method for predicting the relative efficacy of drugs against any common epilepsy, by using its Genome-Wide Association Study summary statistics and drugs’ activity data. The methodological advancement in our technique is that the drug predictions for a disease are based upon drugs’ effects on the function and abundance of proteins, and the magnitude and direction of those effects, relative to the importance, degree and direction of the proteins’ dysregulation in the disease. We used this method to predict the relative efficacy of all drugs, licensed for any condition, against each of the major types and syndromes of common epilepsy. Our predictions are concordant with findings from real-world experience and randomized clinical trials. Our method predicts the efficacy of existing antiseizure medications against common epilepsies; in this prediction, our method outperforms the best alternative existing method: area under receiver operating characteristic curve (mean ± standard deviation) 0.83 ± 0.03 and 0.63 ± 0.04, respectively. Importantly, our method predicts which antiseizure medications are amongst the more efficacious in clinical practice, and which antiseizure medications are amongst the less efficacious in clinical practice, for each of the main syndromes of common epilepsy, and it predicts the distinct order of efficacy of individual antiseizure medications in clinical trials of different common epilepsies. We identify promising candidate drugs for each of the major syndromes of common epilepsy. We screen five promising predicted drugs in an animal model: each exerts a significant dose-dependent effect upon seizures. Our predictions are a novel resource for selecting suitable candidate drugs that could potentially be repurposed for each of the major syndromes of common epilepsy. Our method is potentially generalizable to other complex diseases.
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**Abbreviations:** AC score = abundance correction score; ASM = antiseizure medication; CAE = childhood absence epilepsy; FAM score = function and abundance modulation score; FE = focal epilepsy; FM score = function modulation score; GE = generalized epilepsy; GWAS = Genome-Wide Association Study; HS = hippocampal sclerosis; ILAE = International League against Epilepsy; JME = juvenile myoclonic epilepsy; ROC = area under receiver operated characteristics curve

**Introduction**

A total of 50 million people are affected by epilepsy. Current drug treatments for epilepsy fail to control seizures in \(\sim30\%\) of patients\(^1\) and cause adverse effects in \(\sim88\%\) of patients\(^2,3\); \(\sim20\%\) of people with newly diagnosed epilepsy discontinue their first antiseizure medication (ASM) because of intolerable adverse effects.\(^6\) Hence, there is a need for new ASMs with higher efficacy and/or lower toxicity. Drug repurposing—treating a disease using drugs already licensed for other conditions—offers the potential of significant savings in the time and cost of developing new therapies. Numerous drugs licensed for other conditions have the potential of antiepileptic efficacy.\(^7\) In order to select the best candidate drug(s) to repurpose for epilepsy, it is desirable to predict the relative clinical efficacy that drugs will have in people with epilepsy. One established strategy for discovering potentially effective drugs is to, first, identify the proteins that underlie a disease and, then, identify the drugs that affect the disease-proteins. In such analyses, genes associated with a disease are routinely used as proxies for disease-proteins.\(^8\)

Genetic factors can contribute to the development of epilepsies, either as single-gene mutations in rare monogenic epilepsies, or as multiple genetic variants in common epilepsies.\(^9\) Common epilepsies are complex traits with a polygenic origin, which means that the combined effect of many common risk variants contributes to their genetic risk.\(^7\) Common epilepsies are divided into...
different types and syndromes\textsuperscript{10}; for brevity, we use ‘forms’ as a general term for both types and syndromes. Different forms of common epilepsy have important differences in their genetic determinants,\textsuperscript{11} clinical manifestations and response to medications.\textsuperscript{12} Hence, to be most useful for common epilepsies, methods of drug prediction must use the specific genes/proteins underlying a particular form of common epilepsy, to make drug predictions that are specific for that particular form of common epilepsy. This has not been achieved by any of the published drug prediction studies for epilepsy.\textsuperscript{11,13–17} Some studies have pooled genes/proteins associated with different forms of epilepsy (including rare epilepsies), to produce a single list of drug predictions for all forms of epilepsy\textsuperscript{13–17}; these methods are not readily adaptable to individual common epilepsies, as they require a large number of genes/proteins definitively associated with a disease. Other studies have used genome-wide transcriptomic analysis of human brain tissue from epilepsy surgery\textsuperscript{14,15}, such tissue is only available for a very limited number of epilepsy syndromes, and its analysis is hindered by the lack of suitable control brain tissue that is comparable, normal and has been exposed to ASMs. Of course, any transcriptomic changes detected in epileptic brain tissue could be a consequence, rather than a cause, of disease.

The Genome-Wide Association Study (GWAS) is becoming an increasingly powerful tool for revealing the distinct genetic determinants of different common epilepsies.\textsuperscript{11,18–20} GWAS results are routinely used to predict new candidate drugs for complex diseases. In the standard approach, significant variants from the GWAS are mapped to genes; drugs that are known to affect the (protein products) of the genes, are predicted to affect the disease.\textsuperscript{21} This simplistic approach has a number of methodological deficiencies. It reflects neither the polygenicity of common diseases, nor the polypharmacology of common drugs. It ignores drugs’ effects on disease-protein abundance, even though, in order to exert their therapeutic effect, drugs rectify the activity of disease-proteins by modulating their function or abundance or both.\textsuperscript{22–24} It disregards the magnitude and direction of change in disease-proteins’ activity, and drugs’ effects upon it. Potential causal variants below the genome-wide disease significance threshold are ignored. Practically, it produces an unordered and unranked pool of drug names, with no indication of the relative predicted efficacy of the compounds, to enable selection of the most promising candidates. Ultimately, it is liable to producing poor results. Some limitations of the standard approach are addressed by recently developed enhanced techniques for using GWAS results to identify effective drugs,\textsuperscript{25–28} but these newer methods and their drug predictions for common epilepsy still leave room for improvement. None of the existing methods make drug predictions for a disease based upon drugs’ effects on the function and abundance of proteins, and the magnitude and direction of those effects, relative to the importance, degree and direction of the proteins’ dysregulation in the disease. Our aim was to develop such a method, and to use this method to predict the relative efficacy of drugs for each of the major types and syndromes of common epilepsy, and to make our predictions available as a novel resource for selecting suitable candidate drugs that could potentially be repurposed for each of the major types and syndromes of common epilepsy.

**Materials and methods**

Methods are summarized below; further details can be found in the Supplementary methods.

**Overview**

**Epilepsy types and syndromes**

The common epilepsies are divided into different types, which are further subdivided into different syndromes.\textsuperscript{10} In the current work, we included the main types and syndromes analysed in the most recent epilepsy GWAS\textsuperscript{11}:

i. All epilepsy, which is comprised of generalized, focal and unclassified epilepsies

ii. The two main types of all epilepsy: generalized epilepsy (GE) and focal epilepsy (FE)

iii. Two GE syndromes: juvenile myoclonic epilepsy (JME) and childhood absence epilepsy (CAE)

iv. A FE syndrome: FE with hippocampal sclerosis (HS)

**Method summary**

Genetic variants cause disease by modifying the function or abundance (or both) of proteins derived from the variant genes.\textsuperscript{29} Drugs exert a therapeutic effect by rectifying the abnormal function or abundance (or both) of the proteins underlying a disease.\textsuperscript{22–24} To predict the relative efficacy of drugs against a disease, we developed (Fig. 1) a novel score for drugs’ relative ability to affect the protein function and abundance changes caused by common genetic variations associated with the disease: the disease-protein function and abundance modulation (FAM) score.

For method development and benchmarking, we used the all epilepsy GWAS. Then, we applied the developed method to the GWAS for specific epilepsy types and syndromes.

It should be noted that, to aid brevity and readability, we use the expressions ‘disease-associated proteins’ and ‘disease-proteins’ as proxies for ‘proteins encoded by genes bearing variations associated with the disease’, and we use the expression ‘protein abundance changes’ as proxy for ‘changes in gene expression’.

**The disease-protein FAM score: creation and benchmarking**

The steps taken in developing the method for calculating the FAM score are detailed in Supplementary material.
Below, we summarize the method (Fig. 1) we developed for calculating the FAM score.

The FAM score is calculated by aggregating its two constituent scores:

i. The disease-protein function modulation (FM) score
ii. The disease-protein abundance correction (AC) score

**FM score**
The FM score is based on the following premise: A drug’s ability to affect a disease can be predicted from:

i. the degree of disease-association of each protein whose function is affected by the drug, and
ii. the strength of the drug’s effect on the function of each of those proteins

The degree of disease-association of proteins is derived from GWAS gene-based \( P \)-values. The strength with which drugs affect proteins’ function is derived from drug-target affinity data. Figure 1 presents a conceptual explanation of how the FM score is calculated from these two types of data. A more detailed explanation can be found in the Supplementary material.

**AC score**
The AC score is based upon the following premise: A drug is more likely to be effective for a disease if it is better able to correct abnormalities in protein abundance underlying the disease. Disease- and drug-induced transcriptomes were compared in order to predict each drug’s relative ability to rectify disease-associated protein abundance changes, as previously described and detailed in the Supplementary material. Briefly, the AC score for a drug is calculated as follows: For each disease-associated protein, the algorithm compares the magnitude and direction of change in the protein’s abundance found in the disease, with the magnitude and direction of change in the protein’s abundance caused by the drug. Then, drugs are ranked in accordance with their overall predicted corrective effect on the abundance of all disease-associated proteins. To measure the overall effect, a metric called ‘cosine distance’ is used.

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Figure 1 Premise and conceptual explanation of the disease-protein function modulation (FM) and abundance correction (AC) scores, which are integrated to form the disease-protein function and abundance modulation (FAM) score. Before integration, the FM score is adjusted to control for the different number of proteins affected by each drug (see Supplementary material for details). Cosine distance is the (dis)similarity metric used for calculating the AC score.
Aggregating the FM and AC sores to generate the FAM score
The FM and AC scores were converted into their respective z-scores. The FAM score for each is calculated by averaging its FM and AC z-scores (see Supplementary material for details).

Comparing our method with existing alternative advanced methods
We compared our results with the results from two existing and contrasting advanced methods for GWAS-based drug predictions.

Network-based method
An approach employed in a number of studies is to identify the drugs that target genome-wide significant disease-proteins and, in addition, the drugs that target the proteins interacting with genome-wide significant disease-proteins. We used the GUILDify v2.0 Web Server to identify such drugs.

Gene-set analysis method
In this method, GWAS gene-based P-values are first converted to z-statistics and, then, a single-sided two-sample t-test is used to determine if the mean z-statistic of the genes that are altered in function by a drug is lower than the mean z-statistic of the genes that are not.

Validation of the FAM score
For in silico validation of the FAM score, we examined the following hypotheses:

- The FAM score for all epilepsy specifically prioritizes the drugs that are effective in people with epilepsy: when drugs are ranked by their FAM score for all epilepsy, drugs used to treat epilepsy are ranked higher than drugs used to treat any other human disease
- The FAM score predicts which ASMs are more clinically effective, and which ASMs are less clinically effective, for each common epilepsy syndrome studied
- The FAM score predicts the observed patterns of relative efficacy of individual clinically-effective ASMs for each common epilepsy syndrome studied

The above hypotheses are further detailed in Results and in Supplementary methods.

To test the above hypotheses, we used the following metrics:

1. Identification of effective drugs: we used area under receiver operated characteristics curve (AUROC) analysis to determine the accuracy with drugs’ scores discriminate ASMs from all other drugs, or discriminate more from less clinically-effective subsets of ASMs. AUROC was calculated using the package PRROC (version 1.3.1) in R (version 3.4.3). In assessing the discrimination of ASMs from all other drugs, there is a marked class imbalance, because a very small fraction of all drugs are ASMs. To correct for this imbalance, we employed the standard technique of random under-sampling, which is commonly used in published studies (see Supplementary material for further details and references). Specifically, AUROC was calculated using the set of ASMs and a randomly selected set of other drugs equal in number to the ASMs. This process was repeated 1000 times, and mean (± standard deviation) AUROC was calculated. When discriminating more from less effective ASMs, class imbalance is not an issue and, hence, random under-sampling was not employed.

2. Prioritization of effective drugs: amongst all the drug predictions for a phenotype, we determined the average rank of ASMs, or compared the average rank of more clinically-effective and less clinically-effective ASMs. To ease conceptualization and interpretation of results, we converted ranks to percentile ranks. For example, a drug with a percentile rank of 90 is ranked higher/better than 90% of all drugs. Like numerous published studies, we used the median in order to compute the average of ranks, as it is less liable to skewing by outliers (see Supplementary material for further details and references).

Statistical analysis
We determined the statistical significance of drug identification and prioritization results by comparing the results to those from a null distribution generated by performing $10^6$ random permutations of the scores assigned to drugs.

Determining whether the drug predictions are driven by individual highly disease-associated proteins
For each epilepsy, FAM scores were re-calculated after excluding, one at a time, the top 10 most strongly disease-associated proteins (Supplementary Table 3). Drug ranks obtained after excluding a protein were compared with the original drug ranks, using Kendall’s $\tau$. Kendall’s $\tau$ is a commonly used measure of rank correlation. Kendall’s $\tau$ ranges from $+1$ to $-1$, where $+1$ means that two ranked lists are identical to each other, $-1$ means that they are the exact inverse of each other, and 0 means that there is no relationship between them.

Further details about this analysis can be found in the Supplementary material.

Top candidate drugs
To aid the selection of suitable candidate drugs for experimental validation and clinical evaluation, we demarcated the most promising candidate drugs for
each phenotype: the topmost drug predictions with the greatest enrichment of (more) effective ASMs for that phenotype. A manually curated selection of top candidate drugs for different forms of common epilepsy was also produced.

**Testing top candidate compounds in an animal model**

As we used complex genetic data to make our drug predictions, we used a complex genetic model to test our drug predictions. We used a rodent model with a complex genetic seizure disorder that manifests as audiogenic generalized seizures: the DBA/2 mouse. We tested the five most highly ranked predictions for GE, after filtering out known ASMs, compounds with existing published evidence in the DBA/2 mouse model, drugs lacking evidence of blood–brain barrier permeability, drugs lacking evidence of safe long-term oral use in humans, compounds insoluble in water or saline and ‘controlled substances’ that require exceptional legal authorization for procurement under the laws of France, where the animal experiments were performed by a contract research organization.

The animal experiment protocol followed the method described by Dürmüller et al. The study was conducted in compliance with Animal Health regulations, in particular:

i. Council Directive No. 2010/63/UE of 22 September 2010 on the protection of animals used for scientific purposes and French decree No. 2013-118 of 1 February 2013 on the protection of animals;

ii. Porsolt facility accreditation for experimentation (E 53 1031, renewed on 19 April 2016);

iii. The recommendations of the Association for Assessment and Accreditation of Laboratory Animal Care of which the accreditation was granted in June 2012 and renewed in 2018.

Porsolt has an in-house ethics programme, which covers animal care and use within the facility. Additional experimental details about the animal model testing can be found in the Supplementary material.

**Code availability**

The R code for computing FM and FAM scores is available at [https://figshare.com/projects/Using_common_variants_to_find_drugs_for_common_epilepsies/78330](https://figshare.com/projects/Using_common_variants_to_find_drugs_for_common_epilepsies/78330). The code is for non-commercial use only.

**Data availability**

The following datasets are available for download from the project’s data repository page ([https://figshare.com/projects/Using_common_variants_to_find_drugs_for_common_epilepsies/78330](https://figshare.com/projects/Using_common_variants_to_find_drugs_for_common_epilepsies/78330)):

i. GWAS gene-based and tissue-wide association study (TWAS) datasets used in our analyses.

ii. Ranked list of the top predicted drugs for each phenotype.

iii. Our complete set of predictions, listing each drug and its FAM score, for each phenotype.

**Results**

**The standard method is inadequate for predicting drugs effective against common epilepsies**

In the standard method, drugs are predicted to be efficacious if they modulate the function of proteins that are associated with the disease, according to the GWAS, at a genome-wide level of significance. For all epilepsy, GE and FE, SCN1A is the only gene that both (i) reaches genome-wide level of disease-significance, and (ii) produces a protein that is known to be altered in function by any existing compound. For CAE, JME and HS, there are no genes that both (i) reach genome-wide level of disease-significance and (ii) produce a protein that is known to be altered in function by any existing compound. Predicting candidate compounds for epilepsy based upon their ability to affect the function of sodium channel protein Type 1 subunit alpha (the protein product of SCN1A) yields a recall (from amongst all ASMs, the fraction predicted to be effective) of 35% and precision (from amongst all drugs predicted to be effective, the fraction that are ASMs) of 32%, which equates to an F-score (harmonic mean of the precision and recall) of 33%. The standard method of drug prediction produces an unordered and unranked set of candidate drugs, with no metrics for the relative predicted efficacy of the candidate compounds. This precludes method evaluation based upon predicted drug rankings and AUROC, and hampers the selection of the most promising candidate drugs for experimental validation. The same set of ASMs is predicted to be effective for the two divergent phenotypes of GE and FE, even though some seizure types in the former are aggravated by the ASMs that are most effective for the latter. Hence, for different common epilepsies, this method either fails to identify the majority of known effective drugs, or identifies no candidate drugs at all, or identifies potentially aggravating drugs. By extension, applying the standard approach to common epilepsies will yield no or few candidates for repurposing, will not prioritize amongst the candidates, will fail to identify any or most of the efficacious compounds and will potentially identify aggravating drugs.
Creating and benchmarking a new method for predicting the relative efficacy of drugs against common epilepsies

To predict the relative efficacy of drugs against common epilepsies, we devised the disease-protein FAM score, which is calculated using the method illustrated in Fig. 1.

For benchmarking, we used the FAM score and alternative existing advanced methods to predict drugs for all epilepsy, and compared the methods’ performance. For the identification and prioritization of ASMs, the FAM score achieved AUROC (mean ± standard deviation) of 0.83 ± 0.03 and average percentile of 94, respectively. In comparison, the best performing alternative method achieved AUROC (mean ± standard deviation) of 0.63 ± 0.04 and average percentile of 77. Results of all comparator alternative approaches are shown in Supplementary Table 1.

Validating the FAM score

Next, we present results of the analyses performed to test the validity of the predictions made using the FAM score.

The FAM score for all epilepsy specifically prioritizes the drugs that are effective in people with epilepsy

When drugs are ranked by their FAM score for all epilepsies, drugs used to treat epilepsy are ranked higher than drugs used to treat any other human disease. The median rank of drugs used to treat epilepsy is at least seven percentiles higher than that of drug-sets used to treat other human diseases. Permutation-based $P$-value $= 1 \times 10^{-4}$ that ASMs are ranked highest, and so much higher than all other drug-sets used to treat all other human diseases.

The FAM score predicts which ASMs are more clinically effective, and which ASMs are less clinically effective, for each common epilepsy syndrome

Different ASMs are most effective for different syndromes of common epilepsy. Clinical studies and experience show that, for each common epilepsy syndrome, some ASMs can be classified into a more clinically-effective subset and some into a less clinically-effective subset. For each common epilepsy syndrome, the FAM score predicts which ASMs are amongst the more efficacious in clinical practice, and which ASMs are amongst the less efficacious in clinical practice (Table 1). Specifically, for each common epilepsy syndrome, the FAM score (i) distinguishes the more from the less clinically-effective ASMs and (ii) prioritizes the more clinically-effective ASMs higher than the less clinically-effective ASMs (Table 1).

In order to predict which ASMs are more clinically-effective and which ASMs are less clinically-effective for a syndrome, the best results are obtained by using the FAM score for that syndrome. To illustrate this, we show that the ASMs that are more effective for CAE are favoured over the ASMs that are less effective for CAE, only when drugs are predicted using the FAM scores for CAE (AUROC: 0.79), and not when drugs are predicted using the FAM scores for all epilepsy, GE, JME, FE or HS (max AUROC: 0.49); permutation-based $P$-value $= 1 \times 10^{-5}$ that the AUROC values for CAE and other phenotypes are so contrasting.

For FE, current ASMs are not readily classified into more clinically-effective and less clinically-effective subsets. The FE FAM score identifies and prioritizes ASMs: AUROC (mean ± standard deviation) of 0.85 ± 0.03 and average percentile of 94; the FAM score’ performance is statistically significant (permutation-based $P$-value $= 1 \times 10^{-6}$), and superior to that of its constituent scores.

When considering the ability to distinguish more effective ASMs from all drugs and from less effective ASMs, the FAM score outperforms its constituent scores (Supplementary Table 2).

Table 1 Performance of the FAM score, measured by the identification and prioritization of AEDs

| Epi | Identification of AEDs (AUROC) | Prioritisation of AEDs (average percentile) | $P$ |
|-----|--------------------------------|--------------------------------------------|-----|
|     | More effective AEDs from all drugs (mean ± SD) | Less effective AEDs from all drugs (mean ± SD) | More from less effective AEDs | More effective AEDs | Less effective AEDs |
| HS  | 0.65 ± 0.13                      | 0.36 ± 0.18                                | 0.87 | 73  | 27   | $8 \times 10^{-3}$ |
| GE  | 0.85 ± 0.04                      | 0.69 ± 0.09                                | 0.71 | 93  | 70   | $<1 \times 10^{-4}$ |
| JME | 0.88 ± 0.04                      | 0.76 ± 0.08                                | 0.72 | 96  | 86   | $<1 \times 10^{-4}$ |
| CAE | 0.75 ± 0.05                      | 0.45 ± 0.15                                | 0.79 | 85  | 48   | $2.9 \times 10^{-5}$ |

Constituents of the ‘More effective AEDs’ and ‘Less effective AEDs’ drug-sets are specific to each phenotype. ‘Less effective AEDs’ comprise the set of less effective, ineffective or aggravating AEDs for that phenotype. AUROC is calculated using drugs’ FAM scores. AUROC for identifying AEDs from all drugs is computed using the technique of random under-sampling, and presented as mean ± standard deviation (see Supplementary methods). Prioritization is calculated using drugs’ ranks, when all drugs have been ranked from highest to lowest predicted effect on the phenotype. Prioritization result shown is the average (median) rank of AEDs, expressed as a percentile: it is equivalent to the percentage of all drugs ranked below the middle-ranked AED (see Supplementary methods). AUROC, area under the receiver operating characteristics; CAE, childhood absence epilepsy; Epi, epilepsy type or syndrome; GE, generalized epilepsy; HS, focal epilepsy with hippocampal sclerosis; JME, juvenile myoclonic epilepsy; $P$, permutation-based $P$-value after Benjamini–Hochberg correction; SD, standard deviation.
The FAM score predicts the observed patterns of relative efficacy of individual clinically-effective ASMs

We tested our predictions against the following observed patterns of relative efficacy of individual clinically-effective ASMs.

Valproate is the most effective ASM for GE, whereas carbamazepine is the most effective ASM for FE

It is recognized that the efficacy of valproate for general-ized onset seizures is ‘unsurpassed’, whereas for focal onset seizures, ‘no other drug has been shown to be more effective’ than carbamazepine. In our predictions for GE, valproate is ranked highest of all current ASMs. In our predictions for FE, carbamazepine is ranked highest of all current ASMs. Valproate and carbamazepine are amongst the top two of all drugs in our predictions for GE and FE, respectively; permutation-based P-value = 5.6 × 10⁻⁶ for both valproate and carbamazepine being ranked so highly in our predictions for GE and FE, respectively.

The prioritized order of efficacy of ASMs for GE matches that seen in the SANAD trials

The SANAD studies are the largest published head-to-head comparison of multiple ASMs for GE, and the largest published randomized controlled trial of ASMs for FE. The ASMs compared in the FE arm of SANAD I were lamotrigine, topiramate and valproate. These drugs’ predicted order of efficacy matches the clinically observed order of efficacy in the SANAD I trial. The finding that these drugs are ranked as highly and in the correct order is unlikely to occur by chance (permutation-based P-value = 1 × 10⁻⁵).

Valproate and lamotrigine are effective ASMs but, in the GE arm of the SANAD I trial, valproate was significantly more efficacious than lamotrigine. Valproate and lamotrigine are ranked high in our predictions for GE (percentile ranks 100 and 81, respectively), but valproate is ranked significantly higher than lamotrigine (permutation-based P-value = 3 × 10⁻⁴ for the ranks of both drugs being as high but as disparate as observed).

The ASMs compared in the GE arm of SANAD II were levetiracetam and valproate. Valproate and levetiracetam are effective ASMs but, in the GE arm of the SANAD II trial, valproate was significantly more efficacious than levetiracetam. Valproate and levetiracetam are ranked high in our predictions for GE (ranks 1 and 15, respectively), but valproate is ranked significantly higher than levetiracetam (permutation-based P-value < 1 × 10⁻⁵ for the ranks of both drugs being as high but as disparate as observed).

Topiramate is more effective than lamotrigine for GE, but lamotrigine is more effective than topiramate for FE, in concordance with the SANAD I trial

Lamotrigine and topiramate are the only two ASMs included in both the FE and GE arms of the SANAD I study. In the GE arm of SANAD I, topiramate was more efficacious than lamotrigine, whereas in the FE arm, lamotrigine was more efficacious than topiramate. In our predictions for FE, lamotrigine is ranked higher than topiramate, while for GE, topiramate is ranked higher than lamotrigine. The contrasting ranks of lamotrigine and topiramate for FE and GE are unlikely to occur by chance (permutation-based P-value = 1 × 10⁻⁴).

For JME, valproate is most effective

Valproate is thought to be the most efficacious broad-spectrum ASM for JME but this is based on anecdotal data and retrospective analyses. Amongst our predictions for JME, valproate was amongst the highest ranked drugs (percentile rank 98), but not the highest. The highest ranked prediction was primidone. In the longest retrospective cohort study of JME to date, primidone was most effective, with a 5-year terminal remission rate of 73.3, compared to 50% with valproate.
For CAE, valproate and ethosuximide are most effective
Valproate and ethosuximide are most effective for CAE; both are similarly effective for CAE.54 In our predictions for CAE, valproate is ranked highest of all drugs. Ethosuximide is not ranked highly, but higher than average, amongst our predictions (median percentile rank 58). The P-value for the two drugs being ranked so favourably is $5 = 1 \times 10^{-4}$. Ethosuximide is ascribed a particularly low FM score for CAE, which places it in the 20th percentile of predictions for the phenotype. One possible explanation of ethosuximide’s low FM score is that its mechanism of action is poorly understood, as it is not an extensively studied compound. Indeed, ethosuximide is one of the least studied of the current ASMs: there are 343 MEDLINE articles with the word ethosuximide in their title, compared to a mean of ~1765 for the other current ASMs that are also found in our datasets (as of 2 September 2021; single-sample one-tailed $t$-test $t = 3.7$ and $P$-value $= 6.9 \times 10^{-4}$).

The drug predictions are not driven by individual highly disease-associated proteins
The relative predicted efficacy of drugs does not change significantly after excluding, one at a time, the top 10 most strongly disease-associated proteins that contribute to the FAM score for that epilepsy. The predicted ranks of drugs for each epilepsy remained significantly stable after excluding, one at a time, the top 10 most strongly disease-associated proteins that contribute to the FAM score for that epilepsy. For each epilepsy, FAM scores were re-calculated after excluding, one at a time, the top 10 most strongly disease-associated proteins (Supplementary Table 3) that contribute to the FAM score for that epilepsy. When drug ranks obtained after excluding a protein were compared with the original drug ranks, Kendall’s $\tau$ ranged from 0.80 to 0.93, with all corrected $P$-values $<1 \times 10^{-200}$. In contrast, comparing the predicted drug rankings for two unrelated epilepsies—CAE and HS—yields a Kendall’s $\tau$ of 0.04 ($P = 0.10$).

Top candidate drugs
Ranked lists of the top drugs predicted to be effective for each phenotype, which are most enriched with the drugs that are known to be (more) effective for the phenotype, are available for download (see Data availability). For each phenotype, the top candidate drugs are significantly (Benjamini-Hochberg $P$-value $<0.05$) enriched with the ASMs that are (more) effective for the phenotype, except for HS. For HS, there was no significant enrichment of (more) effective ASMs, which may be a reflection of the often drug-resistant nature of HS, or of the lower power of the HS GWAS, or the relatively smaller size of the more effective subset of ASMs for HS, or a combination of these factors.
A manually curated selection of top candidate drugs that could potentially be repurposed for different forms of common epilepsy is shown in the Table 2.

Predicted drugs have a significant dose-dependent effect on seizures in an animal model
After excluding drugs that are toxic or otherwise unsuitable, the top five predicted drugs for GE were tested in a mouse model with a complex genetic seizure disorder that manifests as audiogenic generalized seizures. Each of the drugs had a significant dose-dependent effect on tonic and clonic convulsions (Table 3). Whilst four of the drugs had a significant dose-dependent anti-convulsant effect, one of the compounds (betahistine) had a significant dose-dependent pro-convulsant effect.

Discussion
We present the relative predicted efficacy of drugs against each of the main types and syndromes of common epilepsy. This dataset is a novel and valuable resource for selecting the best candidate drug(s) to repurpose for any of the main types and syndromes of common epilepsy. Of course, our predicted candidate drugs require further animal model and/or human clinical trial evidence before being considered for deployment in clinical practice.
To generate our predictions, we created a novel method. Our method possesses several strengths that are lacking in previously published approaches. Common epilepsies, like other complex diseases, develop when many different proteins display abnormal activity due to pathological changes in their abundance or function.35 Our method prioritizes drugs according to their relative ability to modulate changes in both the abundance and the function of disease-proteins. Furthermore, drugs are prioritized on the basis of their ability to correct disease-protein abnormalities that are found in people with the disease, rather than in animal models, and that are not consequential to or compensatory for the disease, as they are driven by germline variations. We use genetic variation data specific to each form of common epilepsy, to make drug predictions specific to that form of common epilepsy. The ASMs that are more clinically-effective for a syndrome and the ASMs that are less clinically-effective for a syndrome are predicted more effective and less effective, respectively, for that syndrome only, but not for any other epilepsy type or syndrome—this suggests that our predictions are not systemically biased in favour of a particular set or type of drugs. The methodology is based upon a polygenic model of disease and a multi-targeted approach to treatment, which are desirable for complex diseases. We utilize conventional canonical low-
throughput single-target functional drug activity data, and high-throughput genome-wide transcriptomic drug activity data, so that prioritization of drugs is informed by their on-target and off-target effects, and by their affinities for individual proteins and effects upon genome-wide gene expression. The directionality of drugs’ effects on protein activity also helps inform drug prioritization.

Rather than dichotomous categorization of compounds into drugs that are predicted to be effective or ineffective, our method ranks drugs individually according to relative predicted efficacy, which aids candidate selection for in vivo validation and for development.

Our method produces accurate drug predictions for epilepsy syndromes even if their GWAS results include few genome-wide significant loci. Even excluding the most strongly disease-associated proteins does not significantly change the relative efficacy of drugs predicted by our method (as we show in the Results, under subheading ‘The drug predictions are not driven by individual highly disease-associated proteins’). This is because our method is not reliant on individual highly disease-associated proteins. Instead, our method leverages the gene-set analysis approach, where each gene-set is the set of genes affected by each drug. The disease association of all the genes in a gene-set, even those below the genome-wide significant threshold, is combined; the gene-sets that are more disease-associated overall are more biologically relevant.

The gene-set approach is a long-established and widely-used method in all areas of genomic analysis, including post-GWAS analysis generally and GWAS-based drug repurposing analysis specifically. Utilizing the full distribution of all genetic associations for gene-set analysis is a validated, established and accepted approach, which has been implemented in numerous widely-used post-GWAS analysis tools, for example FUMA, MAGMA, MAGENTA, INRICH and DEPICT, each of which

Table 2 Manually curated selection of candidate drugs for the phenotypes shown in the table

| Epi | Drugs | Evidence of antiseizure efficacy in | Indication | Mode of action |
|-----|-------|-----------------------------------|------------|---------------|
| CAE | Clomipramine | Animal models and humans | Depression | Serotonin–noradrenaline reuptake inhibitor |
| CAE | Doxepin | Animal models | Depression | Tricyclic antidepressant |
| CAE | Pentoxifylline | Animal models | Peripheral vascular disease | Haemorheological agent, increases leukocyte deformability |
| CAE | Phenelzine | Animal models | Depression | Monoamine oxidase inhibitor |
| CAE | Sulindac | Animal models | Pain | Non-steroidal anti-inflammatory |
| CAE | Tolbutamide | Animal models | Diabetes mellitus | Sulphonylurea |
| CAE | Tranycypromine | Animal models | Depression | Monoamine oxidase inhibitor |
| FE | Chlorzoxazone | Rat hippocampal neurons | Muscle spasms | Calcium and potassium channel inhibitor |
| FE | Hydrochlorothiazide | Animal models and human | Hypertension | ACEI antagonist |
| FE | Thalidomide | Animal models | Multiple myeloma | Immunomodulation, unspecified |
| FE | Zaleplon | Animal models | Insomnia | GABA-BZ agonist |
| FE | Zolpidem | Animal models | Insomnia | GABA-BZ/GABA-A agonist |
| HS | Amiodarone | Animal models | Arrhythmia | Potassium channel blocker |
| HS | Clonidine | Animal models | Hypertension | Alpha-2 adrenergic receptor agonist |
| HS | Methoxamine | Animal models | Hypertension | Alpha-1 adrenergic receptor agonist |
| HS | Pergolide | Animal models | Parkinson’s disease | D2 agonist |
| HS | Thiopental | Animal models | Psychosis | D1/D2 antagonist |
| HS | Tizanidine | Animal models | Muscle spasticity | Alpha-2 adrenergic receptor antagonist |
| JME | Aliskiren | Animal | Hypertension | Renin inhibitor |
| JME | Baclofen | Animal model | Muscle spasticity | GABA-B receptor agonist |
| JME | Diazoxide | Animal model | Hypoglycaemia | Potassium channel agonist, inhibits insulin release |
| JME | Icosapent | Animals and humans | Hypertriglyceridaemia | 20-carbon omega-3 fatty acid |
| JME | Iloprost | Animal models | Pulmonary arterial hypertension | Synthetic analogue of prostacyclin PGI2 |
| JME | Nicotinamide | Animal models | Pellagra | Water-soluble form of Vitamin B3 |
| JME | Pranlukast | Animal models and humans | Asthma | Cysteinyl leukotriene receptor-l antagonist |
| JME | Riluzole | Animal models | Amyotrophic lateral sclerosis | Glutamate antagonist |

Candidate drugs for GE, which we tested in an animal model, are listed in Table 3. References, for the evidence cited here, can be found in the Supplementary material. CAE, childhood absence epilepsy; Epi, epilepsy type or syndrome; HS, focal epilepsy with hippocampal sclerosis; JME, juvenile myoclonic epilepsy.
has been employed in a multitude of published GWAS-based studies.

Alongside these strengths, our method has some limitations, discussed below.

Our drug prediction method, like all previously published genetics- or genomics-based drug prediction methods, predicts the efficacy of drugs for a disease. However, the most efficacious drug for a disease in not always the most appropriate drug for every individual with the disease. Important factors to consider when choosing a drug for an individual include the potential of undesirable interactions with other medications and the possible side-effects. Our method, like all previously published genetics- or genomics-based drug prediction methods, does not predict drugs’ interactions with other medications and side-effects. Indeed, the success of an ASM is determined as much by its tolerability as by its efficacy.59–62 As the drugs we have predicted for a disease are already being used for other diseases, their side-effect profiles are known. This allows researchers to select for further development those candidate compounds whose side-effects are less deleterious or even desirable.

Our method predicts drugs effective for a disease from the proteins underlying the disease, after identifying the proteins changed in function by drugs. At present, knowledge of the proteins changed in function by drugs is incomplete, and it is more incomplete for some drugs than for others. The more incomplete the knowledge of the proteins that are changed in function by a drug is incomplete, and it is more incomplete for some drugs than for others. The more incomplete the knowledge of the proteins changed in function by a drug is, the more likely it is that the drug’s FM score will be underestimated. By extension, the FM score is more likely to be underestimated for drugs that are less studied, as their modes of action are less analysed and, hence, knowledge of the proteins changed in function by them is less complete. This may explain the relatively low FM score for ethosuximide.

Our drug predictions are based upon two scores: the FM and AC scores. The FM score relies upon knowledge of the proteins changed in function by drugs. At present, knowledge of the proteins that are changed in function by each drug is incomplete, and it is more incomplete for some drugs than for others. The more incomplete the knowledge of the proteins changed in function by a drug is, the more likely it is that the drug’s FM score will be underestimated. By extension, the FM score is more likely to be underestimated for drugs that are less studied, as their modes of action are less analysed and, hence, knowledge of the proteins changed in function by them is less complete. This may explain the relatively low FM score for ethosuximide.

The AC score is free of this limitation, as the AC score is based upon profiles of drug-induced transcriptomic changes assayed by using the same standardized pipeline for each drug. With over 44 000 compounds already tested; s.e.m, standard error of the mean.

Table 3 Results from testing compounds in a genetic model of generalised seizures: the DBA/2 mouse model of audiogenic seizures

| Drug                  | Latency (s) to convulsions (mean ± s.e.m) | P       |
|-----------------------|------------------------------------------|---------|
| Vehicle (i.p.)         | 10.9 ± 2.6                               | –       |
| Orphenadrine (12.5 mg/kg i.p.) | 40.0 ± 5.6                           | 6.10 × 10⁻⁵ |
| Orphenadrine (25 mg/kg i.p.) | 53.4 ± 3.7                           | 5.40 × 10⁻⁷ |
| Orphenadrine (50 mg/kg i.p.) | 60.0 ± 0.0                           | 4.14 × 10⁻⁷ |
| Dyclonine (5 mg/kg i.p.)   | 31.5 ± 6.2                               | 1.77 × 10⁻² |
| Dyclonine (10 mg/kg i.p.)   | 44.7 ± 5.4                               | 2.16 × 10⁻⁴ |
| Dyclonine (20 mg/kg i.p.)   | 57.7 ± 2.4                               | 4.14 × 10⁻⁷ |
| Trimeprazine (2.5 mg/kg i.p.) | 11.0 ± 0.6                            | 6.52 × 10⁻¹ |
| Trimeprazine (5 mg/kg i.p.)   | 18.1 ± 4.1                               | 1.77 × 10⁻² |
| Trimeprazine (10 mg/kg i.p.)   | 44.5 ± 5.3                               | 4.06 × 10⁻⁸ |
| Acamprosate (125 mg/kg i.p.) | 8.7 ± 0.4                               | 6.40 × 10⁻¹ |
| Acamprosate (250 mg/kg i.p.) | 9.2 ± 0.2                               | 4.56 × 10⁻¹ |
| Acamprosate (500 mg/kg i.p.) | 14.3 ± 2.5                              | 1.20 × 10⁻² |
| Betahistine (75 mg/kg i.p.)    | 9.1 ± 0.5                                | 4.53 × 10⁻⁵ |
| Betahistine (150 mg/kg i.p.)    | 6.9 ± 0.4                                | 2.83 × 10⁻² |
| Betahistine (300 mg/kg i.p.)    | 5.3 ± 0.3                                | 4.48 × 10⁻⁴ |
| Valproate (180 mg/kg i.p.)     | 57.7 ± 1.4                               | 4.89 × 10⁻⁷ |

After activation of a bell, latency to the occurrence of tonic convulsions and clonic convulsions was measured. P, Benjamini–Hochberg-corrected P-value from two-sided Mann–Whitney U test; s.e.m, standard error of the mean.
analysed on this platform (http://lincsportal.ccs.miami.edu/SmallMolecules/catalog; accessed on 1 February 2021), transcriptomic profiles are available for the vast majority of drugs of interest. However, a small number of interesting drugs (for example, brivaracetam and cenobamate) have not been assayed, which means that an AC score and, hence, a FAM score cannot be calculated for them. The platform and pipeline used for generating drugs’ transcriptomic profiles are in the public domain, and have been used by researchers to generate profiles for any compounds of interest not already found in the database, albeit for industrial-scale projects. In addition, any compounds of interest not already found in the database have been used by researchers to generate profiles for transcriptomic profiles are in the public domain, and the platform and pipeline used for generating drugs’ transcriptomic profiles are in the public domain, and have been used by researchers to generate profiles for any compounds of interest not already found in the database, albeit for industrial-scale projects. In addition, any compounds of interest not already found in the database have been used by researchers to generate profiles for drugs’ structures to predict the proteins that they change in function and/or abundance, which is another potential future strategy for predicting the relative efficacy of compounds whose molecular effects are still unknown.

It is noted that the FM score does not predict the ‘directionality’ of drugs’ effects (that is, beneficial or harmful) on disease-protein function. Therefore, drugs predicted by the FM score to affect a phenotype may be alleviating or aggravating for the phenotype. This is a recognized limitation of methods that use data for the ability of drugs to alter the function of genetically-associated disease-proteins in order to predict drugs that can affect the disease, as the direction of change in protein activity occurring in the disease is unknown. On the other hand, the AC score does predict the ‘directionality’ of drugs’ effects (that is, beneficial or harmful) on individual disease-proteins and, thereby, the overall ‘directionality’ of drugs’ effects (that is, beneficial or harmful) on the disease. The AC score takes into account the magnitude and direction of change in proteins’ abundance underlyin...
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Competing interests

The authors report no competing interests.

Appendix I

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