CNS Drugs
https://doi.org/10.1007/s40263-026-01281-0

LEADING ARTICLE

Seletracetam Revisited: A Missed Opportunity for Effective Epilepsy Therapy

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Received: 27 October 2025 / Accepted: 3 February 2026

Abstract

Seletracetam (SEL) is a second-generation racetam derivative of the benchmark antiseizure medication (ASM) levetiracetam, discovered in a drug discovery program conducted by UCB Pharma in the early 2000s to optimize binding to synaptic vesicle glycoprotein 2A (SV2A), the main target of levetiracetam. SEL (administered orally) reached phase IIa clinical trials, but its further development was stopped, and its patent expired in 2021. In preclinical studies, SEL showed very potent seizure suppression in several acquired and genetic epilepsy models, with high CNS tolerability. Phase I human studies indicated rapid and extensive oral absorption (> 90% bioavailability), linear pharmacokinetics, and an elimination half-life of about 8 h, with mostly mild to moderate CNS adverse events. Several phase IIa trials found SEL to be effective and to have a good safety profile in patients with photosensitive epilepsy and drug-resistant focal epilepsy. A unique aspect of SEL is its high potency and water solubility that—unlike any other non-benzodiazepine (non-BDZ) ASMs—allows it to be formulated at therapeutic doses in a very low liquid volume suitable for intranasal administration and potential use in acute seizure rescue therapy. The US-based company PrevEp, Inc. (Bethesda, MD) filed a new US patent application in 2024, followed by a worldwide Patent Cooperation Treaty (PCT) application in 2025 on intranasal and orobuccal SEL formulations and new medical uses as the first potential non-BDZ rescue treatment of acute repetitive seizures and rapid epileptic seizure termination (REST). The clinical development of this novel formulation is derisked by the favorable oral SEL administration phase I and phase IIa clinical data. SEL offers several important advantages for rescue treatment in comparison with BZDs. It is only moderately sedative even at the highest doses tested orally, does not cause respiratory depression, and has no addictive potential. Thus, SEL has the potential to become the first non-BDZ acute rescue therapy. Because SEL has never been approved for use in humans, it is a new chemical entity (NCE). In this review, we describe the pharmacology of SEL, its clinical profile after oral administration, and the development of the new intranasal formulation, including first-in-human data.

1 Introduction

Seletracetam (SEL [ucb 44212]; Fig. 1), a derivative of the benchmark antiseizure medication (ASM) levetiracetam (LEV), was discovered by a drug discovery program at UCB Pharma in which ~ 12,000 compounds were screened in vitro for binding affinity for the LEV binding site (LBS) on brain synaptic plasma membranes, characterized subsequently to be the synaptic vesicle glycoprotein 2A (SV2A), the main target of LEV [1, 2]. Following the in-vitro screening, 1200 compounds were further screened in vivo for seizure protection in an animal model, the audiogenic seizure-prone DBA/2 mouse model of reflex epilepsy; subsequently, about

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Published online: 03 March 2026

Key Points

Racetams such as levetiracetam and brivaracetam, which act by modulating synaptic vesicle glycoprotein 2A, are widely used in the chronic treatment of different types of epilepsy.

The highly potent second-generation racetam, seletracetam, showed promise as an antiseizure drug in preclinical and early clinical studies, but its further clinical development for oral epilepsy therapy was discontinued in favor of the less potent brivaracetam.

The high antiseizure potency, water solubility, and tolerability of this drug make it a promising candidate for rescue treatment of acute repetitive seizures and rapid seizure termination by intranasal administration, thus potentially replacing benzodiazepines, which are currently used in this respect.

30 of these compounds were selected and broadly characterized in a battery of animal models of seizures and epilepsy [2, 3]. This led to the identification of two distinct racetam families with high affinity for SV2A and high antiseizure potency. They were named after their lead compounds: SEL (a difluorovinyl derivative of LEV) and brivaracetam (BRV; a 4-n-propyl LEV homolog; Fig. 1). Both SEL and BRV have at least 10 times higher affinity for SV2A than LEV and are more selective [4, 5]. Both racetams are also much more lipophilic and markedly more potent than LEV in acute and chronic animal models of focal and generalized seizures, SEL being the most potent of all three compounds, especially in the amygdala kindling model [5]. Both SEL and BRV underwent phase I and IIa clinical studies and showed high efficacy and safety after oral administration, but UCB Pharma decided to evaluate only one drug, BRV, in large multicenter phase III trials, leading to US Food and Drug Administration (FDA) approval of BRV in 2015 for the treatment of focal onset seizures [6]. At least in part, the decision to choose BRV and not SEL was based on the broader spectrum of antiseizure activities of BRV in animal models [2, 5]. SEL was progressed by UCB as a BRV backup should the latter fail, which did not occur. The patent for SEL expired in 2021.

Based on the favorable physicochemical properties of SEL, its high antiseizure potency, proof-of-concept (POC) efficacy in several phase IIa trials, excellent pharmacokinetics and safety profile, and no obvious developmental roadblocks, the US-based company PrevEp (Bethesda, MD) decided in 2024 to file a new US patent application followed by a worldwide Patent Cooperation Treaty (PCT) application in 2025 on intranasal and orobuccal SEL formulations and new medical uses for rescue treatment of acute repetitive seizures (ARS), rapid epileptic seizure termination (REST), and prevention of reflex seizures [7]. The clinical development of such a novel formulation is derisked by the favorable phase I and phase II clinical data on the oral administration of SEL. Uniquely among non-benzodiazepine (non-BDZ) ASMs, SEL's potency is such that it allows the formulation of therapeutic doses in the small volume of liquid or spray that can be accommodated by the human nostril, namely about 100 µL per nostril [8, 9]. As will be discussed in this review, SEL provides several important advantages for rescue treatment in comparison with BZDs that have been

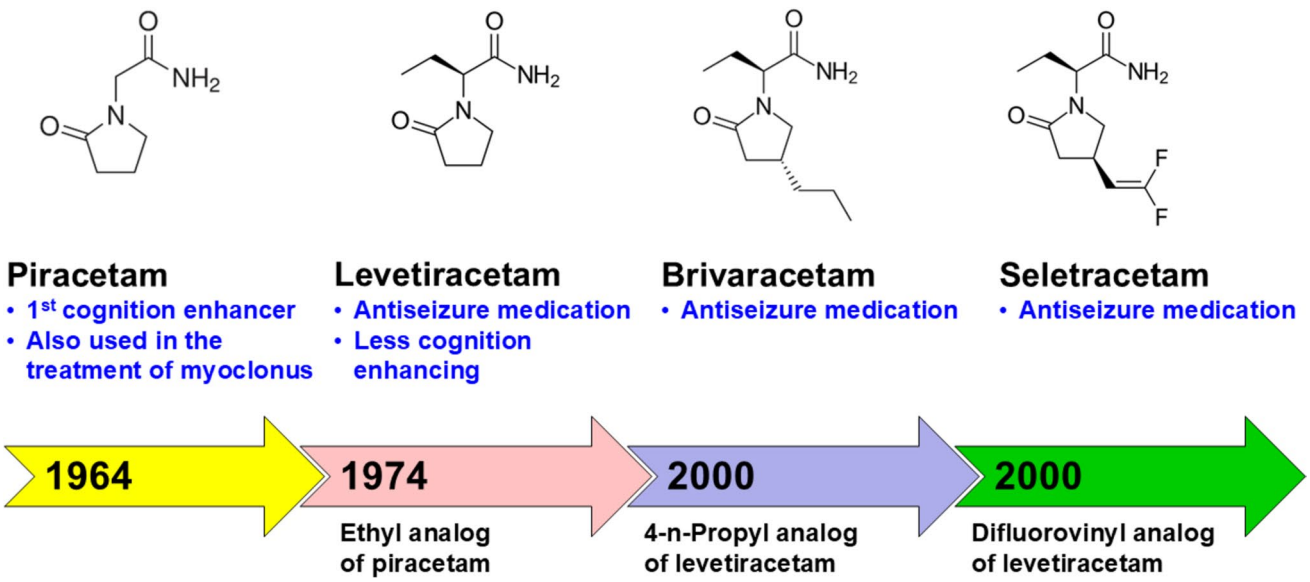

Fig. 1 The discovery of the racetams by UCB Pharma

approved for this indication [10, 11]. Thus, in contrast to BDZs, SEL is only moderately sedative even at the highest doses tested orally in volunteers and patients (see Sects. 5.1 And 5.3), and, similar to LEV and BRV, does not cause respiratory depression and has no addictive potential. Thus, SEL has the potential to become the first non-BDZ for termination of acute seizures, with the potential to replace BDZs for ARS rescue therapies.

As SEL has never been approved for use in humans, it has to be classified as a new chemical entity (NCE). In this review, we will describe the pharmacology of SEL and its clinical profile after oral administration. An update on SEL's potential for acute rescue treatment since its last reviews [4, 12] appears timely in view of recent development of the new intranasal formulation, including first-in-human data [13].

2 Preclinical Pharmacology of Seletracetam

Like LEV and BRV, SEL is an asymmetric (chiral) compound (Fig. 1). LEV ((*S*)-α-ethyl-2-oxopyrrolidine acetamide) is the (*S*)-enantiomer of etiracetam (α-ethylpiracetam), a piracetam derivative developed initially as a nootropic (cognitive-enhancing) drug [14]. Both the nootropic and anticonvulsant effects of etiracetam reside in its (*S*)-enantiomer (LEV; ucb L059), while the (*R*)-enantiomer (ucb L060) has little or no activity [15]. Compared with LEV, the binding affinity of ucb L060 is 1000 times lower [16]. BRV ((2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide), a (4*R*)-propyl derivative of LEV, is a chiral compound with two chiral centers (Fig. 1). The chiral center linking the butanamide moiety to the pyrrolidone ring is highly stereoselective for binding to SV2A, with BRV being > 3000-fold more potent than its (2*R*,4*R*)-diastereoisomer [15]. Like BRV, SEL ((2*S*)-2-[(4*S*)-4-(2,2-difluoroethenyl)-2-oxo-1-pyrrolidinyl]butanamide), a (4*S*)-difluorovinyl derivative of LEV, is a chiral compound with two chiral centers (Fig. 1). Like LEV and BRV, seletracetam binds stereospecifically to SV2A [4]. The enantiomers of SEL behave the same way as those of BRV, that is, a marked loss in affinity for the acetamide chiral center (*S* much more potent than *R*) and a much smaller drop for the pyrrolidone chiral center (4*R* being more potent than 4*S*) (Michel Gillard, personal communication).

As with other racetams such as LEV and BRV, SEL combines high lipophilicity with high water solubility. This allows easy preparation of aqueous solutions of the compound and also explains its rapid absorption following in-vivo administration (see Sect. 2.1). Like BRV (log*P* 0.66), SEL is more lipophilic than LEV (log*P* 0.51 [SEL] vs − 0.64 [LEV]), which favors rapid brain entry after systemic administration [2]. Importantly, SEL is not just another racetam but differs significantly in its mechanisms of action and antiseizure potencies from LEV and BRV.

2.1 Mechanism of Action of Seletracetam

LEV was first synthesized in 1974 during efforts at UCB Pharma to identify a second-generation agent to replace the nootropic drug piracetam (Fig. 1). However, LEV did not show any significant nootropic activity in clinical trials [14]. Instead, pharmacological characterization revealed antiseizure effects in animal models such as genetically sound-sensitive mice and amygdala-kindled rats. Its main mechanism of action was unknown until the early 2000s, when Lynch et al. [17] described that LEV acts by modulating SV2A in the brain, previously described as LBS on brain synaptic plasma membranes [16]. The identification of the molecular target LBS/SV2A allowed UCB to screen in vitro for more effective ligands, resulting in the discovery of BRV and SEL. As shown in Fig. 2, by modulating SV2A, which is expressed in both inhibitory and excitatory synapses and is discussed as being a key player in the control of exocytosis, racetams such as LEV, BRV, and SEL may exert effects on vesicle mobilization, neurotransmitter release, and thus neuronal excitability [5]. However, the exact role of SV2A in neurotransmission is still a matter of debate [18]. Both BRV and SEL are at least 10 times more potent than LEV to interact with SV2A (Table 1).

SV2A forms a transporter-like structure with a central binding pocket that is occupied by racetam anticonvulsants (Fig. 2), providing important insights into the mechanism of action for these drugs [18]. All three racetams bind to a shared primary site of the SV2A protein but interact differently with SV2A [5, 19–21]. Data for LEV and BRV suggest that these drugs recognize, induce, or stabilize different conformations of the SV2A protein, which may provide the molecular rationale for their distinct pharmacodynamic properties. SEL not only differs from LEV in its much higher affinity for SV2A, but it also dissociates much more slowly from SV2A than LEV (Michel Gillard, personal communication). Thus, when comparing SV2A dissociation kinetics in the rat cortex at 4° and 25° (see Noyer et al. [16] for details), dissociation was up to 20 times slower for SEL versus LEV, translating into longer target occupancy. This, together with the higher binding affinity, may explain why SEL is much more potent than LEV both preclinically and clinically (see below). However, all three racetams also affect other targets that may contribute to their antiseizure effects [3].

Importantly, SEL has been shown to inhibit high-voltage-activated Ca^{2+} currents (HVACCs) 50 times more potently than LEV [22]. The half-maximal inhibitory concentration (IC_{50}; 0.27 µM) of SEL for inhibiting HVACCs is close to its IC_{50} at SV2A (Table 1). In vitro experiments with toxins that target different subtypes of HVACCs

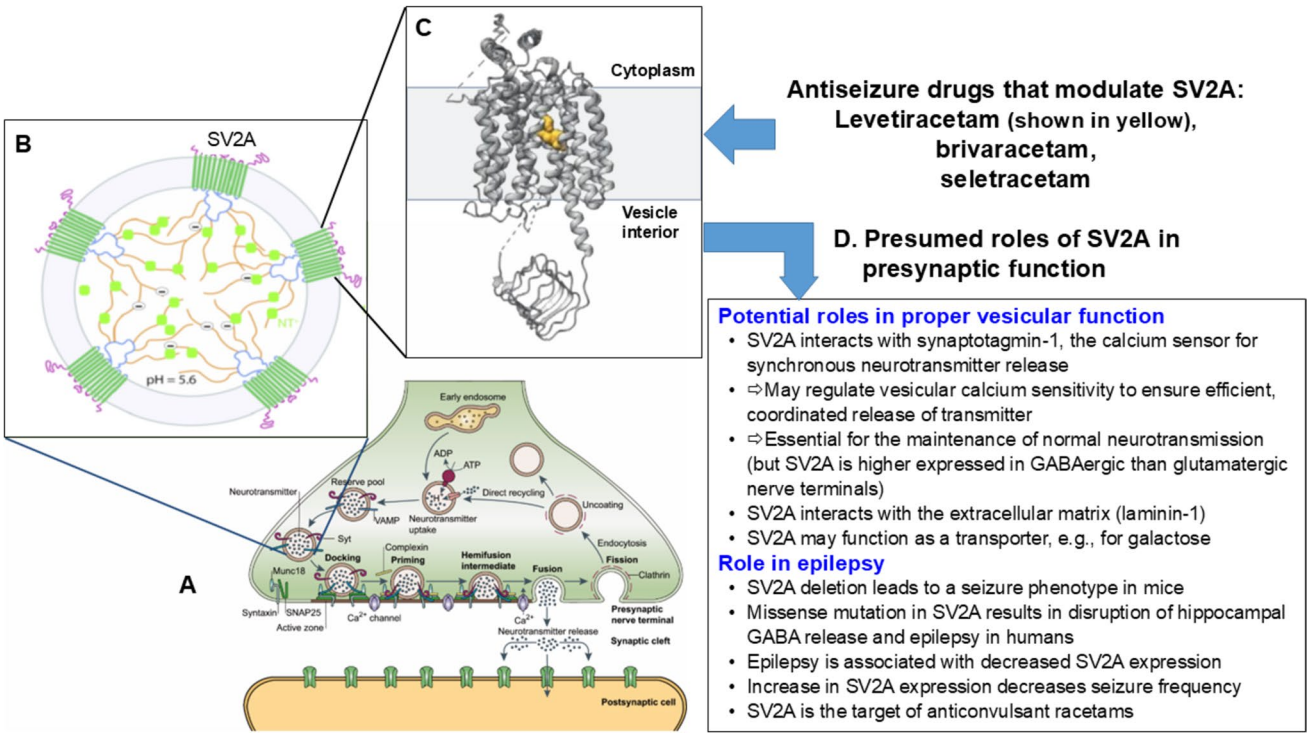

Fig. 2 Schematic representation of the localization, structure, and potential functions of synaptic vesicle glycoprotein 2A (SV2A). **A** Schematic illustration of the dynamics of synaptic vesicles (SVs) at the presynaptic terminal, illustrating the mechanism of neurotransmitter (NT) release and SV recycling. SVs are specialized spheroidal membrane structures that traffic along the axon to the presynaptic terminals, where they internalize and store NTs (blue dots). The SV membrane harbors proteins, some of them highly glycosylated (synapsin, synaptotagmin [Syt], SV2A, and synaptophysin), whose precise sorting is required for efficient neurotransmission. Once SVs are loaded by NTs, several processes lead to exocytosis as illustrated in **A**. SV2A has been proposed to be involved in several of these processes, including control of the expression and localization of Syt1 (the calcium sensor for synchronous neurotransmitter release) at the presynapse, calcium-dependent exocytosis, NT loading/retention in SVs, and SV priming, as well as the transport of vesicle constituents. **B** A magnified view of an SV illustrating SV2A as a vesicular protein. Note that other vesicular proteins and the proton pump are not illustrated. Neurosecretory vesicles typically express 5 copies of SV2A, with little intravesicular variation. The 4th intraluminal loop of SV2A is heavily glycosylated (glycosylated chains are illustrated by orange lines), which leads to negative charges in acidic environments. This allows NTs that are either positively charged (e.g., monoamines, acetylcholine) or zwitterionic (e.g., GABA) to adsorb into the charged proteoglycan matrix, removing them from the concentration gradient and allowing the vesicle to package more NT. **C** Cryo-EM structure of SV2A in complex with levetiracetam (shown in yellow). Racetams (levetiracetam, brivaracetam, seletracetam) specifically bind in a central pocket within SV2A that faces the inside of the synaptic vesicle and act by modulating its functions (see text for details). **D** Suggested functions of SV2A for proper vesicular function and in epilepsy are summarized. Note that SV2A appears to be more highly expressed in GABAergic than glutamatergic neurons, indicating a disproportionate impact on inhibitory neurotransmission. However, although SV2A is one of the most abundant SV molecules, which suggests that it performs a key role in presynaptic function, there is still considerable debate regarding its precise roles. See Löscher et al. [5], Stout et al. [69], Rossi et al. [70], and Hogg and Cousin [71]. The figure was modified and updated from Löscher et al. [5] and Bradberry and Chapman [18]

suggested that N-type Ca^{2+} channels, and partly Q-type subtypes, are preferentially targeted by SEL [22]. Other ASMs that inhibit HVACCs at therapeutically relevant drug levels include lamotrigine, topiramate, and phenobarbital, but not valproate [23]. However, the combination of effects on both SV2A and HVACCs is unique for SEL. It should be noted that BRV does not inhibit HVACCs (Table 1). Like LEV and BRV, SEL is devoid of effect on low-voltage-gated (T-type) Ca^{2+} currents [3].

While SEL and LEV do not inhibit voltage-gated Na^+ currents (Table 1), BRV was shown to produce a concentration-dependent inhibition of such currents, recorded in rat cortical neurons in culture, with an IC_{50} value of 7 µM [24]. It was suggested that this explains the antiseizure activity of BRV in the maximal electroshock seizure (MES) test, in which LEV and SEL are ineffective (see below). However, subsequent studies questioned whether modulation of voltage-gated Na^+ currents plays a role in the antiseizure activity of BRV [2]. Similarly, voltage-gated potassium channels are not affected by racetams at therapeutically relevant concentrations.

Concerning glutamate receptors, SEL did not modify NMDA-, kainate-, or AMPA-gated currents (except for minor inhibition of the plateau phase of the NMDA current)

Table 1 Comparative in vitro potencies of levetiracetam (LEV), brivaracetam (BRV), and seletracetam (SEL) at different targets

Target	Preparation	LEV	BRV	SEL	References
Synaptic vesicle glycoprotein 2A (SV2A)					
SV2A, IC_{50} (μM)	Human SV2A expressed in COS-7 cells	1.9			[17]
SV2A, Ki (μM)	Human SV2A expressed in COS-7 cells	3.16	0.13	0.032	[72, 73]
SV2A, Ki (μM)	Rat cortex	1.3	0.079		[72]
SV2A, IC_{50} (μM)	Rat cortex	0.78		0.14	[73]
Voltage-gated ion channels					
High voltage-activated Ca^{2+} currents (HVACCs), IC_{50} (μM)	Rat cortex	13.9	NE[a]	0.27	[2, 22]
Voltage-gated Na^{+} channels, IC_{50} (μM)	Rat cortical neurons	NE[1]	7	NE[a]	[3]
Transmitter-gated ion channels					
Reversal of inhibition by Zn^{2+} on GABA-gated currents (20 mM)	Hippocampal neurons	Reversal (30–100 μM)	Reversal (1–100 μM)	NE[b]	[3]
Reversal of inhibition by Zn^{2+} on glycine-gated currents (100 mM)	Spinal cord neurons	Reversal (0.1–100 μM)	Reversal (3–100 μM)	Total reversal (from 10 pM)	[3]

HVACCs high-voltage-activated calcium channels, *IC_{50}* half-maximal inhibitory concentration, *Ki* inhibition constant, *NE* not effective, *SV2A* synaptic vesicle glycoprotein 2A

[a]Up to 1000 μM

[b]Up to 100 μM

at pharmacologically relevant concentrations, while LEV possesses an ability to inhibit AMPA-gated currents in rat hippocampal and cortical neurons (IC_{50} 268 μM), which, however, only becomes significant at concentrations above therapeutic relevance [3, 4]. BRV is devoid of any direct interaction with excitatory and inhibitory neurotransmission, except for a weak and minor inhibition of the NMDA receptor current. Neither LEV nor SEL exerts direct effects on $GABA_A$ receptors.

However, LEV and BRV differ from other ASMs by their ability to reverse the inhibition of Zn^{2+} of both GABA-gated currents (in rat hippocampal and dentate granule neurons) and glycine-gated currents (in spinal cord neurons) [3, 25]. Based on the 'sprouted mossy fiber/Zn^{2+}-sensitive $GABA_A$ receptor' hypothesis [26–29], it has been suggested that epileptogenesis involves alterations in both the subunit composition of the $GABA_A$ receptor as well as mossy fiber sprouting from dentate granule cells with Zn^{2+}-containing terminals, which induces a vicious circle of disinhibition in the hippocampus resulting in epileptic discharges—a condition that LEV may counteract [3]. Concerning this hypothesis, there has been some debate that centers around the contradictory effects of zinc on $GABA_A$ receptors, with some studies showing zinc inhibits $GABA_A$ receptors, while others suggest it can also modulate or enhance GABAergic transmission [29]. The discrepancy likely arises from the different contexts and receptor subtypes being studied, as well as the varying concentrations of zinc used in the experiments. In contrast to LEV and BRV, SEL is ineffective in reversing the inhibition of Zn^{2+} of GABA-gated currents, while it is much more potent than LEV and BRV in reversing the inhibition of Zn^{2+} of glycine-gated currents in the spinal cord (Table 1). Glycine is the main inhibitory neurotransmitter of the spinal cord and brainstem, and glycine receptors regulate motor control through inhibitory synaptic signaling [30]. Dysregulation of glycine receptors influences a wide range of conditions, including temporal lobe epilepsy [31].

More recently, SEL was found to increase the activity of the major glial glutamate transporters GLT-1 (rats) and EAAT2 (humans) in vitro at nanomolar concentrations below those that modulate SV2A, indicating that this effect may be critically involved in SEL's mechanisms of action (Krzysztof Kaminski and Agata Faron-Górecka, personal communication). SEL was 1500 times more potent than LEV to increase glutamate transport. Glutamate transporter 1 (GLT-1), also known as excitatory amino acid transporter 2 (EAAT2), plays a crucial role in regulating extracellular glutamate levels in the brain, and its dysfunction is implicated in epilepsy [32]. Specifically, reduced expression of astroglial GLT-1/EAAT2, which is responsible for clearing glutamate from the synapse, is observed in the brain of both animal models of epilepsy and patients with epilepsy [33].

This reduction can lead to excitotoxicity, a process where excessive glutamate overstimulates neurons, potentially triggering seizures. Ceftriaxone, a β-lactam antibiotic that was previously shown to increase GTL-1/ EAAT2 protein expression levels [34], was reported to restore GLT-1 function and to inhibit seizures, revealing a previously unknown link between cerebrovascular factors and epileptogenesis [35]. Furthermore, Goodrich et al. [36] reported that treatment with ceftriaxone after traumatic brain injury restores expression of GLT-1 and reduces post-traumatic seizures in the rat, indicating a critical role of GLT-1 in epileptogenesis. Novel positive allosteric modulators (PAMs) of EAAT2 have recently been identified and are under development, representing a promising approach for the advancement of novel therapeutics for epilepsy [32, 33].

Taken together, SEL differs from LEV and BRV both in its interaction with SV2A and in its off-target effects, particularly its potent inhibitory effect at HVACCs, its powerful ability to reverse the inhibition of Zn^{2+} on glycine-gated currents, and its effects on glutamate transport. These mechanisms together may explain why SEL is more potent than other racetams, BDZs, and other ASMs in certain preclinical seizure models.

2.2 Antiseizure Effects of Seletracetam in Animal Models

As shown in Table 2, SEL, like LEV, showed no anticonvulsant activity in the two classical screening tests for ASMs: the maximal electroshock seizure test (MES; tonic hindlimb convulsions) and the pentylenetetrazol seizure test (PTZ; generalized clonic convulsions), both acute seizure models in naïve mice. In distinct contrast, SEL showed potent seizure suppression in models of acquired or genetic epilepsy (Table 2). Thus, SEL displayed potent protection against audiogenic seizures in genetically seizure-prone DBA/2 mice (median effective dose [ED_{50}] of 0.17 mg/kg) and against absence-like seizures in the GAERS (Genetic Absence Epilepsy Rat from Strasbourg) model (ED_{50} of 0.15 mg/kg). The latter two genetic models are used to test drugs for antiseizure activity against generalized seizures. In kindling models, which are used to evaluate drug activity against focal-onset and secondarily generalized convulsive seizures, SEL displayed potent protection against secondary generalized motor seizures in fully corneally kindled mice (ED_{50} of 0.31 mg/kg). Furthermore, it exerted potent effects against focal and secondary generalized motor seizures in amygdala-kindled rats, a widely used and highly predictive chronic model of antiseizure efficacy in temporal lobe epilepsy [37]. Minimum active doses (MADs) to increase the threshold for focal seizures (after-discharge threshold; ADT) and generalized convulsive seizures (GST) were 0.0074 mg/kg intraperitoneally (i.p.), which is far below the effective doses of any other ASM, including BDZs, previously reported in the kindling model [37].

Figure 3 illustrates the dose-dependent antiseizure effect of SEL on the GST in amygdala-kindled rats in comparison with the respective effects of LEV and BRV. Similar potency differences were obtained for the ADT [38]. SEL was not only about 180 times more potent in increasing the GST (and ADT) than LEV but also more effective, as indicated by the higher percent GST increases obtained with SEL versus LEV. Furthermore, SEL was at least 10 times more potent than BRV in this model.

Overall, SEL is one of the most potent compounds ever tested in genetic and kindling models of epilepsy, even exceeding the potency of BDZs in several of the models shown in Table 2. The finding that SEL is not effective in the MES and PTZ models is not relevant, as LEV is also ineffective in these models but has become one of the most widely used ASMs. Similarly, several other clinically effective ASMs, including vigabatrin, tiagabine, gabapentin, and lamotrigine, are ineffective in the MES and/or PTZ models [39], so these tests are no longer used as gatekeepers in ASM screening but are now integrated into a diversified panel of acute and chronic seizure models [40].

2.3 CNS Tolerability of Seletracetam in Animals

The rotarod test of Dunham and Miya [41] is a classical test commonly used for the determination and quantification of the *minimal neurological deficit* during the characterization of novel ASMs [40]. Based on the performance of mice or rats in this test, the protective index, or the ratio of median neurotoxic dose (TD_{50}) for rotarod toxicity to ED_{50} for seizure protection, is commonly calculated as a measure of the separation between anticonvulsant potency and potency to induce motor impairment [40]. As shown in Table 2, in contrast to its high antiseizure potency, SEL is only weakly effective in inducing motor impairment in the rotarod test with TD_{50} of 503 mg/kg in mice and > 743 mg/kg in rats. Consequently, SEL exhibits a remarkably high protective index, which greatly exceeds that of LEV, BRV, diazepam, and other ASMs. Importantly, such a high protective index is also seen in kindled mice and rats, indicating that the chronic brain alterations associated with kindling do not decrease the tolerability of this drug, as is seen with several other investigational compounds and ASMs [42]. In amygdala-kindled rats, a protective index of > 70,000 was obtained for SEL, far exceeding the protective indices of LEV, BRV, and other ASMs in this model. Overall, SEL showed a potent, broad spectrum of seizure protection and a high CNS tolerability in animal

Table 2 Preclinical profile of seletracetam versus levetiracetam and brivaracetam in rodent models of seizures. Some other antiseizure drugs are shown for comparison. Furthermore, data for 'minimal neurological deficit' (neurotoxicity) determined by the rotarod test are shown

Model	ED_{50} (mg/kg i.p.)							
	SEL	LEV	BRV	DZP	PHT	CBZ	LTG	VPA
Antiseizure effects								
Screening models								
MES test (mice)	> 232	> 540	113	23	5.6	7.8	7.5	260
s.c. PTZ test (mice)	> 232	> 540	30	0.29	> 50	> 50	> 50	220
Genetic models								
Audiogenic seizures in DBA/2 mice	0.17	30	2.4	0.2	3.9	11	2.4	155
SWDs in GAERS (rats)	0.15	5.4 (MAD)	6.8 (MAD)	~ 0.75	NE	NE	NE	< 200
Kindling models								
Corneally kindled mice (secondary generalized seizures)	0.31	7.3	1.2	0.6	67	9	37	110
Amygdala-kindled rats (ADT [focal seizures])	0.0074 (MAD)	1.25 (MAD)	0.68 (MAD)	NE	30	> 20	~ 10 (MAD)	300
Amygdala-kindled rats (GST [secondary generalized seizures])	0.0074 (MAD)	1.25 (MAD)	0.68 (MAD)	2	50	8	?	190
Minimal neurotoxicity (rotarod test)	TD_{50} (mg/kg i.p.)							
Neurotoxicity in naive mice	503	2223	195	4.7	41	45	30	400
Neurotoxicity in naive rats	> 743	1960	~ 370	2.8	140	33	411 (per os)	394
Neurotoxicity in corneally kindled mice	325	1036	55	?	99	33	29	184
Neurotoxicity in amygdala-kindled rats	520	1119	163	5.8	?	32	?	300
Protective indices	TD_{50}/ED_{50}							
Protective index in DBA/2 mice	2958	74	81	23.5	10.5	4.1	12.5	2.6
Protective index in rats (GAERs)	> 4950	363	54	3.7	NE	NE	NE	> 2
Protective index in kindled mice	1048	142	46	NT	1.47	3.7	0.78	1.67
Protective index in kindled rats (TD_{50}/MAD or ED_{50})	70,270	895	240	NE	?	< 1.6	?	1.6

Data are from Löscher et al. [5] and Löscher and White [37]

ADT after-discharge threshold, *BRV* brivaracetam, *CBZ* carbamazepine, CC_{97} current inducing seizures in 97% of mice, *DZP* diazepam, ED_{50} median effective dose, *GAERS* genetic absence epilepsy rat from Strasbourg, *GST* generalized seizure threshold, *i.p.* intraperitoneal, *LEV* levetiracetam, *LTG* lamotrigine, *MAD* minimum active dose providing significant protection against the seizure endpoint, *MES* maximal electroshock seizure, *NE* not effective, *NT* not tested, *PHT* phenytoin, *PTZ* pentylenetetrazol, *s.c.* subcutaneous, *SEL* seletracetam, *SWD* spike-wave discharges, TD_{50} median toxic dose, *VPA* valproate, *?* no data are available

models. The animal data predicted the high tolerability of SEL in patients with epilepsy (see Sects. 5.1 And 5.3).

2.4 Pharmacokinetic Profile of Seletracetam in Animals

Following oral administration, SEL is rapidly and highly absorbed in animals, with linear and time-independent pharmacokinetics [4]. The exposure to the drug is similar in both sexes in all animal species (mice, rats, and dogs) tested. Plasma protein binding is low, and SEL is rapidly distributed to tissues. The major metabolic pathway of SEL, which has been observed in all tested species, consists of the hydrolysis of the acetamide group to form the carboxylic acid metabolite ucb-101596-1, which is pharmacologically inactive. The parent compound, along with its major metabolite, is excreted mainly in the urine.

3 Preclinical Safety Pharmacology and Toxicology of Seletracetam

SEL has a very low acute oral toxicity in mice, rats, and dogs, and presents no significant CNS, cardiopulmonary, or respiratory tract effects, as demonstrated in the safety pharmacology studies [4, 43]. Repeat-dose oral toxicity of SEL has been tested for up to 13 weeks in rats and dogs. The highest tested oral dose was 2000 mg/kg/day in rats and 600 mg/kg/day in dogs. At this high dose level, systemic signs of toxicity were induced, which were primarily CNS-related. Drug-related effects were observed from oral dose levels of 20 mg/kg/day in rats and 50 mg/kg/day in dogs. Results of genotoxicity tests give no evidence for SEL being genotoxic at any of the doses and concentrations tested. The reproductive toxicology studies performed thus far have shown that SEL is neither embryotoxic nor teratogenic.

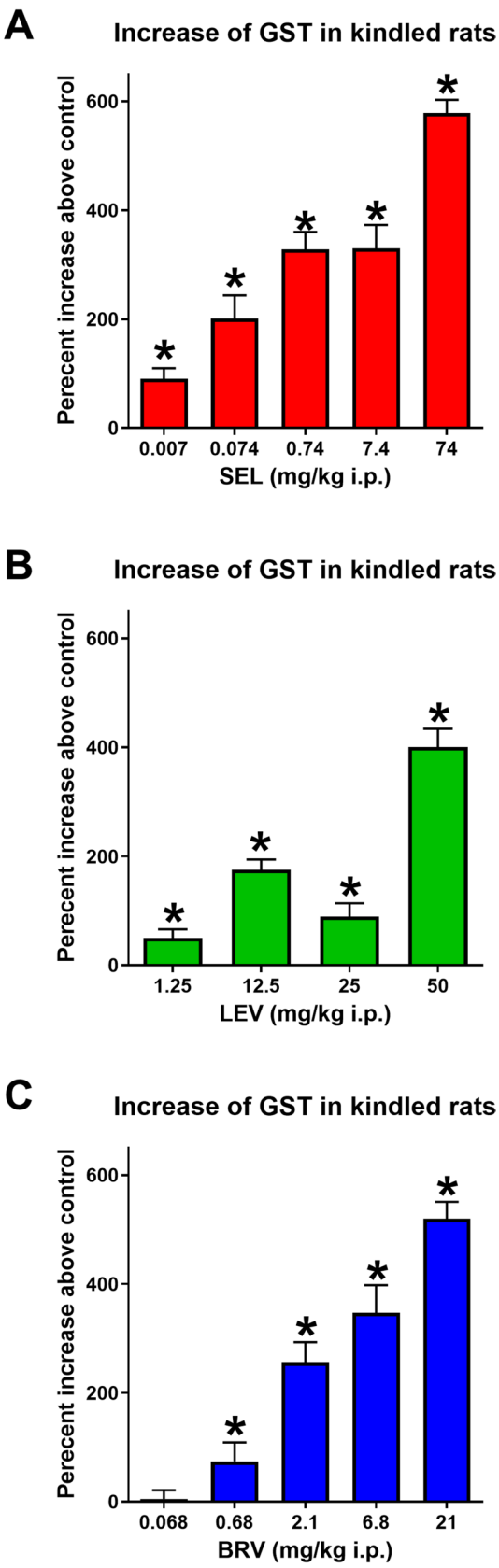

Fig. 3 Antiseizure effect of seletracetam (SEL), levetiracetam (LEV), and brivaracetam (BRV) in amygdala kindled rats. Drug effects on the threshold for secondarily generalized convulsive seizures (GST) are shown. Data are shown as means ± SEM of 9 fully kindled rats in percent seizure threshold increase above vehicle control seizure thresholds. Significant differences to control thresholds are indicated by asterisks ($p < 0.05$). The experiments with the three drugs were done in a blinded randomized fashion in the same group of fully kindled rats by the group of W. Löscher. Note the enormous potency differences among the three drugs, with SEL being by far the most potent racetam. All drugs also significantly increased the threshold for focal seizures (after-discharge threshold; ADT) in kindled rats. The minimum doses increasing GST and ADT are shown in Table 2. For details, see Matagne et al. [38]

4 Drug Interactions of Seletracetam

Based on the in-vitro data currently available, there is a low potential for interaction of SEL on other drugs or of other drugs on SEL [43]. SEL appears neither to inhibit nor to induce the major human drug metabolizing CYP isoenzymes and does not inhibit human epoxide hydrolase. It has low plasma protein binding (<10%), which also suggests a low potential for drug–drug interactions.

5 Clinical Data of Seletracetam

SEL and BRV were developed in parallel by UCB Pharma. Both drugs underwent early-phase clinical trials (phase I and phase IIa) with oral administration, but only BRV was subsequently evaluated in large phase III trials. Results of early-phase clinical trials with oral administration of SEL are reported in the following sections.

5.1 Tolerability of Seletracetam After Oral Administration in Healthy Volunteers

The tolerability of SEL following single and multiple doses was evaluated in healthy volunteers (Table 3). Overall, SEL was well tolerated following single oral doses from 2 mg to 600 mg and following multiple oral doses of 200 mg twice daily [43].

Subjects in the single-dose study reported adverse events typical of ASMs, including dizziness, somnolence, nausea, and headache [4]. The incidence of dizziness tended to increase at doses of ≥50 mg; however, nausea, somnolence, and headache did not seem to be dose-related. All the adverse events reported were of mild or moderate intensity, and the doses tested appeared to be well tolerated.

In the repeated-dose study, the subject-reported adverse events were similar to those observed in the single rising dose study, with CNS adverse events reported most frequently, the majority of which were of mild to moderate

intensity. In general, these adverse effects occurred within 1 hour of initial dosing and decreased in incidence with subsequent dosing [4].

5.2 Pharmacokinetics and Metabolic Profile of Seletracetam Following Oral Administration in Healthy Volunteers

The pharmacokinetics of SEL were studied in healthy male subjects in a single rising dose study, with oral doses ranging from 2 to 600 mg [4]. SEL was rapidly absorbed, as demonstrated by a maximal plasma concentration (C_{max}) that was reached within 1 hour after dosing in the majority of fasted subjects. Coadministration with a high-fat meal resulted in a delayed time to C_{max} (median time delayed from 0.5 to 4 h after the dose) and a 39% reduction in C_{max} but did not affect the overall extent of absorption. The disposition of SEL was characterized by linear pharmacokinetics over the 300-fold dose range studied. The volume of distribution was approximately 0.6 L/kg, which is close to that of total body water, indicating that SEL distributes to all tissues, including the brain. SEL plasma terminal half-life was approximately 8 h in young healthy male subjects; it did not vary with dose. The total apparent clearance was approximately 67 mL/min, or approximately 0.8 (mL/min)/kg; this is much lower than the hepatic blood flow (1500 mL/min), indicating a low extraction ratio by the liver.

A repeated-dose study was performed in 36 healthy male volunteers (Table 3). Subjects received either 20, 60, or 200 mg twice daily for 2 weeks. SEL was shown to have predictable pharmacokinetics. Dose proportionality was confirmed for elimination and half-life. The metabolite concentrations were approximately 10-fold lower than those of the parent compound. After repeated dosing, no unexpected accumulation of either parent compound or metabolite was observed, and no autoinduction of SEL clearance occurred, confirming time-independent pharmacokinetics [4].

A study was conducted to investigate the excretion balance and metabolism of orally administered [^{14}C]SEL (100 mg) in six healthy male volunteers [4]. Absorption of SEL administered as an oral solution was rapid and nearly complete, with 92% of radioactive tracer recovered in urine. The urine metabolic profiling indicated that, besides the parent compound, one major metabolite was identified (ucb-101596-1, the acidic metabolite) and two additional minor metabolites. At 168 h, 3.21% of the dose was recovered in the feces, and 91.9% of the dose was recovered in urine, reflecting a high absorption of the drug. In the urine, the unchanged compound (25%) and the major metabolite measured (53%) represented 78% of the dose. In plasma, radioactivity was measurable until 72 h after the dose for all subjects. The major radioactive component was the parent drug, representing generally > 90% of the circulating radioactivity up to 24 h after administration. The remaining

Table 3 Early-phase clinical trials with oral seletracetam. A total of 171 participants were treated (53 healthy volunteers and 118 patients with epilepsy)

Study type and population	Number of subjects	Age (y)	Study duration	Oral dose	Study results	References
Phase I; SAD healthy volunteers	26	Adults	Single dose	2–600 mg	Favorable pharmacokinetics and good tolerability, with adverse effects limited to mild to moderate CNS effects	[74]
Phase I; MAD healthy volunteers	27	Adults	2 weeks	20–200 mg per day b.i.d.	Adverse effects limited to mild to moderate CNS effects at initial dosing	[74]
Phase IIa POC; IPS/PPR in photosensitive epilepsy patients	28	18–60	Single dose	0.5–20 mg	Rapid and potent dose-dependent suppression of PPR; seen also in patients on comedication with ASMs, including LEV	[44, 46, 75]
Phase IIa; add-on treatment in patients with focal onset seizures	31	18–65	11 weeks	20–160 mg	See Sects. 5.3.2 and 5.5.3	NCT00152451 (clinicaltrials.gov)
Phase IIa; add-on treatment in patients with focal onset seizures	59	18–65	11 weeks	20–160 mg	See Sects. 5.3.2 and 5.5.3	NCT00152503 (clinicaltrials.gov)

ASM antiseizure medication, *b.i.d.* twice daily, *IPS* intermittent photic stimulation, *LEV* levetiracetam, *MAD* multiple ascending dose, *POC* proof of concept, *PPR* photoparoxysmal EEG response, *SAD* single ascending dose

radioactivity (up to 10%) was associated with ucb-101596-1, the acidic metabolite.

5.3 Tolerability of Seletracetam After Oral Administration in Epilepsy Patients

5.3.1 Photosensitive Epilepsy

Of 27 participants with photosensitive epilepsy in whom single oral doses (0.5–20 mg) of SEL and of placebo were administered, 18 participants reported adverse effects after SEL and four after placebo [44]. The most frequently reported adverse effects after SEL were somnolence (32%), dizziness (21%), headache (14%), and feeling drunk (7%). In participants with somnolence, this adverse effect started within one hour in six participants (at SEL doses of 0.5–10 mg) and at 2, 3.5, and 4 h after intake of 1, 10, and 20 mg in other participants, respectively. The duration varied from 19 min to 3 h (SEL doses between 0.5 and 20 mg) in six, while three other participants reported a duration of 4.5 (4 mg), 7 (2 mg), and 19 (1 mg) hours. Dizziness was reported by four other participants with onset between 15 min and 2.5 h, with duration between 23 min (SEL 10 mg) and 5.5 h (SEL 10 mg). No evident association was observed between the incidence of adverse effects reported after SEL administration and the dose or plasma level. All but one of the adverse effects observed were mild to moderate. One subject had severe somnolence after SEL 4 mg lasting 3 h. All treatment-emergent adverse effects were resolved before the end of the study. No serious adverse effects occurred. No effects on mood were observed.

5.3.2 Focal Epilepsy

Two phase IIa open-label studies evaluated the safety, tolerability, and efficacy of SEL adjunctive therapy in adult participants with focal epilepsy (Table 3). The full results of the studies have not been published, but study protocols and results have been posted on the ClinicalTrials.gov site (identifiers NCT00152503 and NCT00152451).

Study NCT00152503 enrolled 59 adults (aged 18–65 years) from May 2005 to May 2006. It was an open-label, exploratory, dose-escalation phase II study of the safety, tolerability, and efficacy of SEL capsules. SEL was administered in doses of 10, 20, 40, and 80 mg twice daily (daily doses of 20–160 mg) as an add-on treatment to patients with drug-resistant focal epilepsy (previously called refractory partial epilepsy) with continued seizures while receiving one to three concomitant ASMs, including LEV. Following 4 weeks at baseline, subjects were treated with SEL for 11 weeks. They were up-titrated every 2 weeks from 20 to 160 mg/day until the maximum tolerated dose was reached. They were maintained at this dose until the end of the 8th week, followed by a 3-week down-titration period.

Of 59 subjects enrolled (52% women), 55 subjects completed the study, and four subjects stopped the study because of adverse events, although the data posted on the site do not identify which adverse effects led to discontinuation, nor whether or not they were treatment-emergent adverse events. SEL appeared well tolerated. There were three serious adverse events, seemingly unrelated to the medication (skin cancer, convulsion, and unstable angina). Side effects with > 5% incidence included dizziness (22%), nausea (20%), headache (15%), fatigue, and somnolence (14% each), followed by nasopharyngitis (12%), vomiting, and urinary tract infection (10% each), cough (8%), nystagmus, diarrhea, abdominal pain, and pharyngolaryngeal pain (7% each) and, at 5% each, decreased appetite, bronchitis, convulsion, dyspnea, herpes simplex infection, irritability, sinus congestion, and tremor.

Study NCT00152451 (UCB study NO1101) enrolled 31 participants (48%), also from May 2005 to May 2006. It was also an open-label, exploratory, multicenter, dose-escalation study of the efficacy, safety, and tolerability of SEL at doses of 10 mg, 20 mg, 40 mg, and 80 mg twice daily (total daily dose of 20–160 mg) with the same 4-week baseline, 8-week up-titration, and 3-week down-titration periods as study NCT00152503. Adult subjects (aged 18–65 years; 48.4% females) with drug-resistant focal epilepsy were treated with one, two, or three ASMs. Like the other study, participants were up-titrated every 2 weeks until the maximum tolerated dose was reached and were maintained at this dose until the end of the 8-week up-titration period, followed by a 3-week down-titration. Of the 31 participants who started the study, 27 completed it. Four stopped early because of adverse events, although the results posted on the ClinicalTrials.gov site do not disclose which adverse effects led to treatment discontinuation or whether they were treatment-emergent adverse events. The most common adverse effects present in > 5% of participants were dizziness (23%), headache and depressed mood (12.9% each), anxiety, decreased appetite and upper respiratory tract infection (10% each), and fatigue, gait ataxia, abnormal coordination, nystagmus, insomnia, irritability, nervousness, and nasal and sinus congestion, at 6% each.

5.4 Pharmacokinetics of Seletracetam Following Oral Administration in Epilepsy Patients

Repeated blood samples were taken in the phase IIa POC study in photosensitive patients, thus allowing for the determination of the pharmacokinetics of SEL in the presence and absence of comedication with ASMs [44]. After each dose (0.5–20 mg) of SEL, maximal plasma concentrations were reached within approximately 2 h and were followed

by a mono-exponential decline. The concentration decreases after C_{max} values were parallel for all doses as evidenced on the semi-logarithmic plot, implying a similar terminal half-life of ~ 8 h across doses. Furthermore, plasma concentrations appeared to increase in a linear proportion with the administered dose, as reported previously for healthy volunteers [4]. Figure 4A illustrates the linear regression between C_{max} and oral dose in the photosensitive participants. Figure 4B shows the linear regression between the area under the plasma concentration curve (AUC; a measure of total drug exposure) and oral dose of SEL in these participants. The linear, time-independent pharmacokinetics of the drug, combined with a rapid and almost complete absorption, indicate that SEL has a straightforward pharmacokinetic profile.

Interestingly, when comparing the median time to the first response on the photoparoxysmal electroencephalographic (EEG) response (PPR; see Sect. 5.5.1) with plasma levels of SEL, the first response was observed before reaching the time of maximal plasma levels (t_{max}) at 0.5–1 h for 1–20-mg doses. The duration of response for the same dose was much longer than the half-life, and ranged from 16 to 31 h. This suggests that very low plasma levels of SEL are sufficient to produce an effect quickly and to maintain it for a long time. Examples of two participants are illustrated in Fig. 5, demonstrating the rapid onset of the anti-PPR effect and the long duration of the effect.

Most of the participants were on steady-state treatment with one or two ASMs. Data on plasma levels of these ASMs did not suggest obvious pharmacokinetic interactions between these ASMs and SEL [44].

5.5 Efficacy Data After Oral Administration of Seletracetam

Three clinical studies have been performed with orally administered SEL, including a phase IIa POC trial in participants with photosensitive epilepsy and two phase IIa add-on studies in patients with focal epilepsy (Table 3).

5.5.1 POC Phase IIa Trial in Patients With Photosensitive Epilepsy

The photosensitivity model has become a widely accepted POC model for testing of diverse new ASMs [45]. Its utility rests on a read-out that is directly related to epilepsy, namely, reflex-induced epileptiform discharges in the EEG of patients with reflex epilepsy in whom there is a tight relationship between reflex photosensitive epilepsy and PPR to intermittent photic stimulation (IPS). PPR is suppressed by ASMs of diverse mechanisms of action and of diverse indication targets, including focal epilepsy, acute rescue therapy, or REST [45]. Data obtained in trials in photosensitive patients are useful to inform dose finding and effective

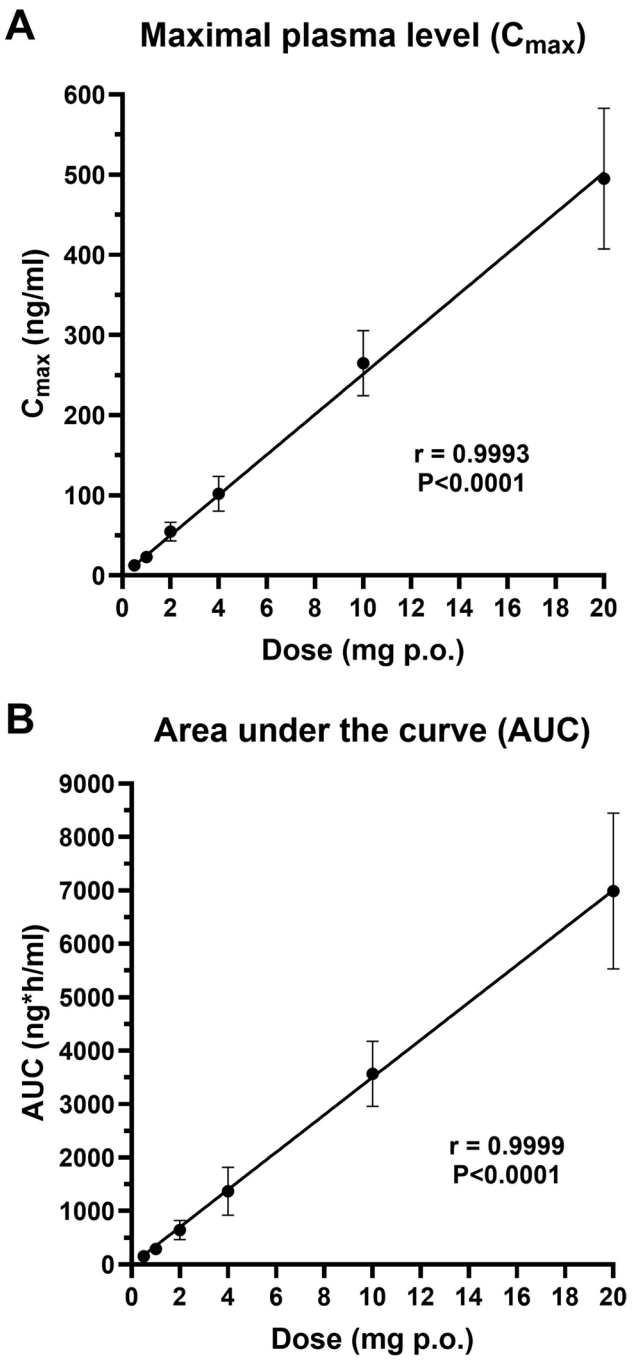

Fig. 4 Pharmacokinetics of seletracetam (SEL) following administration of single oral doses in 27 patients with photosensitive epilepsy. Data are shown as means ± standard deviation (SD). **A** Maximal plasma concentration (C_{max}) of SEL following doses of 0.5, 1, 2, 4, 10, and 20 mg. Note the linear relationship between dose and C_{max}, resulting in a highly significant correlation between the two variables. **B** Area under the plasma concentration–time curve (AUC) determined following oral doses of 0.5, 1, 2, 4, 10, and 20 mg of SEL. Note the linear relationship between dose and AUC (i.e., total drug exposure), resulting in a highly significant correlation between the two variables. See Kasteleijn-Nolst Trenité et al. [44] for additional pharmacokinetic parameters of SEL

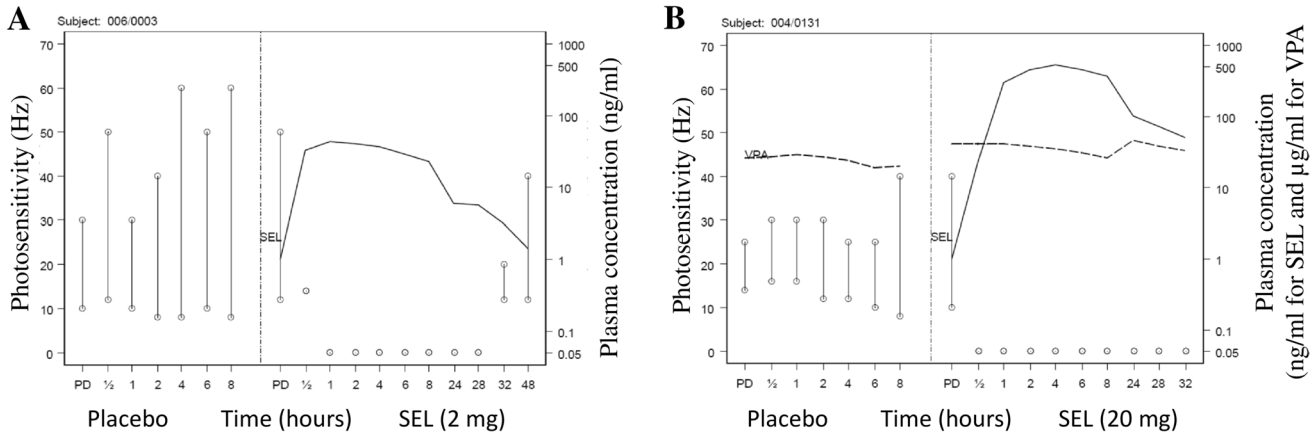

Fig. 5 Example of two individual photosensitive epilepsy patients who were treated with seletracetam (SEL). In each trial, the patient received a placebo (day − 1; left part of each graph) and SEL (day 1; right part of each graph). Placebo or SEL were orally administered immediately after predrug (PD). The patient shown in **A** did not receive comedication with antiseizure medication (ASM), while the patient in **B** received valproate (VPA) on a chronic basis. The effect of oral intake of SEL on the photosensitivity range (upper and lower photosensitivity limits in Hz, depicted as a bar) is shown. The limits themselves are graphically expressed as small circles. The left *y* axis shows the photosensitivity in Hz, while the right y-axis shows the plasma drug concentration of SEL (in ng/mL) or VPA (in µg/mL). Drug levels are indicated by the dashed (VPA) or solid (SEL) lines. SEL (2 or 20 mg) completely abolished the photoparoxysmal response in both patients. Note the rapid onset and long duration of the effect. The two patients are from the trial published by Kasteleijn-Nolst Trenité et al. [44]

plasma levels of an investigational drug for subsequent clinical trials in other patient populations or with other routes of administration (see Sect. 6).

The primary objective of the POC phase IIa trial with SEL was to identify the lowest single oral dose of SEL producing suppression of the IPS-evoked PPR in photosensitive epileptic subjects [44]. A secondary objective was to assess the relationship between plasma concentrations of SEL, changes in the photosensitivity frequency range, time of onset, and duration of the effect (see also Sect. 5.4). In this multicenter, single-blind, phase IIa study, adults with photosensitive epilepsy, with and without concomitant ASM therapy, underwent IPS under three eye conditions (at eye closure, eyes closed and eyes open) after a single oral dose of placebo (day − 1) or SEL (day 1; 0.5, 1, 2, 4, 10, or 20 mg). Complete suppression was a standardized photosensitivity range (SPR) reduction to 0 over one or more time points for all eye conditions. Partial suppression was a ≥ 3-point reduction over three or more testing times versus the same time points on day − 1 in one or more eye condition. In addition, pharmacokinetics and safety were assessed. Of 27 evaluable participants, nine reentered to receive a second drug exposure 1–6 months later, providing a total of 36 individual exposures. At all doses administered, even the lowest, several subjects reached a complete abolishment of PPR, with a rapid onset of effect. Overall, complete abolishment of PPR was obtained in 40–71% of the participants; the effect increasing with the dose. Comparing effective doses to suppress PPR, SEL was at least 1500 times more potent than LEV and 10–20 times more potent than BRV. The effects of SEL in two individual participants are illustrated in Fig. 5, demonstrating the rapid onset and long duration of SEL's effect on PPR.

Concerning the relationship between plasma concentrations of SEL and its effect on PPR, a PPR-suppressing effect was already observed in some participants at the lowest dose (0.5 mg), at which C_{max} was only ~ 13 ng/mL (Fig. 4A), underlining the high potency of the compound.

This POC study in photosensitive epilepsy patients showed that SEL is a promising ASM candidate, one with high potency, straightforward pharmacokinetics, and good tolerability in epilepsy patients. Photosensitive POC trials are useful for quantitatively predicting efficacy in focal or generalized epilepsies [45]. It is worth noting that SEL is the only non-BDZ ever tested in the human photosensitivity model that exerts effects on PPR at doses as low as effective BDZ doses.

5.5.2 Comedication With Levetiracetam Does Not Counteract the Effect of Seletracetam in Patients With Photosensitive Epilepsy

Most (78%) of the participants in the study of Kasteleijn-Nolst Trenité et al. [44] were on comedication with one or two ASMs (including LEV, lamotrigine, valproate, topiramate, carbamazepine, phenobarbital, and phenytoin) that did not suppress the PPR response in these participants (see Fig. 5B). However, a group of six participants was not taking any ASM, and groups of similar size received different ASM comedications, thus allowing the determination of which, if any, of the ASMs reduced (or increased) the effect of SEL

on PPR in individual participants [46]. Overall, a response to SEL was seen in 32 of the 36 exposures (Fig. 6; right column). In participants without any comedication, SEL completely suppressed PPR in 86% of the exposures (see Fig. 5A as an example). In participants on comedication with LEV, complete suppression was only observed in 33% of the exposures, which, however, was not statistically significantly different from participants without comedication (Fig. 6). Overall, in 78% of the SEL exposures in participants on concomitant LEV, a response (either partial or complete) was observed, indicating that comedication with LEV may reduce, but not abrogate the effect of SEL. As discussed in Sect. 2.1, the unique combination of effects on both SV2A and HVACCs may explain why SEL inhibits PPR even in the presence of LEV. This finding may suggest that in clinical practice, the two drugs could be combined and yet derive benefits from SEL. Similarly, none of the other ASMs examined in the phase IIa POC trial significantly counteracted the effect of SEL (Fig. 6). Indeed, given the fact that the PPR in these participants was resistant to treatment with steady-state doses of ASMs (see Fig. 5B as an example), the study shows that ASM failure could be overcome with add-on treatment with SEL in most (32/36) participants.

5.5.3 Phase IIa Add-on Trials in Patients With Drug-Resistant Focal Onset Seizures

Two Phase IIa add-on trials with SEL were performed in participants with drug-resistant focal onset seizures (Table 3), but results of only one of these trials are available in the public domain.

In study NCT00152503 ($n = 59$), efficacy was evaluated as focal (partial) seizures during 7-day periods, comparing treatment periods during the up- and down-titration stages of the 11-week total treatment period with the 4-week baseline period. The evaluation included partial simple (focal preserved consciousness using current International League Against Epilepsy [ILAE] terminology [47]) seizures with a motor component, partial complex (focal impaired consciousness) seizures, and partial seizures with secondary generalization (focal to bilateral tonic-clonic seizures). SEL, administered as capsules in a twice-daily schedule, resulted in median percent seizure frequency reduction of 26% (20 mg/day), 32% (40 mg/day), 42% (80 mg/day), and 32% (160 mg/day) during the up-titration period. Of note, in this study, participants were on concomitant treatment with LEV, without seizure control, before entering the study. In the NCT00152451 study ($n = 31$), SEL treatment reduced seizure frequency (median percent reduction) by 40% (20 mg/day), 37% (40 mg/day), 28% (80 mg/day), and 40% (160 mg/day). During the up-titration period, 3% of participants achieved > 75 to < 100% seizure frequency reduction, and 6.5% achieved seizure freedom during treatment week 8, the last week of the up-titration period.

6 Development of Seletracetam as a Novel Immediate-Use Seizure Medication

Even with appropriate daily ASMs, a significant proportion of patients with epilepsy, variably estimated at ~ 10 to 70%, have frequent ARS episodes, also known as seizure clusters [11, 48–50]. ARS place an undue burden of care on patients and caregivers, increasing the likelihood of status epilepticus, mortality and morbidity, emergency room visits, hospitalizations, and ICU admissions [51, 52]. BDZs are the current standard of care for the treatment of such acute seizure emergencies [10, 53–55]. Intranasal drug delivery provides certain advantages over other routes of administration [56–59]. Currently, intranasal formulations of diazepam (Valtoco®) and midazolam (Nayzilam®) are approved for the treatment of ARS [59]. The intranasal route is attractive due to its non-invasiveness, potential for direct nose-to-brain delivery, high vascularity, relatively large absorptive surface area, and avoidance of intestinal/liver metabolism, all resulting in faster target engagement than oral formulations [60]. It is more convenient and user-friendly than rectal or potential subcutaneous or intramuscular injections and can be readily used in out-of-hospital settings, unlike intravenous administration [9].

Following intranasal administration, drugs are either absorbed into the capillaries of the nasal mucosa and then transported from the venous circulation across the blood–brain barrier (BBB) into the brain, or the drug is transported directly from nose to brain, bypassing the bloodstream (Fig. 7). Nose-to-brain transport of intranasally applied medications may accelerate target engagement and therapeutic onset of action of nasally delivered CNS-active drugs. Nose-to-brain delivery of drugs is believed to occur along olfactory nerve projections to the olfactory bulb and trigeminal nerve projections to the brainstem [61, 62]. Thus, nose-to-brain delivery results in inhomogeneous brain drug distribution with high drug levels in the olfactory bulb (but low plasma levels), while drugs (such as BDZs) that are primarily absorbed into the capillaries of the nasal mucosa and then transported from the venous circulation across the BBB into the brain exhibit high plasma levels and homogeneous brain drug distribution [63]. As shown for intranasal administration of allopregnanolone, direct nose-to-brain delivery results in greater speed of antiseizure action and less propensity for adverse effects [63]. At present, there are no data for SEL in this respect.

The direct nose-to-brain route may be particularly attractive for CNS delivery of drugs with poor permeability

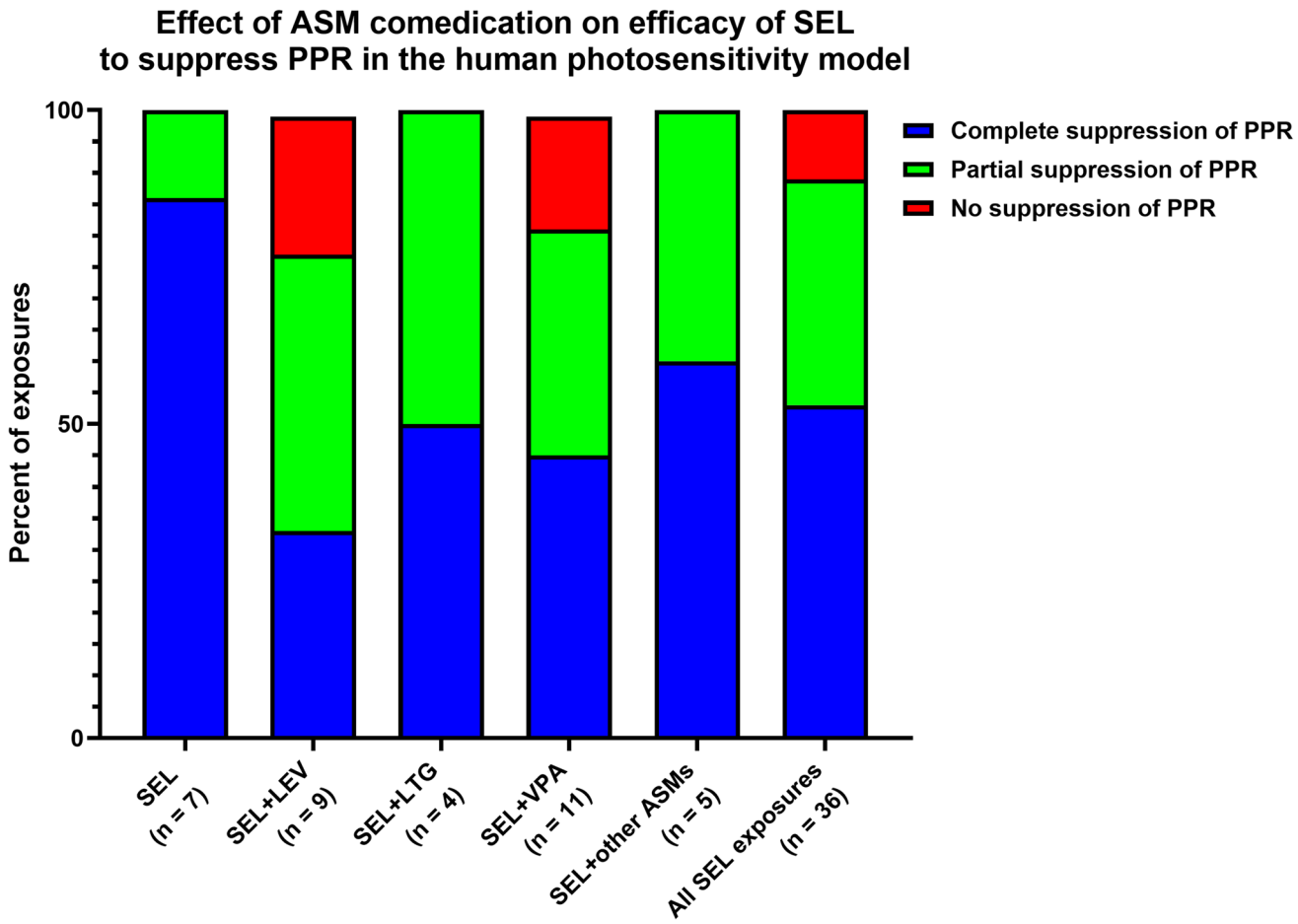

Fig. 6 Effects of comedication with antiseizure medications (ASMs) on the efficacy of seletracetam (SEL) to suppress the photoparoxysmal EEG response (PPR; eye closure) after intermittent photic stimulation in patients with photosensitive epilepsy. PPRs were analyzed by an independent central EEG reader. Overall, SEL was tested in 36 exposures in 27 patients. SEL was tested following oral administration of single doses, ranging from 0.5 to 20 mg. Since the same dose range was tested in all subgroups, all values are shown together for each group. Data are illustrated as complete suppression of PPR, partial suppression of PPR, or no suppression of PPR for the following groups: SEL without ASM comedication; SEL in patients comedicated with levetiracetam (LEV); SEL in patients comedicated with lamotrigine (LTG); SEL in patients comedicated with valproate (VPA); SEL in patients comedicated with other ASMs (carbamazepine, topiramate, phenobarbital, phenytoin); and all SEL exposures. The effect of SEL seemed to be highest in the group without ASM comedication; however, statistical analysis of the data by Barnard's test did not indicate any significant intergroup differences. Data are from Löscher et al. [46]

through the BBB, especially if they can be formulated with suitable mucoadhesives [60]. However, for intranasal administration of the highly lipophilic BDZs, animal data indicate minimal brain-to-nose delivery; the bulk of distribution to the brain is via the venous circulation, followed by transport across the BBB [60, 63]. In contrast, the neurosteroid allopregnanolone confers rapid seizure protection by direct nose-to-brain delivery [63]. It is not known whether SEL is also transported directly from the nose to the brain, bypassing the bloodstream.

The limited volume of the nasal cavity allows for intranasal administration only if there is antiseizure potency at very low doses, precluding nasal administration of all licensed ASMs other than BDZs and neurosteroids such as allopregnanolone (brexanolone). In addition, poor water solubility of most ASMs further restricts absorption, leading to insufficient therapeutic brain levels after intranasal administration [60]. SEL is an exception, unique among non-BDZ ASMs, because its favorable water solubility and high antiseizure potency allow for it to be dissolved at anticonvulsant doses in low volumes.

While intranasal BDZs are suited for rescue therapy for seizure clusters or periods of increased seizure activity [54, 59], the use of BDZs is associated with significant disadvantages, including marked sedation and the risk of respiratory depression and addiction [10]. Indeed, BDZs can cause psychological and physical dependence and withdrawal reactions, especially if used too frequently [64]. The FDA has

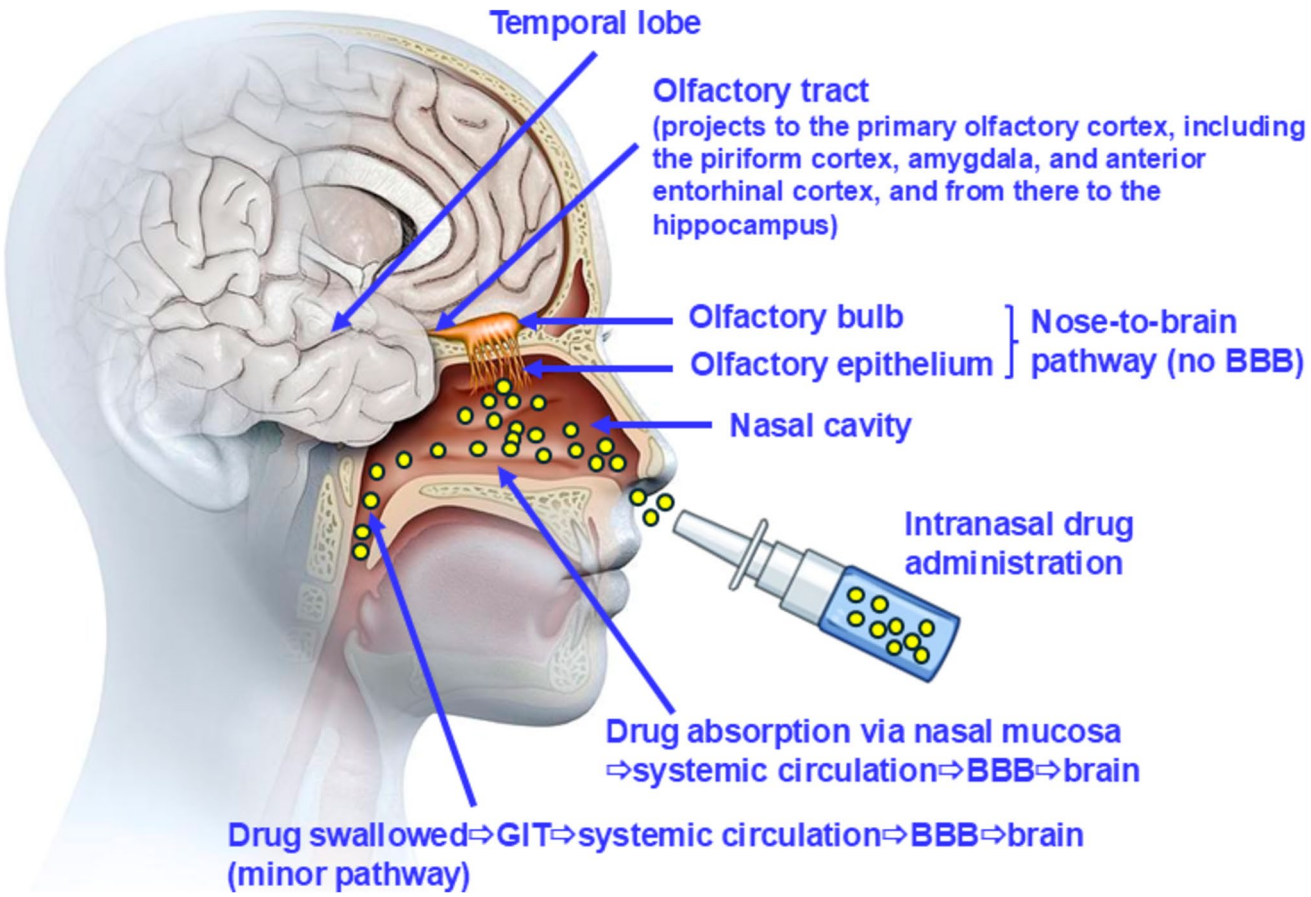

Fig. 7 Simplified scheme of the nose-to-brain pathway. Substances applied via the nasal cavity will reach the olfactory epithelium. Two major nerves innervate the olfactory epithelium, the olfactory nerve and the trigeminal nerve (not shown). Intranasally applied substances will be taken up by the olfactory nerve and reach the olfactory bulb. From there, substances may be transported via the olfactory tract to regions of the temporal lobe, including the amygdala, piriform and entorhinal cortices, and hippocampus. In addition, part of the intranasally administered drug is absorbed into the capillaries of the nasal mucosa, thereby reaching the systemic circulation. Further, drops of the intranasal solution may drain into the nasopharynx and be swallowed. *BBB* blood–brain barrier, *GIT* gastrointestinal tract

restricted the use of intranasal diazepam and midazolam to no more than one seizure episode every 3 (Nayzilam®) or 5 (Valtoco®) days and no more than five episodes per month, limiting its usefulness for many patients. Thus, there is a need for non-sedating, non-addictive alternatives to BDZs, such as SEL, for ARS rescue therapy.

6.1 Novel Intranasal Formulation of Seletracetam

PrevEp has submitted a worldwide patent application for novel intranasal and oromucosal spray formulations of SEL [7] and is currently optimizing an intranasal spray formulation of SEL for use in preclinical POC experiments and first-in-human use. For intranasal administration, a mucoadhesive phosphate-buffered aqueous vehicle was developed, utilizing hydroxyethylcellulose as a gel-forming agent. The hydroxyethylcellulose type and concentration were selected to combine sprayability with sufficient mucoadhesion; pH was adjusted to 7.4. At the selected concentration of 200 mg/mL (resulting in an intranasal dose of 30 mg in 150 µL), the solution presented as a mildly hypertonic mucoadhesive solution [7].

Studies on the pharmacokinetics and antiseizure efficacy of this formulation with intranasal administration in dogs and rodents, respectively, are in development. The genotoxicity and repeat dose toxicity of the intranasal spray SEL formulation will be evaluated in rats and dogs.

Because of the limited volume of the nasal cavity in humans, the optimal volume of an intranasal dose is limited to 100–150 µL per spray application per nostril [60]. Based on the clinical effects observed with different oral doses of SEL in patients with epilepsy (Sect. 5.5), a suitable targeted dose for the intranasal formulation of SEL is in the range of 10–40 mg per nostril with spray administration.

6.2 First-in-Human Use of Intranasal Seletracetam

A 42-year-old male with reading epilepsy, a type of reflex epilepsy characterized by reading-induced facial myoclonic seizures (as previously reported by Vaudano et al. [65]), agreed to participate in a study with intranasal SEL [13]. Epilepsy history included past bilateral tonic-clonic seizures controlled with LEV. Facial myoclonic seizures were incompletely controlled. The treatment with intranasal SEL was performed at the Department of Neurology at the Paracelsus University of Salzburg, Austria, which was permitted under the Named Patient Use regulations in Austria. SEL was synthesized by MedChemExpress (Monmouth Junction, NJ, USA). Intranasal administration was performed under EEG control inside a magnetoencephalography (MEG) scanner, as described previously in the same patient [65].

Baseline recording was done to find the most seizure-provoking text (a mathematical textbook), capturing nine spikes at a rate of 1.3/min, only whilst reading; no spikes were observed at rest. Then, a test dose of NaCl 150 µL (placebo) was given via syringe with a special nasal spray adaptor to prepare the patient for the sensation of intranasal administration. About 2 min after administration of the placebo, the patient started to read, and the first seizure occurred at 1:56 min after the onset of reading (Fig. 8). Reading was stopped after the third unequivocal seizure, which occurred at about 4 min. Then, the first 30-mg SEL dose (in 150 µL aqueous mucoadhesive buffer) was administered into the left nostril. After about 2 min, the patient resumed reading the same text. After SEL 30 mg, the first reading-induced seizure was delayed to 4:17 min. As the seizure was more subtle than following placebo, the patient continued to read for another 3 min until he experienced his third unequivocal seizure. He stopped reading, and the second 30-mg SEL dose was administered into the right nostril. About 2 min later, the patient resumed reading and continued to read for another 25 min without any self-reported seizures. MEG recording continued throughout until 30 min after the second SEL administration. MEG recording consistently showed left frontal spikes at the rate of 3.1/min while reading at baseline (after 0.9% NaCl), declining to 1.9/min after the first, and to 1.6/min after the second 30-mg nasal SEL administration. Importantly, before SEL, spikes propagated to the left posterior insula and returned. After SEL, activity remained localized, demonstrating that SEL constrained not only the frequency but also the spatial dynamics of the epileptic network [13].

The patient experienced a transient, mild bitter taste after the first (but not second) dose of SEL, with no other adverse events, and no sedation [13]. Serum samples were taken before and at different times after the first and second SEL dose administrations (see Fig. 8). SEL serum level at first drawing was 70 ng/mL (301 nM), increasing to 260 ng/mL (1120 nM) immediately after the second 30-mg SEL dose, and reaching 500 ng/mL (2153 nM) ~ 27 min after the second 30-mg SEL dose. For comparison, following oral

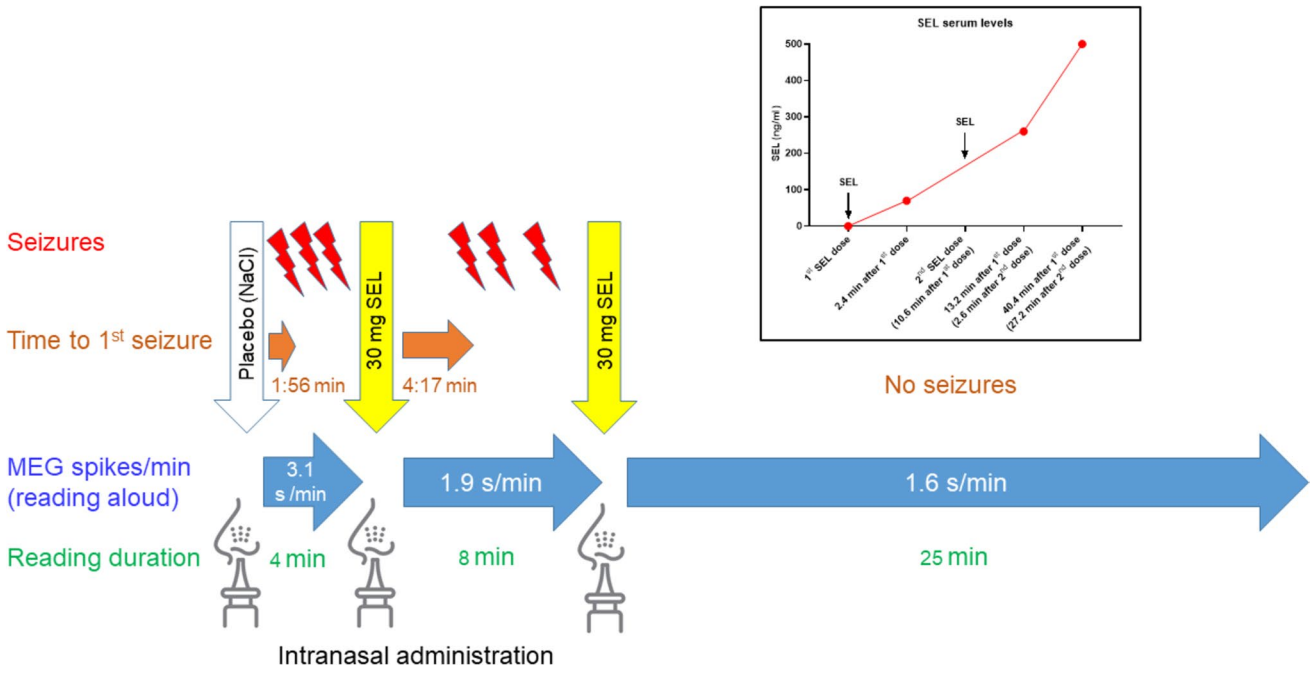

Fig. 8 Effect of intranasal administration of seletracetam (SEL) in a patient with reading-induced focal aware seizures. See text for details. Figure modified from Koepp et al. [13]. *MEG* magnetoencephalography

administration of a single dose of SEL 50 mg in healthy volunteers, C_{max} values (reached within 1 h after dosing) were about 1000 ng/mL [4]. Furthermore, as described in Sect. 5.5.1, in photosensitive patients, SEL plasma levels as low as 13 ng/mL were associated with a PPR-suppressing effect. As described in Sect. 4, SEL is < 10% protein bound and highly lipophilic, so the serum levels may reflect brain exposure. The plasma concentration range (0.3–2.15 µM) of SEL determined after intranasal administration is in the range that reduced epileptiform activity in rat hippocampal slices [38], which is consistent with termination of clinical seizure activity observed in vivo.

This clinical case supports the potential of SEL as a safer, non-sedating, fast-acting, intranasal non-BDZ treatment for acute seizure management and prevention of reflex seizures.

6.3 Other Topical Administration Routes of Seletracetam

In addition to intranasal administration, the same formulation of SEL can be used for orobuccal administration (e.g., in the pediatric population with seizures). In fact, the orobuccal administration route allows the administration of higher concentrated solutions, as the plate epithelium of the oral mucosa is not sensitive to hyperosmolar solutions, enabling concentrations well exceeding 40-mg/spray actuation while maintaining a low spray volume, preventing the swallowing of the solution. Orobuccal administration is a topical route of administration by which drugs applied in the buccal area diffuse through the oral mucosa and enter directly into the bloodstream [66]. Orobuccal administration may provide better bioavailability and a more rapid onset of action compared with oral administration because the medication does not pass through the gastrointestinal tract and thereby avoids first-pass metabolism in the liver. Orobuccal administration of midazolam is used for the treatment of prolonged acute convulsive seizures in childhood and adolescence [10, 67], and buccal midazolam (Buccolam®) is licensed in the European Union for this indication. The efficacy of buccal midazolam to terminate acute seizures is not different from intranasal or intramuscular administration, but sedation occurs with all three administration routes [56, 57, 68]. As with intranasal administration, orobuccal SEL is thought to be better tolerated than BDZs.

7 Conclusions

SEL is a second-generation racetam derivative of LEV with 10 (BRV) to 100 (LEV) times higher antiseizure potency than commercially available racetam ASMs. SEL is one of the most potent compounds ever tested in chronic models of epilepsy, exceeding the potency and efficacy even of BDZs in the amygdala kindling model. In photosensitive epilepsy patients, SEL is the only non-BDZ that exerts effects on PPR at doses as low as effective doses of BDZs; PPR-suppressive effects were observed at 0.5 mg of SEL. This marked potency of SEL is associated with high water solubility while maintaining sufficient lipophilicity for rapid absorption. Up to ~ 1000 mg/mL of SEL (or 1 mg/µL) can be easily dissolved in water. The high potency of SEL allows its formulation in therapeutic doses in a low liquid volume, which enables its administration as an intranasal (and orobuccal) spray treatment. Its highly favorable pharmacokinetic profile, unrivaled high efficacy, low toxicity, and high therapeutic ratio in animal models, and high efficacy and good safety and tolerability profiles with oral administration in humans in phase I–IIa studies make it a promising candidate for possible non-BDZ acute seizure rescue therapy. Its recent successful first-in-human intranasal spray treatment in this setting provides early support for its clinical development as a new generation, first-in-class, non-BDZ acute seizure rescue therapy. Furthermore, intranasal SEL may be suited for REST and, as indicated by both the data from photosensitive patients and the patient with reading epilepsy, the prevention of reflex seizures.

Acknowledgements We thank Prof. Krzysztof Kaminski (Jagiellonian University Medical College, Department of Medicinal Chemistry, Kraków, Poland) for providing data on SEL's effects on glutamate transport and Dr Michel Gillard (UCB Pharma, Brussels, Belgium) for providing data on SV2A kinetics of SEL and the stereoselectivity of SEL.

Funding Open Access funding enabled and organized by Projekt DEAL. No funding was received to support the writing or submission of this manuscript.

Declarations

Conflicts of interest The authors are cofounders of PrevEp, Inc. (Bethesda, MD, USA). Wolfgang Löscher has received consulting fees (2020–2024) from Addex/Neurosterix, Angelini Pharma, Atlas Venture, Axonis, Lundbeck, Axonis Therapeutics, Clexio Biosciences, Cogent Biosolutions, Ovid, Idorsia, ND Capital, Sintetica, SynapCell, and Selene Therapeutics, and has received research support from the German Research Foundation (Bonn, Germany). Pavel Klein has served as a consultant, advisory board member or speaker (2020–2024) for Abbott, Angelini Pharma, Aquestive, Arvelle Therapeutics, Aucta Pharmaceuticals, Dr Reddy's, Eisai, GRIN Therapeutics, Jazz Pharmaceuticals, Longboard Pharmaceuticals, Neurelis, Inc., Neurona, Paladin, SK Life Science, Sunovion, UCB Pharma, UNEEG, UniQure, and Xenon Pharma, is a member of the Medical Advisory Board of Stratus and of the Scientific Advisory Boards of OB Pharma and of NEUmirna, and has received research support from CURE/Department of Defense and from the NIH/SBIR. Eugen Trinka reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Alexion, Medtronic, BIAL, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Lundbeck, Eisai, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, STOKE Therapeutics, Rapport, and Actavis. He is co-director of the European Consortium on Epilepsy Trials (ECET). His institution received grants from Biogen, UCB

Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Österreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. None related to the presented work. Eugen Trinka is an Editorial Board member of CNS Drugs. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Matthias Koepp or his department has received grants from Angelini, Biohavn, UCB, and Xenon, has received consulting fees from Angelini, Bial, Biocodex, Eisai, Jazz Pharma, LivaNova, Sanofi, and UCB Pharma, is co-founder of PrevEp, Inc., and has received research funding from the MRC, Wellcome Trust, Epilepsy Research UK, Epilepsy Society UK, UCLH Foundation Trust, and Henry Smith Foundation.

Availability of data and materials The datasets generated during and/or analyzed during the current review are available from the corresponding author on reasonable request.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Authors' contributions Idea origination—WL; outline creation/revision—WL, PK, and CR; literature search/data analysis—WL, PK, and CR; drafted manuscript—WL, PK, and CR; critically revised manuscript—WL, PK, CR, MK, and ET; all authors have read and approved the final submitted manuscript and agree to be accountable for the work.

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