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REVIEW

Computational approaches for innovative antiepileptic drug discovery

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ABSTRACT

Introduction: Despite the approval of a large number of antiepileptic agents over the past 25 years, there has been no significant improvement in efficacy of treatments, with one third of patients suffering from intractable epilepsy. This scenario has prompted the search for innovative drug discovery solutions. While network pharmacology and explanations of the drug resistance phenomena have been proposed to drive the search for more efficacious therapeutic solutions, such alternative approaches have not fully taken hold within the antiepileptic drug discovery community so far.

Areas covered: Herein, the author discusses the impact that network pharmacology and the current hypotheses of refractory epilepsy and drug repurposing could have if integrated with anti-epileptic computer-aided discovery.

Expert opinion: With many complex diseases, the advancement in the understanding of disorder pathophysiology in addition to the contribution of systems biology have rapidly translated into the discovery of novel drug candidates. However, antiepileptic drug developers have fallen a little behind in this regard, with fewer examples of computer-aided antiepileptic drug design and network-based approximations appearing in scientific literature. New generation single-target agents have so far shown limited success in terms of enhanced efficacy; in contrast, multi-target agents could possibly demonstrate improved safety and efficacy.

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1. Introduction

Epilepsy, a large group of disorders consisting in recurrent unprovoked seizures, is the most common brain disorder, affecting around 0.4–1% of the world population [1]. Despite more than 15 third-generation antiepileptic drugs (AEDs) have been approved from 1990 to date, including selective drugs discovered through target-driven approaches, such as vigabatrin or tiagabine [2], no significant improvement in the overall efficacy has been achieved [3,4]: seizures are not controlled with pharmacotherapy in about one-third of the patients, a condition known as refractory or intractable epilepsy.

The failure of existing AEDs to meet the expectations has led to growing disappointment at different levels of the drug discovery community, from basic scientists to the pharmaceutical industry, and to a perceived loss of industry interest [3,5]. Faced with this situation, leading experts in the field of AED discovery have underlined the need of new concepts and fresh thinking to improve novel AED discovery [3].

While computational models are presently used in virtually all fields of drug discovery, computational approaches for the screening or design of novel AEDs have been underexplored in comparison with other therapeutic categories. This may arise from a persistent and major obstacle to apply structure-based approximations in the field of AED development: most validated molecular targets for AEDs are either voltage- or ligand-based ion channels whose structure has not been experimentally solved yet, which forces drug designers in the epilepsy field to resort to homology modeling or ligand-based approximations. For instance, homology models of relevant targets such as gamma-aminobutyric acid transaminase (GABA) transaminase, GABA transporters, and synaptic vesicle protein 2A (SV2A) have recently been reported [6–8]. A notorious exception is carbonic anhydrase, a putative AED target whose human isoforms have already been solved and are being actively used to search for novel antiepileptic therapies [9–12].

In order to provide innovative and more efficacious solutions for the management of epilepsy, computational modeling should integrate the most recent experimental data on the underlying causes of epilepsy and drug-resistant epilepsy and address paradigm shifts in the field of drug discovery for the treatment of complex disorders. Here, we will discuss how (and why) recent knowledge related to the physiopathology of epilepsy (including available hypothesis on the nature of refractory epilepsy) should be incorporated into the process of computer-guided AED design and identification. A flow diagram illustrating some of the ideas discussed in the review is presented in Figure 1.

2. Are selective and potent drugs the most adequate solution for epilepsy?

2.1. Incorporating systems biology principles to the AED discovery field

Some decades back, the pharmaceutical industry adopted target-driven (allegedly 'rational') approaches to drug discovery. The general idea behind this paradigm was that exquisitely

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Article highlights

- Last generation antiepileptic drugs have failed to meet the expectations regarding improved efficacy in the treatment of refractory patients.
- Novel strategies towards the development of new antiepileptic agents are required.
- Modern approaches (e.g. multi-target drugs, computer-guided drug design) that have been widely used to discover new treatments for other diseases of complex etiology have been underexplored in the case of epilepsy.
- Knowledge on the hypothetic causes of drug resistant epilepsy should be translated to the antiepileptic drug discovery field.
- Target-driven approaches towards antiepileptic drug discovery should be complemented with phenotypic-based approximations in line with the network pharmacology perspective.
- Systematic drug repurposing poses excellent opportunities for the antiepileptic drug discovery community.

This box summarizes key points contained in the article.

selective agents interacting with a validated target would avoid off-target interactions, thus arriving to safer therapeutic solutions. While 'clean' drugs developed through target-based approaches seem well suited to find therapeutic agents to treat monogenic diseases, they are generally less efficacious for the treatment of complex disorders and are usually cited as one of the reasons for the decline of new drugs that reach the market despite the increased investment in drug discovery [13–15], a reality that is particularly marked in the field of central nervous system (CNS) pharmacology [16,17]. Inquiringly, the number of small-molecule first-in-class drugs emerging from phenotypic screening seemingly outnumbers those emerging from target-centered discovery [18].

In some cases, the clinical reality has challenged the theoretically improved safety of target-based therapeutics. For instance, in the case of retigabine, a first-in-class K+ channel opener for the adjunctive treatment of partial-onset seizures, back in 2013, the Food and Drug Administration (FDA) approved changes to drug label (black boxed warning) in order to warn that the drug can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina that may lead to permanent vision loss [19]. Accordingly, the FDA advises periodic eye examinations to people taking retigabine; the drug should be discontinued if ophthalmic changes are observed. Similarly, retigabine indication was restricted to last-line use in UK, and patients taking the drug should be subjected to comprehensive ophthalmic examination every 6 months [20]. Furthermore, interaction of this drug with Kv7 potassium channels expressed in the smooth muscle of the urinary bladder explains other adverse reactions such as urinary retention, hesitation, and dysuria, which have led to a Risk Evaluation Mitigation Strategy program for urinary retention [21].

It is to be noted, though, that the contribution of very recently approved selective AEDs such as the allosteric alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist perampanel has still to be seen, while vigabatrin is the first-line drug against infantile spasms due to tuberous sclerosis [22,23]. Thus, whereas introduction of selective AEDs to the market has still not shown an overall improvement on the successful rate in the management of epilepsy, selective agents could be advantageous against specific types of epilepsy, and the impact of recently approved selective agents will not be known until some years from now.

From the perspective of systems biology, biological organisms are resilient to perturbation, and disease is often an also resilient state that emerges from multiple and simultaneous perturbations of an intricate network of elements [14], a viewpoint that seems particularly valid to explain complex disorders. A number of authors have begun to realize that epilepsy, as a complex, multifactorial, multigenic, and dynamic pathology is particularly suited to be approached through systems biology [24–28]. One of the current hypotheses that provide explanation to the drug resistance phenomenon in epilepsy points to the role of the disturbed state in complex networks of interacting components that are reorganized following epileptogenic activity [29,30]. How could the 'system pharmacology' approach be translated into the drug discovery field? Mainly, in four ways.

First, by complementing single-target approaches with multi-target ones (either through multidrug therapeutics or

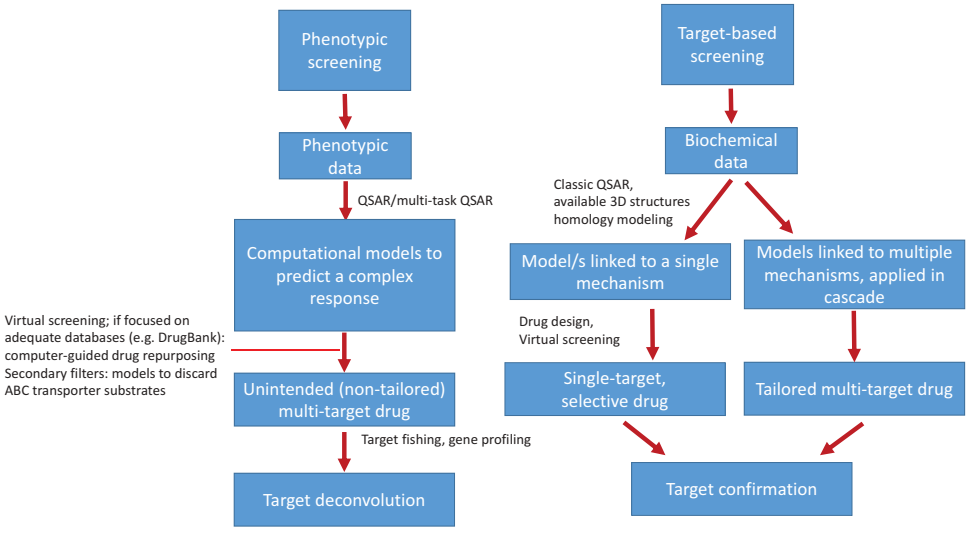

Figure 1. Flow diagram illustrating some of the points discussed in this review.

through multi-target single drugs) [24,28]. Whereas highly selective agents may display greater efficacy in selected patient subgroups (i.e. to treat specific syndromes) [5], many of the existing and more used AEDs are in fact (unintended) multi-target agents that have been selected through phenotypic approaches [25,27]. A diversity of studies in animal models of seizure and epilepsy suggest that the combination of drugs associated to different mechanisms tends to enhance the efficacy of the treatment [3,31–34]. Remarkably, the protective effects of other AEDs are enhanced by levetiracetam (an AED with distinctive mechanisms of action) despite the seizure model or drug combination studied [31]. Second, by conferring genome-wide analysis a prominent role in the drug discovery process, exploiting modern technologies (high-content technological platforms, 'omics') that allow exploring the interactions among thousands of genes and their products in different states [3]. Third, by scrutinizing 'the more potent the better' paradigm of hit selection under the light of the network pharmacology approach. And fourth, by developing quantitative structure–activity relationships (QSARs) using biological responses obtained in animal or cellular models, instead of the classical suggestion of preferring binding affinity data obtained at the *in vitro* level. It should be remembered that, as mentioned previously, the term epilepsy encompasses a large number of complex disorders with distinctive etiology and manifestations. Being so, it is possible than some types of epilepsy could be better addressed through single-target agents, while others could require therapeutic agents linked to a more complex pharmacology. Accordingly, we would like to highlight that, in our opinion, the evolution of the AED discovery does not call for the *replacement* of target-driven approximations by network-based approaches, but for the integration of system pharmacology thinking to existing paradigms.

As we discuss in further subsections, the network pharmacology paradigm has vast applications in the realms of cheminformatics and bioinformatics, including tailored multi-target agents, automated network analysis tools, and automated comparison of gene signatures. These tools have, however, been scarcely applied in the field of AED development, thus far.

2.2. Tailored multi-target/multifunctional AEDs – arguments in favor of and against hybrid molecules: recent applications

Before target-driven drug discovery, new leads emerged from serendipitous discovery, traditional medicine, or phenotypic screening in cellular or animal disease models. Although it was possible to find multi-target agents through such approaches, those targets were, if lucky, defined a posteriori, and the combination of targets attacked was unpremeditated and sometimes not fully understood. As an example, note that even today, the molecular mechanisms of action of aspirin itself are not completely uncovered, and new modes of action of this centennial drug are constantly being reported [35–37].

In the discussion on phenotypic- versus target-based strategies, tailored multi-target agents can be regarded as the middle way. They are an extension of the target-centered approach that incorporates the perspective of network pharmacology. Tailored (or designed) multifunctional agents are purposely conceived to selectively modulate a number of chosen targets of interest, frequently relying on computer-aided design and data analysis tools and simplifying (costly) target deconvolution. In principle, multi-target agents are equivalent to the combined therapy with different single-target agents, but they are advantageous in terms of reduced probability of drug interactions, simplified pharmacokinetics, and better patient compliance [38]. The pharmacodynamics of the components of a hybrid drug should be, however, compatible [39]; in other words, the ratio of activities at the different targets should usually be adjusted so that the multi-target drugs hit every target with approximately the same potency, and thus the same dose could be used to modulate a diversity of targets, a requirement which could prove complicated to attain [40]. Furthermore, multi-target agents display, comprehensibly, higher probability of off-target interactions.

While tailored multi-target agents to address other complex CNS conditions (including neurodegenerative diseases and mood disorders) have been abundantly explored [41–43], this strategy has been (at most) meagerly applied in the search of novel solutions for epilepsy (Figure 2) [23]. The application of this type of hybrid drugs in epilepsy is restricted by our incomplete understanding of the pathophysiology of this disorder, which limits our possibilities to rationally choose an appropriate combination of mechanisms (however, limited knowledge on the underlying pathological mechanisms has not hampered the development of multi-target agents as

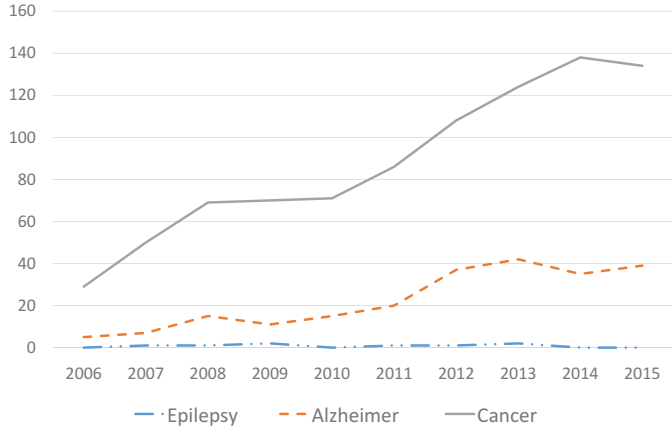

Figure 2. Comparison of the number of published scientific articles per year related to the multi-target approach and epilepsy, Alzheimer's disease and cancer. Whereas the three compared disorders are undeniably complex and their underlying pathological mechanisms are not fully understood, the differences in the number of articles are overwhelming. In the author's opinion, these differences reflect not only differences in the R&D investment for these disorders (cancer is, probably, the disorder that attracts the most funding) but also particular challenges posed by epilepsy and some delay in the antiepileptic drug discovery community to embrace innovative strategies. The search was performed in titles, abstracts and keywords of scientific articles indexed by Scopus. Search criteria where: for epilepsy, 'epilepsy' and 'hybrid molecule' or 'hybrid drug' or 'hybrid approach' or 'multi-target'; for Alzheimer's disease, 'Alzheimer' and 'hybrid molecule' or 'hybrid drug' or 'hybrid approach' or 'multi-target' and; for cancer, 'cancer' and 'hybrid drug' or 'hybrid approach' or 'multi-target' or 'tumor' and 'hybrid drug' or 'hybrid approach' or 'multi-target'.

potential solutions to other complex disorders, e.g., cancer). On the other hand, empirical evidence indicates that some AEDs could be effective to address some epilepsy types while paradoxically worsening seizures in others [44–46]; therefore, the combination of mechanisms of action and the clinical applications of the resulting hybrid molecules should be carefully examined to avoid seizure aggravation. The previous scenario is complicated by the inherent complexity of defining 'causes' in epilepsy [47,48]: while causal conditions of epilepsy based on notable structural change and monogenic illnesses have been identified, mechanisms of genetic influences and proximate molecular mechanisms are less clearly established [47]. The self-perpetuating nature of epilepsy and the relatively low availability of brain tissue samples from epileptic patients constitute other major obstacles to differentiate causes from effects.

Despite the intrinsic limitations to the development of tailored multi-target AEDs, the theoretical applications of hybrid molecules in the field of epilepsy are enormous. First, multi-target agents could be a viable solution to deal with drug-resistant epilepsy linked to acquired or constitutive target modifications [49]. Second, multi-target agents could be designed to address, simultaneously, the symptoms and underlying causes of the disease. For instance, it is suspected that seizures and inflammation take part in a complex interplay that results in a negative circle [40,51] where inflammation may be both cause and consequence of seizures. Clinical evidence, particularly in children, suggests that steroids and other anti-inflammatory treatments display anticonvulsant activity in some drug-resistant epilepsy syndromes. Furthermore, some of the most efficacious AEDs (valproic acid, levetiracetam, and carbamazepine) have also shown anti-inflammatory effects [52–54]. Thus, it could be speculated that a combination of anticonvulsant and anti-inflammatory properties (and other properties with positive impact on disease progression, e.g., neuroprotective effect) in novel tailored multi-target agents could have a positive impact on epilepsy treatment. Finally, since a very high percent of epilepsy patients (and in particular, refractory patients) suffer from comorbid psychiatric disorders (e.g. anxiety, depression, and suicidal ideation) [55,56], the simultaneous treatment of epilepsy and comorbid manifestations of epilepsy would be a third possible application of multi-target agents. Remarkably, many widely used AEDs have shown benefits against mood disorders [57–60], while others seem to possibly aggravate or trigger negative behaviors linked to epilepsy [60–63]. Even so (positive or negative), collateral effects of AEDs are not usually considered when making treatment decisions (the choice of which AED the neurologist will prescribe in the treatment of epilepsy is most frequently based on the classic benefits, i.e., seizure control efficacy) [59,64]. Clinical and epidemiological studies on epileptic patients examining the behavioral effects associated with particular AEDs are still limited and in some cases conflicting (see for instance [60, 65–67]).

Some hybrid molecules for the treatment of epilepsy have recently been designed, with interesting results. Hassan and coworkers, for example, developed a series of *N*-(substituted benzothiazol-2-yl)amide combining riluzole (an anticonvulsant with phenytoin-like spectrum of activity and neuroprotective properties) with a moiety containing a GABA-like pharmacophore on a benzothiazole nucleus [68]; the most promising candidate presented median effective doses (ED_{50}s) around 41 and 85 mg/kg in the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) tests, respectively. Similarly, hybrid molecules of ameltolide and GABA amides have been obtained by Yogeeswari et al. [69]. One of the resulting compounds, 4-(2-(2,6-dimethylaminophenylamino)-2-oxoethylamino)-*N*-(2,6-dimethylphenyl) butanamide, emerged as the most potent derivative effective in three different animal models of seizure: MES, scPTZ, and subcutaneous pricrotoxin test.

An attractive application of the hybrid molecule concept in the field of AED discovery was reported some years back by Wang and colleagues. Based upon a CoMFA model, they proposed novel compounds containing both the phenytoin pharmacophore or the hydroxyamide pharmacophore and the local anesthetic lidocaine, which were predicted as potent binders to the neuronal sodium channel as they would potentially have the ability to bind to an expanded binding region encompassing both the phenytoin and local anesthetics-binding sites [70]. The idea of designing a compound capable of binding two distinct sites of the same target could be interesting to address target-based drug resistance, under the notion that it is less probable that target modifications lead to loss of sensitivity to such kind of hybrid agents.

2.3. Tailored multi-target agents: some general and specific considerations to guide their computer-aided search

Multi-target drugs are based on the general idea of merging two pharmacophores into a single molecule (which can display different degrees of overlapping; Figure 3) [71] or, alternatively, finding a common pharmacophore between two molecular targets of interest. In the absence of commonalities between the pharmacophoric requisites, distinct pharmacophores can be joined together through a linker (fragment-based approach). Such arrangement corresponds to what Sturm and coworkers have called bianchor ligands, which use different sets of atoms to interact with each target protein [72]. The fragment-based approach tends to produce ligands that violate drug-like criteria [24,73,74]; logically, the chance of violating drug-likeness rules and compromising bioavailability

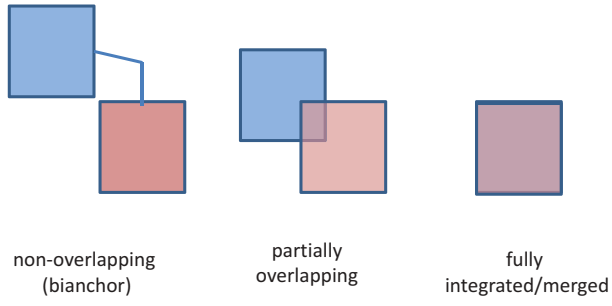

Figure 3. The design of multi-target drugs can integrate pharmacophores with completely distinctive features (left) or common structural features. Fully overlapping pharmacophores are advantageous considering biopharmaceutical and ligand efficiency metrics. Nevertheless, it is possible that two given molecular targets present mutually excluding pharmacophores or a complete absence of commonalities.

increases as the number of distinct anchors does. The designer must thus carefully watch for possible bioavailability issues of the resulting molecule, a statement that is particularly relevant in the case of AED design owing to the special restrictions on physicochemical properties imposed by the blood–brain barrier (BBB). In this regard, Wager and coworkers have developed an interesting yet simple Central Nervous System Multiparameter Optimization and Desirability Score to decide if a given drug candidate is likely to display favorable pharmacokinetic and safety properties for its use as a CNS therapeutic agent [75]. The score is easily calculated through computation of six theoretical physicochemical properties: calculated partition coefficient (clogP), calculated distribution coefficient at pH = 7.4 (clogD), molecular mass, topological polar surface area, number of hydrogen bond donors, and the pKa of the most basic center. A direct relationship between this desirability score and alignment of key *in vitro* attributes of drug discovery (absence of P-glycoprotein efflux, metabolic stability, and safety) has been observed by Wager and colleagues in marketed CNS drugs as well as in Pfizer's candidate set.

The ligand efficiency of the multi-target agents is another aspect that should not be ignored during the design process [24,74,76]. In 1999, the empirical study by Kuntz et al. showed that, across a wide variety of small molecule–macromolecule complexes, maximal contributions to binding free energy per ligand non-hydrogen atom are similar to −1.5 kcal/mol; these authors also noticed a trend to a smaller free energy contribution per atom as the molecular mass of the ligand increases [77]. From then, ligand efficiency metrics have gained increasing acceptance within the drug discovery community, with retrospective analysis of recently marketed oral drugs showing that they usually have highly optimized ligand efficiency values for their targets [78]. In the case of the bianchor agents, it might be speculated that efficiency metrics will tend to be low since only a fraction of the molecule takes part in an efficient interaction between the ligand and each molecular target. The 'density' of efficient contacts between the drug and the targets will consequently tend to be low. Highly integrated pharmacophores may serve to solve the binding efficiency and bioavailability issues typical of fragment-based approximations. Sturm et al. have observed a class of multi-target agents that they called 'flexible ligands,' which includes ligands that can adopt different conformations in the binding sites of the different targeted proteins; whereas the same set of heavy atoms locates in the binding sites, different atoms are involved in direct interactions with each of the targets [72]. It should be warned, though, that an excessive flexibility could conspire against the binding free energy owing to the entropy loss associated to decreased conformational freedom resulting from drug–target recognition event.

There are many other molecular features that have shown a correlation with promiscuity and can presumably be tuned during the drug design process to adjust the degree of promiscuity. For instance, several studies suggest that ligand promiscuity is inversely related to molecular weight [72,79,80] though some other studies have failed to find a correlation or have shown an opposite trend [78,79,81], suggesting that the correlation between molecular mass and promiscuity is context dependent [80]. Sturm et al. identified a class that multi-target compounds that they labeled as 'superpromiscuous,' which could bind to nonhomologous targets, with the same ligand-atoms being involved in direct interactions with each of the targets. Remarkably, these superpromiscuous ligands tend to present either low or high complexity [72]. Direct correlations have also been found between promiscuity and clogP [82,83] or the fraction of molecular framework (for large molecular framework values) among other properties [83]. Since the fraction of molecular framework is defined as the number of heavy atoms in the molecular framework divided by the total number of heavy atoms in the molecule, a smaller molecular framework and more side chain atoms will improve selectivity.

Regarding the application of *in silico* screening campaigns, one should bear in mind that application of independent models to identify multi-target agents is expected to yield lower hit rates than virtual screening campaigns oriented to single-target drug candidates [16,73,74,76]. If it is assumed that being a ligand for one of the pursued targets does not increase or decrease the chance of being a ligand for another one (a situation that corresponds to neither overlapping nor mutually exclusive pharmacophores), each model used in the *in silico* screening process functions as a structural restriction that filters out the molecules that do not gather the model's requisites; thus, the more models used, the less probable it is to find chemical compounds accomplishing all the models' structural constraints. Considering this situation, when choosing the score thresholds to consider a compound as a predicted (multi-target) active drug, it can be a reasonable alternative to sacrifice specificity in favor of sensitivity; such strategy, of course, will result in an increment of experiment-related costs (diminished active enrichment). Alternatively, choosing the pursued targets on the basis of empirical or theoretical evidence on common determinants of specificity could be a good advice to improve the likelihood of success. There is a plenty of evidence on the existence of molecular coevolution (coordinated changes that occur in pairs of biomolecules to maintain or refine functional interactions between them), and a number of bioinformatics tools have been developed to detect it [84]; these could be used to identify pairs of molecular targets with similar binding sites.

2.4. Gene signature comparison

Gene expression profiles offer a picture of globally measured transcript levels in a given cell, tissue, or organism at a specific point of time [85]; gene signatures are characteristic of particular conditions, i.e., disease states or exposure to a certain drug. They can be particularly relevant to characterize the phenotypic response to long-term drug exposure (which is the general case for drugs used to treat chronic condition, e.g., AEDs) to shed light about the mechanisms of action of drugs and to identify potential treatments for a given disease. The Broad Institute has pioneered such applications through its Connectivity Map. It is a publicly available resource conceived to connect disease and small molecules through gene profiles [86]. It compiles gene expression profiles derived from the treatment of human cells cultured with a large number of perturbagens,

including more than 1300 FDA-approved drugs. Query expression signatures can be compared to the stored ones through pattern-matching algorithms: those at the top and bottom of the resulting similarity rank are considered related to the query state by shared (direct similarity) or opposite (inverse similarity) expression changes, in that order. It is presumed that compounds eliciting similar expression changes than the ones observed in a given disease state will aggravate such condition, whereas compounds displaying inverse signatures to the disease state would likely work as therapeutic agents. Naturally, robustness of gene signature-based studies is highly dependent on the quality of the expression profiles from which they are generated.

Gene expression profiling studies have been conducted in the past years to help comprehending the molecular changes underlying epilepsy and epileptogenesis and identifying potential molecular targets for intervention [87–91]. More recently, gene profiling was used to investigate gene expression in the hypoxic seizure model of acquired epilepsy in the rat, with and without treatment with an AMPA receptor antagonist, a compound under investigation as modulator of epileptogenesis [92]. The gene profiles obtained in the previous studies could be a good starting point to reveal novel drugs with disease-modifying properties, by application of the inverse similarity idea proposed by the Connectivity Map.

At this point, it is worth mentioning emerging approaches to AED target discovery based on the targeting of transcriptional processes. Epigenetic mechanisms involved in transcriptional regulation of multiple molecular pathways are attractive therapeutic interventions for epilepsy, since single-target therapies are unlikely to provide both anticonvulsant and disease-modifying effects. Mazzuferi and coworkers found a significant increase in nuclear factor erythroid 2-related factor 2 (Nrf2) (a transcription factor that promotes the expression of anti-inflammatory, antioxidant, and neuroprotective gene products) in human epileptic hippocampal tissue and in mice following pilocarpine-induced status epilepticus [93]. A review on Nrf2 as a therapeutic target for epilepsy has recently been published [94]. McClelland et al. found that interfering with the repression of numerous genes by the transcriptional repressor neuron-restrictive silencer factor can attenuate the development of epilepsy in the short term, supporting a mechanistic role in epileptogenesis [95]. Through application of system genetics to surgically acquired hippocampal tissue from temporal lobe epilepsy patients, Johnson et al. identified a gene-regulatory network genetically associated with epilepsy that contains a specialized, highly expressed transcriptional module encoding proconvulsive cytokines and Toll-like receptor signaling genes [96]. The proconvulsant module was mapped to the SESN3, and it was verified that it was conserved across species. These reports illustrate the potential of system genetics to unveil pathways related to epilepsy onset and progression. Such pathways could be targeted to arrive to next-generation disease-modifying therapeutic solutions in line with some of the most recent hypotheses of drug-resistant epilepsy (i.e. the network hypothesis).

2.5. Are the most potent drugs the best choice to move forward?

From a network pharmacology perspective, targeting hubs (highly connected nodes in a biochemical network) might not be the best strategy, especially if we are targeting sensitive organs (such as the brain). Using low-affinity, multi-target ligands to modulate multiple non-crucial nodes adjacent to key nodes sounds as a more rational approach to restore the network to its normal functioning without severe side effects [97]. Partial weakening of regulatory networks at a small number of selected nodes may have a greater impact than the complete elimination of a single selected node [98]. As clearly expressed by Bianchi and coworkers, 'the complexity of neural processes underlying seizure activity may be more amenable to multiple small perturbations than a single dominant mechanism' [27].

Memantine (Figure 2) constitutes a good example of the potential benefits of low-affinity multi-target ligands on CNS disorders [99,100]. It is currently prescribed for the treatment of moderate-to-severe Alzheimer's disease and other types of dementia when acetylcholinesterase inhibitors are not tolerated; memantine produces moderate decrease in clinical deterioration. Unlike high-affinity uncompetitive inhibitor of the N-methyl-D-aspartate receptors (NMDAR) dizocilpine, which has not reached the market due to severe side reactions including psychotic reactions, cognitive disruption, and Olney's lesions, memantine possesses surprising low-affinity binding to NMDARs (in the high nanomolar to low micromolar range), fast on/off kinetics, and almost no selectivity among NMDARs subtypes [99], being much better tolerated. It also shows uncompetitive antagonism on other receptors, including serotonin type 3 [101], nicotinic [102], and dopamine D2 receptors [103] (in all cases, with comparable potency than for the NMDA receptors) (Figure 4).

The AED imepitoin (approved in the US and Europe for the treatment of epilepsy in dogs) constitutes another example of the potential of low-affinity ligands for the treatment of epilepsy [104]. It is a broad-spectrum AED that acts as a low-affinity partial agonist for the benzodiazepine-binding site in $GABA_A$ receptors. Identified through a pharmacophore-based screening, it was originally thought as a novel AED for humans, but development was terminated because of pharmacokinetic differences between smokers and nonsmokers. Effectiveness was demonstrated in a wide range of preclinical models of seizure and epilepsy, including electrically and chemically induced seizures, genetic models of seizures and amygdala, and hippocampal kindling models. Observed

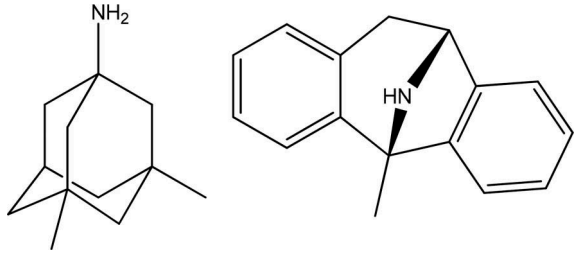

Figure 4. Memantine (left) illustrates the potential advantages of low-affinity multi-target ligands compared with high affinity drugs like dizocilpine (right), questioning the predominant 'the more potent the better' paradigm.

Ki values are in the low micromolar range. Interestingly, the drug has a similar activity profile than benzodiazepines but is much better tolerated and lacks the tolerance and abuse liability of other full and more potent agonists.

However, the old paradigm (the more potent and the better) still prevails in the primary screening for novel AEDs (and novel drugs, in general). Note that the National Institutes of Health's Anticonvulsant Screening Program still considers the acute potency of drug candidates in acute seizure models to decide which candidates will progress to further testing [105], a decision-making scheme that may underestimate the efficacy of the drugs in on a long-term basis [106]. The same principle is often applied in the context of a computer-aided screening campaign, where the best scored hits (e.g. those having higher predicted affinities) are more likely to progress to experimental testing.

Remarkably, it has been underlined that levetiracetam (a new-generation AED that enjoys increasing attention within the epilepsy community and probably the new-generation antiepileptic agent with the most innovative pharmacologic profile) exerts multiple, mild, and modulatory actions on neurons, rather than a straightforward dose-dependent inhibition of one single effect [25]. In this regard, it should also be noted that in 2016 the European Commission and the FDA approved brivaracetam, a selective, high-affinity ligand of the SV2A (one of the known molecular targets of levetiracetam) [107], as an add-on treatment to other medications to treat partial-onset seizures in patients with epilepsy aged 16 years and older. Brivacetam was discovered during a large-scale drug discovery program aimed at optimizing the pharmacodynamics activity at such novel molecular target. In preclinical models, brivaracetam displayed more potent seizure suppression and greater antiepileptogenic potential than levetiracetam. It has a 15- to 30-fold increased affinity for SV2A compared with levetiracetam. Accordingly, the coming years could prove crucial to judge whether low-affinity multi-target agents like levetiracetam are clinically more efficacious than high-affinity and selective drugs such as brivaracetam and what are the clinical implications of their differential pharmacological profiles.

2.6. What response should be modeled?

In the context of classical QSAR theory, and particularly in the case of 3D QSAR, it is preferred that the training example used for model building share the same mechanism of action (and the same binding mode) [108–110]. It is argued that all 3D QSAR methods were conceived to describe only one interaction step in the lifetime of ligands [108], a statement that is supported by the fact that many 3D QSAR methods are highly alignment dependent. Furthermore, it is recommended to consider *in vitro* biological data only, since *in vivo* data reflect a number of parallel processes (e.g. transport, binding to multiple targets, biotransformation, and bioactivation) [108,109]. It is true that *in vitro* data are cleaner than *in vivo* data, in the sense that interpretation of the test results is more straightforward and less affected by confounding factors, while cellular models and living organisms undergo significant time-dependent changes. However, as stated previously, such excessive reductionist approach could be insufficient when dealing with complex disorders such as epilepsy. Against dogmatic or conservative viewpoints, very common biological data obtained from phenotypic models are used to build QSAR models and despite that the models attain considerable descriptive and predictive ability (see, for instance [111–114]). In this line, several successful QSAR models and *in silico* screening applications for the discovery of AEDs rely on *in vivo* biological data for modeling purposes [115–122], including reports by leading experts in the QSAR field [115]. What is more, QSAR theory has greatly evolved in the last years; multitasking QSAR models are suitable to predict multiple features complex behaviors, exploiting latent commonalities across tasks [123,124].

On the basis of already alleged advantages of multi-target ligands over single-target ones against epilepsy, building predictive models from biological responses obtained in phenotypic screening might be the best choice to obtain efficacious novel AEDs (transferring the philosophy of phenotypic screening to *in silico* screening). Most of the previously cited articles report models to predict the effect of a drug in (traditional) seizure models (prominently, MES test). The current challenge in this field is to intend modeling biological data obtained from actual models of epilepsy or at least other acute models so far understudied through the QSAR theory (e.g. 6-Hz test).

3. Incorporating refractory epilepsy hypotheses into computer-guided AED design

Biological mechanisms underlying drug-resistant epilepsy have not been fully elucidated yet [5]. There exist five predominant hypotheses that try to explain the nature of this phenomenon: the transporter hypothesis [125,126], the target hypothesis [126,127], the neural network hypothesis [29], the gene variant hypothesis [128], and the intrinsic severity hypothesis [129]. Chronologically, the transporter and target hypotheses have been proposed earlier and have therefore been more extensively examined from an experimental perspective.

Briefly, the transporter hypothesis sustains that refractoriness could emerge from the local overactivity of polyspecific adenosine triphosphate-binding cassette (ABC) transporters at the BBB and/or the epileptic foci. If an AED was recognized by such efflux pumps, these could impede achieving effective levels of the therapeutic agents at the site of action. A major argument against the transporter hypothesis is that not all AEDs are substrates for the ABCB1 transporter (Pgp). Seemingly contradictory evidence exists regarding which AEDs are substrates and which are not [130,131], but it should be kept in mind that results are highly dependent on the experimental setting, including type of assay (*in vitro, ex vivo*, or *in vivo*; animal or human models; and nonequilibrium conditions or concentration equilibrium transport assay). Still, it seems safe to say that some AEDs are unlike Pgp substrates or weak Pgp substrates at best. Does this entirely preclude the validity of the transporter hypothesis? Not really. First, Pgp is one among many other efflux transporters possibly involved in drug-resistant epilepsy. Most of the studies determining the directional transport of AEDs have focused on Pgp; however, some of the AEDs are transported by other members of the

ABC superfamily. For instance, recent studies using double knock-out Mdr1a/1b(−/−)/Bcrp(−/−) mice and the concentration equilibrium transport assays suggest that some AEDs are breast cancer resistance protein (BCRP) substrates [132,133]. Moreover, due to the partial overlapping of the substrate specificity of different ABC transporters (together with co-localization and co-expression patterns that suggest a cooperative role in the disposition of common substrates) [132–134], the role of a certain ABC transporter might be obscured owing to the function of others, their concerted function, and the possible compensatory regulation, thus requiring complex models to study the phenomena. The difficulties to quantify the levels of expression of a given transporter in different regions of the brain of patients who have not been subjected to surgical procedures and the uncertainties regarding the ability of experimental models to reflect the absolute and relative expression levels of the different ABC efflux transporters at the BBB and the epileptic foci contribute are other obstacles to investigate the influence of a given transporter in the regional AED bioavailability in the brain (note that high local levels of an efflux transporter could even limit the bioavailability of weak substrates). The current definition of refractory epilepsy itself [135] implies that the transporter hypothesis may hold even if some of the known AEDs are not recognized by ABC transporters. The definition indicates that a patient should be diagnosed refractory after failure of two well-tolerated and appropriately chosen and used AED trials; the key to the preceding reasoning lies in what is considered an appropriate drug choice. The definition of drug-resistant epilepsy weakens the transporter hypothesis if and only if one of the two appropriate therapeutic interventions was in fact a non-substrate for ABC transporters. At present, in the absence of definitive clinical proof of the transporter hypothesis, clinical guidelines for the management of epilepsy do not recommend to try at least one non-substrate AED; thus, the quality of substrate or non-substrate is presently unrelated to the appropriateness of the intervention. As a result, the current figures on refractory epilepsy could be related to a suboptimal treatment choice related to the lack of definite validation of the transporter hypothesis at the clinical level.

The target hypothesis suggests that the reduced sensitivity to AEDs could be associated to acquired modifications in the functionality and/or structure of AED molecular targets. The gene variant hypothesis postulates genetic causes of drug resistance (e.g. polymorphic variants of drug biotransformation enzymes, molecular targets, or transporters) [5]. The neural network hypothesis maintains that recurrent episodes of excessive neural activity lead to plastic modifications of the neural network; the resulting anomalous networking might in turn relate to the drug resistance phenomena. The hypothesis is supported by the fact that surgical resection of the seizure focus frequently results in seizure freedom [5], though the differences between the alterations in brain plasticity in responsive and nonresponsive patients are yet to be elucidated [29]. The intrinsic severity hypothesis is based on epidemiologic studies showing that the most important factor linked to the prognosis of epilepsy is the number of seizures at the epilepsy onset. Again, the biological basis of disease severity is not fully understood to the moment, so currently the influence of the intrinsic severity hypothesis on treatment choice or treatment development is limited. Finally, a possible role of epigenetics in drug resistance epilepsy has also been suggested (establishing a sixth hypothesis for refractory epilepsy) although presently the experimental basis supporting this mechanism remains scarce [136].

None of the previous hypotheses provides a universal, satisfactory explanation to nonresponsive patients: a particular hypothesis might be appropriate to a particular subgroup of patients or, otherwise, some patients could require multiple hypotheses to explain their refractoriness [5,49,137]. The network hypothesis appears so far as the more holistic explanation to drug resistance, since some of the others (e.g. the target hypothesis) could be applied in its context. It is worth emphasizing that the treatment approach should be highly dependent on the drug resistance mechanisms present in a particular patient [49].

The formerly discussed systems biology approach (Section 2), relying on the design of novel multi-target AEDs, seems as a possible solution to the target and network hypotheses of drug resistance, considering that it is less likely that two separate drug targets are altered simultaneously in a single patient. Concordantly, even if one of the molecular targets of a multi-target agent has lost sensitivity, it can be speculated that the other/s will remain sensitive, thus maintaining drug efficacy. Some particular types of epilepsy, though, may require drugs with specific mechanisms of action; in such cases, as discussed previously, loss of sensitivity to a drug could be prevented by designing drugs which are capable of interacting with multiple binding sites of the same target.

In relation to therapeutic solutions to drug-resistant epilepsy associated to ABC transporter overactivity, inhibition of ABC transporters by co-treatment with on transporter inhibitors could, theoretically, result in enhanced efficacy. However, clinical trials with transporter inhibitors in the field of anticancer treatment have been unsatisfactory ([49,138,139] and refs. therein) due to severe safety issues. The physiologic role of ABC transporters as a general detoxification mechanism and their involvement in the traffic of endogenous substrates conditions the use of add-on inhibitors in the context of long-term drug treatments (such as AEDs). Weak inhibitors of ABC transporters and agents directed to the signaling cascade that regulate efflux transporters expression could emerge as possible solutions [139]. An extensive review on such approaches can be found in the excellent articles by Potschka and Potschka and Luna-Munguia [139,140]. Second, one may mention the use of a 'Trojan horse' subterfuge to achieve therapeutic concentrations of the ABC transporters substrates to the epileptic focus, avoiding the recognition of the efflux pumps. Pharmaceutical nanocarriers can be included in this category [141,142]. In concordance with the preceding strategy, we can mention the design of prodrugs of AEDs either lacking affinity for ABC transporters or displaying affinity for influx transporters that could compensate the efflux pumps influence on BBB permeability [139].

The computer-assisted design of novel AEDs which are not recognized by ABC transporters and the early screening

during drug development to discard substrates (regarding efflux transporters as anti-targets) constitute interesting but mostly underexplored alternative solutions. Despite a multiplicity of models and algorithms for the computer-aided recognition of substrates for ABC transporters have been reported [143–145], few have been applied in the field of AED discovery [122,146].

Some model developers offer their models online or in software packages, either freely or commercially (see, for instance, Biozyne [147,148] and Althotas Virtual Laboratory [149,150]). Other models can be reproduced from literature provided that the user has access to the required software tools. In any case, it is always a good idea to inspect the original articles in which such models are described, in order to assess the suitability and limitations of the procedures that have been used for model building. Very frequently reported models related to ABC transporters are based on unbalanced training sets in which substrates significantly outnumber non-substrates, resulting in possible bias towards the prediction of the prevailing category. What is more, several reported models have been derived from congeneric series of molecules, severely restricting their applicability domain.

Due to the polyspecificity that characterizes ABC transporters and the high inter-laboratory variability in experimental data, predicting whether a substance is or is not a substrate for members of the ABC superfamily is challenging. Back in 2007, based on the high variability of Pgp experimental affinity data, Zhang and colleagues estimated the upper bound of accuracy for Pgp models in those days in 85% [151], which is quite low compared with the accuracy achieved for other modeling tasks. Accordingly, most of the reported models on ABC transporters display an overall accuracy around 80%. Normally, modeling efforts rely on biological data and chemical data sets compiled from literature: classification models can be used to alleviate the noise associated to such heterogeneous experimental data and large inter-laboratory variability [152]; as stated by Polanski and coworkers, extensive data independence implies qualitative rather than quantitative solutions [153].

The intrinsic difficulty of predicting affinity for ABC transporters has led many researches in the field to contemplate more flexible techniques such as nonlinear models [145] and robust approximations such as ensemble learning/consensus QSAR or locally weighted methods [144,154–160]. Also note that there is evidence that ensemble learning could reduce the necessity of applicability domain assessment, assuring broader coverage of the chemical space [161].

4. Computer-guided drug repurposing

Drug repurposing comprises finding new medical uses for existing drugs, including marketed, investigational, discontinued, and shelved ones. Repurposed drugs present higher probability of surviving clinical trials than *de novo* drugs (about 2.5 higher chances of surviving Phase II and 1.3 probabilities of surviving Phase III) and a reduced development timeline (3–5 years shorter) [162,163], since indication expansion builds on already available safety, pharmacokinetic, stability, and manufacturing knowledge. While numerous AEDs have been approved for other medical uses and/or possess different off-label uses [57,164–168], the opposite is not true: few drugs from other therapeutic category (with the exception of hypnotics and anxiolytics) has so far been approved as antiepileptic agent, and off-label prescription of drugs with other indications for epilepsy is not a common practice. It can thus be stated that drug repurposing for epilepsy is at present quite underexplored. A critical question deserves examination: is the relationship between epilepsy and other conditions bidirectional? A large number of AEDs have been successfully repurposed for other indications (either off-label or by gaining regulatory approval); does this imply that drugs used for any of those indications could potentially be used to treat epilepsy? Could some therapeutic categories display systematic connections? Interestingly, it has recently been reported that drugs affecting the renin–angiotensin system do provide protection in seizure animal models, either alone or in combination with approved AEDs [168–171].

A diversity of approaches can be used to propose second medical uses of existing drugs, from exploitation of serendipitous clinical observations regarding possible unexpected beneficial effects of a drug to epidemiological retrospective studies. Another option is systematic drug repurposing, which includes knowledge-based and computer-assisted drug repurposing, in which chemical and pharmacological information on the drugs and pathophysiological knowledge on the diseases are examined to guide the indication shift. Due to the unprecedented rate at which scientific data are generated today, computational data analysis approaches can provide a valuable support to organize information and gain knowledge which can in turn be used to guide repurposing initiatives.

4.1. Bioinformatics-based drug repurposing

One of the general principles that supports computer-aided drug repositioning is that health disorders linked to the same or similar dysregulated or dysfunctional proteins may be treated with the same drugs (disease-centric approach). Bioinformatic applications, from sequence alignment to domain similarity identification tools, are useful to reveal unknown protein–protein similarities. While experts in a particular disorder are logically familiarized with the function and/or molecular structure of target proteins associated to their specific matter of study, they might well ignore which other diseases are linked to the same or closely related targets. Several online public resources can be used to find curated information on gene–disease associations. For instance, DisGeNET [172] is a discovery platform that contains hundreds of thousands of associations between genes and diseases (including both Mendelian and complex disorders). Other interesting resources include the Comparative Toxicogenomics Database [173], which delivers information about interactions between environmental chemicals and gene products and their relationship to diseases; the Online Mendelian Inheritance in Man [174], an online catalog of human genes and genetic disorders; and PsyGeNET [175], which focuses on links between genes and psychiatric disorders. The simpler way of inferring gene or protein homology is

probably through sequence similarity; however, homologous sequences do not always share significant sequence similarity but are clearly homologous based on statistically significant structural similarity or strong sequence similarity to an intermediate sequence [176]. Using different approaches to find homologs could be convenient for a wider coverage; homology identification based on sequence alignment can be complemented by structural homology approaches based on manual or automated comparison of 3D protein structures. For instance, Vector Alignment Search Tool (VAST) [177] detects similar 3D protein structures solely by geometric criteria and can identify distant homologs which are lost by sequence comparison. Its extension, VAST+, explores structural similarity on the level of biological assemblies or macromolecular complexes [178], an attractive possibility in the field of epilepsy since several AEDs such as ligand-operated ion channels are macromolecular complexes. Once homologous with suspected similar functions and conserved determinants of specificity have been found, the previously discussed public resources compiling associations between gene/gene products and disease can be used to propose new medical uses for existing drugs.

Connections between ligand promiscuity and binding site and global structure similarity have been established by Haupt and coworkers [179]. Their results suggest that binding site similarity and global structure similarity can be used as criteria to guide drug repositioning initiatives. Interestingly, many algorithms have been developed to identify, in an automated manner, similarities between binding sites (see reference [180]). Connectivity mapping is another bioinformatics approach that can prove helpful to guide drug repurposing [85]. By application of this approach, Zhuo et al. recently revealed that valproate is able to reverse acquired erlotinib resistance of lung cancer [181]. Likewise, Dudley and coworkers discovered that topiramate is a potential therapy for inflammatory bowel disease [182]. It is still to be seen if this methodology will prove useful to assist repurposing in the opposite direction, i.e., to detect drugs from other therapeutic classes which could be useful to treat epilepsy.

4.2. Cheminformatics-based drug repurposing

The most common cheminformatic-based drug repositioning approach involves virtual screening campaigns in which the screened chemical repository/database is focused on approved, discontinued, abandoned, and/or investigational drugs. The methods used in cheminformatic-based drug repositioning are thus classified in the same way that for general virtual screening approaches [183]. DrugBank and Sweetlead [184,185] are excellent resources to carry out *in silico* drug repurposing: they compile approved, discontinued, and investigational drugs from the FDA and other regulatory agencies. It was recently highlighted that the importance of bioactivation in the context of *in silico* drug repurposing campaigns might have been underestimated [186,187]. Since around 10% of the known 'drugs' are in fact unintended or intended prodrugs [188], it is advised to explicitly consider possible active metabolites of the potentially repurposed compounds during the screening protocol.

A different and conceptually interesting approach has been presented by Wu and coworkers [189], in line with previous work by Keiser and collaborators [190,191]. The general idea behind their studies is that different therapeutic indications could be related if each of them includes chemically similar drugs. This approach provides a rational basis to decide which pairs of therapeutic classes are more favorable to explore possible cross-repurposing.

A current trend in computer-aided drug repurposing consists in integrating large volumes of heterogeneous types of data (e.g. experimental and predicted, chemical similarity, and protein similarity) into large-scale drug protein networks or even drug–protein–disease networks [192–194]. Small-scale application of the previous concept led to the identification of the anticonvulsant effects of artificial sweeteners cyclamate and acesulfame [195,196], which in turn allow identifying the anticonvulsant effects of natural sweeteners (steviol glycosides) [197]. Saccharin and cyclamate have also shown selective and potent inhibitory effects on one carbonic anhydrase VII, a putative AED target [12,198]. Large-scale networks provide similar possibilities, but in a more automated, high-throughput manner.

5. Expert opinion

New-generation antiepileptic agents have failed to produce a significant improvement in the efficacy of AEDs, with about one-third of the patients still failing to attain a seizure-free condition. Despite recent authoritative opinions on the potential contribution of network-based approaches to the development of more efficacious antiepileptic treatments, these considerations have been scarcely translated into novel drug candidates, unlike what happened in other complex diseases, such as neurodegenerative conditions. While it is true that the impact of some recently approved highly selective agents (perampanel and brivaracetam) on the overall success of pharmacologic antiepileptic treatment has still to be seen, our opinion is that there is a need to increase the presence of the network pharmacology philosophy in the AED discovery field, integrating such way of thinking to the lately dominating target-focused strategies. The ultimate goal in the field is to develop therapeutic solutions that (a) restore the life quality of the patients, which implies attaining an enduring seizure-free state and addressing frequent comorbidities that threat the social integration of the people with epilepsy and (b) limit or reverse the progression of the disorder. Inexorably, these challenges require a holistic approach at both the drug discovery level and the treatment choice stage.

Besides the need to rethink the rationality behind the current drug discovery paradigms, attention should also be paid to a couple of additional issues. First, current drug resistance hypotheses have to date not been fully exploited for drug development either. Second, computer-assisted drug discovery campaigns related to epilepsy are scarce in comparison with other diseases.

We have discussed four strategies to incorporate a network pharmacology perspective in the field of computer-aided AED discovery: tailored multi-target agents; gene signature comparison; examining the suitability of 'the more potent the better'

paradigm as selection criteria at the AED screening stage; and building QSAR models based on biological responses emerging from phenotypic models, with emphasis on epilepsy models and novel seizure models associated to novel mechanisms of action. When seeking for multifunctional therapeutic answers, it is highly relevant to consider other criteria (e.g. possible impact on comorbidities) besides seizure control when selecting existing therapeutic agents and designing new ones.

The application of some of the previous innovative approaches (in particular, the tailored multi-target approach) is presently hindered by our incomplete knowledge of the underlying causes of epilepsy and the molecular basis of epileptogenesis, an obstacle that is stressed by our difficulties to differentiate epilepsy causes from effects. We must also take into consideration that epilepsy encompasses a wide range of disorders, and one possible answer to generate more efficacious therapeutic alternatives could well involve focusing on particular types of epilepsy (a growing trend in the field) instead of searching broad-spectrum drugs. Facing this challenge, however, would also ideally require a fine knowledge on the specific mechanisms that lead to onset and progression of each type of epilepsy. How can we expect to design effective agents if the specific molecular and cellular mechanisms behind the pathophysiology of the epilepsies are still unclear? If adopting the designed multi-target approach, how shall we decide, on a rational basis, on the suitable combination of targets that will result in a better therapy?

In regard to current refractory epilepsy hypotheses, multi-target agents seem as plausible solutions to the network and target hypotheses, whereas the design of AEDs that are not recognized by ABC transporters appears as a reasonable alternative to approach the transporter hypothesis, seemingly constituting a safer strategy than add-on therapies based on transporter inhibitors. Ensemble learning, nonlinear techniques, and locally weighted methods are interesting computational approximations to deal with the polyspecificity of those anti-targets; in turn, classification models are probably good solutions to address the high inter-laboratory variability of experimental data from transport assays.

Finally, we would like to draw the reader attention to the fact that, while many AEDs have been successfully repurposed for other therapeutic indications (and many more indication expansions for AEDs seem on the way), the opposite direction has not been explored with equivalent enthusiasm. There is abundant evidence supporting two-way systematic relationships between therapeutic classes, representing interesting drug repurposing opportunities. Accordingly, the time may have come to approach the exploration of other drug classes for their potential as antiepileptic treatments.

Hopefully, as the impact of novel AEDs is examined and the epilepsy community incorporates modern drug discovery strategies, the next few years will bring a reformulation of the way in which AED development is approached, enhancing the probability to achieve a better therapeutic outcome.

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