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REVIEW

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Potassium channel agonists emerging as treatment options for focal epilepsy: are we breaking new ground?

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ABSTRACT

Introduction: Focal epilepsy is a leading cause of neurological disability, with about one-third of patients failing to achieve seizure freedom despite numerous antiseizure medications (ASMs) are available. Most current therapies broadly modulate synaptic transmission, leading to dose-limiting cognitive, psychiatric, and systemic adverse effects. Kv7 (KCNQ) potassium channels, responsible for the neuronal M-current, represent a high-precision therapeutic target that regulates intrinsic excitability and provides a fundamental 'molecular brake' against pathological firing.

Areas covered: This mini-review summarizes the clinical evolution of Kv7 modulation, from the first-generation prototype ezogabine to more selective second-generation candidates. We outline the scientific rationale for targeting the M-current, review emerging clinical data for agents such as azetukalner (XEN1101) and opakalim (BHV-7000), and highlight preclinical strategies including dual-mechanism modulators and drug repurposing.

Expert opinion: Kv7 agonists offer a mechanistically elegant approach to restoring seizure resistance. Second-generation agents provide encouraging mechanistic and clinical proof-of-concept, but long-term success will depend on clear advantages in patient-centered outcomes over established ASMs. Future value is likely to lie in precision-medicine strategies for KCNQ2/3-related encephalopathies and a carefully defined role in managing neuropsychiatric comorbidities.

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1. Background

Focal epilepsy is common in both children and adults and a major cause of neurological disability, causing interference with education, employment, driving, and social participation. Comorbidities are frequent and include depression, anxiety and, at times, cognitive dysfunction [1]. Beyond the clinical burden, the disease carries significant social and financial implications, with high costs for healthcare systems and lost productivity for patients and caregivers. Although more than 40 drugs are currently labeled as antiseizure medications (ASMs), approximately one-third of patients remain drug-resistant [2].

To overcome this therapeutic challenge, research has increasingly focused on the brain's intrinsic ability to maintain electrical balance. At the heart of this process are voltage-gated potassium (Kv) channels, which function as the primary 'molecular brakes' of the central nervous system (CNS). Among these, the Kv7 (KCNQ) subfamily has emerged as a particularly critical target, as it generates the M-current, a steady electrical flow that prevents neurons from reaching the firing threshold for a seizure. By regulating the outward flow of potassium ions from the cell, these channels counteract the excessive firing characteristic of epilepsy and provide a fundamental stabilizing influence on neural networks [3].

In this mini-review, we examine the therapeutic potential of Kv7 (KCNQ) potassium channel agonists, tracing their clinical evolution from the first-generation prototype ezogabine to the latest breakthrough second-generation candidates. We further evaluate emerging research pipelines, including dual-mechanism modulators and drug repurposing strategies, while discussing their expanding role in precision medicine for genetic encephalopathies and the management of neuropsychiatric comorbidities.

2. Medical need

Drug-resistant epilepsy (DRE) is defined as the failure of two appropriately chosen and tolerated ASMs to produce sustained seizure freedom [4]. In the refractory population, recurrent seizures continue to drive injury risk, cognitive decline, psychosocial stigma, and a higher risk of premature mortality.

In affected individuals, the cumulative burden of seizures is compounded by the adverse effects of polytherapies on the CNS, which may include cognitive slowing, sedation, and mood disturbance [5]. Polytherapy is common in focal DRE and often involves three or more ASMs, amplifying the risk of drug–drug interactions, systemic toxicity, and poor adherence. Many patients face a trade-off between partial seizure control and an unacceptable burden of side effects.

Surgical options (resective surgery, laser ablation) and neuromodulatory interventions (vagus nerve stimulation, deep brain

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stimulation, responsive neurostimulation) provide important alternatives but are not widely accessible and are unsuitable or ineffective for a substantial proportion of patients. Thus, there remains a clear medical need for better-tolerated, mechanism-based pharmacologic therapies that can either complement or, in selected individuals, delay or obviate the need for invasive procedures. Furthermore, there is an urgent need for genuine disease-modifying therapies that can alter the course of the disorder, particularly in genetic forms where standard drugs often fail to provide adequate relief.

3. Existing treatment

Most established ASMs act by globally dampening neuronal activity. Sodium and calcium channel blockers limit action potential propagation and synaptic release, whereas GABAergic agents enhance synaptic inhibition [6]. While effective at raising the seizure threshold, these strategies often cause nonselective suppression of network activity, leading to dose-dependent toxicity of the CNS. Sodium-channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, lacosamide) and SV2A ligands (levetiracetam, brivaracetam) are among the most widely used agents for mono- and adjunctive therapy in focal epilepsy. In randomized controlled adjunctive trials, these agents demonstrate clinically meaningful reductions in seizure frequency and responder rates superior to placebo [7–9]. However, long-term retention is frequently limited by adverse events: sodium-channel blockers may cause dizziness, diplopia, ataxia, hyponatremia, rash, and cognitive slowing; SV2A ligands are associated with behavioral and mood disturbances in a significant proportion of patients; and broad GABAergic drugs can exacerbate sedation and cognitive impairment [5,6]. Newer agents targeting AMPA receptors or exhibiting multiple mechanisms (e.g., perampanel, cenobamate) have broadened therapeutic options but still largely operate through the nonselective suppression of neuronal excitability at the network level [6].

Consequently, there remains a substantial unmet need for treatments that selectively stabilize pathological hyperexcitability while sparing physiological network function, particularly in patients whose quality of life is more constrained by adverse effects than by residual seizures.

4. Market review

The global market for ASMs is substantial and steadily expanding, reflecting the high prevalence of epilepsy and the persistent unmet need in drug-resistant populations. Recent analyses estimate the global epilepsy therapeutics market to exceed 11 billion USD per year, with projected compound annual growth rates (CAGR) of approximately 5–6% over the next decade [10]. Growth is driven by improved diagnosis, broader access to treatment in emerging economies, and the introduction of newer ASMs with improved tolerability profiles.

North America and Europe currently account for the largest share of the ASM market, supported by established healthcare infrastructures, high diagnostic rates, and widespread use of newer branded therapies. However, the Asia–Pacific region is expected to show the fastest growth, reflecting increasing healthcare investment and improved access to neurological care [10]. Despite the availability of more than 40 approved ASMs, a significant proportion of patients with focal epilepsy remain drug-resistant, creating a sustained demand for novel therapeutic options with differentiated mechanisms of action.

The current market is dominated by well-established drug classes, including sodium-channel blockers and GABAergic agents. Many of these compounds are now available as generics, which substantially lowers treatment costs but also raises the threshold for adoption of newer, higher-cost therapies. Recently introduced agents such as cenobamate have demonstrated improved efficacy in some refractory populations, but their uptake remains influenced by safety considerations and physician familiarity [11].

Within this competitive landscape, Kv7 potassium channel modulators represent a mechanistically distinct class with the potential to address a well-recognized therapeutic gap. Their ability to selectively enhance intrinsic neuronal stability, rather than broadly suppress synaptic transmission, may position them as high-value adjunctive therapies, particularly in patients who experience dose-limiting adverse effects with existing ASMs. However, their market penetration will depend on several factors, including demonstration of clear clinical advantages in comparative trials, long-term safety, and cost-effectiveness relative to generic standards of care.

Pricing and reimbursement will be critical determinants of adoption. Given the widespread availability of inexpensive generic ASMs, new Kv7 modulators will likely need to demonstrate either superior efficacy in drug-resistant populations or meaningful improvements in patient-centered outcomes—such as cognition, mood, or treatment adherence—to justify premium pricing. In addition, their potential role in precision medicine, particularly in genetically defined epilepsies, particularly those related to loss-of-function variants in potassium channel subunits, such as KCNQ2/3-related disorders, may support niche but high-impact indications.

Overall, the ASM market is mature but remains receptive to innovation that delivers clear clinical differentiation. Kv7 modulators enter this space with strong mechanistic rationale, but their commercial success will ultimately depend on translating this into tangible and sustained benefits for patients.

5. Current research goals

Current research in epilepsy pharmacotherapy is moving beyond nonspecific synaptic suppression toward more refined modulation of neuronal network stability. A major focus is on intrinsic mechanisms of excitability, particularly the Kv7 channel family, to stabilize neurons from within while preserving physiological network function. Key aims include improving cognitive and psychiatric tolerability, aligning pharmacologic mechanisms with defined genetic etiologies (e.g., KCNQ2/3 loss-of-function), and optimizing pharmacokinetics for once-daily dosing to enhance adherence. Within this framework, next-generation Kv7 agonists are being designed to strengthen the neuronal ‘molecular brake’ at critical excitability checkpoints, such as the axon initial segment (AIS), to selectively suppress pathological

bursting without compromising normal firing. Additional goals include achieving high selectivity for channel subtypes specific to the brain over those found in peripheral tissues, particularly the heart, to eliminate systemic side effects. Research also prioritizes removing reactive chemical structures linked to the toxicity of earlier prototypes to ensure long-term safety. Finally, current efforts aim to evaluate potential disease-modifying effects in genetic encephalopathies and the broader benefits of these agents on neuropsychiatric comorbidities.

6. Scientific rationale

The scientific basis for targeting Kv7 channels lies in their unique ability to regulate intrinsic excitability, acting as a high-precision filter for neuronal electrical signals. In the CNS, heteromeric channels composed of Kv7.2 and Kv7.3 subunits generate the M-current, a low-threshold, non-inactivating potassium conductance active near the membrane potential [12]. These channels are strategically enriched at the AIS and nodes of Ranvier —the key sites of action potential initiation — through interactions with the scaffolding protein Ankyrin-G [13]. By positioning this 'molecular brake' at the point of spike generation, the M-current exerts maximal control over neuronal output. Beyond simple threshold modulation, the M-current represents a prototypical mechanism of Spike Frequency Adaptation (SFA), a fundamental form of neuronal gain control. As a slow-activating, non-inactivating negative feedback loop, it dynamically adjusts neuronal responsiveness to sustained excitatory inputs. By introducing an active leak conductance at these checkpoints, the M-current acts as a dynamic filter, suppressing high-frequency pathological bursting without necessarily silencing the neuron's ability to fire single, physiologically relevant action potentials.

This mechanistic framework is powerfully supported by human genetics: loss-of-function variants in *KCNQ2* and *KCNQ3* cause benign familial neonatal seizures and severe developmental and epileptic encephalopathies (DEEs), suggesting that impaired Kv7 function is sufficient to generate epilepsy phenotypes [14–16]. Therefore, the therapeutic hypothesis is that positive allosteric modulators can rescue this stabilizing current, effectively restoring the physiological brake. Furthermore, the expression of these channels in limbic circuits provides a rationale for their impact on mood disorders, as the M-current regulates the neuronal gain of reward-related pathways [17].

Overall, these findings suggest that pharmacologic modulation of Kv7 channels targets a disease-relevant regulatory system rather than a purely downstream symptom.

7. Competitive environment

The landscape of Kv7 modulation has evolved from the clinical proof-of-concept provided by first-generation agents to a sophisticated pipeline of selective, second-generation candidates and novel pharmacological strategies (Table 1).

7.1. The first-generation prototype: ezogabine

Ezogabine (retigabine, developed by Valeant Pharmaceuticals and GlaxoSmithKline) is a positive allosteric modulator that binds within the pore domain of Kv7 channels and stabilizes the open state. Its efficacy in reducing focal seizure frequency was demonstrated in three randomized, double-blind trials in adults with refractory focal-onset seizures [18–20]. On this basis, the drug was approved in 2011 as adjunctive therapy for focal-onset seizures. However, its clinical use was curtailed by several liabilities. Ezogabine exhibits limited selectivity among Kv7 subtypes, resulting in modulation of the peripheral channels in addition to neuronal Kv7.2/7.3. Because Kv7.4 and Kv7.5 are expressed in smooth muscle, a proportion of patients experienced urinary retention and related urological adverse events [21]. Moreover, ezogabine can activate cardiac Kv7.1 channels, causing QT interval prolongation at higher doses, raising additional cardiac safety concerns [22]. More concerning were pigmentary abnormalities of the skin, mucosa, and retina, thought to arise from reactive metabolites (including N-acetyl ezogabine) that undergo oxidative dimerization and interact with melanin [23–25]. These safety signals led to progressive regulatory warnings and eventual market withdrawal in 2017.

Ezogabine provided clinical proof of concept that targeted enhancement of Kv7 function can suppress focal seizures. At the same time, its nonselective Kv7 subtype profile likely contributed to cardiac and urological adverse events. This experience has driven the design of next-generation modulators with stronger preference for neuronal Kv7.2/7.3 over peripheral isoforms, improved chemical stability, and a wider systemic safety margin, while preserving robust M-current facilitation and antiseizure efficacy.

7.2. Advanced second-generation clinical candidates

7.2.1. Azetukalner (XEN1101)

Azetukalner (XEN1101, developed by Xenon Pharmaceuticals) is the most clinically advanced second-generation Kv7 modulator. It is a selective opener of neuronal Kv7.2/7.3 channels with no detectable effect on cardiac Kv7.1. Structurally, it avoids the anilide motifs associated with pigmentary complications and exhibits an extended half-life of approximately 10 days, supporting once-daily dosing [26,27].

In preclinical testing, XEN1101 showed potent antiseizure activity across standard *in vivo* models, including maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ), and the 6 Hz psychomotor seizure models, considered to be predictive of efficacy in drug-resistant epilepsy [28]. Compared with ezogabine, XEN1101 exhibited a higher protective index, reflecting a wider margin between efficacious and neurotoxic doses.

A randomized, double-blind, placebo-controlled study in 325 adults with focal epilepsy (Phase 2b X-TOLE trial) demonstrated dose-dependent reduction in monthly seizure frequency (NCT03796962) [26]. At the highest dose, the median percent reduction approached 50%, compared with 18% for placebo. Dizziness and somnolence were the most common adverse events, typically mild to moderate. No

instances of retinal or cutaneous pigmentation and no major urinary complications were reported within the exposure period.

Building on these findings, a pivotal Phase 3 program (X-TOLE2; NCT05614063) has been designed to evaluate the efficacy and safety of adjunctive azetukalner in adults with focal seizures. According to company communications, top-line results are expected to inform regulatory interactions and potential submission of a New Drug Application (NDA) [29].

A second Phase 3 multicenter adjunctive therapy trial in adults with focal seizures is ongoing (NCT05716100), and a Phase 3 study is also ongoing to test adjunctive XEN1101 in primary generalized tonic-clonic seizures (PGTCS) (NCT05667142). An open-label extension study of those three Phase 3 clinical studies will evaluate long-term safety, tolerability, pharmacokinetics, and efficacy of XEN1101 in patients with focal-onset seizures or PGTCS for up to 3 years (NCT05718817). Detailed, peer-reviewed data from these Phase 3 studies will be essential to define the comparative efficacy and tolerability of azetukalner relative to existing adjunctive ASMs.

Although these efficacy signals are encouraging, their interpretation should be considered in the context of contemporary adjunctive therapy trials in focal DRE. Across modern epilepsy studies, placebo responses have increased over time, a phenomenon attributed to factors such as trial design, patient selection, and improved background therapy. As a result, cross-trial comparisons between emerging Kv7 modulators and established ASMs must be interpreted cautiously. Reported seizure-frequency reductions and responder rates may not be directly comparable across studies because of differences in baseline seizure burden, trial duration, and patient populations. Consequently, the apparent effect sizes observed in these pivotal trials of Kv7 modulators should be viewed as preliminary indicators rather than definitive measures of comparative efficacy.

Building on CNS effects observed in early studies, azetukalner is also being developed as a monotherapy for major depressive disorder (MDD). A Phase 2 randomized, placebo-controlled trial showed signal of antidepressant efficacy with an acceptable tolerability profile (NCT05376150), and two Phase 3 studies in MDD are underway (NCT06775379, NCT07076407) [30]. These parallel programs may accelerate characterization of long-term safety and neuropsychiatric effects.

7.2.2. Opakalim (BHV-7000)

Opakalim (BHV-7000, developed by Biohaven Pharmaceuticals) represents a parallel second-generation strategy emphasizing high selectivity for Kv7.2/7.3 heteromers and reduced off-target activity. *In vitro*, BHV-7000 potently activates Kv7.2/7.3 while showing minimal interaction with GABAA receptors and other common pharmacologic targets [27]. In rodent seizure models, it confers dose-dependent antiseizure protection with limited impact on motor performance in rotarod testing, suggesting a favorable separation between efficacy and motor/cerebellar toxicity.

Phase 1 studies in healthy individuals, including an exploratory pharmaco-EEG study, have indicated low propensity to cause sedation or marked slowing of background rhythms [27,31,32]. Ongoing Phase 2 and Phase 2/3 trials are assessing efficacy and safety of BHV-7000 as adjunctive therapy in focal epilepsy (NCT06132893, NCT06309966), PGTCS (NCT06425159), and as monotherapy in MDD and bipolar disorder (NCT06419608, NCT06419582). According to company communications, the clinical program for BHV-7000 in MDD has been discontinued after a Phase 2 trial (NCT06419608) did not meet its primary antidepressant endpoint [33]. Consequently, development efforts are now focused on BHV-7000 for epilepsy, where the mechanistic rationale for suppressing network hyperexcitability remains robust.

7.2.3. Pynegabine (HN 37)

Pynegabine (HN-37, developed by the Shanghai Institute of Materia Medica) is an ezogabine-derived Kv7 opener engineered to exhibit greater chemical stability and prevent the formation of pigment-associated metabolites. It preferentially enhances neuronal Kv7 isoforms while sparing cardiac Kv7.1. HN-37 increases M-current, and exhibits improved oxidative stability compared with ezogabine, potentially reducing the risk of tissue pigmentation. It also achieves favorable brain-to-plasma ratios in animal models, potentially allowing effective CNS exposure at lower systemic doses [34].

A randomized, double-blind, placebo-controlled, dose-escalating Phase 2a trial in patients with focal epilepsy reported dose-related seizure reductions and acceptable tolerability, with no clear evidence of cutaneous pigmentary changes over the study period [35]. Larger and longer-term studies are needed to confirm these early findings and define the role of HN-37 relative to XEN1101 and BHV-7000.

7.3. Novel Kv7 modulators in preclinical development

7.3.1. Ezogabine-derived compounds

A growing set of Kv7 channel modulators is in preclinical development, extending beyond the second-generation clinical agents XEN1101, BHV-7000, and pynegabine. Many of these compounds are ezogabine-derived or structurally related Kv7.2/7.3 activators (e.g., ETX-123, IDOR-1104-0086, several resin acid derivatives, sulfide analogs of flupirtine/ezogabine, and other ezogabine derivatives) [36–40]. They are being optimized primarily for greater chemical stability, improved Kv7 subtype selectivity, and a more favorable safety window, while preserving robust M-current facilitation and antiseizure efficacy. Several of these compounds also exhibit promising analgesic activity in pain models. These efforts represent a progressive refinement of the selective Kv7-modulation strategy already exemplified at the clinical level by XEN1101, BHV-7000, and pynegabine.

7.3.2. Dual-mechanism approaches

A second line of innovation involves dual-mechanism molecules that combine Kv7.2/7.3 activation with modulation of other targets. One example is GRT-X, which combines Kv7.2/7.3 activation with engagement of the mitochondrial translocator protein TSPO, potentially adding neuroprotective,

neurodegenerative, anti-inflammatory, and antidepressant effects via enhanced neurosteroidogenesis [41,42].

Other compounds, such as BS421, BS627, and BS661, pair Kv7.2/7.3 opening with the modulation of the transient receptor potential vanilloid type 1 (TRPV1) ligand-gated ion channel, a strategy pursued mainly for acute and chronic pain but conceptually relevant to epilepsy, where comorbid pain and neuroinflammation may be present [43]. Whether these dual mechanism approaches will translate into clinically meaningful advantages—or introduce new tolerability constraints—remains an open question.

7.3.3. Repurposing strategies

A conceptually distinct and particularly attractive avenue is the repurposing of existing CNS drugs with previously unknown Kv7 activity. JNJ-37822681, a fast-dissociating D2 receptor antagonist originally developed as an antipsychotic, was identified as a potent neuronal Kv7 opener [44]. *In vitro* and *in vivo* studies showed that JNJ-37822681 binds the canonical retigabine hydrophobic pocket and enhances Kv7.2–Kv7.5 currents with retigabine-like potency. In a KCNQ2-DEE patient-specific model of cortical neurons, JNJ-37822681 hyperpolarized the resting membrane potential and reduced spontaneous burst firing, normalizing excitability, and highlighting its precision-medicine potential for KCNQ2 encephalopathy. *In vivo*, it conferred robust protection in PTZ-induced seizure models, an effect abolished by the Kv7 blocker XE-991, confirming a Kv7-dependent mechanism. JNJ-37822681 has undergone extensive human safety evaluation, which demonstrated a generally favorable toxicological profile and a safety profile comparable to that of other atypical antipsychotics [45–47]. Should its Kv7-mediated effects prove separable from dopaminergic actions at clinically relevant exposures, repurposing this compound could represent a feasible, lower-risk translational approach for epilepsy and other Kv7-related hyperexcitability disorders.

8. Potential development issues

Kv7 agonists have progressed from a mechanistic concept to a growing clinical pipeline, but several issues will determine whether they become established pillars of therapy or remain niche options. The ezogabine experience highlights how serious adverse effects, including pigmentary and urological complications, may emerge only after prolonged and widespread use. This precedent emphasizes that the current lack of reported long-term toxicity for second-generation Kv7 modulators must be interpreted with caution, as chronic safety signals may only manifest after cumulative exposure in a broader clinical population. For azetukalner, BHV-7000, and pynegabine, available data point mainly to dizziness, somnolence, and gastrointestinal complaints, with no clear signal of pigmentary, ophthalmologic, or major urinary toxicity to date.

Nonetheless, cumulative tissue effects, subtle cognitive or mood changes, and residual off-target activity at peripheral Kv7 isoforms or other channels remain important unknowns. This concern is not unique to Kv7 modulators; other long-half-life CNS drugs, such as certain atypical antipsychotics and mood stabilizers, illustrate how cumulative metabolic, neurologic, or psychiatric adverse effects may emerge after years of continuous exposure. For Kv7 agonists, particular attention should be paid to potential shifts in mood, motivation, or apathy that might be subtle yet functionally significant, especially given the expression of these channels in limbic circuits.

In monogenic epilepsies, where treatment may be started in infancy and continue lifelong, even low-frequency adverse events could have a substantial cumulative impact, underscoring the need for decades-long surveillance and dedicated patient registries.

A critical challenge in this context is the developmental timing of intervention, particularly in KCNQ2/3-related DEEs. During early neurodevelopmental windows, impaired M-current function may drive hyperexcitability, disrupting synaptogenesis and circuit refinement and promoting maladaptive network reorganization. Once established, these alterations may not be fully reversible; thus, Kv7 modulation initiated later in life could improve seizure control without fully improving cognitive or developmental outcomes. These considerations support early precision-based intervention aimed not only at suppressing seizures but also at preventing long-term neurodevelopmental impairment.

Given these risks, regulators are likely to require extended open-label follow-up and post-marketing surveillance with systematic dermatologic, ophthalmologic, and urinary assessments.

Furthermore, development programs have so far followed a conventional path: adjunctive therapy in adults with drug-resistant focal-onset seizures, using seizure-frequency endpoints. In addition, the interpretation of efficacy outcomes in modern epilepsy trials requires attention to broader clinical metrics beyond median seizure reduction. Responder rates, treatment retention, and patient-centered outcomes such as cognitive performance, quality of life, and mood stability are increasingly recognized as critical indicators of real-world therapeutic value. These measures are particularly relevant when comparing emerging Kv7 modulators with established adjunctive therapies such as sodium-channel blockers, which have demonstrated durable retention and well-characterized safety profiles in long-term clinical use.

The recent success of the Phase 3 X-TOLE2 trial is a landmark for the field, yet the exceptionally low placebo response observed in that study highlights the volatility of contemporary trial designs. Similarly, the discontinuation of the BHV-7000 psychiatric program in January 2026, following a failed Phase 2 trial in MDD, serves as a reminder that biological plausibility does not always translate into clinical success across all indications.

Pediatric and precision medicine indications —especially in KCNQ2/3-related DEEs—are mechanistically attractive, but long-term safety expectations will be stringent. Prolonged exposure to long-acting Kv7 modulators, such as XEN1101, may increase the risk of unexpected developmental or neuropsychiatric effects, underscoring the need for conservative dosing and rigorous monitoring. Mechanistic data suggest a potential disease-modifying role, yet clinical evidence that early intervention can alter the natural history of the encephalopathy—beyond seizure control—remains limited, highlighting the balance of promise and caution required in pediatric precision-therapy strategies.

Table 1. Voltage-gated potassium channel subfamily 7 (KCNQ, Kv7) modulators in clinical development.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Azetukalner (XEN1101)	XenonPharmaceuticals	Aza-anthracenone derivative (Non-anilide)	Focal-onset seizures (FOS); Primary generalized tonic-clonic seizures (PGTCS); Major depressive disorder (MDD)	Phase 3	Selective neuronal Kv7.2/Kv7.3 opener that stabilizes the open channel state
Opakalim (BHV-7000)	Biohaven Pharmaceuticals	Pyridone-based selective opener	FOS; PGTCS	Phase 2/3	Highly selective Kv7.2/Kv7.3 opener with minimal off-target activity
Pynegabine (HN-37)	Shanghai Institute of Materia Medica	Fluorinated ezogabine derivative	FOS	Phase 2	Neuronal Kv7.2/7.3 opener engineered for improved oxidative and chemical stability

9. Conclusion

Kv7 potassium channel agonists represent one of the most mechanistically coherent advances in antiseizure therapy in recent decades. By targeting intrinsic neuronal excitability rather than downstream network effects, they offer a fundamentally different approach to seizure control. Second-generation agents have addressed many of the liabilities that limited ezogabine and show encouraging efficacy and tolerability in DRE and, potentially, mood disorders. These features, together with a clear genetic link between KCNQ2/3 dysfunction and epileptogenesis, provide solid grounds for optimism.

The milestone achievement of the X-TOLE2 primary endpoint in March 2026 and the anticipated NDA submission for azetukalner in Q3 2026 signal that this class is moving toward clinical implementation.

10. Expert opinion

Whether these agents 'break new ground' depends on their long-term clinical performance and their potential to demonstrate clear advantages in patient-centered outcomes over established therapies. Clinical failure for next-generation Kv7 modulators might not arise from lack of efficacy alone, but rather from a combination of marginal therapeutic gains compared to established, lower-cost ASMs and the emergence of unexpected chronic toxicities or neuropsychiatric side effects. If these drugs fail to demonstrate a clear advantage in patient-centered outcomes—such as cognitive stability or the prevention of disease progression in genetic channelopathies—they may remain niche options rather than becoming pillars of therapy. Furthermore, early efficacy signals from Phase 2 trials should be interpreted within the broader landscape of adjunctive therapy studies in focal epilepsy, where increasing placebo responses and heterogeneous trial designs complicate direct comparisons of effect size across different drug classes.

In the near term, Kv7 agonists are likely to be used primarily as adjunctive treatment in adults with focal DRE, as high-value additions to existing ASMs. Their once-daily dosing and apparently limited sedative potential may be particularly advantageous in patients whose functioning is constrained by adverse effects of sodium channel blockers or broad GABAergic drugs. Beyond this broad indication, they hold promise for monogenic channelopathies such as KCNQ2/3 loss-of-function disorders, in which restoration of M-current is directly disease relevant. In these genetic epilepsies, their disease-modifying potential stems from addressing the underlying channelopathy (loss of Kv7.2/7.3 function) rather than merely suppressing symptoms. Restoring M-current early in development could, in principle, limit maladaptive circuit reorganization and improve long-term neurodevelopmental trajectories. At the same time, biological plausibility does not guarantee disease modification: durable improvements in development or cognition will need to be demonstrated empirically, beyond seizure metrics, in carefully designed longitudinal studies.

Despite their mechanistic appeal, Kv7 agonists are unlikely to replace first-line ASMs. Current standards benefit from extensive safety data and low costs, which these new agents must overcome with evidence of clear clinical superiority. Phase 3 trials will clarify whether efficacy and tolerability justify early positioning in treatment algorithms. To fully understand the role of these drugs, future studies should include comparative trials versus established adjunctive ASMs, particularly sodium-channel blockers and SV2A ligands, and incorporate patient-centered outcomes such as cognition, mood, quality of life, responder rates, and long-term treatment retention. More realistically, they may become high-value adjunctive therapies in focal DRE and as precision-medicine anchors for selected KCNQ2/3-related epilepsies.

An additional emerging aspect is the potential role of Kv7 modulators in mood disorders. Converging data indicate that aberrant excitability within fronto-limbic circuits underlies both depression and mania. In this context, the M-current acts as a neuronal gain regulator: its potentiation stabilizes firing patterns without abolishing physiological synaptic transmission. This targeted modulation may dampen limbic hyperreactivity, offering a mechanistic advantage over certain broad-spectrum ASMs. However, as shown by the divergent clinical results of azetukalner and opakalim in MDD, realizing such precision applications will require routine access to genetic testing, functional annotation of variants, and the development of biomarkers—electrophysiologic or imaging-based—that report on impaired M-current or network hyperexcitability. If long-term safety proves acceptable, Kv7 modulators may meaningfully reshape the pharmacological management of focal epilepsy, shifting the focus toward targeted, disease-modifying strategies.

Author contributions

CRediT: **Cristiana Pelorosso:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing; **Simona Balestrini:** Conceptualization, Investigation, Writing – review & editing; **Renzo Guerrini:** Conceptualization, Investigation, Supervision, Writing – review & editing.

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