XENON

ASENT 2021

VIRTUAL NEUROTHERAPEUTICS CONFERENCE

"K_V7 Modulators in Epilepsy and Depression"

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EVP, STRATEGY & INNOVATION | XENON PHARMACEUTICALS INC.

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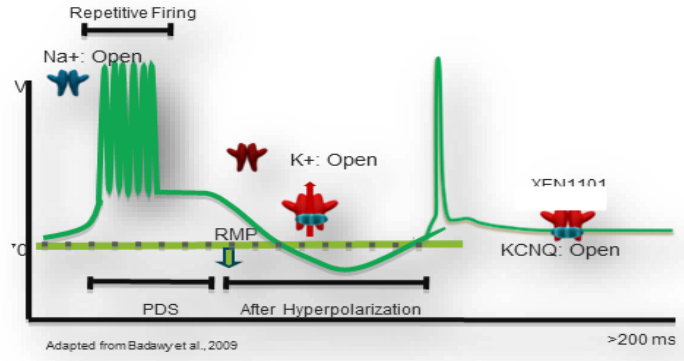
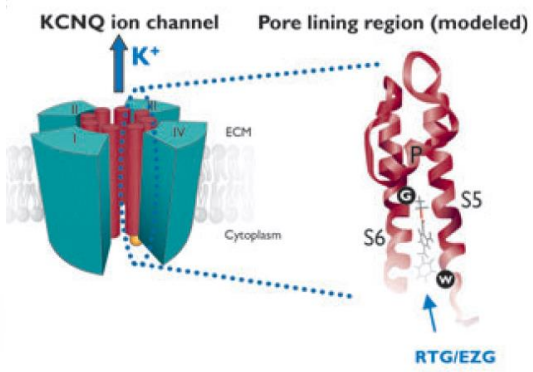
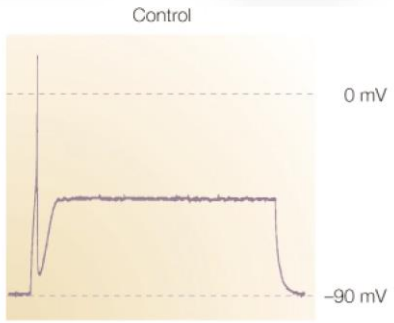
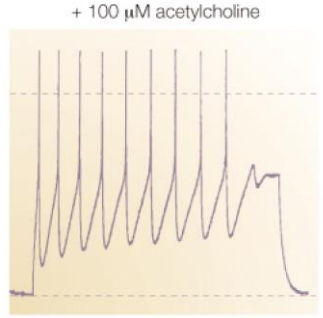
K_V7 Potassium Channels Control Neuronal Firing

- K_V7 channels have important inhibitory control over burst firing maintaining normal neuronal firing in the CNS
- They form hetero or homotetramers
- Modulated by muscarinic receptors, referred to as the M-current
- Loss of the M-current leads to neuronal hyperexcitability
- $K_V7.2/7.3$ heterotetramers are the major M-current in the CNS
- Loss of function mutations cause epilepsy

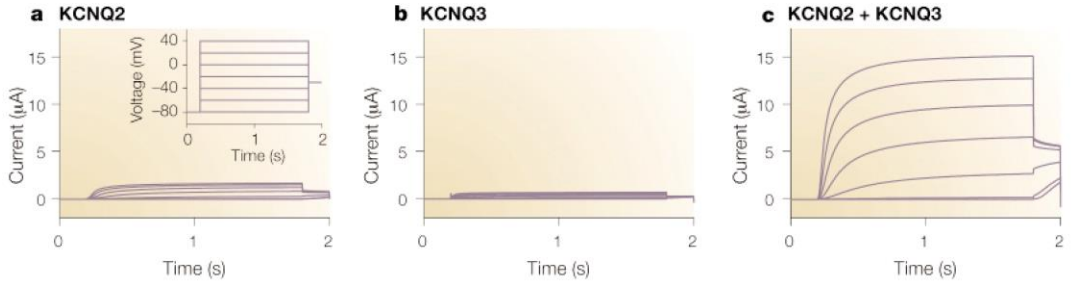








M1 RECEPTOR ACTIVATION



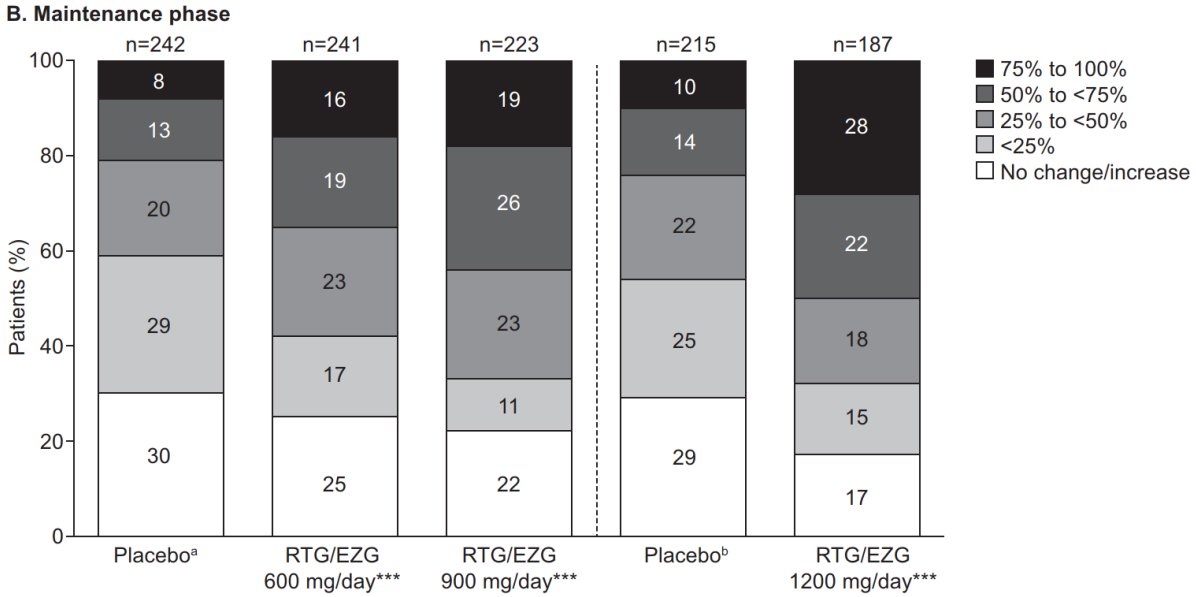
Gunthorpe, Epilepsia 2012; Jentsch, Nature Reviews 2000

K_V7 Openers Proven Mechanism for Control of Seizures

- Ezogabine demonstrated potent seizure reduction in registration trials

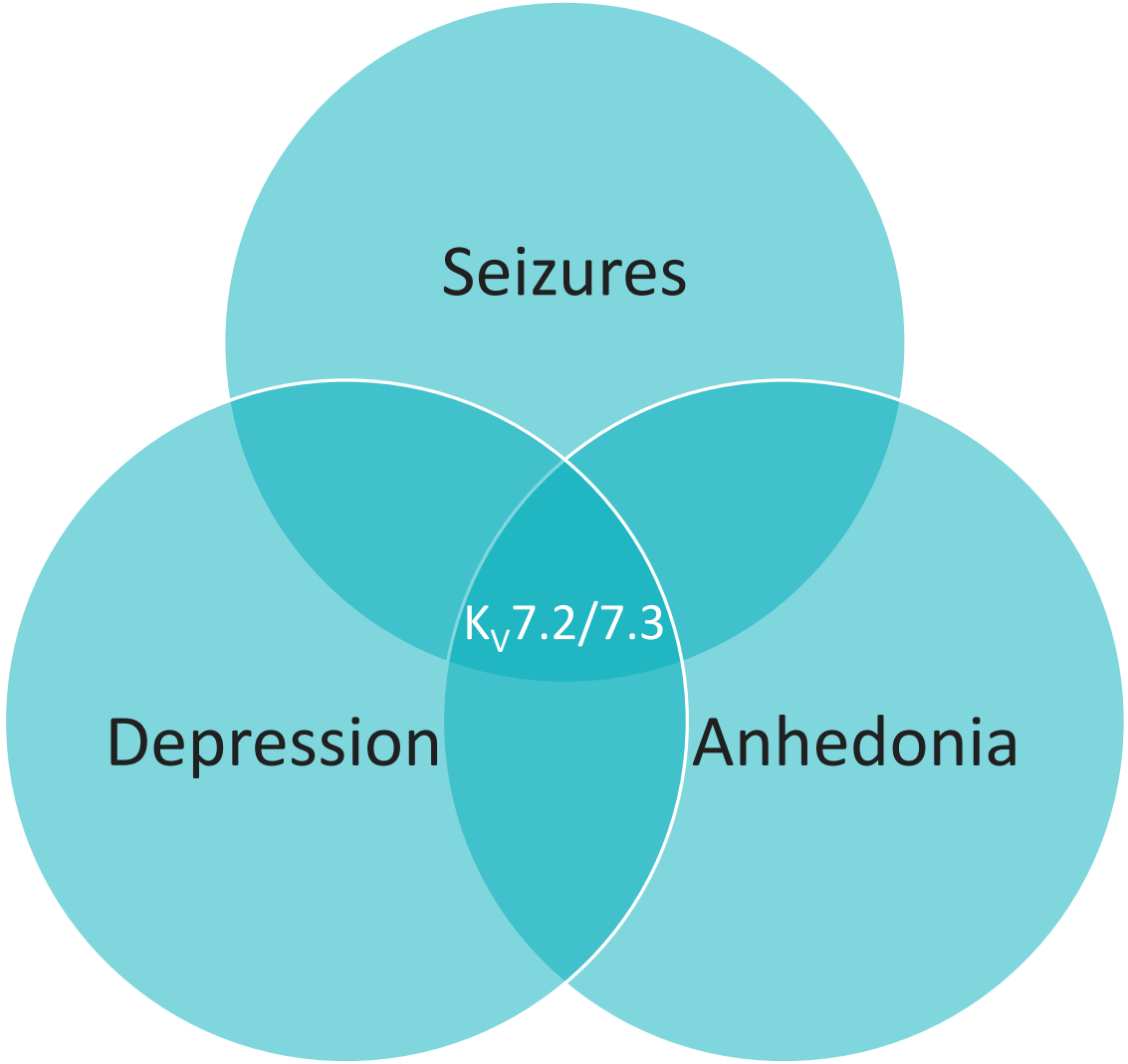
Table 1. KCNQ channels: the primary site for RTG/EZG MoA

Pharmacological action	Effect	Level of activity or EC_{50} or IC_{50} where determined[a]	Ratio of activity : Free C_{max} or C_{ave} at 1,200 mg/day in patients with epilepsy[b]
KCNQ	Positive allosteric modulator	EC_{50} = 1.6 μM at KCNQ2/3	~1
GABA	Positive allosteric modulator at $GABA_A$ receptors (non–benzodiazepine site)	Significant effects at ≥10 μM in the majority of studies	≥10-fold
	Effects on GABA metabolism	Significant effects at 20 μM	~20-fold
Calcium channels	Weak inhibitor	IC_{50} > 100 μM at neuronal Ca_v channels (29% inhibition at 100 μM)	>100-fold
Sodium channels	Weak inhibitor	IC_{50} > 100 μM at neuronal Na_v channels (25% at 100 μM)	>100-fold
Glutamate receptors	No effect at NMDA, AMPA, or kainate receptors	No effect up to 10 μM	>10-fold
Other: Broad selectivity profile	No additional activities detected	No significant interactions in 62 assays of ion channels, transporters, enzymes, and 2nd-messenger systems at 10 μM[c]	>10-fold



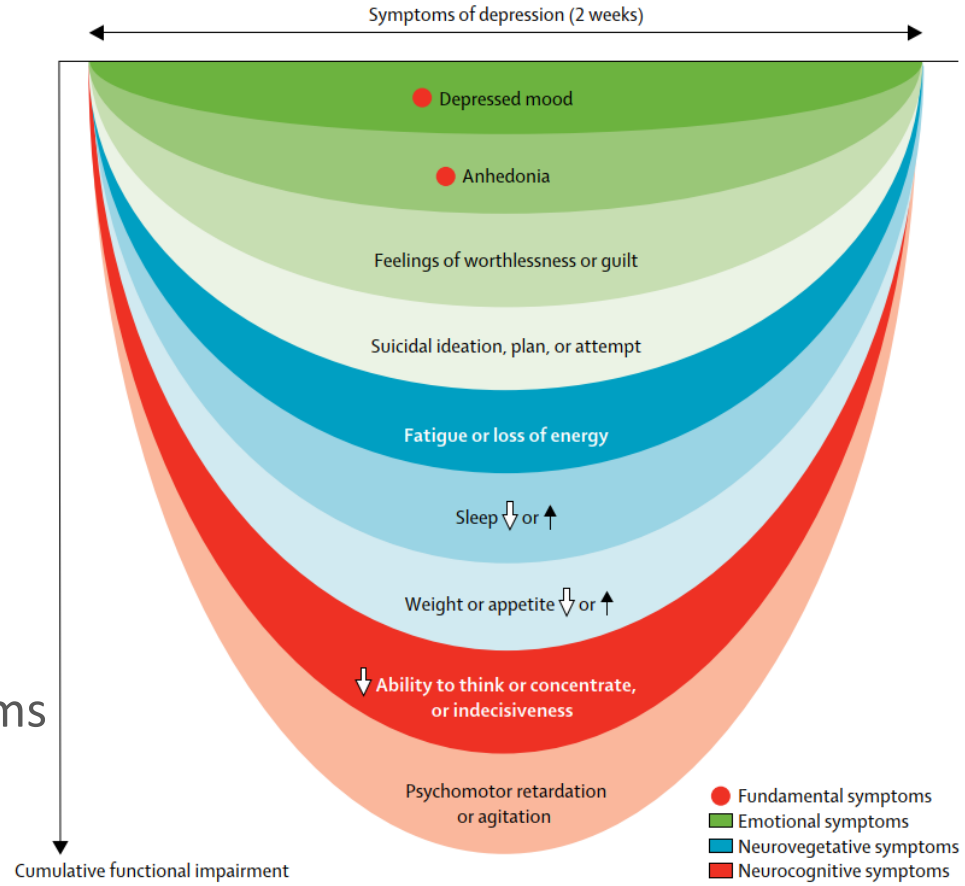
Gunthorpe, Epilepsia 2012; Porter, Epilpesy Res 2012

K_V7 Therapeutic Target for Seizures and Potentially Depression



Burden of Disease for MDD with Anhedonia

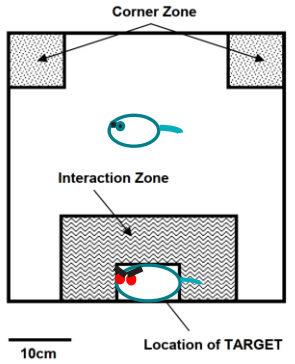
- WHO ranked major depressive disorder (MDD) as the 3rd cause of burden of disease worldwide
  - 12 month prevalence ~6%
  - Lifetime prevalence ~15-18%
  - ~30% considered treatment resistant (TRD)
- Anhedonia is a core symptom of MDD
  - Associated with poorer treatment outcomes
  - Lengthens time to remission and reduces depression free days in SSRI-TRD with second line therapy
  - Associated with suicidality independent of depressive symptoms in a large cohort of undergraduate students (n = 1,122) and physicians (n = 557)

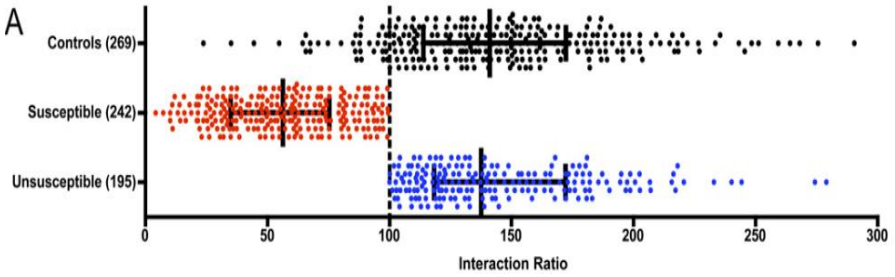


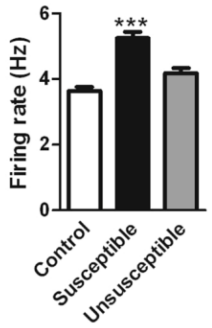
Malhi, Lancet 2018; Little, Am Fam Physician 2009; Vrieze, J Affect Disord 2014; Khazanov, Behav Res Ther 2020; McMakin, J Am Acad Child Adolesc Psychiatry 2012; Winer, Archive of Sucide Research 2016; Loas, PLOS 2018

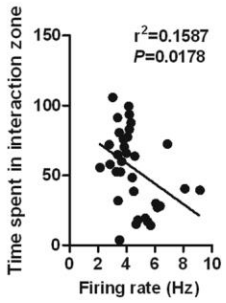
Chronic Social Defeat Stress Model of Depression

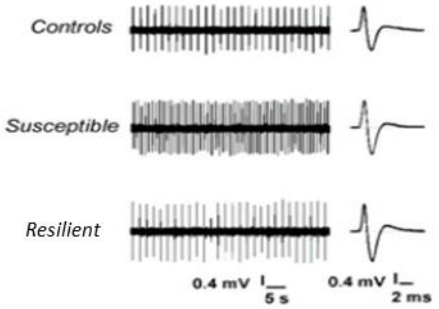
- Model of stress related depression
- Discordant behavioural outcomes to CSDS with both susceptible and resilient animals
- Studied to understand the molecular basis of resilience to stressed induced depression
- Tonic firing rather than hyperexcitability of the VTA in the reward system leads to resilient mice
- Gene expression studies showed upregulation of potassium channel including $K_V7.3$ (KCNQ3) correlate with resilient phenotype
- $K_V7.2/7.3$ heterotetramers effect M-current and blunt VTA hyperexcitability
- Suggests resilience to CSDS is an active molecular process of stress-coping











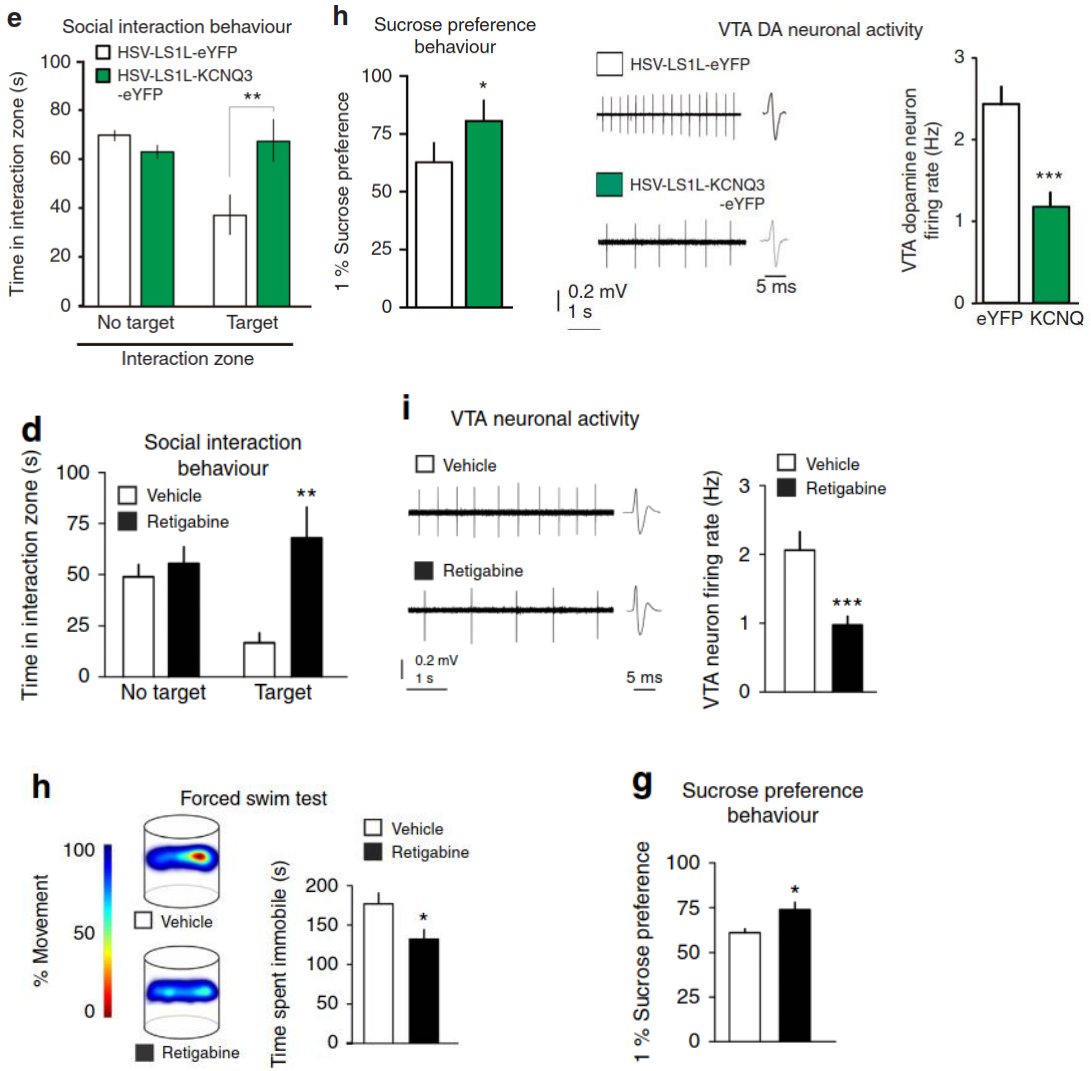
Ventral Tegmental Area

***Gene* (Definition)**	Susceptible	Unsusceptible
Gal (Galanin)	⇑	⇔
Gdnf (Glia derived neurotrophic factor)	⇔	⇑
Kcnf1 (Voltage gated K^+ channel F1)	⇔	⇑
Kcnh3 (Voltage gated K^+ channel H3)	⇔	⇑
Kcnk4 (K^+ channel K4 [TRAAK])	⇔	⇑
Kcnq3 (Voltage gated K^+ channel Q3)	⇔	⇑
Kif1b (Kinesin family member 1B)	⇔	⇓
Lcn2 (Lipocalin-2)	⇑	⇑

Krishman, Cell 2007; Cao, J Neuroscience 2010

K_V7 Channels' Role in Active Resilience

- $K_V7.3$ forms heterotetramers with $K_V7.2$ to effect the M-current and blunt VTA hyperexcitability
- Viral expression of $K_V7.3$ in VTA reverses the CSDS susceptible phenotype and hyperexcitability and improved anhedonia
- K_V7 opener (ezogabine/retigabine) dosed 8-days (1 mg/kg ip) reversed the susceptibility phenotype mimicking the resilient phenotype
  - Blunted VTA hyperexcitability and normalized social interaction
  - Demonstrated antidepressant activity in the forced swim test of behavioural despair
  - Improved sucrose preference a measure of anhedonia



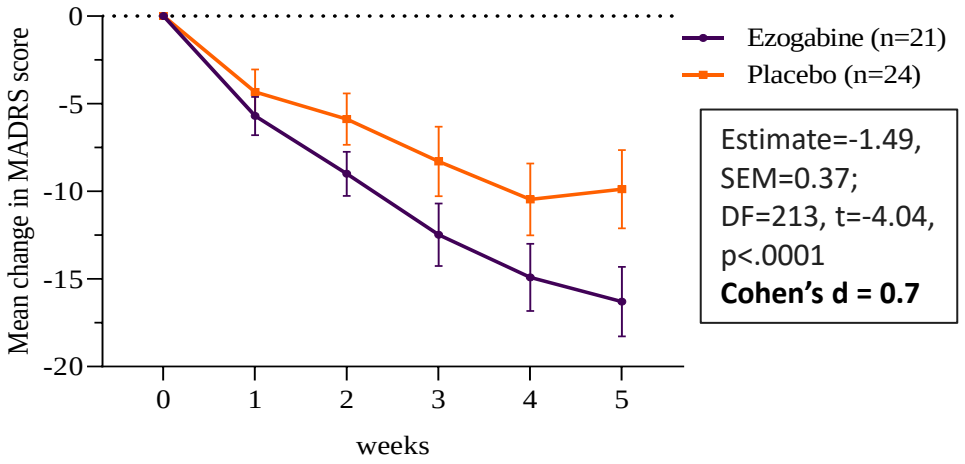
Friedman, Nature Communications 2016

K_V7 Opener Results in Meaningful Clinical Efficacy in MDD

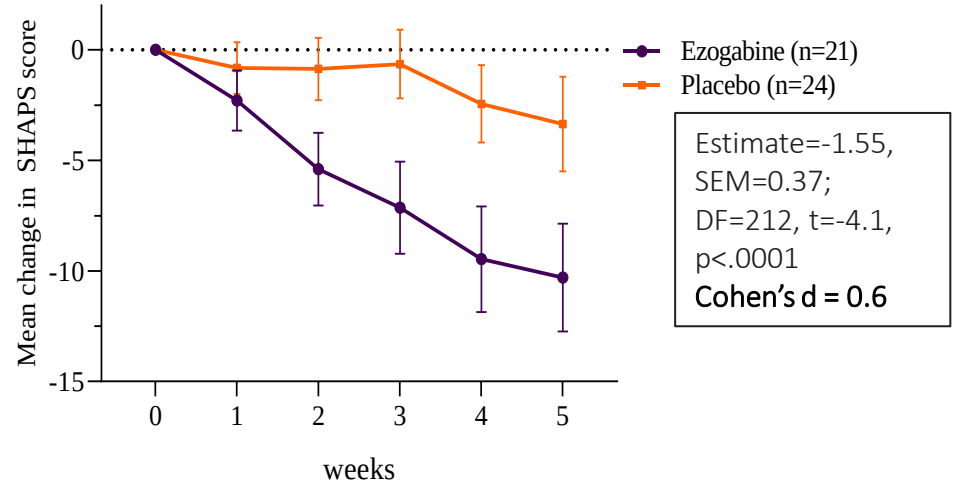
- Based on the preclinical work, the K_V7 mechanism was evaluated in a proof-of-concept randomized placebo controlled clinical trial (n=45)
  - Ezogabine dosed 300mg TID

Inclusion		
DSM-V MDD or PDD		
Clinically significant anhedonia (SHAPS ≥ 20)		
Illness severity moderate or greater (CGI-S ≥ 4)		
Highlighted Demographics	**Active**	**Placebo**
Baseline MADRS	28.4	26.8
Baseline SHAPS	38.7	33.7

Montgomery–Åsberg Depression Rating Scale



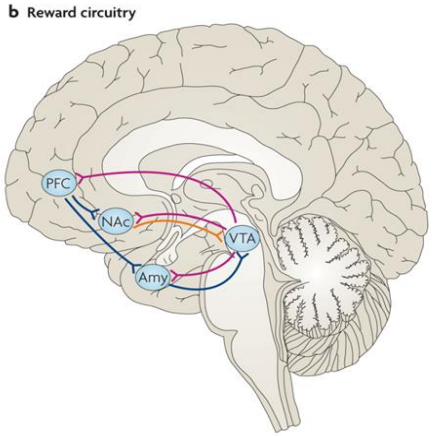
Snaith-Hamilton Pleasure Scale



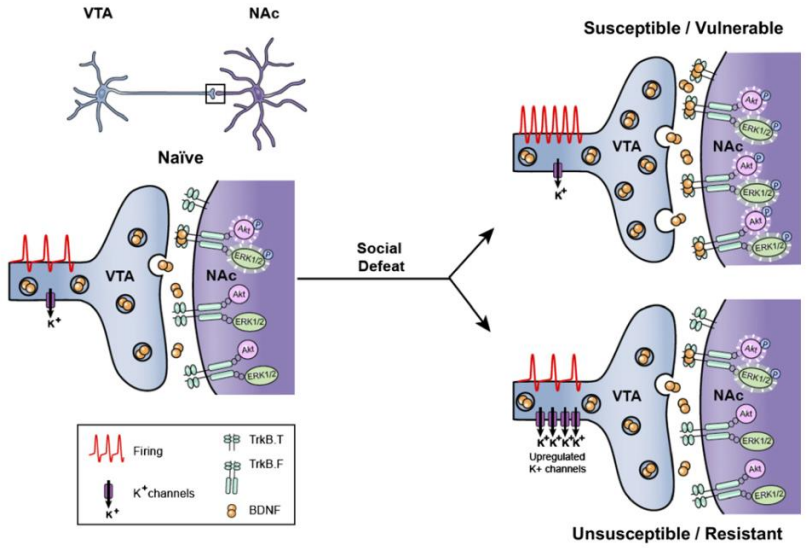
Murrough, JW ACNP 2019 Orlando, FL; Costi S, et al., in press

K_V7 and Depression and Anhedonia Review

- Resilience is proposed to be an active coping mechanism to stress induced depression
- Hyperexcitability of the VTA DA neurons underpins susceptibility to CSDS
- Upregulation of voltage gated K^+ channels including $K_V7.3$ associated with resilient phenotype
- $K_V7.3/7.2$ mediated M-current blunts the VTA hyperexictability and reverses the susceptibility phenotype
- Ezogabine demonstrated beneficial effects in MDD patients including for anhedonia
- A novel molecular mechanism to potentially treat depression through modulation of the reward system



Pink = Dopamine
Orange = GABA
Blue = glutamate



Krishnan, Cell 2007; Feder, Nat Rev Neurosci 2009

Depression and Anhedonia Present in Animal Models of Epilepsy

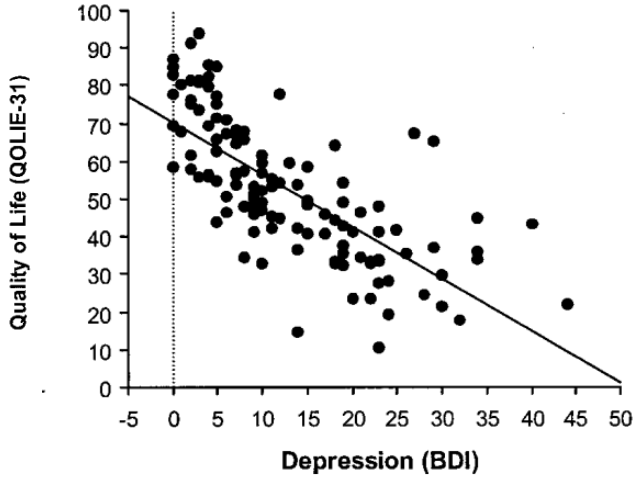
Epilepsy Model	Forced Swim Test Immobility	Sucrose/Saccharin Preference
Rapid amygdala kindled TLE rats	↑	↓
Pilocarpine induced status epilepticus rats	↑	↓
LiCl-pilocarpine non-convulsive status epilepticus*	↑	↓
WAG/Rij genetic absence seizure rats	↑	↓
Hippocampal kindled TLE rats	ND	↓
Amygdala kindled TLE rats	ND	↓

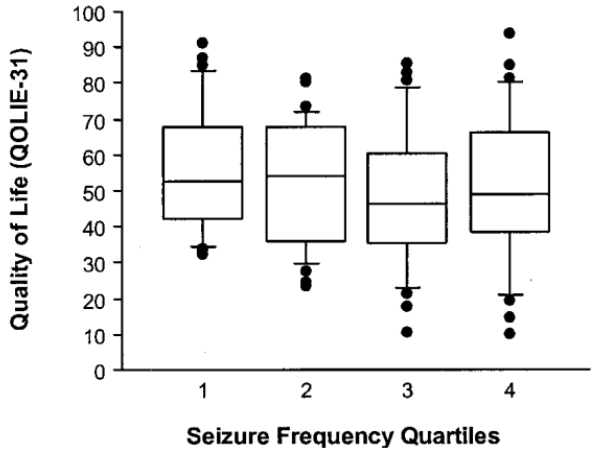
* Resistant to fluoxetine and depressive impairments not dependent on frequency of spontaneous recurrent seizures

Mazarati, Brain 2008; Pineda, Epilepsia 2010; Sankar, Jasper's Basic Mechanisms of the Epilepsies 2012; Chen, Frontiers in Behavioural Neuroscience 2016; Medel-Matus, Epilepsia 2017; Boldt, Epilepsy & Behavior 2021

Depression Burden in Persons with Epilepsy

- Is a common co-morbidity of epilepsy lifetime prevalence rate reported in the literature ~30-50%
- Greater severity of depression associated with higher seizure frequency
- Is a strong and independent predictor of reduced QOL
  - Depression severity but not seizure frequency predicts QOL in treatment resistant epilepsy
- Lifetime history of depression may predict of resistance to treatment
- Significant cause of non-adherence to anti-seizure medications (ASMs)





Boylan, Neurology 2004; Kanner, Epilepsy Currents 2006; Hitiris, Epilepsy Research 2007; Kanner, Neurol Clin 2009; Kanner, Epilepsy & Behavior 2012; Ettinger, Epilepsy & Behavior 2014; Guo, Epilepsy & Behavior 2015; Shallcross, Epilepsy & Behavior 2015; O'Rourke, Seizure 2017; Kumar, J Nerv Ment Dis 2019

Physicians' Perspectives

- Market research with 20 Epileptologists examined the impact of depression in epilepsy patients with focal onset seizures
- Physicians reported ~35-45% of actively managed focal onset seizure patients suffer from depression
- Physicians highlighted the critical need for ASMs offering a mood benefit for patients that suffer from comorbid depression
  - Current ASMs do not adequately address depression
  - ASM side effect profiles can exacerbate mood-related comorbidities (e.g. levetiracetam)
  - In later lines of treatment, physicians indicated the potential need to choose between improving seizure control at the expense of potentially worsening mood-related comorbidities

Quotes from U.S. KOL Epileptologists

"A great unmet need is improving the treatment of these patients with psychological / psychiatric co-morbidities, due to the disabling effect to patients."

"If a product can improve both seizures and a comorbidity, I think I could use it to help lessen the treatment burden due to the number of medications a patient is on."

XEN1101's Differentiated Profile in Adult Focal Epilepsy

- Potential for a **highly differentiated profile** within the **adult focal epilepsy space**:

Ease of Use

- ☑ Once daily (QD) dosing
- ☑ No titration; at efficacious doses immediately
- ☑ No significant DDI predicted
- ☑ Low daily dose
- ☑ No drug allergic reactions observed
- ☑ Slow elimination could provide coverage for missed doses

Efficacy

- ☑ Proven anti-seizure mechanism of action
- ☑ Broad efficacy in multiple pre-clinical seizure models as monotherapy or in combination with other ASMs
- ☑ Greater effect on TMS target engagement
- ❑ Phase 2b trial modeled for median monthly seizure reduction in the range of currently used ASMs

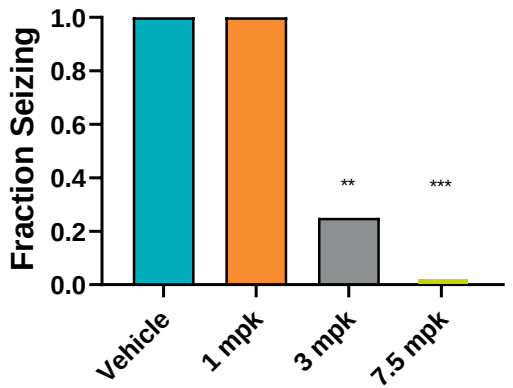
Safety / Tolerability

- ☑ Favorable safety profile and well-tolerated in Phase 1
- ☑ Evening QD dosing with C_{max} (and related CNS AEs) during sleeping hours
- ☑ Low C_{max} to C_{min} provides better tolerability
- ☑ To date, low drop out rates and high conversion rates to OLE in ongoing blinded Phase 2b trial

XEN1101 in Preclinical Models of Epilepsy and Depression

Maximal electrical shock (MES) is a model of generalized seizures

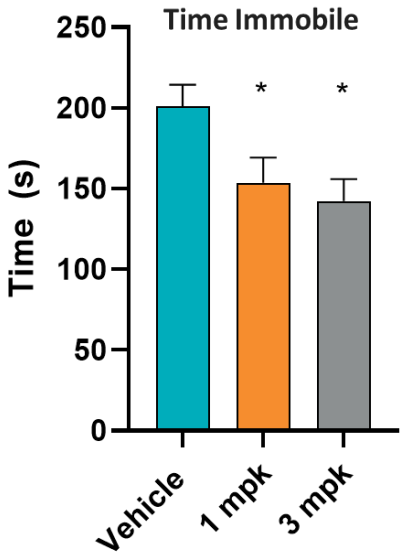
- XEN1101 demonstrated a significant reduction in seizures



(**p<0.01, ***p<0.001)

The forced swim test (FST) is a depression model of behavioral despair

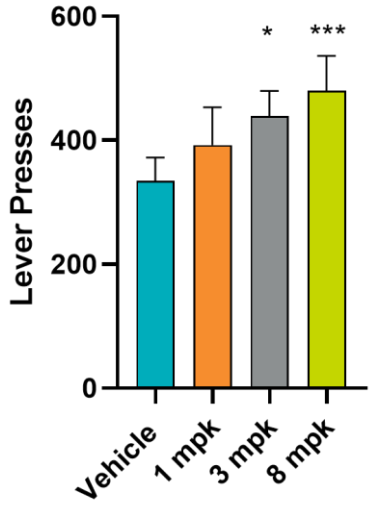
- XEN1101 demonstrated a significant reduction in time spent immobile, indicating an anti-depressant effect



(*p<0.05 compared to vehicle)

The progressive ratio test (PRT) is a model of motivational performance and decisional anhedonia

- XEN1101 significantly increased the total number of lever presses in the test session



(* p<0.05; *** p<0.001 compared to vehicle)

Conclusions

- XEN1101 is a differentiated, next-generation K_V7 potassium channel modulator
- K_V7 channels mediate resilience to chronic stress related depression in animal models through blunting of VTA excitability within the reward system
- Ezogabine a K_V7 opener significantly improved depression and anhedonia in MDD patients
- The results from the two preclinical studies presented at ASENT 2021 support a potential benefit of XEN1101 in mood disorders
- Major depression is a common co-morbidity of persons with epilepsy and significantly impacts their quality of life
- The Phase 2b "X-Tole" clinical trial is underway to evaluate the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in approximately 300 adult patients with focal epilepsy
  - Topline results are expected in the third quarter of 2021
- Anticipate initiating a Phase 2 proof-of-concept clinical trial examining XEN1101 in MDD with anhedonia in 2021

Please refer to these additional presentations at ASENT 2021 to learn more:

Dr. Alison Cutts,
"*Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated K_V7 Potassium Channel Modulator*"

Dr. Ernesto Aycardi,
"*Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel K_V7 Modulator*"

Dr. J.P. Johnson, Jr.,
"*Anticonvulsant Effects of the Differentiated K_V7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs*"

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