THE TREATMENT OF ANXIETY: ONE FOCAL PERSPECTIVE

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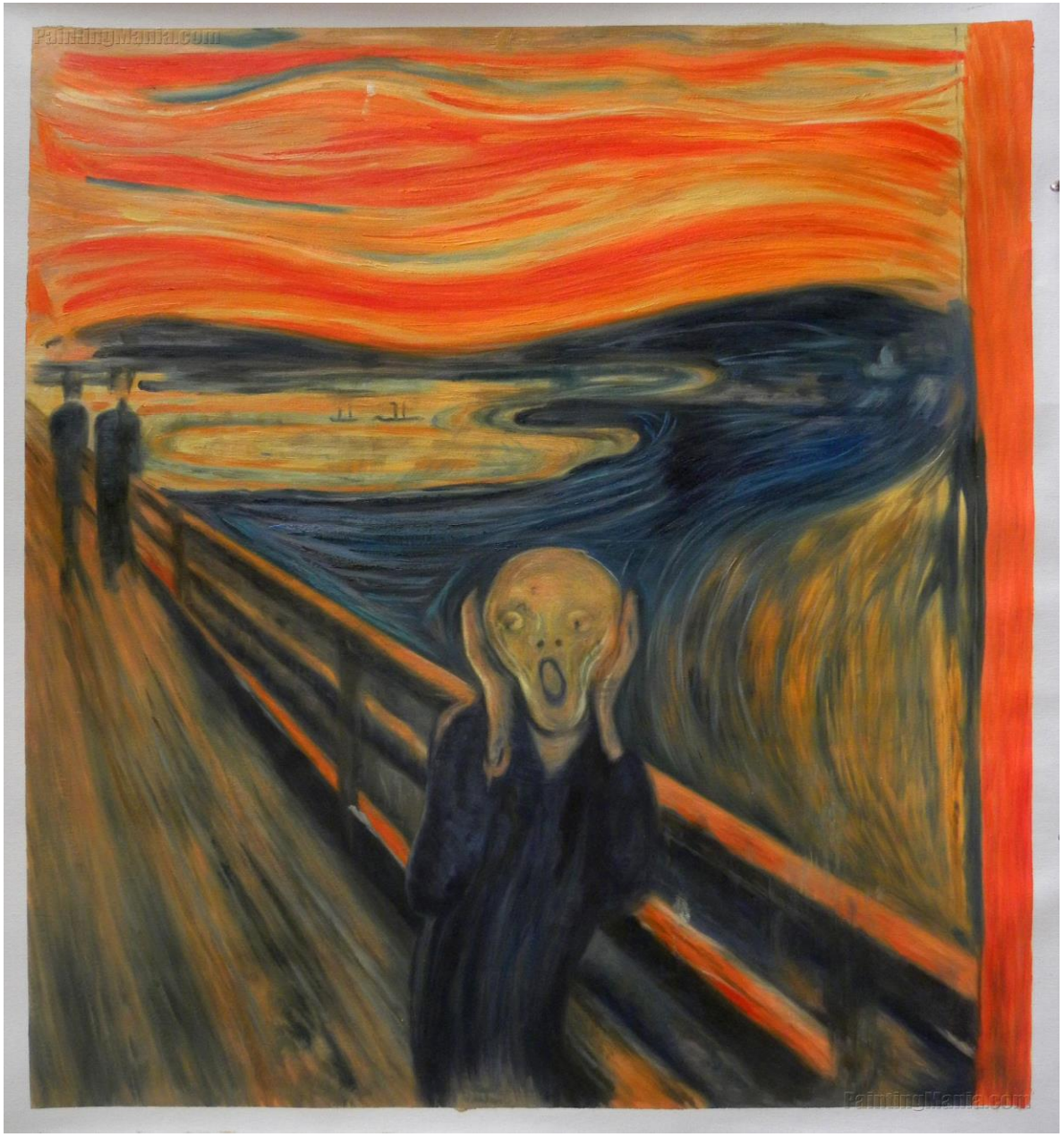
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Flow of presentation

- Anxiety: Epidemiology
- Types of anxiety disorders
- Case study
- Severity of anxiety disorder
- Management of anxiety disorders
- Pharmacological options
- Selecting a right anxiolytic agent for mild-moderate anxiety
- Focus on clobazam in anxiety management
- Summary

Anxiety

- Anxiety disorders are **common** conditions seen in clinical practice[1]
- Most frequently seen mental disorders in primary care, followed by depression[2]
- **Lifetime prevalence** of anxiety disorders **is about 29%**[1]
- Despite this:
  Frequently under-diagnosed in primary care[1]

1. International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84
2. BPJ | Issue 25:20-27

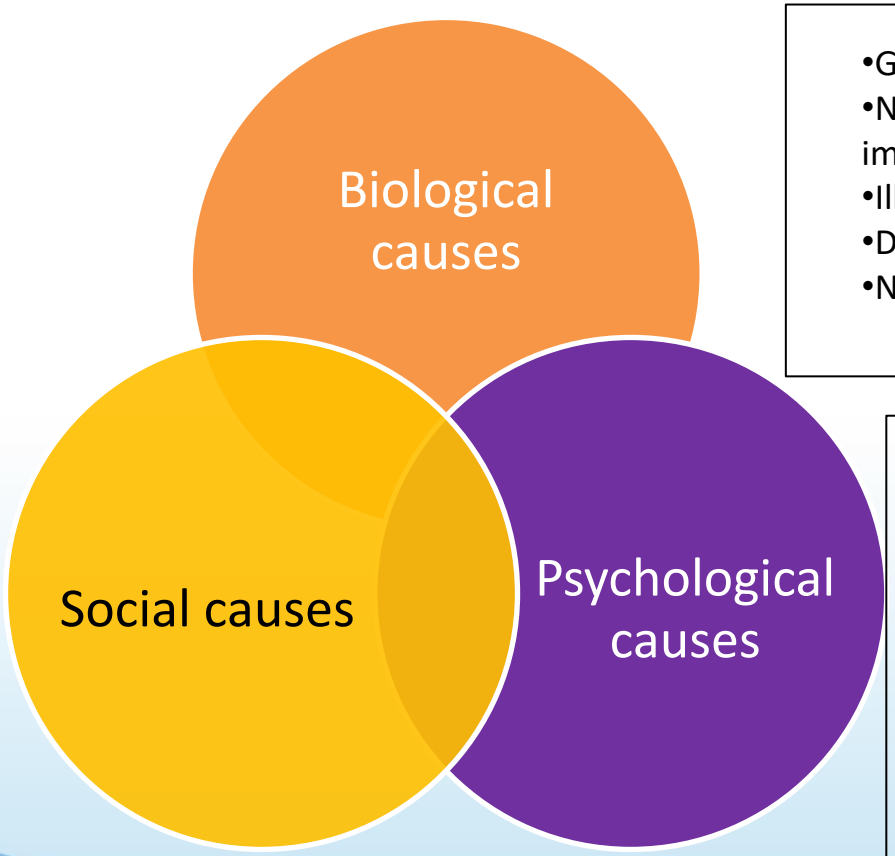
Anxiety disorders

- Panic disorder (PD)
- Agoraphobia
- Generalized anxiety disorder (GAD)
- Specific phobia
- Social phobia (social anxiety disorder)
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)

Disorder	Lifetime prevalence
Generalized anxiety disorder	5.1%
Obsessive-compulsive disorder	**2%**
Panic disorder	3.5%
Post-traumatic stress disorder	7.8%
Phobias	11.3%
Social anxiety disorder	13.3%

International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84
Kaplan EM, DuPont RL. Current Medical Research and Opinion2005;21;6:941–950

Anxiety: Pathophysiology



- Genetic factors
- Neurotransmitter imbalance
- Illness
- Drugs
- Nutritional causes

- Adverse life experiences
- Lack of social support
- Work stress
- Lack of social skills
- Changing values
- Conflict of societal norms
- Natural calamities

- Personality traits
- Low self esteem
- Cognitive dissonance
- Negative emotions
- Inter and/or intra-personal conflicts
- Developmental crises : Trauma & Abuse
- Perception f situational factors

http://bsris.swu.ac.th/journal/i5/Page100-118.pdf

Anxiety: Pathophysiology

- Neurobiological vulnerability
- **Risk factors:** Genetic, childhood adversity
- **Environmental factors:** Stress, trauma

Interaction of a specific neurobiological vulnerability and environmental factors

International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84

Anxiety: Pathophysiology

- **Dysfunction of** neurotransmitter systems: GABA, **s**erotonin, norepinephrine etc.
- Increased activation of the hypothalamic-pitutary-adrenal axis
- Increased corticotropin-releasing factor
- Reduced levels of GABA, serotonin

International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84
http://bsris.swu.ac.th/journal/i5/Page100-118.pdf

CASE STUDY

- A 30 years female **executive working in a bank**
- Married 5 years, but not conceived
- Apparently alright until 4 years ago
- **History of feeling anxious** every time when she has to make a presentation or speak in front of colleagues since 4years
- **Disturbed sleep** many days before such an event
- **Sweating and palpitation** during presentation
- Difficulties while going to parties, chatting up with male colleagues since 10 years

- Weight: 65 kg
- Height: 140 cm
- **BMI: 33.16 kg/m^2**
- MSE: **Anxious subjectively and objectively; some fidgetiness. Otherwise NAD**

Diagnosis: Generalized Anxiety disorder

Hamilton Anxiety Rating Scale (HAM-A)

No	Item	No	Item
1	Anxious mood	8	Somatic (sensory)
2	Tension	9	Cardiovascular symptoms
3	Fears	10	Respiratory symptoms
4	Insomnia	11	Gastrointestinal symptoms
5	Intellectual	12	Genitourinary symptoms
6	Depressed mood	13	Autonomic symptoms
7	Somatic (muscular)	14	Behavior at interview

Every item scored on 4 point scale: 0 = Not present, 1 =Mild, 2= Moderate, 3 =Severe, 4= Very severe
Total score range of 0–56

Total score	Severity
Mild	<17
Moderate	18-24
Severe	25-30

Hamilton M.The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55

Case continued…
HAM-A score

No	Item	Score	No	Item	Score
1	Anxious mood	**3**	8	Somatic (sensory)	**1**
2	Tension	**3**	9	Cardiovascular symptoms	**2**
3	Fears	**3**	10	Respiratory symptoms	**0**
4	Insomnia	**1**	11	Gastrointestinal symptoms	**0**
5	Intellectual	**1**	12	Genitourinary symptoms	**2**
6	Depressed mood	**1**	13	Autonomic sym	
7	Somatic (muscular)	**1**	14	Behavior at	

Diagnosis:

Moderate anxiety

Total HAM-A score: 23

Hamilton M.The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55

Why should anxiety be treated?

- Can result in emergency
- High risk for suicide attempts
- High risk of substance abuse

International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84

What does a patient want?

- Rapid symptom relief i.e. fast onset of action
- No impairment in the work
- Desire to improve quality of life
- A medicine that is easy to tolerate

What does a patient want?

- Rapid symptom relief i.e. fast onset of action
- No impairme
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- A medicine th

Factors considered while selecting treatment option

- Patient ’s preference
- Severity of illness
- Co-morbidity
- Concomitant medical illnesses
- Complications (substance abuse, suicide risk)
- Previous treatments/ response, including family h/o treatment/ response
- Availability of treatment

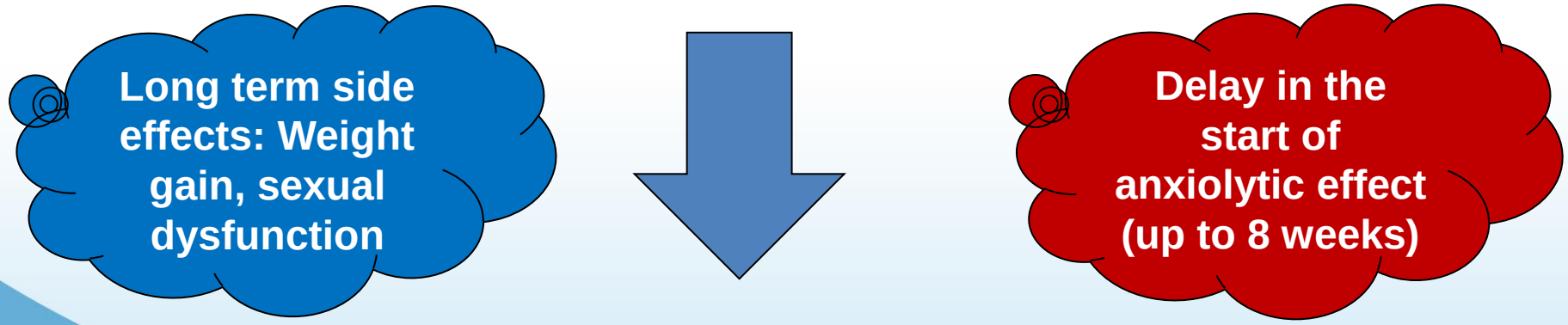
International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84

Treatment options

- Explain mechanisms underlying psychic and somatic anxiety before starting therapy
- **Pharmacotherapy:** SSRIs, SNRIs, pregabalin, benzodiazepines
- **Psychological therapy**
- Explain advantages and disadvantages of the drugs: Can improve compliance

Limitations of SSRIs

Restlessness, jitteriness, an increase in anxiety symptoms, insomnia or headache in the first days or weeks of treatment



Risk of reduced patient compliance

Limitations of SNRIs

- **Onset of action:** 2 – 4 weeks
- **Side effects at the beginning of treatment:** Nausea, restlessness, insomnia or headache
- Sexual dysfunctions, discontinuation syndromes
- Rise in blood pressure
- Risk of reduced patient compliance

International Journal of Psychiatry in Clinical Practice, 2012; 16: 77–84

Benzodiazepines

- Mainstay in the treatment of anxiety
- Can be used as monotherapy as well as adjunctive therapy

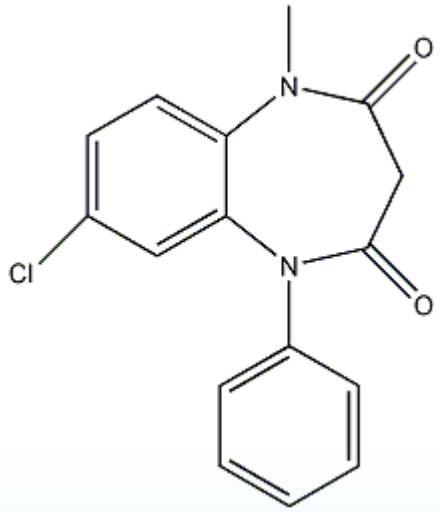
Advantages

- Quick onset of action
- Generally well tolerated

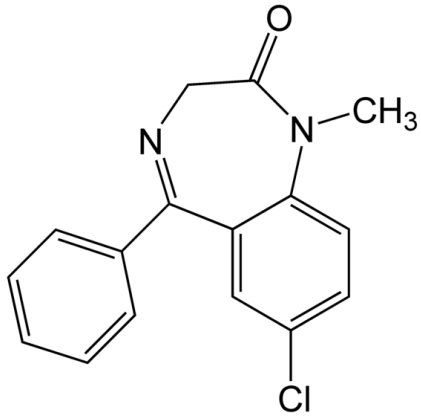
Kaplan EM, DuPont RL. Current Medical Research and Opinion2005;21;6:941–950

Why is clobazam a better choice?

Structural difference between clobazam and 1,4-benzodiazepines



Clobazam

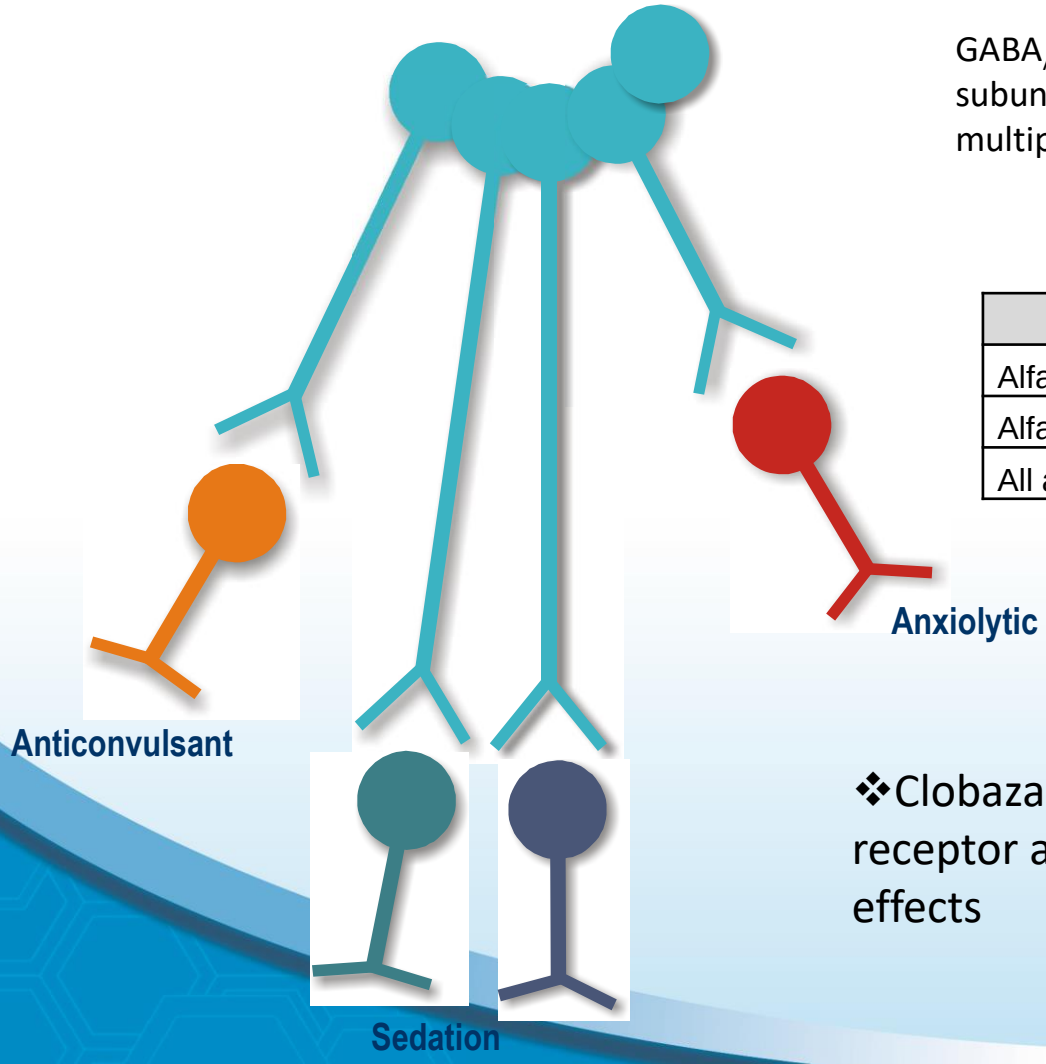


1,4-benzodiazepines

- Clobazam contains nitrogen atoms at the 1 and 5 positions on the B ring, which is the differentiating feature from other conventional 1,4-benzodiazepines

Gauthier AC et al CNS Neuroscience & Therapeutics 2015; 21: 543–548

Specific actions of alfa subunits



$GABA_A$ receptor is composed of five subunits i.e. two alfa-subunits, two beta-subunits, and one gamma-subunit with multiple types among each subunit

Receptor subunit	Action
Alfa 1 subunit	Sedation
Alfa 2 subunit	Anxiolytic action
All alfa subunits	Anti-convulsant action

❖Clobazam binds allosterically to the $GABA_A$ receptor and results in anticonvulsant and anxiolytic effects

Gauthier AC et al CNS Neuroscience & Therapeutics 2015; 21: 543–548

Clobazam: Structural advantages

- Higher selectivity for alfa 2 subunits over alfa 1 subunits compared with 1,4-benzodiazepines, decreases the risk of sedation[1]

- Selective binding may be responsible for reduced risk for efficacy tolerance[1]

- Ten fold lesser sedative effect than conventional 1,4-benzodiazepines[2]

1. Gauthier AC et al CNS Neuroscience & Therapeutics 2015; 21: 543–548
2. Mehndiratta MM et al.*Seizure* 2003; 12: 226–228

Comparison of different BZDs

Drug	Elimination half life (hrs)	Common dose in anxiety disorder (mg/day)	Dosing frequency
Short acting			
Alprazolam	**6.3-26.9**	**0.75-6**	**QD or TID**
Lorazepam	10-20	2-6	BD or TDS
Intermediate acting Clonazepam	30-40	0.5-1	BD
Long acting			
Clobazam	**12-60**	**20-30**	**QD or BD**
Diazepam	20-100	4-40	BD, TDS or QID

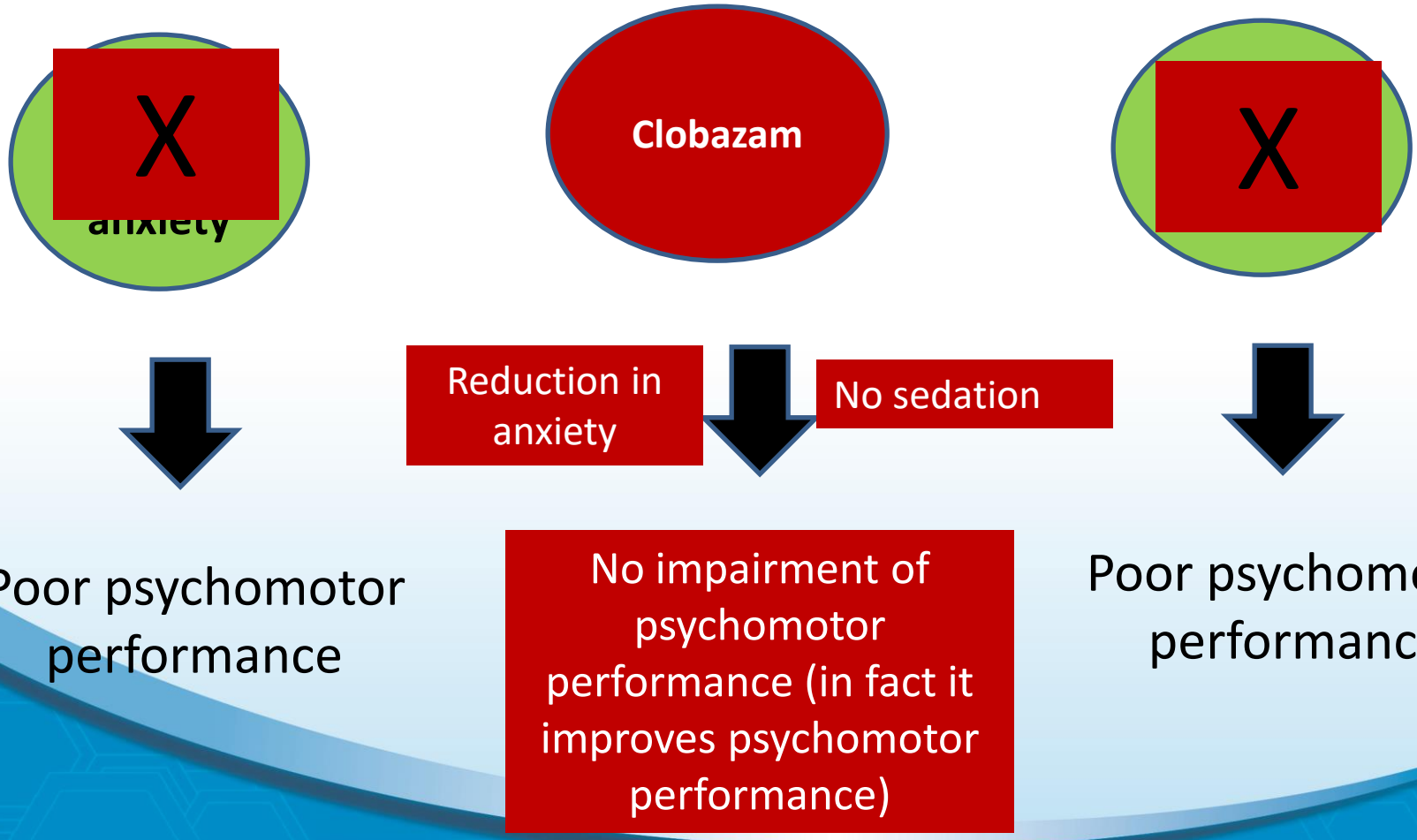
Kaplan EM, DuPont RL. Current Medical Research and Opinion2005;21;6:941–950

Clobazam: Improvement in psychomotor performance

- Performance on sensorimotor tasks is affected by person's level of alertness or arousal
- Adversely impact on the psychomotor performance caused by conventional 1,4-benzodiazepines is contributed by sedation or hypnosis caused by them
- Clobazam does not produce an impairment of psychomotor performance; in fact it can improve performance on a complex psychomotor task

1. Gauthier AC et al CNS Neuroscience & Therapeutics 2015; 21: 543–548
2. Mehndiratta MM et al.*Seizure* 2003; 12: 226–228

Clobazam: Improvement in psychomotor performance



Hindmarch I. Br J Clin Pharmacol. 1979;7 Suppl 1:77S-82S

Clobazam: Dosage

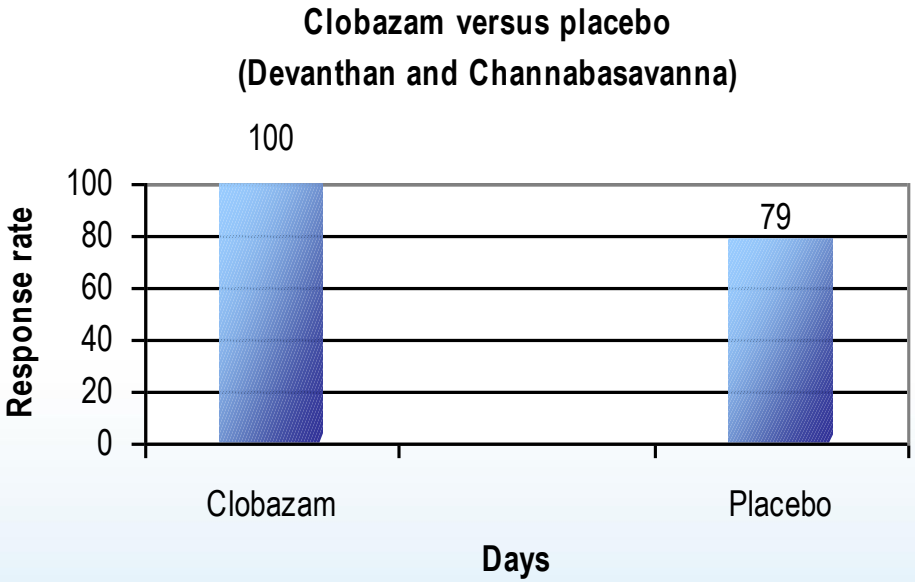
- Different studies have used different dosing schedules of clobazam

- 10 mg twice daily in the first week
- Increased to 10 mg three times daily during second and third week[1]
- Used up to 80 mg/day in a clinical trial[2]

Dose is adjusted based on the response and side effects[2]

1. Bohm C, et al. J Clin Psychopharmacology 1990;10:38S-42S
2. Jacobson AF, et al. J Clin Psychiatry 1983;44:296-300

Clobazam: High response rate



N = 47

Clobazam = 30 mg/ d

Response rate 100% with clobazam

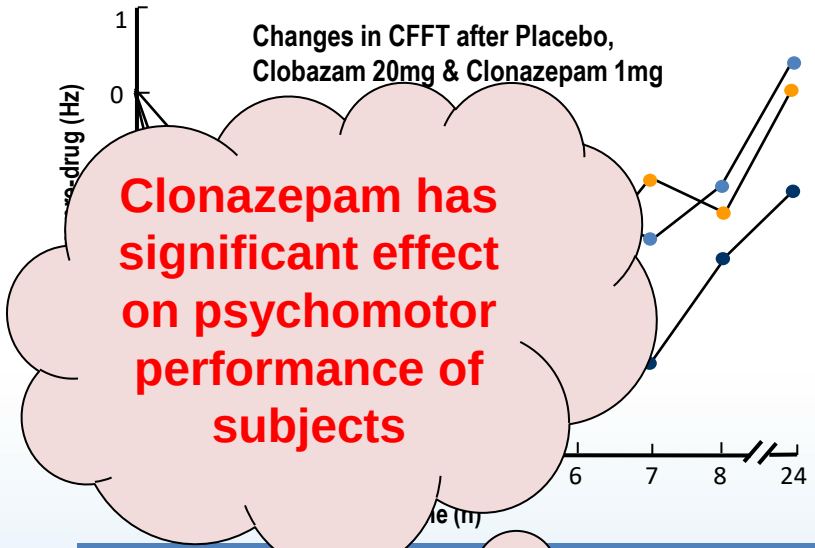
Randomised, double blind study in Patients with anxiety neurosis, t=4 weeks, n=47: clobazam (n=25), placebo (n=22), Arms : Clobazam or placebo Results assessed using : HARS, CGI & symptom checklist

Devnathan S,Channabasavanna SM;Current Therapeutic Research Vol21, No3, March 1977

How does clobazam compare with clonazepam?

Clobazam vs clonazepam

A. Study by Wildin et al.



Clonazepam has significant effect on psychomotor performance of subjects

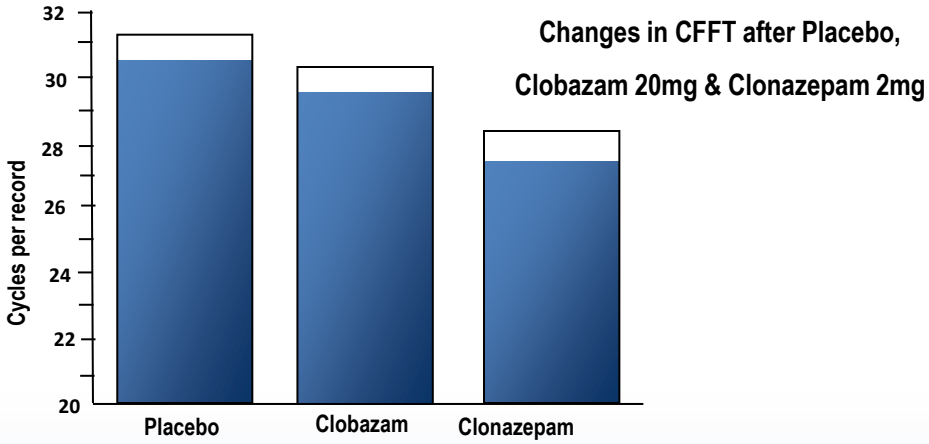
Clobazam is considerably less sedating than clonazepam

- Results show that clobazam is relatively free from CNS depressant actions when compared to clonazepam.
- Clonazepam produced a higher incidence of drowsiness and sedation during the first few weeks of therapy.

Wildin JD et al. Br. J. clin. Pharmac. 1990;29:169-177

Clobazam vs clonazepam

B. Study by Meyden CH, Bartel PR et al.



N = 10 Healthy volunteers

- Clobazam causes no impairment of saccadic eye movements and other aspects of psychomotor function *viz*. critical flicker fusion (CFF) threshold as compared to clonazepam.
- Clonazepam is mainly used in panic attacks as opposed to clobazam which is used in various other anxiety disorders.

A Randomised, cross over, double blind placebo controlled study with a 7 day washout period between two arm assessment in 10 healthy volunteers, Arms : Placebo, Clobazam & Clonazepam, Results assessed using before and after 1.5 hours of intake of medication. CFF test, Sternberg CRT, saccadic eye movement test.

Van Der Meyer et al.; European Journal of Clinical Pharmacology 1989; 37; 365-369

Clobazam vs clonazepam

	Clonazepam	Clobazam
Type of benzodiazepine[1]	1,4-benzodiazepines	1,5-benzodiazepine
Approved indications	**Seizure disorders and panic disorder[2]**	**Uncontrolled epilepsy; acute and chronic anxiety [3]**

- In a comparative trial in healthy volunteers clonazepam showed impairment of cognitive and psychomotor functions[4]
- Clobazam was remarkably free of cognitive and psychomotor side-effects[4]

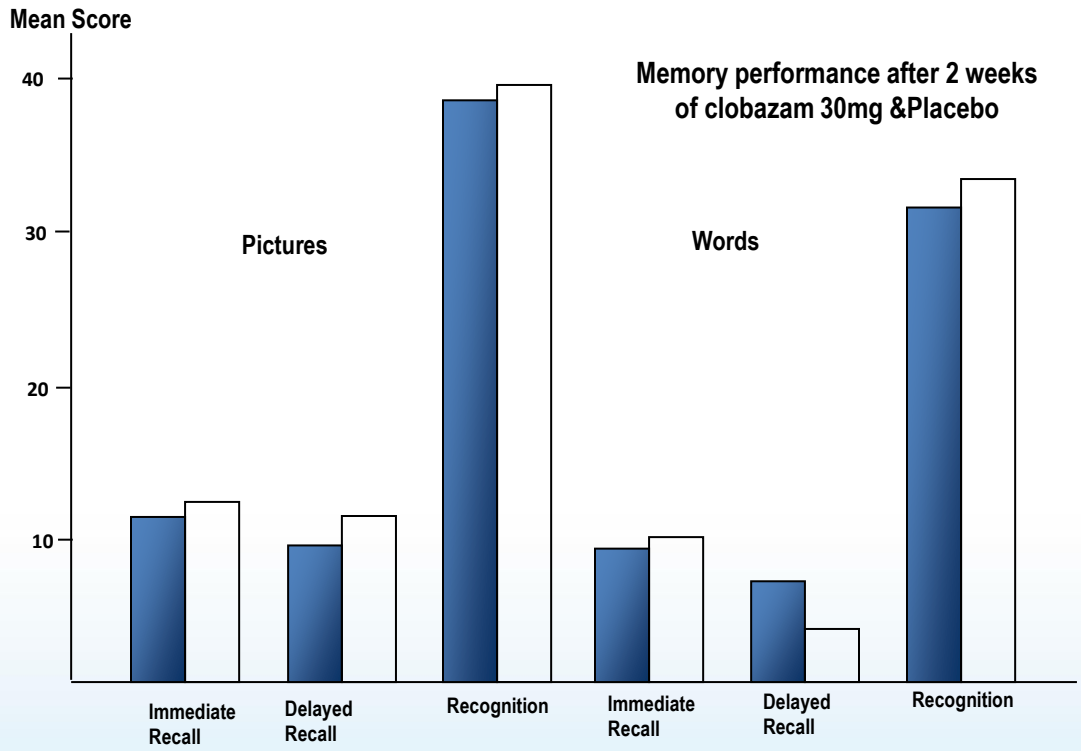
1. Robertson MM. Epilepsia. 1986;27 Suppl 1:S27-41
2. Clonazepam PI 4/2009
3. van der Meyden CH, et al. Eur J Clin Pharmacol. 1989;37(4):365-9
4. Frisium PI June 2014

Clobazam: Dependence and withdrawal symptoms

- Less potential for clobazam dependence
- Less potential for withdrawal symptoms
- Less sedation

Beaumont G. Human Psychopharmacology. 1995;10: S27-S41

Clobazam: Effect on memory



N = 10; healthy volunteers for 2 weeks; double blind placebo controlled cross over study with a 1 week washout period

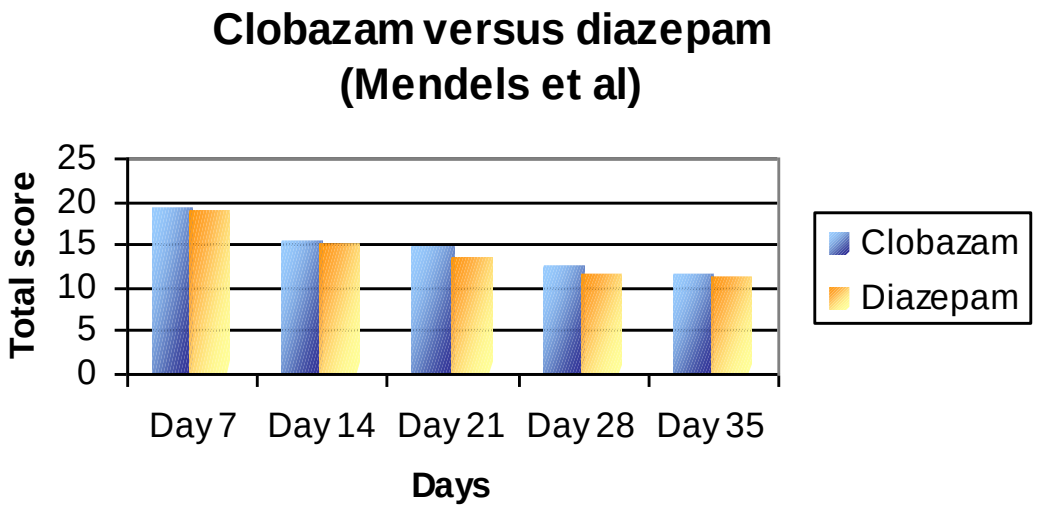
- **Clobazam did not affect any memory function**, neither immediate or delayed recall nor recognition of the learning material.

Thompson and Trimble, 1981

How does clobazam compare with diazepam?

Clobazam vs diazepam

A. Study by Mendels, Secunda, Schless, et al.

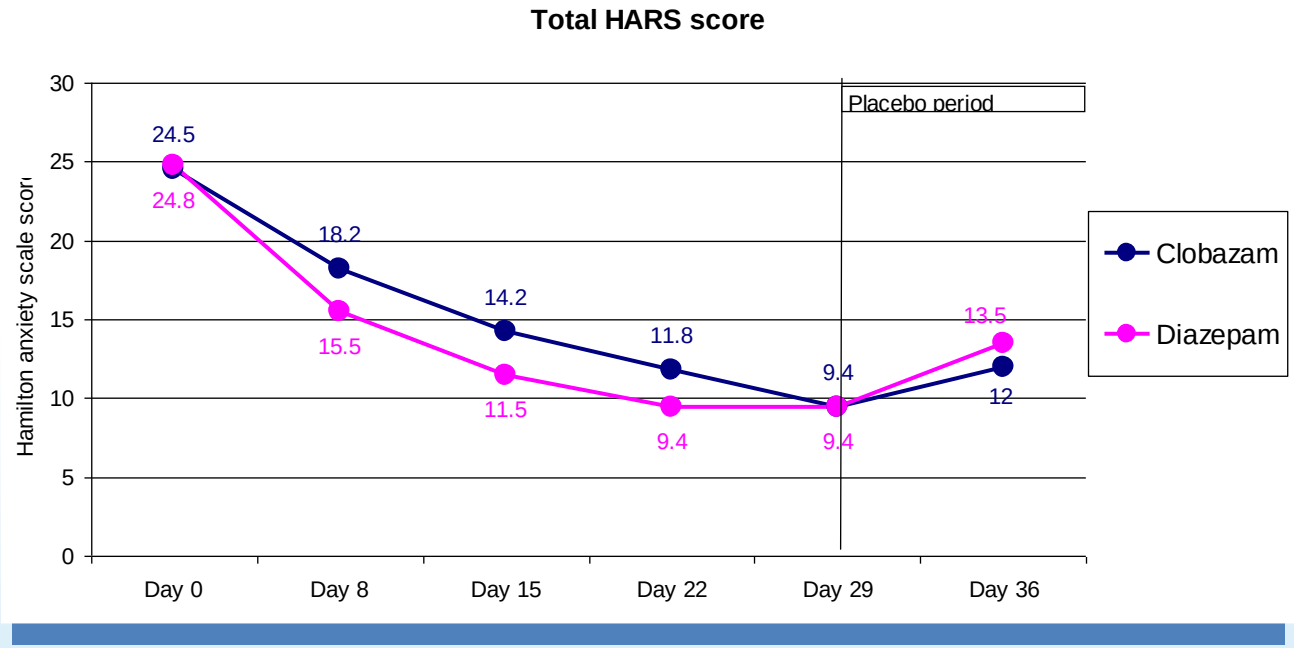


N = 61; 42 completers; 5 weeks

Results show clobazam (20-80 mg) to be as effective as diazepam (10-40 mg) in reducing symptoms of anxiety and tension.

B. Study by Doongaji et al

N = 40; clobazam = 30 – 40 mg/ d; DZM = 15 - 20mg/ d; 5 weeks (4 +1)



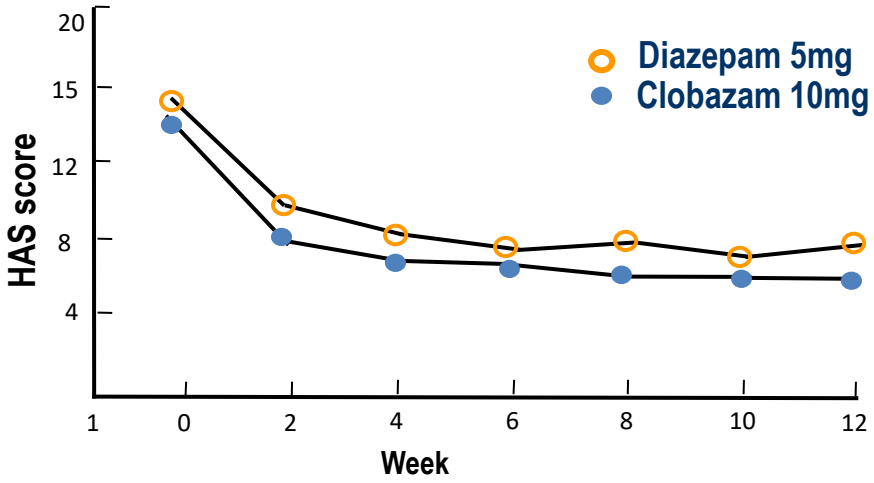
- No significant difference in both groups on the CGI scale.
- Motor coordination tests (hand steadiness test) showed greater improvement with clobazam.

Doongaji Dr, Sheth A, Apte J,Khare Cs, Thatte SS,Lakdawala PD;' Clobazam versus diazepam;a double blind study in anxiety neurosis'; J Clin Pharmacol.18(1978) p358-364

C. Study conducted by Schjonsby et al.

N = 60; DZM = 15mg/d, CLB = 30mg /d

Duration of study = 3mths



- Clobazam was shown to be as effective as diazepam in reducing symptoms of anxiety (as assessed by HARS and CGI improvement)
- The greatest anxiolytic response occurred relatively early during the treatment course
- CLB better than DZM in improving anxious moos whereas DZM better than CLB in improving tension and muscular symptoms

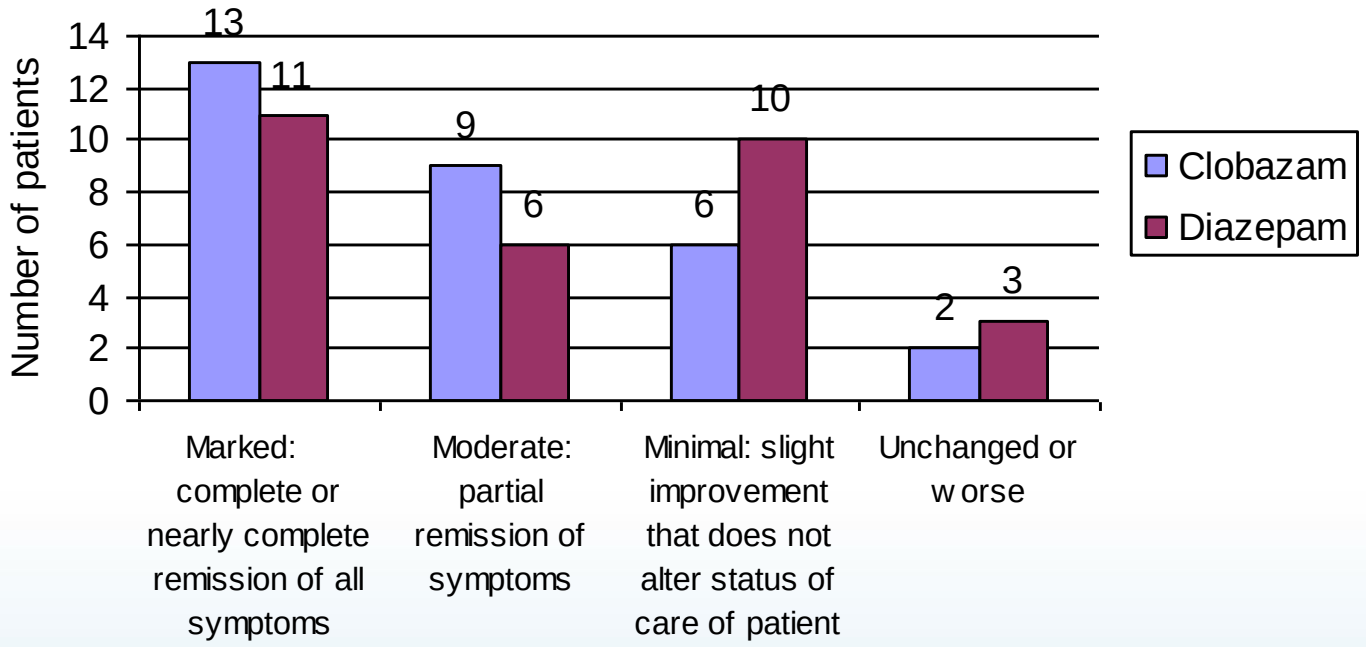
Randomised, double blind study in Patients with neurotic disturbances including patients with anxiety neurosis (WHO code 300.0) & depressive neurosis (WHO code 300.4), t=3months, n=60 : clobazam (n=30), diazepam (n=30), Arms : Clobazam & diazepam Results assessed using : HAS & CGI

Schjonsby HP, et al J Int Med Res (1997)7:404-410

Schjonsby et al.

N = 60; DZM = 15mg/d, CLB = 30mg /d

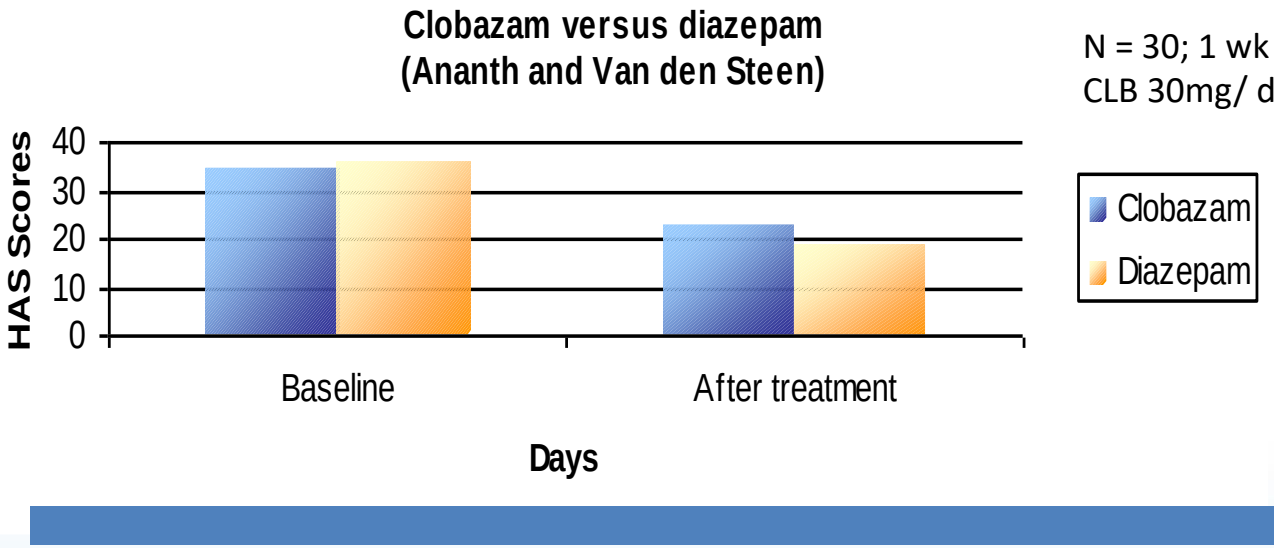
Duration of study = 3mths



- 22 patients on clobazam showed marked to moderate improvement, compared to 17 patients of diazepam group, though it was not statistically significant.

Schjonsby HP, et al J Int Med Res (1997)7:404-410

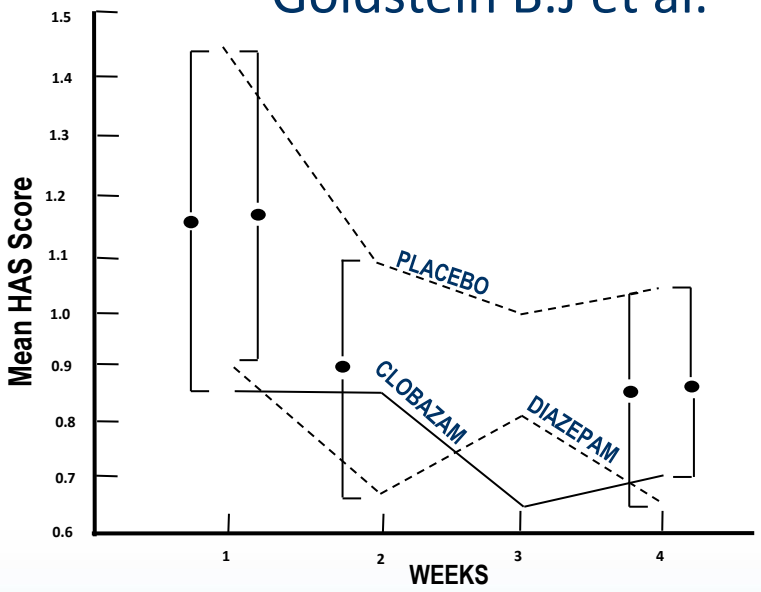
D. Study conducted by J. Ananth and Nancy Van Den Steen.



N = 30; 1 wk placebo washout →
CLB 30mg/ d, DZM = 15mg/ d

- No significant difference between the treatment groups with less side-effects with clobazam than diazepam.
- Therefore, with respect to the efficacy index, clobazam produces therapeutic effect without provoking troublesome side-effects better than diazepam.

E. Study conducted by Jacobson A.F, Goldstein B.J et al.



N = 133; 49 drop outs; CLB = initiated at 10mg/ d, DZM = 5mg/ d up titrated to achieve maximum response

No differences between 3 groups on overall HAS scores at week 4; cause – high dropout rate

- Both clobazam and diazepam demonstrated a significant reduction in somatic symptoms as compared to placebo at weeks 1 and 4
- Clobazam patients were more improved on the HAS somatic factor than the placebo at the end of week 2, while diazepam patients did not differ from either group.
- Significantly lesser number of dropouts in CLB group vs. DZM

Randomised, double blind study in Anxious out patients, t=5 weeks, n=133: clobazam (n=45), diazepam (n=45), placebo (n=43), Arms : Clobazam, Diazepam placebo Results assessed using : HAS, CGI, Hopkins symptoms checklist

Jacobson a, et al J Clin Psychiat.44:296-300

Clobazam vs diazepam

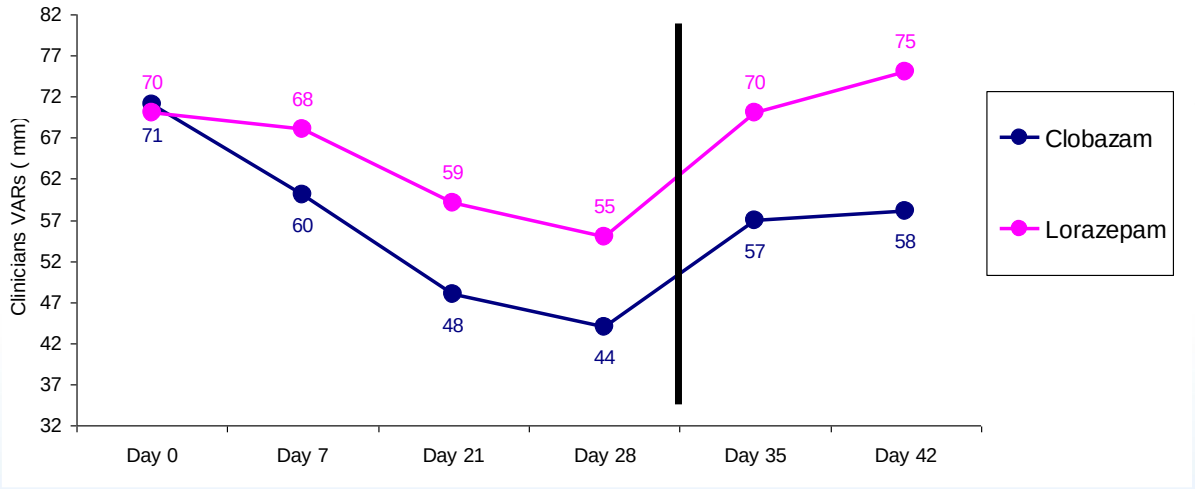
	Diazepam	Clobazam
Type of benzodiazepine[1]	1,4-benzodiazepines	1,5-benzodiazepine,
Sedation	**Yes[1]**	**No[2]**
Impairment of psychomotor performance	Yes[1]	No[2]
Improvement in psychomotor performance	No[1]	Yes[2]

1. Oblowitz H, Robins AH. Br. J. clin. Pharmac. (1983), 16, 95-99
2. Hindmarch I. Br J Clin Pharmacol. 1979;7 Suppl 1:77S-82S

How does clobazam compare with lorazepam?

Clobazam vs lorazepam

A. Study conducted by M. Paes De Sousa, M.L.Figuiera and F. Loureiro.



N = 30 elderly anxious patients; LZM = 3mg /d , CLB = 30 mg/d for 4 weeks

- Both drugs are equally effective in reducing the HARS.
- Worsening of the somatic anxiety component upon withdrawal from active treatment with lorazepam.

Randomised, double blind study in elderly patients with primary symptoms of anxiety, t=6 weeks, n=20 : clobazam (n= 11), lorzepam (N= 9), 9), Arms : 10 mg t.id of clobazam and 1 mg tid of Lorazepam for 4 weeks and both arms shifted to placebo for two weeks Results assessed using : HARS, Leeds self assesment & VARS

B. Study conducted by K. Siegfried, D. Koeppen, K. Taeuber et al. *(healthy volunteers)*

Test	Measure
"Complex memory test"	Short-term memory
"Telephone numbers" "Objects"	Retrograde amnesia
"Triplets" "City map"	Anterograde amnesia
Choice Reaction Task	Psychomotor performance
Critical Flicker Fusion	Vigilance
100 mm Visual Analogue Scales	Subjective mood state

- Lorazepam produces significant anterograde amnesia.
- Clobazam has less detrimental effects than lorazepam.

Clobazam vs lorazepam

C. In a study cited by Aceves Flores, 1979.

- Efficacy and safety of clobazam in generalized anxiety disorders, anxiety neurosis and anxiety secondary to underlying physical disease were reviewed.
- **Anxiolytic efficacy was significantly greater after treatment with clobazam 40 mg daily for 1wk than with lorazepam 4 mg daily**.
- Anxiolysis was maintained on withdrawal of clobazam therapy.

Clobazam does not produce impairment of performance and alertness found with lorazepam[1]

1. Hindmarch I, et al. Br. J. clin. Pharmac. 1980;10:145-150

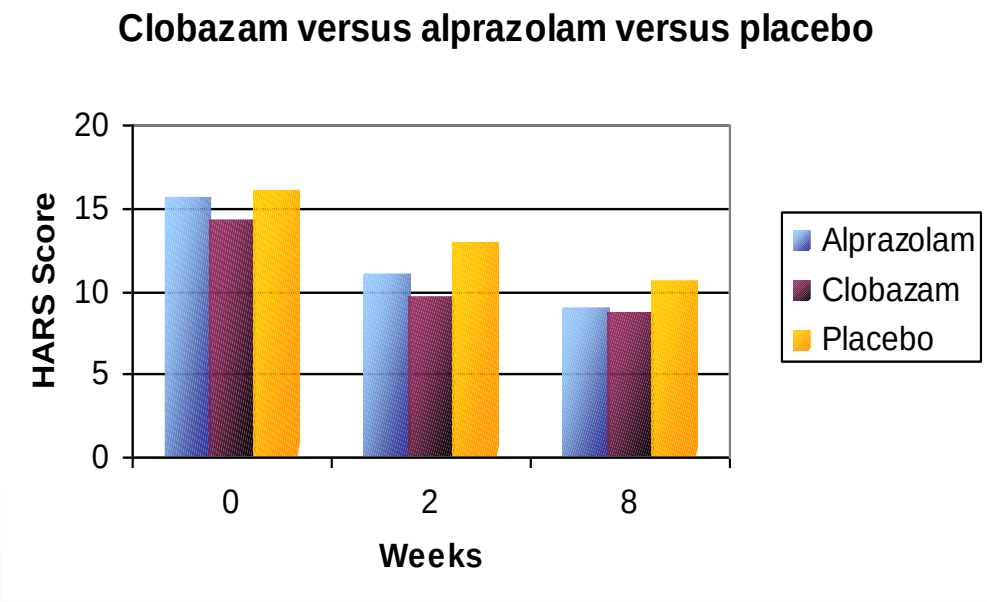
Clobazam vs lorazepam

	Lorazepam	Clobazam
Type of benzodiazepine[1]	1,4-benzodiazepines	1,5-benzodiazepine
Sedation	**Yes[1]**	**No[2]**
Impairment of psychomotor performance	Yes[1]	No[2]
Improvement in psychomotor performance	No[1]	Yes[2]

1. Oblowitz H, Robins AH. Br. J. clin. Pharmac. (1983), 16, 95-99
2. Hindmarch I. Br J Clin Pharmacol. 1979;7 Suppl 1:77S-82S

How does clobazam compare with alprazolam?

A. Study conducted by Castillo A, Sotillo C, Mariategui J.



Results show that both alprazolam and clobazam result in greater reduction of anxiety over the 1st wk than does placebo.

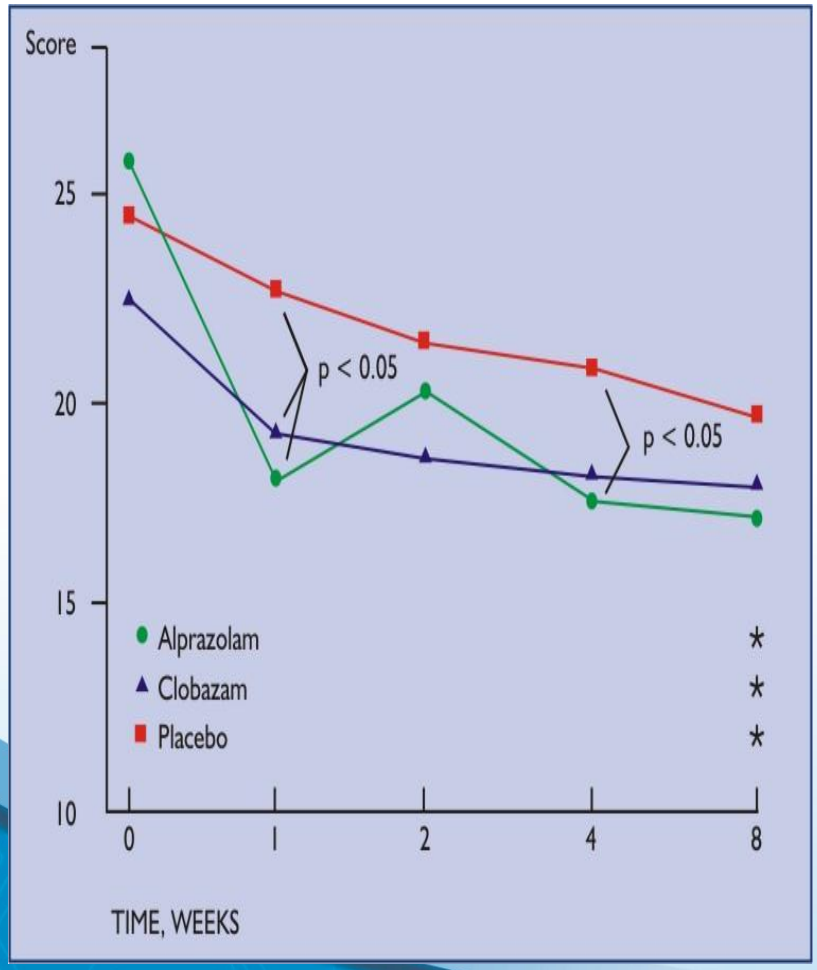
Only alprazolam maintained this difference at week 4

Randomised, double blind study in Patients with GAD as per DSM III for atleast one month, t=8 weeks, n=98: alprazolam (n=32), clobazam (n=33), placebo=(n=33), Arms : Clobazam, Alprazolam or placebo Results assessed using : HARS AND CGI

Castillo A et al. Neuropsychobiology 1987;18:189-194

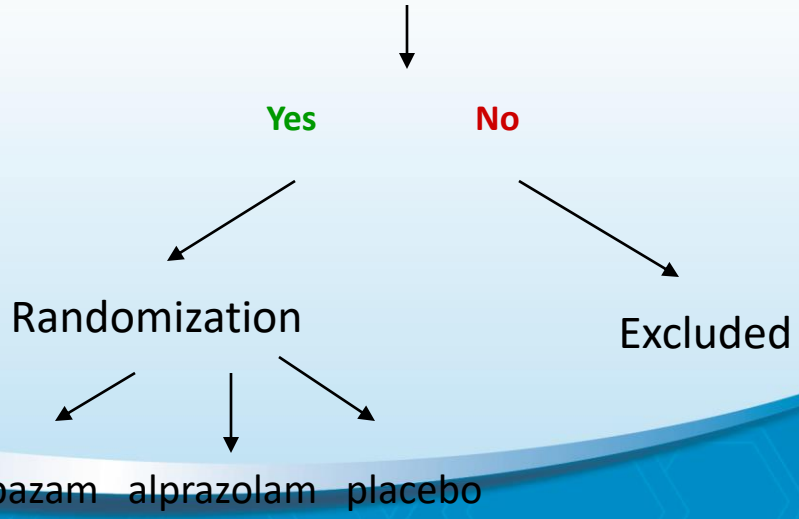
Randomized double blind, placebo controlled study of Clobazam vs. Alprazolam in out patients with GAD

Castillo A,Sotillo C, Mariategui *J Neuropsychobiology* 1987;18:189-194



- N = 98 (M, F); 18 – 50 yrs.
- Outpatients; DSM III GAD
- Min. score of 18 on 14 item HARS

- Washout period – 7days; placebo capsules TID
- Revaluation -- still qualified?



Study conducted by Perez-Rincon and Trujillo, 1985

- Compared alprazolam with clobazam
- Clobazam in equipotent doses is as effective as alprazolam in reducing symptoms of anxiety
- Both drugs reached a similar therapeutic efficacy and side-effect profile

Clobazam vs alprazolam

	Alprazolam	Clobazam
Type of benzodiazepine	1,4 benzodiazepine[1]	1,5-benzodiazepine [2]
Sedation	**Yes[3]**	**No[4]**
Impairment of psychomotor performance	Impairs psychomotor performance (impairs alertness, decreases mental activation)[5] Vester	Does not impair psychomotor performance; in fact can improve psychmotor performance in anxiety[4]

- Clobazam is as effective as alprazolam[6]

1. Xanax PI March 2006
2. Oblowitz H, Robins AH. Br. J. clin. Pharmac. (1983), 16, 95-99
3. Cohn JB, Wilcox CS. J Clin Psychiatry 1986;47;8:409-12
4. Hindmarch I. Br J Clin Pharmacol. 1979;7 Suppl 1:77S-82S
5. Vester JC, et al. Neuropsychopharmacology 2002;27;2:260-9
6. Castillo A, et al. Neuropsychobiology 1987;18:189–194

Clobazam in somatic anxiety

- Effective in reducing anxiety associated with CV symptoms *viz. tachycardia, precordial pain or anginal pain (*Krantz *et al).*
- Alleviating anxiety associated with psychosomatic genito-urinary symptoms in menopausal women (de Souza).
- Effective in reducing anxiety and tension-related psychosomatic gastrointestinal symptoms (Figueiredo Penteado).

Case study..

- A 30 years female **executive working in a bank**
- Apparently alright until 4 years back
- **History of anxiousness** every time when she has to make a presentation or speak in front of colleagues since 4years
- **Disturbed sleep** many days before such an event
- **Sweating and palpitation** during presentation
- Difficulties while going to parties, chatting up with male colleagues since 10 years

- Weight: 65 kg
- Height: 140 cm
- **BMI: 33.16 kg/m^2**
- Married 5 years, but not conceived

Diagnosis: Moderate anxiety (HAM-A score 23)

Clobazam is a suitable choice for working executives for mild to moderate anxiety

Duration of therapy

- At least 6 – 24 months after remission
- Reduce the risk of relapse
- May be stopped only if all, or almost all, symptoms disappear

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Before I Conclude...

- We have here looked at one specific agent for the effective and safe treatment of anxiety. Namely, CLOBAZAM
- The importance of non pharmacological treatment cannot be overemphasized.
- Ideally a combination of the two modalities should be attempted, and it works best.
- A word about side effects: Much less than other BDZs
-

Conclusion

- Anxiety disorders are common psychiatric disorders
- They result in a significant amount of impairment in quality of life
- Among pharmacological options benzodiazepines offer faster onset of action
- Clobazam is 1,5 benzodiazepine and offers advantages over 1,4 benzodiazepines
- Clobazam does not cause sedation
- It is thereby a useful agent in the treatment of outpatients with mild-moderate anxiety disorders in adult working patients

THANK YOU

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