새로운 항불안약물

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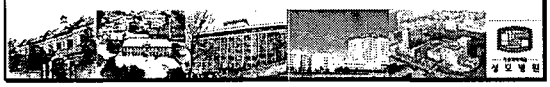


항불안약물
Current options

- **Benzodiazepines**
- **Azaspirone: buspirone**
- **SSRIs**
- **SNRIs**

그럼에도 불구하고...

- **Side-effect burden**
- **Tolerance/Dependency issues**
- **Premature discontinuation of medications**
- **Failure to achieve remission**

다른 계통의 약물 차용
- Off label use

- **Propranolol; SAD, PTSD**
- **Atypical antipsychotics**
  - Risperidone, Olanzapine, Quetiapine…
- **Prazocin: nightmare**
- **Anticonvulsants…**
  - GABAnergic

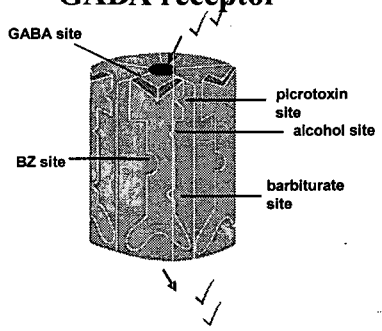
Future drugs
- Pipelines

- **CRH antagonists**
- **NMDA receptor antagonists**
- **NK1 antagonists**
- **Glutamate related drugs**
  - LY 354740 (metabotropic glu agonist)
  - Riluzole
  - Memantine

새로운 (Not 미래의)
feasible 항 불안약물

- **Tiagabine**
- **Pregabalin**
- **D-Cycloserine?**

GABA receptor



GABA-A receptors and mood

- **GABA-A receptors regulate rapid mood changes:**
  - anxiety
  - panic
  - stress response
- **Drugs that stimulate GABA-A receptors (BZs, PB) have anticonvulsive effects and anxiolytic effects**

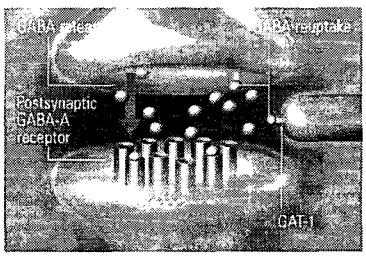
주 GABA 작용 약물

- **Allosteric GABA-A modulations**
  - Barbiturates, benzodiazepines, topiramate, neurosteroids
- **Direct GABA receptor agonists**
  - Alcohol, barbiturates (high dose), chloral hydrate, abecarnil
- **Incresed GABA synthesis**
  - topiramate, valproate
- **Inhibit breakdown**
  - valproate, vigabatrin
- **Inhibit reuptake**
  - tiagabine
- **GABA analogues**
  - gabapentin, pregabalin

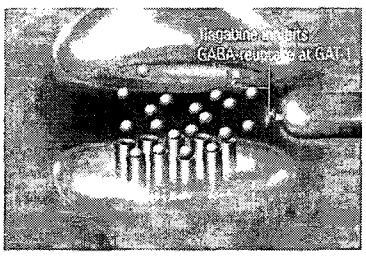
Tiagabine (Gabitril®)

Cephalon

Normal release and reuptake of GABA



Activity of tiagabine at the GAT-1 transporter



GAD: Tiagabine vs Paroxetine

	Tiagabine (n=20)	Paroxetine (n=20)
Age, years	32(19-50)	38(20-60)
Female:male (n)	12:8	11:9
Duration of GAD, years	1(0-10)	2(0-11)
HAM-A	24(20-35)	22(18-41)
HAM-D	13(9-17)	12(6-18)
PSQI	11(4-16)	10(4-15)
CGI-S "Markedly ill" "Moderately ill"	 8 12	 4 16
SDS	15(1-30)	13(5-28)

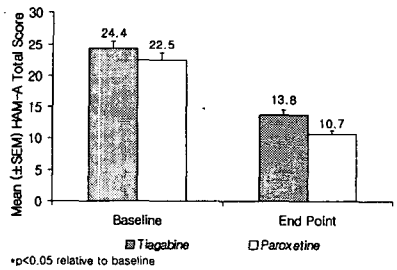
*No significant differences in baseline demographics/clinical characteristics between the two treatment groups

Rosenthal M.J Clin Psychiatry. 2003;64:1245-9.

Dose: Tiagabine and Paroxetine

- **Tiagabine**
  - Mean: ~10 mg/day (divided between AM and PM dose)
  - Range: 4-16 mg/day
- **Paroxetine**
  - Mean: ~27 mg/day (nightly)
  - Range: 20-40 mg/day

Anxiety: HAM-A Total Score

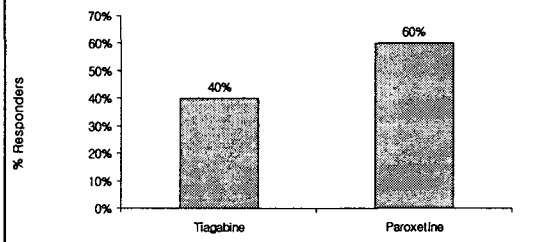


*p<0.05 relative to baseline

No significant difference between treatments

Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

Effect of Tiagabine and Paroxetine in Patients with GAD

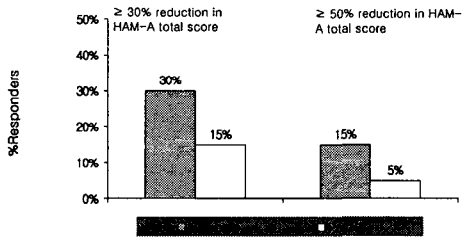


Treatment response is defined as a reduction of ≥50% in HAM-A total score at endpoint. (LOCF values)

No significant difference between treatments

Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

Responders: Achieving Sustained Onset

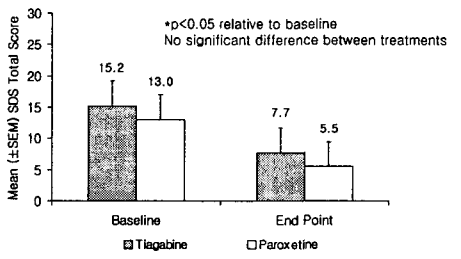


Sustained onset is defined as meaningful improvement that occurs between weeks 1-2 and is maintained to week 10.

No significant difference between treatments

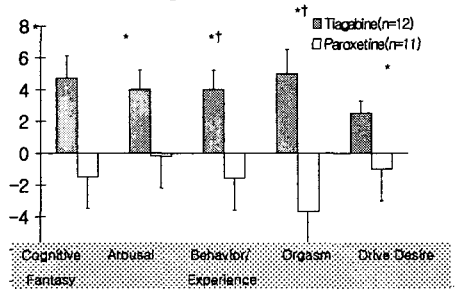
Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

Level of Disability: SDS Total Score



Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

Sexual Functioning: DISF Components (Female)



Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

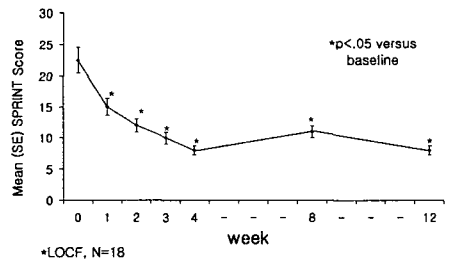
*p<.05 relative to baseline
†p<.05 versus paroxetine

Tiagabine: PTSD

- Objective: To evaluate the effect of tiagabine in patients with PTSD
- 12-week, open-label followed by 12-week douvle-blind discontinuation study (target N=30)
- Patients (N=18) with PTSD-study ongoing
- Tiagabine was initiated at 2 mg bid and titrated to optimal dosage (tolerance/response, maximum dosage of 16 mg/d (8 mg bid)
- Efficacy assessments included measures of
  - *PTSD-Short PTSD Rating Interview (SPRINT)*
  - PSQI (total and single item scores)

Davidson J and Connor K, et al. Tiagabine for PTSD. Presented at the 156th Annual Meeting of the American Psychiatric Association: May 17-22, 2003: San Francisco, California.

Effect of Tiagabine in PTSD



*LOCF, N=18

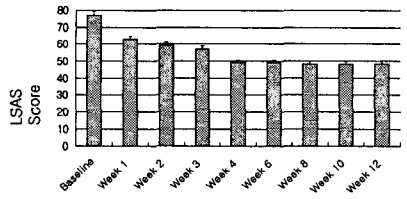
Davidson J and Connor K, et al. Tiagabine for PTSD. Presented at the 156th Annual Meeting of the American Psychiatric Association: May 17-22, 2003: San Francisco, California.

Tiagabine: Social Anxiety Disorder (SAD)

- Objective: To evaluate tiagabine in SAD patients
- 12-week, open-label followed by 12-week DB discontinuation study
- Study ongoing: 63 enrolled, 57 treated, 51 included
- Tiagabine was initiated at 2 mg bid and titrated to optimal response, maximum dosage of 8 mg bid
- Efficacy assessments included measures of :
  - Liebowitz Social Anxiety Scale (LSAS)
  - Clinical Global Impression-change

Davidson J and Connor K, et al. Tiagabine for PTSD. Presented at the 156th Annual Meeting of the American Psychiatric Association: May 17–22, 2003: San Francisco, California.

Open-label Trial of Tiagabine in Social Anxiety Disorder



P<.0001 relative to baseline

N=27

Phil Ninan, MD 2003. Unpublished data.

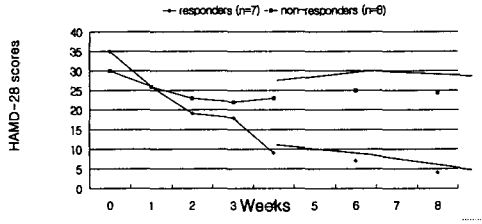
Open Label Study of Tiagabine in MDD with Anxiety

	Baseline	Endpoint(LOCF)
Age (mean±SD)	47.8 ± 6.4	-
Sex (n, %female)	9; 60	-
Weight (lbs; mean±SD)	154.4 ± 34.0	159.3 ± 39.6
CGI severity (mean±SD)	4.47 ± 0.52	2.93 ± 1.58[a]
HAM-D28 total (mean±SD)	31.9 ± 6.1	17.1 ± 12.3[b]
HAM-A total (mean±SD)	22.7 ± 4.9	12.7 ± 8.7[c]
IDS-SR total (mean±SD)	67.1 ± 10.1	50.9 ± 15.0[d]
PSQI sleep (mean±SD)	10.4 ± 3.8	8.6 ± 4.9[e]
End tiagabine dose (mean±SD mg/d) Entire group	-	12.8 ± 5.8
Weeks on drug (mean±SD) Entire group	-	6.1 ± 1.2

[a]p=.003 [b,c]p=.002 [d]p=.0004 [e]p=.10

Carpenter L, et al. 2003. Unpublished data.

Effect of Tiagabine in Patients with MDD with Anxiety: Results of an Open-label Study



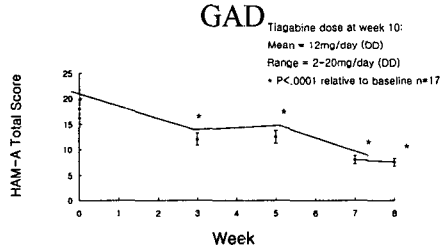
Carpenter L. et al. 2003. Unpublished data.

Tiagabine as SSRI Augmentation Therapy for Anxiety Disorders

- **Evaluate the safety and efficacy of tiagabine as augmentation therapy in anxiety treatment**
- **Open-label augmentation therapy**
- **8-week treatment period**
  - Weeks 1-2 titration:
    -Days 1-2 (2mg/day) followed by 4 mg/day
  - Weeks 3-8
    -Adjusted to optimal dose (tolerance/efficacy) at a rate of 4 mg/week (2 mg increments at investigator discretion)
    -Tiagabine maximum dosage 20 mg/day (10mg bid)
  - Weeks 8-11 post-study taper
- **Concurrent treatment is maintained constant throughout the study**
- **LOCF data presented for 17/18 patients**

Schwartz T. Tiagabine as Augmentation Therapy for Anxiety Disorders. Presented at the 156th Annual Meeting of the American Psychiatric Association: May 17-22, 2003: San Francisco, California.

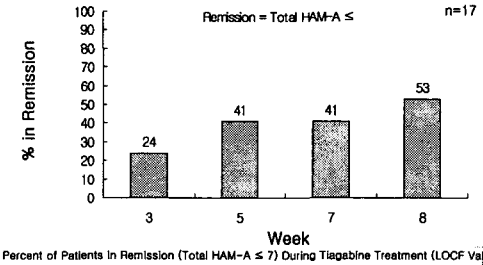
Effect of Tiagabine on HAM-A Total Score on Patients with GAD



Time Course of Mean (±SEM) Total HAM-A Score During Tiagabine Treatment (LOCF value)

Schwartz T. Tiagabine as Augmentation Therapy for Anxiety Disorders. Presented at the 156th Annual Meeting of the American Psychiatric Association: May 17-22, 2003: San Francisco, California

Proportion of Patients in Remission Following Tiagabine as SSRI Augmentation Therapy



Percent of Patients in Remission (Total HAM-A ≤ 7) During Tiagabine Treatment (LOCF Va

Schwartz T. Tiagabine as Augmentation Therapy for Anxiety Disorders. Presented at the 156th An Meeting of the American Psychiatric Association: May 17-22, 2003: San Francisco, California

Treatment-emergent Adverse Events (Incidence>10%)

	Tiagabine	Paroxetine
Headache	**11 (55%)**	**8 (40%)**
Nausea	**7 (35%)**	**4 (20%)**
Anorexia	**6 (30%)**	-
Dizziness	**6 (30%)**	-
Somnolence	**5 (25%)**	**3 (15%)**
Diarrhea	**4 (20%)**	-
Dry mouth	**3 (15%)**	**5 (25%)**
Vomiting	**3 (15%)**	-
Vasodilation	**3 (15%)**	-
Increased appetite	**3 (15%)**	-
Insomnia	-	**4 (20%)**

Rosenthal M. J Clin Psychiatry. 2003;64:1245-9

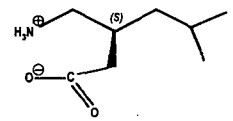
Tiagabine Dosing in Anxiety Disorders: Messages from Clinical Studies

- **Start low**
  - 2-4 mg/day
  - At night or in divided dosages
  - With food
- **Go slow**
  - Titrate to clinical effect or maximum tolerated does
  - Increase by no more than 2-4 mg/week
- **Expected effective doses**
  - Effective doses will vary in individual patients
  - Expected effective dose in anxiety is 4-16 mg/day

Pregabalin (Lyrica®)

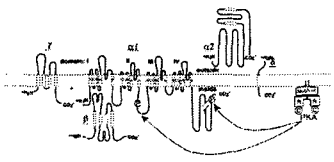
Pregabalin

Molecular Structure

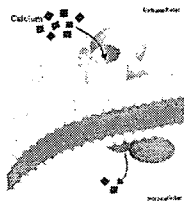


- *Amino acid*
- *Readily crosses blood-brain barrier*
- *Inactive at GABA receptors*

Pregabalin (CI-1008) (S)-3-(aminomethyl)-5-methylhexanoic acid



- **It binds with high affinity to the alpha(2)-delta subunit of voltage-gated calcium channels and is a substrate of the system L neutral amino acid transporter.**



Pregabalin

- **A structural analogue of -aminobutyric acid, is a novel compound with broad-spectrum efficacy**

- **diabetic neuropathy**
- **postherpetic neuralgia**
- **partial epilepsy.**

Prescribing Information

- **Indications**
  - adjunctive therapy in adults with partial seizures with or without secondary generalization
  - peripheral neuropathic pain in adults
- **Contraindication**
  - Hypersensitivity to the active substance or to any of the excipients
- **Adverse events**
  - The most common adverse events: **dizziness and somnolence**
- **Renal impairment**
  - Pregabalin dosage reduction is necessary in patients with renal impairment (Clcr < 60 mL/min). Pharmacodynamic interactions
  - Pregabalin appears to be additive in the impairment of cognitive and gross motor function
    caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam

Pregabalin Demonstrates Favorable Tolerability by Dose

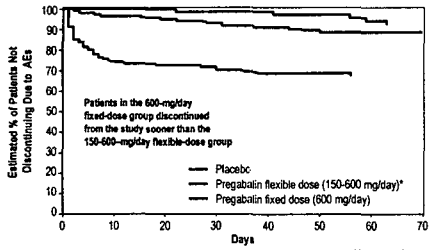
Pooled Fixed-Dose Epilepsy Trials

Adverse Event	Placebo n=294 (%)	Pregabalin 150 mg/day n=185 (%)	Pregabalin 300 mg/day n=90 (%)	Pregabalin 600 mg/day n=395 (%)
Dizziness	10.5	17.8	31.1	38.0
Somnolence	10.9	11.4	17.8	28.4
Ataxia	4.1	5.9	10.0	19.5
Asthenia	8.2	10.8	12.2	12.4
Weight gain	1.4	4.9	6.7	15.9
Accidental injury	5.4	7.0	11.1	9.9
Headache	11.6	7.6	5.6	11.1
Amblyopia (blurred vision)	4.4	5.4	7.8	12.2
Diplopia	3.7	5.4	6.7	11.9
Tremor	3.7	3.2	6.7	10.6
Thinking abnormal (difficulty concentrating)	2.0	3.8	7.8	9.1

Most events were mild to moderate and dose related

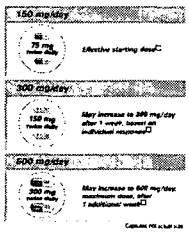
More Patients Remain on Therapy With Flexible Dosing of Pregabalin

Kaplan-Meier Analysis



*Average daily dose=349 mg/day; flexible-dose trial.
AE=adverse event.

Simple Dosing and Administration



Pregabalin may also be administered 3 times daily. Efficacy and safety profiles in 2- and 3-times-daily regimens were similar.

- **Effective starting dosage is 150 mg/day given in 2 divided doses***
- **Dosage may be increased to 300 mg/day after 1 week if needed**
- ***Dosage may be increased to a maximum of 600 mg/day after an additional week if needed***
- **Pregabalin may be taken with or without food**
- **Capsule strengths available†**
  - 75 mg, 150 mg, 300 mg

Discontinuation of pregabalin should occur gradually over a minimum of 1 week.
*Dosage reduction is necessary in patients with compromised renal function.
†*25 mg, 50 mg available for renally impaired patients.*

No Known Pharmacokinetic Drug-Drug Interactions

Carbamazepine	***Insulin***
Gabapentin	***Oral hypoglycemics***
Lamotrigine	***Diuretics***
Lorazepam	***Combined oral contraceptive***
Phenytoin	***Oxycodone***
Valproic acid	***Alcohol***
Phenobarbital*	
Tiagibine*	
Topirimate*	

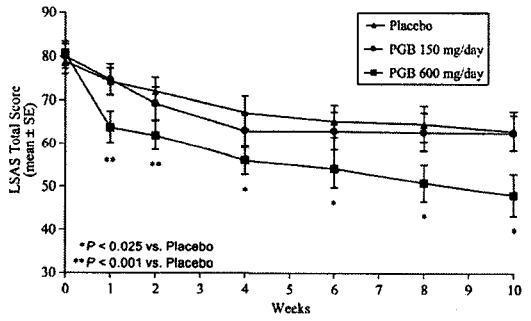
- Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration.
- Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone and may potentiate the effects of ethanol and lorazepam.

*Based on population pharmacokinetic analysis.
Brockbrader et el. AES 2001. Data on file, Pfizer Inc

Pregabalin: SAD

- **Double-blind, multicenter clinical trial in which 135 patients with SAD were randomized to 10 weeks of double-blind treatment with either pregabalin 150 mg/d, pregabalin 600 mg/d, or placebo.**

Pande et al (2004). Journal of Clinical Psychopharmacology: Volume 24(2) April 2004 pp 141-149

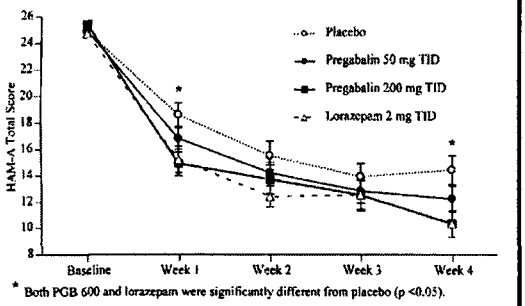


Pande et al (2005). Journal of Clinical Psychopharmacology: Volume 24(2) April 2004 pp 141-149

Pregabalin: GAD

- **A double-blind, fixed-dose, parallel-group, placebo and active-controlled multicenter 4-week study that compared 271 patients randomized**
  - pregabalin 50 mg tid (N = 70)
  - pregabalin 200 mg tid (N = 66)
  - placebo (N = 67)
  - lorazepam 2 mg tid (N = 68)

Feltner et al (2003). Journal of Clinical Psychopharmacology: Volume 23(3) June 2003 pp 240-249

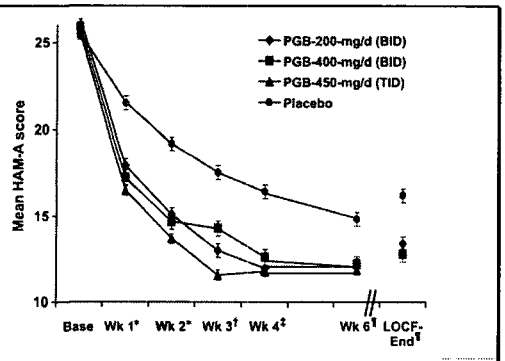


Feltner et al (2003). Journal of Clinical Psychopharmacology: Volume 23(3) June 2003 pp 240-249

Pregabalin: GAD - bid vs tid dosing

- **Randomized to 6 weeks of double-blind treatment**
- **Pregabalin**
  - 200 mg/d (BID; N = 78)
  - 400 mg/d (BID; N = 89)
  - 450 mg/d (TID; N = 88)
  - placebo (N = 86).

Pohl et al (2005). Journal of Clinical Psychopharmacology: Volume 25(2) April 2005 pp 151-158

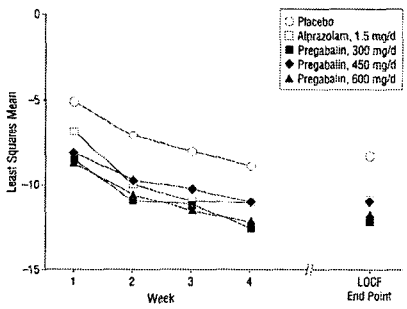


Pohl et al (2005). Journal of Clinical Psychopharmacology: Volume 25(2) April 2005 pp 151-158

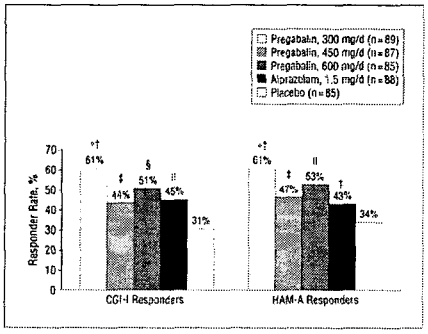
Pregabalin: GAD

- **Double blind placebo controlled active comparator trial**
- **4 weeks of treatment with**
  - Pregabalin
    - 300 mg/d (n = 91)
    - 450 mg/d (n = 90)
    - 600 mg/d (n = 89)
  - alprazolam, 1.5 mg/d (n = 93)
  - placebo (n = 91).

Rickels et al. (2005) Arch Gen Psych 62(9)



Rickels et al. (2005) Arch Gen Psych 62(9)



Rickels et al. (2005) Arch Gen Psych 62(9)

Pregabalin: summary

- Pregabalin (S-[+]-3-isobutylgaba) was designed as a lipophilic GABA (gamma-aminobutyric acid) analogue
- pregabalin interacts with the same binding site and has a similar pharmacological profile as its predecessor, gabapentin (1-[aminomethyl] cyclohexane acetic acid).
- Its main site of action appears to be on the alpha(2)delta subunit of voltage-dependent calcium channels
- Pregabalin appears to produce an inhibitory modulation of neuronal excitability.
- It is well-tolerated and associated with dose-dependent adverse effects (ataxia, dizziness, headache and somnolence) that are mild-to-moderate and usually transient.
- There are no known pharmacokinetic drug-drug interactions reported to date.
- beneficial effects in both ethological and conflict models of anxiety, as well as having some sleep-modulating properties.
- promising anxiolytic action when compared to placebo in generalised anxiety disorder, social phobia and panic disorder.

Pregabalin in anxiety disorders

- Well tolerated
- Low rate of discontinuation due to AEs
- Most AEs were mild of moderate intensity
- Profile consistent with CNS-active agent
  - Dizziness and somnolence most common
- Onset 1-5 days; resolution within 1 month (median)
- No significant sexual dysfunction
- Low incidence of discontinuation-emergent AEs
  - *No evidence of withdrawal phenomena*

Take home message

- No perfect drugs
- Appropriate use current options
- Take consider off label usage
- Newer pipelines
- Newer options
  - Tiagabine, Pregabalin…