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CRITICAL REVIEW

Antiseizure medication discovery: Recent and future paradigm shifts

Alan Talevi[1,2]

[1]Laboratory of Bioactive Research and Development (LIDeB), Faculty of exact Sciences, University of La Plata (UNLP), Buenos Aires, Argentina

[2]Argentinean National Council of Scientific and Technical Research (CONICET), Buenos Aires, Argentina

Correspondence
Alan Talevi, Laboratory of Bioactive Research and Development (LIDeB), Faculty of exact Sciences, University of La Plata (UNLP), 47 & 15, La Plata (B1900AJK), Buenos Aires, Argentina.
Email: alantalevi@gmail.com

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Abstract

Despite the ever-increasing number of available options for the treatment of epilepsies and the remarkable advances on the understanding of their pathophysiology, the proportion of refractory patients has remained approximately unmodified during the last 100 years. How efficient are we translating positive outcomes from basic research to clinical trials and/or the clinical scenario? It is possible that fresh thinking and exploration of new paradigms are required to arrive at truly novel therapeutic solutions, as seemingly proven by recently approved first-in-class antiseizure medications and drug candidates undergoing late clinical trials. Here, the author discusses some approximations in line with the network pharmacology philosophy, which may result in highly innovative (and, hopefully, safer and/or more efficacious) medications for the control of seizures, as embodied with some recent examples in the field, namely tailored multi-target agents and low-affinity ligands.

KEYWORDS

disrupting innovation, drug discovery, epilepsy, innovation, low-affinity ligand, multi-target, multi-target drugs, network pharmacology, partial agonist, radical innovation, systems pharmacology

1 | INTRODUCTION

Even though at present more than 40 antiseizure medications (ASMs) are available to treat epilepsy, either as monotherapies or in drug combinations, around one third of the patients with epilepsy are unable to fully control seizures through pharmacotherapy.[1,2] Whereas several hypotheses have been formulated to explain the drug-resistant phenotype (some of which may show a considerable degree of overlap), they have not been generally validated at the clinical level and/or translated into therapeutic interventions.[1] It is now commonly accepted, though, that a single mechanism is unlikely to wholly explain the drug resistance phenomenon, which is possibly multifactorial and could vary from patient to patient.[1-3]

The disappointment at unfulfilled expectations on third-generation ASMs has led to reconsider the preclinical strategies for the identification of potential new treatments against epilepsy,[4] which are progressively shifting from models that identify symptomatic therapies to other that may be useful to screen for disease-modifying treatments and medications that may be more effective in the refractory population. This has clearly crystallized in modifications to the traditional Anticonvulsant Screening

Program of the National Institute of Neurological Disorders and Stroke, which has recently been renamed to Epilepsy Therapy Screening Program,[5] expressing the philosophical change and the substantial transformations made to the program. In the last decades, the scientific community has made significant efforts to move beyond the classical models of acute seizures that gave us most of the available ASMs, toward animal models of epilepsy and, interestingly, animal models that express a drug-resistant phenotype. For instance, amygdala kindling and post-status epilepticus models of temporal lobe epilepsy allow selection of responder and non-responder animals.[4] The lamotrigine-resistant amygdala kindling model uses repeated administration of lamotrigine during the kindling process to induce a resistance to lamotrigine and to some other ASMs, such as carbamazepine.[6,7] Administration of increasing doses of 3-mercaptopropionic acid to mice has been reported to provide a drug-resistant phenotype linked to P-glycoprotein upregulation.[8] The model has later been used to screen for drug candidates that could be used to prevent the development of resistance.[9]

2 | TYPES OF INNOVATION WITHIN THE PHARMACEUTICAL SECTOR: A POSSIBLE CLASSIFICATION

Innovation can be classified in very different manners depending on the context and the degree of novelty[10-12]; allocation to a given class, as in any classification exercise, could sometimes include a subjective component. Here, we will adopt a triadic categorization scheme, considering *radical*, *semi-radical,* and *incremental* innovation. It should be underlined that, in the drug discovery field, despite the different degrees of novelty associated to each type of innovation (Figure 1), all of them can provide significant advantages in terms of efficacy, safety, or convenience (radical innovations, naturally, are supposed to represent breakthrough advances).

Radical innovations reformulate the behavior and the structure of the market, often making obsolete earlier generation products; they may respond to an unmet or an unrecognized need.[11] In the pharmaceutical sector, a radically innovative therapeutic solution would address an orphan disease, or, alternatively, provide a substantial improvement in terms of efficacy, safety, cost-efficiency, and/or ease of use in comparison with existing medications for a given pathology. We could include in this category novel mechanistic approaches for the treatment of a certain disease (*first-in-class drugs*). It could be hypothesized that radical innovations within the pharmaceutical sector *arise from novel chemical matter exhibiting a novel (previously unseen) pharmacological profile within a given therapeutic category*. For instance, sildenafil is often regarded as a radical innovation, which offered the first efficacious oral treatment for erectile dysfunction: before sildenafil, this condition was (under)treated invasively with alprostadil.[13] Treatment of erectile dysfunction was the first approved use of sildenafil (though not the first use investigated). Its subsequent approval for the treatment of pulmonary arterial hypertension[14] can be regarded as much less innovative, as already known chemical matter was approved for a new medical use for which other treatment alternatives were available. What is more, sildenafil's mode of action as anti-hypertensive does not substantially differ from its mode of action for the treatment of erectile dysfunction (corresponding to *on target drug repositioning*). Note that the first indication approval of sildenafil corresponds to the upper right quadrant in Figure 1 (highly innovative), while its second indication approval in 2005 would correspond to the lower left quadrant (less innovative). Other common examples of breakthrough innovations are monoclonal antibodies and selective inhibitors of serotonin re-uptake. In general terms, radical innovations represent a rather small fraction of all innovations[10] and are even less prevalent in the pharmaceutical sector.[15]

Semi-radical and incremental innovations occur much more frequently. Possible examples of the former would be chemically novel drugs with similar mechanisms to already known medications (which, for instance, may have improved pharmacokinetics, diminished incidence of drug-drug interactions or enhanced selectivity). Also note that there may be different degrees of "chemical novelty." Some new drugs have similar mode of action than existing ones but represent a completely new active scaffold, whereas others (the "me too" or "follow-on" drugs) display relatively minor modifications on a known active scaffold. Repurposed drugs could also probably fit into this

Key points

- Systems pharmacology can provide more efficacious and safer treatments for epilepsy.
- Tailored multi-target drugs could provide improved seizure control for those patients where drug resistance is associated to reduced sensitivity of the target.
- Partial agonists and low-affinity drugs may display improved tolerability in comparison with full agonists and high-affinity ligands.

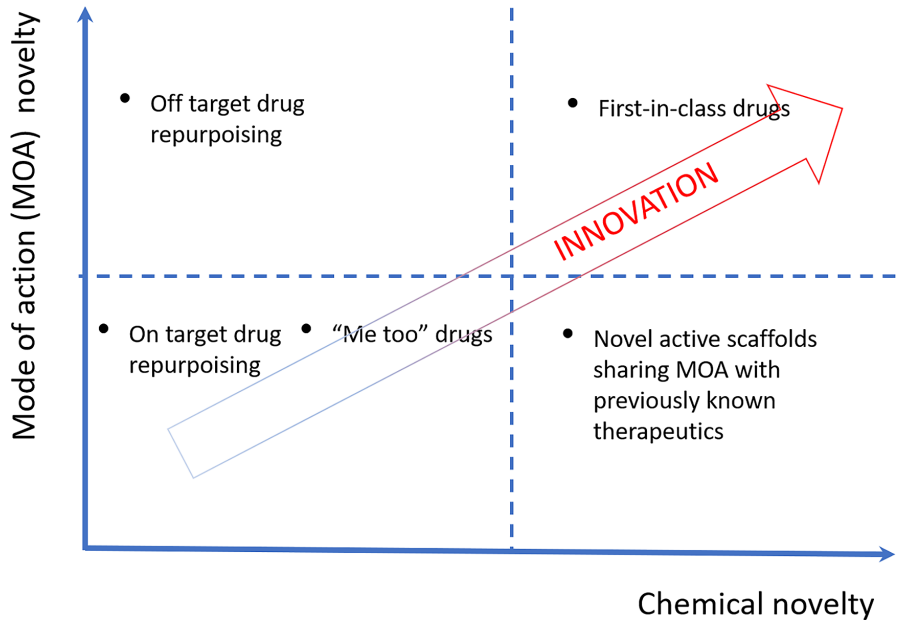

FIGURE 1 In the drug discovery field, different degrees of innovation can be envisioned based on the degree of chemical and/or pharmacological novelty, with radical innovations typically belonging to first-in-class medications. It must be underlined that beyond the drug discovery field, innovations in the pharmaceutical sector can also occur at the levels of drug delivery devices (for instance, an oral delivery system for insulins would, with no doubt, revolutionize the treatment of type-1 diabetes) or at the level of process innovation, which are out the scope of the present article

category: they imply innovative medical uses of known chemical matter.

Prodrugs might be good examples of incremental innovation, as the active pharmacological entity persists the same to previously known medications, but it is delivered into systemic circulation and/or the action site in some novel, advantageous manner through addition of a metabolically labile component. Other examples could be the conversion from add-on therapy to monotherapy and expanded approvals. For instance, lacosamide originally received approval as an add-on therapy for partial-onset seizures in adults (in 2008), it was next approved as monotherapy for adults (2014), and as monotherapy or adjunctive therapy in patients aged 4 years and older with focal onset seizures (2017). More recently, it was approved to treat generalized tonic-clonic seizures. Note that neither semi-radical nor incremental innovations replace, in general, previous therapeutic options, but instead offer an improved therapeutic profile and may result in market competition or displacement of existing products.

So, are antiseizure medications approved in the last 10 years and candidates for the treatment of epilepsy currently undergoing clinical trials examples of radical or semi-radical innovation? A bit of each, actually (see Table 1 for more details). Whereas third-generation ASMs have to some extent displaced drugs from the preceding generation, these are far from obsolete. For instance, first-generation ASM ethosuximide is the drug of choice for epilepsy patients with non-motor (absence) seizures as the only seizure type, and second-generation ASM valproate remains the most effective one for idiopathic generalized epilepsy with generalized tonic-clonic seizures.[16]

Among recently approved ASMs, retigabine and perampanel could be regarded as radical innovations, as they are first-in-class drugs with novel mechanism(s) for the treatment of seizures.[16-18] Unfortunately, retigabine has been withdrawn due to bluish pigmentation in the nails, skin, and retina associated to long-term use. On the other hand, perampanel is associated to psychiatric and behavioral disorders, as indicated in its black box warning in the United States. Cannabidiol may also fall into the category of radical innovations, as its mechanism(s) of action as ASM has not been fully elucidated. Also 2-deoxyglucose, an antiseizure medication that reached clinical trials and acts by glycolytic inhibition: its broad antiseizure effects involve decreased glycolytic flux and reduced cell energy production.[19] Cenobamate, in contrast, can be possibly regarded as a semi-radical innovation: while based on previously known modes of action (positive allosteric modulation of GABAergic inhibition plus block of persistent sodium currents and enhancement of the inactivated state of voltage gated sodium channels), it is a dual action that combines these complementary mechanisms uniquely.[18] Also, possibly, everolimus: it has been approved as immunosuppressant since 2003, but was only recently repositioned for the treatment of refractory seizures associated with tuberous sclerosis complex[20]; in other words, the already known mechanism (mTOR

TABLE 1 Degree of innovation represented by antiseizure medications approved in the last 10 years

Drug	Degree of innovation	Comment
Eslicarbazepine acetate	Incremental / semi-radical	Eslicarbazepine acetate was first approved as adjunctive therapy against partial-onset seizures, followed by a monotherapy indication after successful completion of monotherapy conversion trials[16,56]; this is a third-generation relative of carbamazepine and oxcarbazepine that is less prone to drug interactions and better tolerated. It acts as a prodrug that is rapidly convert to eslicarbazepine by the first pass hepatic effect. Moreover, it is available in a convenient once-daily regimen. As carbamazepine, it acts by blocking voltage-operated sodium channels stabilizing the inactive state. Eslicarbazepine does not alter fast inactivation of the voltage-gated sodium channel (carbamazepine and oxcarbazepine do) but seemingly reduces the channel availability through enhancement of slow inactivation.[57] All in all, this drug has provided rather slight chemical and mechanistic novelty.
Retigabine	Radical	Whereas retigabine was a first-in-class ASM with a novel mechanism of action as a potassium channel opener, its use decreased when it was associated to bluish pigmentation in the skin, nails, and retina, which eventually led to its withdrawal from the market in 2017.[57] Interestingly, XEN1101 is a novel positive allosteric modulator of KCNQ2/3 which is currently undergoing phase 2 clinical trials. It has improved selectivity and is free of the structural requirements needed for the formation of chromophoric phenaziniumtype dimers that have been implicated in the pigmentary abnormalities observed with long-term retigabine exposure.[58] Furthermore, its pharmacokinetics are compatible with once daily dosing.[59]
Perampanel	Radical	Perampanel is a selective and non-competitive antagonist for post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptor.[60] It is indicated for the treatment of partial seizures, and as adjunctive treatment for generalized tonic-clonic seizures. However, psychiatric and behavioral adverse events seem to be more common with perampanel than with other ASMs, especially in refractory patients.
Brivaracetam	Semi-radical	Brivaracetam shares active scaffold with the first-in-class ASM levetiracetam; however, it was designed to display higher selectivity and about 20 times higher affinity to Synaptic Vesicle Glycoprotein 2A (SV2A) than its predecessor.[16,31] It also possesses better permeability through the blood-brain barrier. It is approved for the treatment of partial-onset seizures. All in all, it may be said that it has limited chemical novelty and limited mode of action novelty.
Everolimus	Incremental / Semi-radical	In 2018, oral everolimus was approved for the adjunctive treatment of adult and pediatric patients above 2 years with tuberous sclerosis complex (TSC)-associated partial-onset seizures.[20,61] Since it has also been shown to improve other TSC manifestations such as subependymal giant cell astrocytomas and renal angiomyolipomas. This represents an on-target drug repurposing example, as the indication of a known drug has been expanded based on its previously known mechanism (mTOR inhibition). While we might say, thus, that the approval represents no chemical or mechanistic novelty, it is worth highlighting that everolimus addresses the underlying pathophysiology of tuberous sclerosis complex, which is not the general case for ASMs.
Cannabidiol	Radical?	Highly purified cannabidiol has been approved for the treatment of seizure associated to Dravet and Lennox-Gastaut syndromes, and its being evaluated as treatment for other difficult-to-treat epileptic syndromes such as tuberous sclerosis complex and infantile spasms.[17] Its exact mechanism of action is not still known, though a complex pharmacology is suspected.[62] Cannabidivarin, the propyl analog of cannabidiol, is another candidate in the pipeline.[17]
Fenfluramine	Semi-radical	Fenfluramine was introduced in Europe in the 1960s as an appetite suppressant but was later withdrawn due to reports of heart valve disease and continued findings of pulmonary hypertension. Recently, though, it has been approved as treatment of Dravet syndrome.[18] It acts primarily as a serotonin-releasing agent. In addition, it has been shown to non-selectively bind to sigma-1 receptor.[63] While we cannot speak of chemical novelty (since this is an example of drug rescue), these mechanisms are indeed a novelty within the field of epilepsy.
Cenobamate	Semi-radical / Radical	Cenobamate is a novel multi-target drug whose mode of action combines potentiation of GABAergic transmission plus voltage-gated sodium channels blockade.[18] This combined mechanism adds to its chemical novelty. It has been approved for the treatment of partial-onset seizures in adults.

inhibition) of a known chemical substance has been innovatively repurposed for the treatment of a very specific type of seizure.

3 | THE ADVENT OF TAILORED MULTI-TARGET AGENTS FOR THE TREATMENT OF COMPLEX DISORDERS

Before the emergence of target-driven "rational" drug discovery in the late 20th Century, new lead compounds with therapeutic potential emerged ether from serendipitous observations, traditional medicine, or phenotypic screening in cellular or animal models of disease[21]. The target-focused drug discovery paradigm proposes that safer medications may be developed if exquisitely selective, "clean" drugs (devoid of off-target events) are pursued. In practice, this implies the early selection of drug candidates based on in vitro screening to assess their binding to predefined molecular targets; the resulting hits are only then confronted with phenotypic screening in cellular and animal models. The target-focused philosophy is also the basis of classic computer-aided drug design approximations.

However, it has been increasingly realized that complex disorders represent robust states that are unlikely to be reverted with single-target therapeutics but rather with polytherapy or through multi-target agents (as Kitano has neatly expressed, *"complexity has to be controlled by complexity"*).[22,23] This strategy has been actively applied in some branches of neurology (in particular, in the field of neurodegenerative conditions[24]). In the field of epilepsy Bianchi et al have indicated that *"the complexity of neural processes underlying seizure activity may be more amenable to multiple small perturbations than a single dominant mechanism"*[25] (note the notion of *small* perturbations, which will be further addressed in the next section of this article).

As a matter of fact, some authors have underlined that old drugs for CNS conditions which were discovered through phenotypic models are in general unintended multi-target drugs with complex pharmacology.[21,25] This *network pharmacology* paradigm[26] has manifested in the renewed interest in phenotypic screening[27,28] and, particularly, in the quest for tailored multi-target therapeutic agents that somehow encompass both the reductionist, target-oriented approximations, and the systems pharmacology perspective.[29] In the field of epilepsy, multi- target drugs might not only be intrinsically more efficacious but also more likely to provide symptomatic control in those patients that present a less sensitive variant of a given drug target. In other words, if the target combination addressed by the multi-target agent (or, occasionally, by a drug combination) is adequately chosen, this multiple intervention is expected to provide better pharmacological response in those refractory patients whose resistance is explained by the target hypothesis. The underlying premise is intuitive: it is unlikely for an individual to simultaneously express two less sensitive intrinsic or acquired variants of the pursued molecular targets.[30]

Levetiracetam could be an interesting example of the potential of low-affinity multi-target drugs, in line with the above-mentioned premise by Bianchi and coworkers. This drug not only displays a rather high Ki of about 1.6 μmol/L against SV2A[31] but also inhibits neuronal high voltage-gated calcium at clinically relevant concentrations, an effect that seems to arise from selective binding to N-type calcium channel.[32-34] Notably, levetiracetam elicits a protective effect in the 6 Hz model, and in drug-resistant amygdala kindled rats,[4,35] two animal models that have been included as primary and secondary screening tools in the Epilepsy Therapy Screening Program. Also remarkably, this drug has consistently proven to reduce focal onset seizure frequency when used as adjunctive treatment for adults and children with drug-resistant focal epilepsy.[36] The molecularly similar analog brivaracetam, in contrast, displays considerably more affinity and selectivity for SV2A and a broader spectrum in preclinical models of seizure.[31] In a way, the comparison of efficacy and tolerability of both medications could provide important clues on the benefits of the system-focused vs the target-focused approximations. Preliminary evidence in that respect arising from small-scale studies or indirect comparisons seems to be conflictive and still inconclusive.[37-40]

Another exponent of multi-target drug is the recently approved cenobamate (see Table 1), and padsevonil, a dual-acting drug candidate specifically designed to interact with pre- and post-synaptic targets: respectively, the three isoforms of synaptic vesicle protein 2 (SV2A, SV2B and SV2C1) and the benzodiazepine recognition site on the $GABA_A$ receptor, where it acts as a partial, low-to-moderate-affinity agonist.[17]

Proof-of-concept of the validity of the network pharmacology perspective has recently been provided through the use of adequately chosen ASM combinations.[41]

The reach of precision medicine has lately been amplified by the opportunity to assess a person's genome and transcriptome using DNA microarrays and next-generation sequencing. For instance, a recent transcriptomic analysis on cortical tissue samples from 86 patients with mesial temporal lobe epilepsy with hippocampal sclerosis served to identify epilepsy-relevant gene networks implicating neuronal and glial mechanisms, mesial temporal lobe epilepsy +hippocampal sclerosis-associated splicing changes in ion channel and non-ion channel genes, and

different genetic loci that affect the expression of genes and/or transcripts that have been involved in epilepsy.[42] Dysregulated genes included not only genes usually associated with epilepsy, such as those codifying for subunits of voltage-operated sodium channels, but also genes implicated in immune response and vascular development, which may involve opportunities for innovative therapeutic interventions. Noteworthy, the network of genes and gene products impacting on a disease state and/or drug sensitivity is not static but may change over time with the progression of the disease, that is, it has a highly dynamic nature. For instance, Winden et al performed a systems level, functional genomic analysis in the intrahippocampal kainite model of temporal lobe epilepsy and observed that Sv2a, the main molecular target of levetiracetam and brivaracetam, has a much higher connectivity in the epileptic network than in the non-epileptic modules, suggesting that it gains a more relevant role in synaptic function in epilepsy than under normal conditions.[43] A corollary of the preceding discussion is that a (single point) transcriptomic analysis inadequately reflects a transient, dynamic state; therefore, a therapeutic intervention informed by it will not necessarily work permanently, but might require adjustments upon the clinical evolution of the patient. In the case of epilepsy, the possibility of sampling tissue at multiple times is complicated by the intrinsic risks of brain biopsies. Intuitively, multi-target agents or polytherapy could provide more robust control of seizures, as the patient will be protected from the loss of sensitivity to a given drug at the drug target level.

4 | WHEN LESS IS MORE: THE POTENTIAL OF LOW-AFFINITY LIGANDS AND PARTIAL AGONISTS

Under the dominant paradigm in the pharmaceutical industry, drug discovery campaigns initiate with a hit identification stage, where novel active scaffolds with the desired activity (typically with a potency of 100 nmol/L-5 μmol/L at the drug target[44]) are sought. A chemistry program is then initiated to improve the potency and selectivity of these hit molecules. In general, after the hit-to-lead stage, the potency of the lead compound(s) lies in the low nM, or even sub-nM, range. This may be synthesized under the moto *"the most potent, the better."*

However, from a network pharmacology perspective, hitting hard on key nodes (eg, hubs) in biochemical networks might not be the best strategy from a safety/tolerability perspective, especially if sensitive organs like the brain are being targeted. Partial weaking of a small number of carefully selected targets could be a more adequate approximation to safely restore physiological systems to well-functioning[45-47]. In the field of drug discovery, this may be accomplished using low-affinity ligands and partial agonists (the latter produce submaximal tissue responses at any degree of receptor occupancy). The safety aspect of medications is not trivial in relation to refractory epilepsy, as the current consensus definition of the International League Against Epilepsy specifies that refractory epilepsy should be diagnosed when adequate trials of two *well-tolerated* and appropriately chosen ASM schedules have failed to achieve sustained seizure freedom.[48] Note that the definition does not comprise therapeutic interventions that could be efficacious but have been disregarded due to poor tolerability. Therefore, the development of new drugs to address the challenge of refractory epilepsy should not only focus on more efficacious medications but also in safer ones.

There are already some examples of successful low-affinity, multi-target ligands in the field of neurology. Memantine, for instance, is a low-affinity drug prescribed for the treatment of moderate-to-severe Alzheimer's disease and other types of dementia.[49,50] Unlike the high-affinity inhibitor of N-methyl-D-aspartate receptors (NMDARs) dizocilpine (which did not reach the market due to severe adverse events that included Olney's lesions), memantine displays low-affinity binding (in the submicromolar range) to NMDARs, almost no selectivity across NMDARs subtypes and antagonism on other receptors, including serotonin, nicotinic, and dopamine receptors.

There are also relevant examples of the use of low-affinity ligands in the field of epilepsy. Imepitoin is a broad-spectrum ASM initially investigated for the treatment of human epilepsy, but later approved for the treatment of canine epilepsy owing to pharmacokinetic issues in humans.[51,52] This drug was identified though a pharmacophore-based approximation and acts as a low-affinity partial agonist of the benzodiazepine binding site of the $GABA_A$ receptor, eliciting up to about 20% of the maximal potentiation obtained with diazepam, a full agonist of such site (the Ki of imepitoin lies in the low μM range, in comparison with Ki = 6.8 nmol/L for diazepam or Ki = 1.7 nmol/L for clonazepam). The low-affinity and partial agonist nature of imepitoin correlates with much better tolerability, reduced tolerance, and absence of the abuse liability characteristic of other full and potent agonists, such as benzodiazepines or barbiturates. The already mentioned padsenovil is another example of partial agonist with rather low affinity for the benzodiazepine site.

Although out of the scope of this article, inverse agonists (ligands which preferentially bind and stabilize receptors in the inactive state, resulting in a reduction in spontaneous receptor activity in those receptors with

constitutive activity) have raised considerable interest within the community of epileptologists. For example, pitolisant, a histamine H3 receptor inverse agonist, has been subjected into clinical Phase 3 for the treatment of epilepsy.[53,54] Recently, it was reported that cannabidiol itself, at high concentrations, acts as an inverse agonist of 5-HT1A receptors.[55]

5 | CONCLUSIONS

Whereas around 20 third-generation ASMs have been approved in the last decades, they have not contributed to a significant reduction in the number of refractory patients. Unfortunately, some of these treatments have found rather limited application (or have even been withdrawn, as in the case of retigabine) due to unfavorable safety profiles, despite exhibiting innovative modes of action (other examples that have found limited application might be tiagabine and vigabatrin).[16] Although drug-resistant epilepsy is commonly perceived as a "lack of efficacy" problem, it should also be considered in terms of the safety of the novel therapeutic options that make it to the market. The current definition of refractory epilepsy only regards as refractory those patients who fail to achieve seizure remission after trial of two adequately and *well-tolerated* drug regimens. Nevertheless, potentially efficacious treatments for epilepsy might be avoided prospectively or interrupted due to safety issues / lack of tolerability. Therefore, the quest for novel medications should emphasize not only the efficacy but also the safety profile of the intended drug candidates.

Here, we have provided a brief, subjective comment on the innovation degree of recently approved ASMs and it was discussed the benefits that a paradigm shift toward a system pharmacology perspective could represent in the field. Fortunately, many of the recently approved medications and some of the drug candidates undergoing advanced development stages are clear examples of radical innovations (first-in-class medications embodying both chemical and pharmacological novelty). Some of these medications are in good agreement with a network pharmacology perspective (representing tailored multi-target drugs and/or partial / low-affinity agonists). This adds to the complementary investigation of other modern paradigms out of the scope of this article such as drugs with subtype selectivity toward ASM molecular targets or drugs addressing the underlying etiology of epilepsy (eg, neuroinflammation).

Hopefully, these novel approximations in the field will achieve the long-pursued goal of significantly reducing the frequency of refractory patients with epilepsy.

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CONFLICT OF INTEREST

The author has no conflict of interest to declare.

ETHICAL STATEMENT

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

ORCID

Alan Talevi https://orcid.org/0000-0003-3178-826X

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