**The Prescribable Drugs with Efficacy in Experimental Epilepsies (PDE3) Database for Drug Repurposing Research in Epilepsy**

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**Summary**

**Objective:**

Current antiepileptic drugs (AEDs) have several shortcomings. For example, they fail to control seizures in 30% of patients. Hence, there is a need to identify new AEDs. Drug repurposing is the discovery of new indications for approved drugs. This drug ‘recycling’ offers the potential of significant savings in the time and cost of drug development. Many drugs licensed for other indications exhibit antiepileptic efficacy in animal models. Our aim was to create a database of ‘prescribable’ drugs, approved for other conditions, with published evidence of efficacy in animal models of epilepsy, and to collate data that would assist in choosing the most promising candidates for drug repurposing.

**Methods:**

The database was created by: (1) computational literature-mining using novel software that identifies Medline abstracts containing the name of a prescribable drug, a rodent model of epilepsy and a phrase indicating seizure reduction; then (2) crowdsourced manual curation of the identified abstracts.

**Results:**

The final database includes 173 drugs and 500 abstracts. It is made freely available at [www.liverpool.ac.uk/D3RE/PDE3](http://www.liverpool.ac.uk/D3RE/PDE3). The database is reliable: 94% of the included drugs have corroborative evidence of efficacy in animal models (for example, evidence from multiple independent studies). The database includes many drugs that are appealing candidates for repurposing as they are widely-accepted by prescribers and patients—the database includes half of the twenty most commonly prescribed drugs in England—and they target many proteins involved in epilepsy but not targeted by current AEDs. Importantly, the drugs are of potential relevance to human epilepsy—the database is highly enriched with drugs that target proteins of known causal human epilepsy genes (Fisher’s exact test p-value < 3x10-5). We present data to help prioritise the most promising candidates for repurposing from the database.

**Significance:**

The PDE3 database is an important new resource for drug repurposing research in epilepsy.

**Keywords**: Epilepsy; Repurposing; Database; Animal models; Literature-mining; Crowdsourcing

**Key points:**

* 173 prescribable drugs have published evidence of efficacy in animal models of epilepsy
* 94% of the drugs have corroborated evidence of efficacy in animal models
* Many of the drugs are widely-accepted by prescribers and patients—the database includes half of the twenty most commonly prescribed drugs
* Many repurposable drugs target proteins implicated in epilepsy but not exploited by current AEDs
* The database is enriched with drugs that target proteins of causal human epilepsy genes and, hence, is of relevance to human epilepsy

**Introduction:**

Currently available antiepileptic drugs (AEDs) have several significant shortcomings: they fail to control seizures in 30% of patients;1 and they cause adverse effects in ~88% of patients.2,3 There is an unmet clinical need for new AEDs with better efficacy and tolerability.

For every 5,000 to 10,000 prospective drugs that enter research and development, only one is approved for human use.4,5 Developing one drug and winning marketing approval for it takes 10–15 years and $2.6 billion.6 However, it is estimated that approximately 90% of approved drugs possess secondary indications and can be used for other purposes.7 Drug repurposing is the discovery of new indications for approved drugs. This drug ‘recycling’ offers the potential of significant savings in the time and cost of identifying new therapies.

There is increasing interest in finding new treatments for epilepsy through drug repurposing.8,9 It has been recognised that a number of commonly-used well-tolerated drugs licensed for other conditions have the potential of antiepileptic efficacy. 8,10 In other disease areas, databases of potentially repurposable drugs have been created in order to facilitate selection of the best candidates for further development.11,12 We are not aware of any existing initiative to create a database of drugs that are potentially repurposable for the treatment of epilepsy in order to facilitate selection of the best candidates for further development.

*In vivo* drug testing in animal models of epilepsy is the strongest class of pre-clinical evidence for demonstrating potential antiepileptic efficacy in humans. Rodent models of epilepsy are the most long-established, well-characterised, widely-used and broadly-accepted animal models for antiepileptic drug validation. Success in these models precedes consideration for clinical trials in humans. We set out to create a database of ‘prescribable’ drugs, approved for other conditions, with published evidence of efficacy in rodent models of epilepsy, and to collate data that would assist in choosing the most promising compounds for further study.

**Methods:**

Literature-mining of Medline abstracts has been used to identify potential new indications and disease associations of drugs.13-16 Hence, we employed literature-mining of Medline abstracts in order to create the database. Data was extracted from Medline abstracts through computational literature-mining followed by ‘crowdsourced’ manual curation (Figure 1).

*Computational literature-mining:*

A Medline search was performed on the 19th of January 2017 for ‘epilepsy or seizure or convulsion’, and all returned abstracts were downloaded.

Computational literature-mining was used to identify abstracts that are most likely to include relevant information. Our strategy was based on the precept that abstracts of interest would include:

1. the name of a US Food and Drug Administration (FDA)-approved drug,
2. the name of a relevant rodent species (mouse, rat, guinea pig, or synonyms),
3. the name of a rodent model of epilepsy or seizures, and
4. a sentence containing the terms ‘reduction’ and ‘seizures’ (or synonyms thereof).

Identifying the relevant abstracts presented two particular challenges: (1) abstracts had to be searched for 1608 drug names, and (2) sentence-level concurrence of the terms ‘reduction’ and ‘seizures’ (and dozens of synonyms) had to be identified within the abstracts. This task was accomplished by using custom bash scripts (available upon request) created by modifying ones we have previously published.10 Some compounds also enhance the action of licensed AEDs; to identify these compounds, we searched for sentence-level concurrence of the terms ‘enhances’ and ‘action’ (or synonyms thereof) and the name of a licensed AED. Sentence-level concurrence of search terms increases specificity and precision of data retrieval.17 A random selection of 100 abstracts from those excluded by our scripts was manually reviewed by one of the senior investigators (NM) to ensure that relevant abstracts meeting our inclusion criteria were not being erroneously excluded by the scripts.

The names of FDA-approved drugs were taken from a recently-published comprehensive map of molecular targets of approved drugs; this would allow us to reliably map the identified drugs to their targets.18 We excluded the names of all recognised AEDs, of benzodiazepines and their derivatives, and of barbiturates, as these drugs are already known to have antiepileptic efficacy. Also excluded were the names of compounds that are unlikely to be repurposable for the treatment of epilepsy, for example, reagents used for generating rodent models of epilepsy. Please see Supplementary Methods for further details.

*Crowdsourced manual curation*

Crowdsourcing is defined as a model that outsources tasks which are traditionally performed by experts to a crowd of ordinary people.19 Members of the crowd were recruited through word-of-mouth from amongst medical undergraduates, junior doctors and laypeople. The crowd comprised 9 individuals. Computationally-parsed abstracts were divided into 9 sets for manual curation. In order to standardise responses, manual curation was performed according to a set of written instructions and the results were recorded on an electronic data collection form. For each abstract, the investigators recorded if the drug being studied was reported to have antiepileptic efficacy and in which model. If the drug being analysed was reported to enhance the action of conventional AED(s), the name(s) of the latter were also recorded.

Each set of abstracts was studied independently by two investigators. Any conflicting responses were arbitrated by one of the senior co-authors (NM, SS or MK). Lastly, each of the abstracts selected in the previous step was again reviewed by one of the senior co-authors in order to remove any erroneous inclusions.

From the final selection of abstracts, we collated names of drugs and the relevant PubMed identifiers (PMIDs) and animal models. For each potentially repurposable prescribable drug identified, we also collated licensed indication(s), and a relative measure of its ‘popularity’ (the number of prescription items of the drug dispensed in England last year) and its ‘longevity’ (year of first known worldwide approval).18 This information was converted into a sortable searchable online database. Please see Supplementary Methods for details.

*Data analytics*

Analyses were performed on the collected data in order to demonstrate that:

1. The database is a reliable source of drugs effective in experimental epilepsies.
2. The included drugs are appealing candidates for repurposing.
3. The included drugs are of potential relevance to human epilepsy.

*Is the database a reliable source of drugs effective in experimental epilepsies?*

If any studies included in the database are effected by error causing incorrect attribution of antiepileptic effect to the drug(s), this will mar the reliability of the database. To ensure that this was not a pervasive problem, we assessed how many of the included drugs have corroborative evidence of antiepileptic efficacy.

The following types of corroborative evidence were gathered:

1. Evidence of antiepileptic efficacy from multiple independent studies
2. Evidence of antiepileptic efficacy in multiple rodent models
3. Evidence of both an independent and enhancing antiepileptic effect
4. Evidence of antiepileptic efficacy of other drugs with the same mechanism of action
5. Evidence of antiepileptic efficacy of other drugs belonging to the same WHO ATC therapeutic/pharmacological/chemical subgroup

Drug names were mapped to mechanism of action and ATC code, as provided by Santos and colleagues.18

*Are the drugs appealing candidates for repurposing?*

Drugs that are widely-recognised, widely-accepted and widely-used are more appealing candidates for repurposing than drugs that are not. Similarly, drugs that have a long history of successful continuous licensed use are more appealing candidates for repurposing than drugs that do not. We analysed data for the number of prescription items of each drug dispensed in England last year, and year of first known worldwide approval for each drug.

Repurposable drugs could be used to treat the disorder for which the drug is licensed and co-morbid epilepsy, thereby reducing cost, pill burden, side-effects and the risk of deleterious drug interactions, and improving compliance. Drugs indicated for common conditions are appealing candidates as these conditions will also be prevalent amongst people with epilepsy and, hence, the compounds will be utilizable for a greater number of people. We determined if the drugs are indicated for common and prevalent conditions.

In order to overcome the limitations of old AEDs, new drugs with novel targets are needed.20 We collated information about the protein targets of the identified drugs, and determined if these are different from those already exploited by established AEDs. Drug names were mapped to target protein and protein class, as provided by Santos and colleagues.18

*Are the drugs of potential relevance to human epilepsy?*

We wished to demonstrate that the set of drugs effective in animal models of epilepsy is likely of relevance to human epilepsy. We determined if more of these drugs target proteins of known causal human epilepsy genes than expected by chance alone. This was calculated as follows. Drug names were mapped to target protein and protein class, as provided by Santos and colleagues.18 Of all drugs included in the initial literature search, we determined the proportion that target proteins of known causal human epilepsy genes. Of the drugs effective in animal models of epilepsy, we determined the proportion that target proteins of known causal human epilepsy genes. The two proportions were compared using a two-sided Fisher’s exact test, with the level of statistical significance set at p-value < 0.05. The set of known causal human epilepsy genes was taken from our recent paper,21 in which we extracted from the Online Mendelian Inheritance in Man database (www.omim.org) genes that cause familial Mendelian disorders in which epilepsy or seizures are a cardinal feature. Symbols for causal genes listed in our previous paper, and UniPort identifiers for drug targets listed by Santos and colleagues were mapped ([www.uniprot.org/uploadlists/](http://www.uniprot.org/uploadlists/); accessed 01/09/2017) to Entrez gene identifiers, and overlaps were calculated.

Can the database help in the search for new causal epilepsy genes? If the set of proteins targeted by the identified drugs is enriched with known causal human epilepsy genes, it is more likely to harbour yet undiscovered causal human epilepsy genes, and be a valuable resource for their discovery. We determined the proportion of known causal human epilepsy genes within the set of proteins targeted by the repurposable drugs, and the proportion of known causal human epilepsy genes within all UniProt proteins. The two proportions were compared using a two-sided Fisher’s exact test, with the level of statistical significance set at p-value < 0.05.

**Results:**

196,573 abstracts were downloaded from Medline. From these, computational literature-mining identified 1,966 abstracts that contained the name of a prescribable drug, a rodent model of epilepsy, and a phrase indicating seizure reduction. A random selection of 100 abstracts from those excluded by our computational scripts was manually reviewed: this did not contain any abstracts meeting our inclusion criteria. Manual review of the 1,966 computationally-selected abstracts identified 500 abstracts that contained evidence of the efficacy of a prescribable drug in an animal model of epilepsy.

The PDE3 online database, comprising 173 drugs and 500 abstracts that evidence their effectiveness in experimental epilepsies, is freely available at [www.Liverpool.ac.uk/D3RE/PDE3](http://www.Liverpool.ac.uk/D3RE/PDE3). The online database allows free-text searching for drug names, drug indications and rodent models. The database can be sorted by the number of independent studies, number of independent models, the number of prescription items dispensed in the community and the year of first approval for each drug. All abstracts for each drug can be accessed directly and easily from the database by clicking a link.

*Is the database a reliable source of drugs effective in experimental epilepsies?*

94% of the identified drugs have at least one type of corroborative evidence of efficacy in experimental epilepsies (Table 1 and Table S2).

The utility of corroborating evidence from multiple independent studies is self-evident. We cite below some examples of how the other types of corroborative evidence can be useful for highlighting promising candidate drugs for further study.

* Evidence of efficacy in multiple rodent models: Whilst the anticonvulsant efficacy of piperonyl butoxide is examined in only one published study,22 it had a higher protective index than conventional AEDs in both the maximal electroshock and pentylenetetrazol mouse models.
* Evidence of both an independent and enhancing antiepileptic effect: Whilst one study reveals the independent antiepileptic effect of probenecid,23 multiple independent studies demonstrate its ability to enhance the efficacy of a number of conventional AEDs24,25
* Evidence of efficacy of other drugs with the same mechanism of action: While guanabenz is shown to be anticonvulsant in only one study and one model,26 a number of other drugs with the same mechanism of action—clonidine, dexmedetomidine, and tizanidine—are effective in multiple studies and models, lending credence to the reported antiepileptic efficacy of guanabenz.
* Evidence of efficacy of other drugs belonging to the same WHO ATC therapeutic/pharmacological/chemical subgroup: While pergolide is shown to be anticonvulsant in only one study and one model,27 other drugs within the same ATC therapeutic/pharmacological/chemical subgroup—apomorphine and bromocriptine—are effective in multiple studies and models, lending credence to the reported antiepileptic efficacy of pergolide.

*Are the drugs appealing candidates for repurposing?*

*The database includes many commonly-used drugs for many common conditions*

The database includes half of the twenty most commonly prescribed drugs in England. Altogether, drugs included in the PDE3 database accounted for 336,707,099 prescription items dispensed in the community in England in 2016, which is 32% of all prescription items dispensed in the community in England in that year.

The database includes drugs currently used to treat 9 of the 10 most prevalent chronic conditions (Table 2).28

The identified drugs have been in use, for their original indications, for a median of 34 years. The oldest of the drugs has been in use for 73 years.

*The identified drugs have novel protein targets relevant to epilepsy*

Currently approved AEDs target 17 different proteins. In contrast, drugs in the database target 155 unique proteins (Table S3). 42% of the proteins are targeted by ≥2 different drugs. Within the set of proteins targeted by conventional AEDs, the vast majority are ion channels. G protein-coupled receptors (GPCRs) and transcription factors are conspicuous by their absence from the set of proteins targeted by conventional AEDs. Drugs in the database target a diverse range of proteins, including GPCRs and transcription factors (Fig 2). Many of the proteins targeted by these drugs have published evidence of functional relevance in epilepsy, but are not targeted by current AEDs (see Table 3 for examples).

Examples of promising drugs identified from the PDE3 database are shown in Table 3. These drugs target proteins involved in epilepsy but not targeted by current AEDs, have multiple types of corroborative evidence supporting their efficacy in experimental epilepsies, exert a dose-dependent effect in experimental epilepsies, are effective in rodent models of epilepsy at human-equivalent doses smaller than licensed human doses, and are widely-used for their licensed indications. None of these drugs have been tested in appropriately-powered randomised controlled human clinical trials for epilepsy.

*The identified drugs are of putative relevance to human epilepsy*

Significantly more drugs in the PDE3 database target proteins of known causal human epilepsy genes than expected by chance alone (two-sided Fisher’s exact test p-value < 3x10-5). The set of proteins targeted by the identified drugs is significantly enriched with known causal human epilepsy genes (two-sided Fisher’s exact test p-value < 1x10-13).

**Discussion**

We present the PDE3 database ([www.Liverpool.ac.uk/D3RE/PDE3](http://www.Liverpool.ac.uk/D3RE/PDE3)). This database shows that there are many prescribable drugs that can potentially be repurposed for the treatment of epilepsy. These repurposing opportunities should be explored and exploited.

We envisage that the database will be used as follows. Based on the data provided, an appealing candidate drug (see examples in Table 3) will be selected for more detailed review of published animal and human studies, pharmacokinetic data and side effects profile. Fruitful reviews should then be published in order to publicise potential drug repurposing opportunities. Such a model of, first, creating a database of potentially repurposable drugs and, then, iteratively selecting the most promising candidate drugs for detailed review and publication has been enacted in other disease areas, for example, the Repurposing Drugs in Oncology (ReDO) Project.12,29-32 We advocate the adoption of this paradigm for epilepsy, based upon the PDE3 database. The reviewed and highlighted potentially repurposable drugs can be further analysed through retrospective analysis of electronic health record data and, finally, taken into human clinical trials. In the near future, we plan to begin the process of selecting, from the PDE3 database, appealing candidate drugs for detailed review and publication.

The data presented can aid the prioritisation of repurposable drugs based upon any or all of multiple criteria:

1. Drugs with the strongest published evidence of efficacy in rodent models.
2. Drugs with a long track record of extensive clinical use.
3. Drugs with novel protein targets implicated in epilepsy but not exploited by current AEDs.
4. Drugs licensed for common conditions. The disorder for which the drug is licensed and co-morbid epilepsy could both be treated with one medication, hence, reducing cost, pill burden, side-effects and the risk of deleterious drug interactions, and improving compliance.
5. Drugs that enhance the efficacy of conventional AEDs in rodent models of epilepsy (Table 4) and, putatively, could be used as adjuncts to improve seizure control in people with epilepsy. Hence, the repurposed drug could be used to treat the condition for which it is licensed, whilst improving the efficacy of concomitantly prescribed conventional AED(s).

The database contains many drugs that are appealing candidates for repurposing because they have corroborated evidence of efficacy in experimental epilepsies, have been in use for many decades, are widely-accepted by prescribers and patients, are approved for the treatment of the most common chronic conditions, and target proteins implicated in epilepsy but not exploited by current AEDs.

It is also envisaged that the data presented can aid the search for new causal human epilepsy genes. The set of proteins targeted by the identified drugs is highly enriched with known causal human epilepsy genes. Hence, it is postulated, that this set of proteins is likely to harbour yet undiscovered causal human epilepsy genes, and be a valuable resource for their discovery.

The PDE3 database is a novel resource for drug repurposing research in epilepsy. To create this novel resource, novel methodologies were necessary. Specifically, custom bash scripts were created that can (1) efficiently search for thousands of drug names within hundreds of thousands of abstracts, and (2) identify abstracts in which particular search terms of interest occur together in a single sentence. Sentence-level concurrence of search terms increases specificity and precision of data retrieval.17 To the best of our knowledge, no pre-existing software offers such functionality. Such a sophisticated search strategy cannot be executed using any of Medline’s online interfaces. For us, our scripts reduced the number of abstracts to be manually reviewed by 100-fold. Without these novel scripts, such comprehensive large-scale literature-mining would not have been possible. Our scripts will be of use to other researchers undertaking large-scale data-mining projects of a similar nature. We are in the process of creating a user-friendly graphical user interface for our scripts. In the meantime, the scripts and instructions on how to use them will be readily shared upon request.

Computational literature-mining was followed by manual curation through crowdsourcing, which is an emerging methodology in biomedical research. Crowdsourcing has found particular utility in data-mining from published scientific texts,33-35 using crowds assembled from laypersons,33 medical undergraduates,36 or other groups.

We acknowledge limitations of the study. The database has been assembled from information present within Medline abstracts; the full publications have not been analysed or critically appraised. Some of the included studies could be of poor quality or erroneous in their attribution of an antiepileptic effect to a drug. However, we are reassured that this is unlikely to be a pervasive problem as 94% of drugs have corroborative evidence of efficacy in experimental epilepsies. Also, Medline abstracts have been successfully used to collate drug indications and drug-disease associations.13-16 Reading the complete texts of all 500 publications included in the database would be impracticable. However, researchers using the database to identify promising drugs should perform detailed review and critical appraisal of the studies cited for those drugs. Of course, even if the drugs in the database are efficacious in animal models of epilepsy, they might not be effective in people with epilepsy. However, we have shown that drugs in the database are of potential relevance to human epilepsy, as the database is highly enriched with drugs that target proteins of known causal human epilepsy genes. Any promising drugs identified from the database should be tested in human clinical trials before being utilised in clinical practice.

It is noteworthy that the database includes some drugs thought to lower the seizure threshold in man, for example selective serotonin reuptake inhibitors (SSRIs). However, recent analyses suggest that SSRIs do not increase but, rather, reduce seizure frequency in people with epilepsy.37,38 It may be that similar misconceptions explain the supposed proconvulsant effects of some of the other drugs in the database. Alternatively, the drugs could have divergent effects in different species or at different doses. Similarly, some drugs may exhibit both pro- and anticonvulsant activity in experimental epilepsies, depending on the species, model and drug dose.39

Some would argue that if commonly used drugs, such as the ones listed in the database, have antiepileptic efficacy in people with epilepsy, this effect would have been detected in epilepsy clinics through serendipity. We would suggest that modern busy clinical practice is not conducive to spontaneous unprompted discovery of temporal connections between the addition of seemingly unrelated drugs and improved seizure control, or between the discontinuation of seemingly unrelated drugs and worsened seizure control. Clinicians and patients might attribute such changes in seizure control to natural variation in seizure frequency. Additionally, an individual epileptologist might not see sufficient numbers of patients started on an individual repurposable drug to appreciate a pattern of improved seizure control with the initiation of that drug.

In conclusion, the PDE3 database is a novel and valuable resource for drug repurposing research in epilepsy. We plan to iteratively select the most promising candidate drugs from the database for detailed review and further study through retrospective analysis of electronic health record data. The database will be updated on a periodic basis with new published evidence.

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**Disclosures**

None of the authors has any conflict of interest to disclose

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Figures**

Figure 1 Overview of methodology used for literature-mining.



Figure 2 Classes of proteins targeted by conventional AEDs and by prescribable drugs with efficacy in experimental epilepsies. GPCRs: G protein-coupled receptors.



*Table 1* Corroborative evidence of efficacy in experimental epilepsies. WHO: World Health Organisation; ATC: Anatomical Therapeutic Chemical.

|  |  |  |
| --- | --- | --- |
| Corroborating evidence | Number of drugs | % of drugs |
| Evidence of efficacy from multiple studies | 93 | 54 |
| Evidence of efficacy in multiple rodent models | 90 | 51 |
| Evidence of both an independent and enhancing antiepileptic effect | 49 | 28 |
| Evidence of efficacy of other drugs with the same mechanism of action | 119 | 69 |
| Evidence of efficacy of other drugs belonging to the same WHO ATC therapeutic/pharmacological/chemical subgroup | 101 | 58 |
| At least one type of corroborative evidence | 162 | 94 |

*Table 2* The 10 most prevalent chronic conditions,28 and repurposable drugs from the PDE3 database that are used for their treatment. GORD: gastro-oesophageal reflux disease

|  |  |  |
| --- | --- | --- |
| Chronic condition | Prevalence (%) | Drugs |
| Hypertension | 34 | Amlodipine, Captopril, Clonidine, Diltiazem, Enalapril, Felodipine, Furosemide, Guanabenz, Isradipine, Losartan, Nicardipine, Nifedipine, Nisoldipine, Nitroprusside, Pindolol, Prazosin, Propranolol, Telmisartan, Verapamil |
| Hyperlipidemia | 33 | Atorvastatin, Lovastatin, Pravastatin, Simvastatin |
| Depression | 19 | Amitriptyline, Bupropion, Citalopram, Desipramine, Doxepin, Duloxetine, Fluoxetine, Fluvoxamine, Imipramine, Pargyline, Quetiapine, Sertraline, Venlafaxine |
| GORD | 15 | None |
| Diabetes mellitus | 12 | Liraglutide, Metformin, Pioglitazone, Sitagliptin |
| Obesity | 12 | Methamphetamine |
| Osteoarthritis | 10 | Capsaicin, Celecoxib, Rofecoxib |
| Asthma | 9 | Montelukast |
| Osteoporosis and osteopenia | 7 | Cholecalciferol, Estrone |
| Migraine | 6 | Amitriptyline, Atenolol, Buclizine, Butorphanol, Methysergide, Metoprolol |

*Table 3* Examples of promising drugs identified from the PDE3 database. Evidence of drug targets’ relevance to epilepsy is in the papers cited in ‘Target and evidence of target’s relevance to epilepsy’ column. Evidence of efficacy in experimental epilepsies (1-5) is one or more of the five types pf corroborative evidence listed in ‘Methods’. The human equivalent of minimum effective dose in rodents was calculated by converting rodent doses to the equivalent for a 70 kg human using published formulae.40 The maximum licensed dose, according to the BNF, is shown. Number of prescriptions is the number of prescription items dispensed in the community in England in 2016. HED: human-equivalent dose; LTCC: L-type voltage-gated calcium channel; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; GABABR: GABAB receptor; AT1R: angiotensin II type 1 receptor; CysLT1R: cysteinyl leukotriene receptor 1; PPARγ: peroxisome proliferator-activated receptor gamma; β1-2-AR: β1 and β2 adrenergic receptors. References cited in this table are listed in the Supplementary Results, in order to save space.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Target and evidence of target’s relevance to epilepsy** | **Evidence of efficacy in animal models** | **Dose-**  **dependent effect?** | **HED of**  **dose in**  **rodents (mg)** | **Dose**  **in man (mg)** | **Number of prescriptions** |
| **Amlodipine** | LTCCS1-S20 | 1, 2, 3, 4, 5 | YesS21 | 5.7S21 | 10 | 26,639,873 |
| **Aspirin** | COXS22-S39 | 1, 2, 3, 4, 5 | YesS40 | 56S40 | 75 | 26,358,016 |
| **Atorvastatin** | HMGCRS41-S47 | 1, 2, 3 ,4 5 | YesS48 | 28S49 | 80 | 32,321,934 |
| **Baclofen** | GABABRS50-S82 | 1, 2, 3, 5 | YesS83 | 22.4S84 | 100 | 1,041,141 |
| **Losartan** | AT1RS85-S87 | 1, 2, 3, 4, 5 | YesS88 | 112S89 | 150 | 9,029,338 |
| **Memantine** | NMDARS90-S105 | 1, 2, 3 | YesS106 | 5.6S107 | 20 | 969,106 |
| **Montelukast** | CysLT1RS108,S109 | 1, 2, 3 | YesS108,S110 | 5.7S108 | 10 | 2,406,711 |
| **Pioglitazone** | PPARγS111-S118 | 1, 2 | YesS113 | 5.7S119 | 45 | 952,808 |
| **Propanolol** | β1-2-ARS120-S125 | 1, 2, 3, 4, 5 | YesS126 | 0.56S127 | 160 | 4,694,616 |

*Table 4* Some of the prescribable drugs that enhance the efficacy of licensed AEDs. The full list can be found in the PDE3 online database and in Table S1. AUD: audiogenic; electro: maximal electroshock; kin: kindling; PTZ: pentylenetetrazol.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name | Indications | AEDs enhanced | Number of studies | Models |
| Nimodipine | Subarachnoid haemorrhage | Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin, Valproate, Other | 7 | PTZ, Electro, AUD |
| Propranolol | Hypertension; portal hypertension; phaeochromocytoma; angina; arrhythmia; hypertrophic cardiomyopathy | Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin, Valproate, Other | 5 | Electro, AUD |
| Sildenafil | Pulmonary hypertension; erectile dysfunction | Carbamazepine, Ethosuximide, Levetiracetam, Oxcarbazepine, Phenobarbital, Tiagabine, Topiramate, Valproate, Vigabatrin, Other | 4 | PTZ, Electro, Other |
| Fluoxetine | Depression; bulimia nervosa; obsessive-compulsive disorder | Carbamazepine, Phenobarbital, Phenytoin, Valproate, Other | 4 | PTZ, Electro |
| Diltiazem | Angina; hypertension | Ethosuximide, Phenytoin, Topiramate, Valproate | 4 | PTZ, Electro, AUD |
| Nifedipine | Angina; hypertension; raynaud's phenomenon; premature labour | Ethosuximide, Phenobarbita, Topiramate, Valproate | 4 | PTZ, AUD |
| Enalapril | Hypertension; heart failure | Carbamazepine, Lamotrigine, Topiramate, Valproate, Other | 3 | Electro, AUD |
| Probenecid | Gout | Oxcarbazepine, Phenytoin, Other | 3 | Pilo, Electro, Kin |