Elimination half life of benzodiazepines and new hypnotics

Long-acting

Chlordiazepoxide

Diazepam

Flurazepam

Intermediate

Lorazepam

Oxazepam

Ultrashort

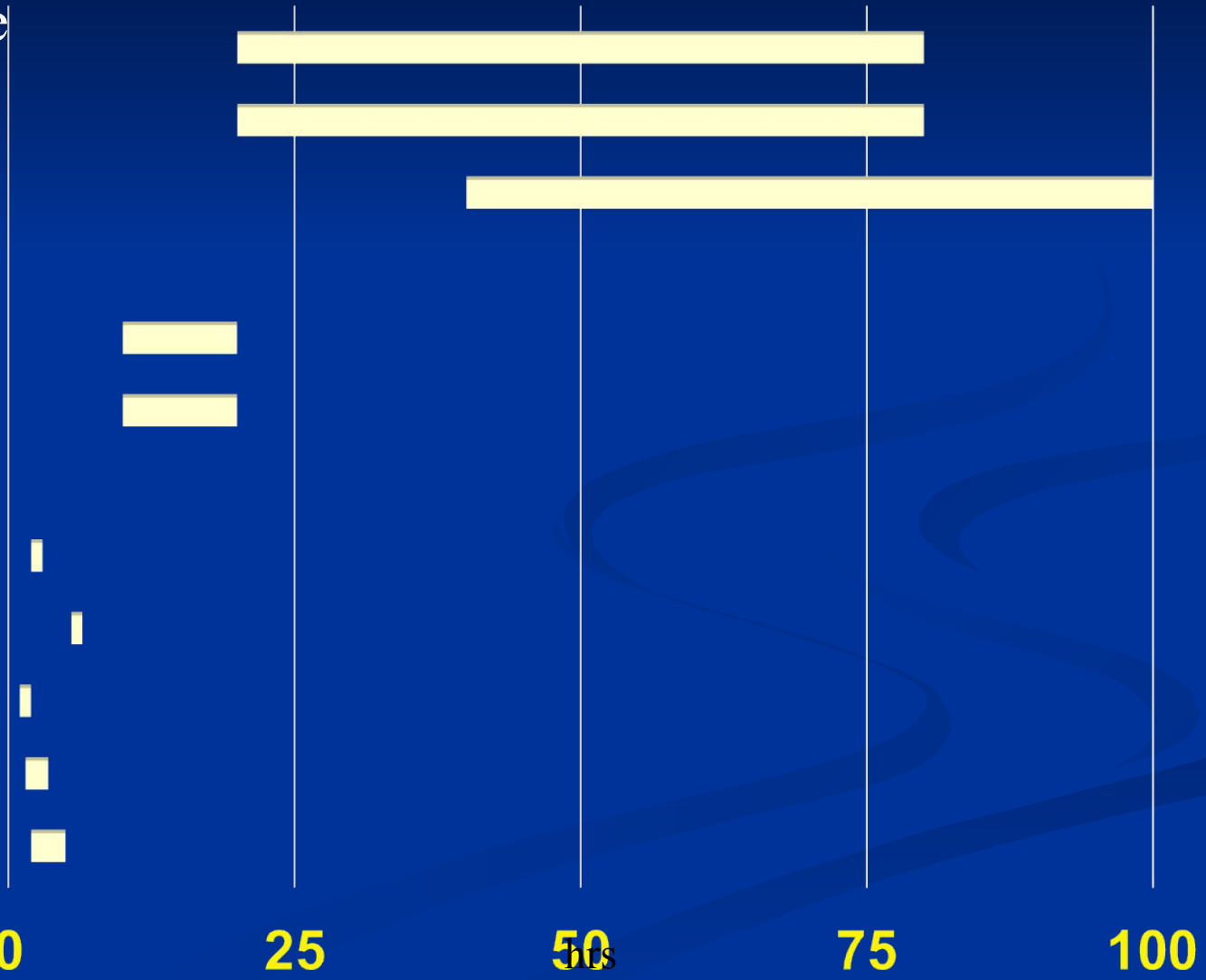
Triazolam

Escozopiclone

Zaleplon

Zolpidem

Ramelteon



Benzodiazepines adverse effects

General	Mood disturbance/rebound anxiety in 30% Amotivation Dependence (within 3-4 weeks) Dangerous in pregnancy or lactation Enhancement of EtOH/opioid euphoria	
Cognitive	Memory Concentration Attenttion	May persist up to 6 month post withdrawal!
Behavioural	Sedation/drowsiness Driving/industrial accidents Slurring of speech Falls Irritability, aggression/hostility (esp. high potency)	

Side effects, hazards

- oversedation
- increase in appetite
- tolerance –pharmacokinetic minimal if any
  pharmacodynamic significant
- physical dependence, withdrawal symptoms
- **suicide proof**
- drug interactions
  - additive with other CNS depressants incl. alcohol
  - metabolism
  oxidation impaired by cimetidine, estrogen, disulfiram, isoniazid, etc.
  glucuronide conjugation unaffected

Benzodiazepines

Amnesic effect

- anterograde amnesia
- cognitive impairment

Warning

- **COPD** — יכול להפריע בנשימה
- **Sleep apnea** — יכול להפריע בנשימה
- **קשישים** — סיכוי יותר גבוה לטוקסיות ולתגובה פרדוקסלית
- **לאנשים עם ליקוי קוגניטבי או דיכוי CNS** — סיכוי יותר גבוה לטוקסיות ולתגובה פרדוקסלית
- **מחלות כבד** — סיכוי יותר גבוה לטוקסיות
- **מחלות כליתיות** — סיכוי יותר גבוה לטוקסיות

- **Narrow angle glaucoma** — החמרת המחלה הבסיסית
- **Porphyria** — החמרת המחלה הבסיסית

זהירות ואסור..

++ טרטוגני אסור בהריון ובהנקה.

- יכול לגרום לסנדרום גמילה בילוד עד כדי פרכוסים ואגטציה אם נלקח בשליש אחרון.
- יתכנו גם דיספנאה, טשטוש, ברדיקרדיה.
- מומים כגון חיך שסוע

++ כשיש רקע של התמכרות)נרקומנים(

- שכן יש סיכוי גבוה להתמכרות או לטוקסיות

Types of withdrawal symptoms after stopping benzodiazepines

Major withdrawal symptoms

Epileptic fits

Confusional state

Abnormal perception of movement

Depersonalisation or derealisation

Muscle twitchings

Lowered perceptual threshold to sensory stimuli

'Psychosis'

Minor withdrawal symptoms

Increased anxiety

Insomnia

Irritability

Nausea

Palpitations

Headache and Muscle tension

Tremor

Dysphoria

Tolerance and dependence

1. Tolerance is a phenomenon that develops with many chronically used drugs. The body responds to the continued presence of the drug with a series of adjustments that tend to overcome the drug effects.
2. In the case of benzodiazepines, compensatory changes occur in the GABA and benzodiazepine receptors which become less responsive, so that the inhibitory actions of the GABA and benzodiazepines are decreased.
3. As a result, the original dose of the drug has progressively less effect and a higher dose is required to obtain the original effect.

Tolerance and dependence

1. Dependence is understood to be the inability to control intake of a substance to which one is addicted.
2. **Dependence has two components:**

a. **psychological** dependence, which is the subjective feeling of loss of control, cravings and preoccupation with obtaining the substance; and

b. **physiological** dependence, which is the physical consequences of withdrawal and is specific to each drug.

1. For some drugs (e.g. alcohol) both psychological and physiological dependence occur; for others (e.g. LSD) there are no marked features of physiological dependence.

Prevention of benzodiazepine dependence

1. Recognize persons likely to become dependent, e.g. alcoholics and those with passive dependent personality traits
2. Avoid continuous, high dosage.
3. Discourage regular consumption for long periods of time
4. Encourage flexible dosage up to an agreed maximum

Withdrawal syndrome and discontinuation syndrome

1. Any drug consumed regularly and heavily can be associated with withdrawal phenomenon on stopping.
2. Clinically significant withdrawal phenomena occur in dependence to alcohol, benzodiazepines, opiates and are occasionally seen in cannabis, cocaine and amphetamine use.
3. In general, drugs with a **short half-life** will give rise to more rapid but more transient withdrawal.

Benzodiazepine Withdrawal Symptoms

Psychological symptoms – excitability, sleep disturbances, increased anxiety, panic attacks, agoraphobia, social phobia, perceptual distortions, depersonalisation, derealisation, hallucinations, misperceptions, depression, obsessions, paranoid thoughts, rage, aggression, irritability, poor memory and concentration, intrusive memories and craving.

Benzodiazepine Withdrawal Symptoms

Physical symptoms – Headache, pain, stiffness, tingling, numbness, altered sensation, weakness, fatigue, influenza-like symptoms, muscles twitches, jerks, tics, "electric shocks", tremor, dizziness, light-headedness, poor balance, visual problems, tinnitus, hypersensitivity to stimuli, gastrointestinal symptoms, appetite change, dry mouth, metallic taste, unusual smell, flushing, sweating, palpitations, over breathing, urinary difficulties, skin rashes, itching.

Mechanisms of withdrawal reactions

Drug withdrawal reactions in general tend to consist of a mirror image of the drugs' initial effects.

In the case of benzodiazepines, sudden cessation after chronic use may result in dreamless sleep being replaced by insomnia and nightmares; muscle relaxation by increased tension and muscle spasms; tranquillity by anxiety and panic; anticonvulsant effects by epileptic seizures.

Mechanisms of withdrawal reactions

These reactions are caused by the abrupt exposure of adaptations that have occurred in the nervous system in response to the chronic presence of the drug.

Rapid removal of the drug opens the floodgates, resulting in rebound overactivity of all the systems which have been damped down by the benzodiazepine and are now no longer opposed.

Mechanisms of withdrawal reactions

Nearly all the excitatory mechanisms in the nervous system go into overdrive and, until new adaptations to the drug-free state develop, the brain and peripheral nervous system are in a hyperexcitable state, and extremely vulnerable to stress.

BDZ withdrawal

Mind	Hyperarousal: restlessness, agitation, anxiety, irritability tremor panic attacks, light/sound hypersensitivity, reduced concentration, insomnia Depersonalisation
Body: ANS	dry mouth, sweating, palpitations

Severe withdrawal:

Seizures

Psychotic : del/hal

Benzodiazepines: withdrawal

Nerves	Nervousness Irritability Seizures
The body	Tremor Myalgia
Vegetative	Insomnia ↓appetite

Treatment:

CBZ may work

Buspirone, propranolol, clonidine DON'T work

Management of benzodiazepine withdrawal

1. Withdrawal of the benzodiazepine drug can be managed in primary care if the patients in consideration are willing, committed and compliant.
2. Clinicians should seek opportunities to explore the possibilities of benzodiazepine withdrawal with patients on long-term prescriptions.
3. Interested patients could benefit from a separate appointment to discuss the risks and benefits of short and long term benzodiazepine treatment.
4. Information about benzodiazepines and withdrawal schedules could be offered in printed form.
5. One simple intervention that has been shown to be effective in reducing benzodiazepine use in long-term users is the sending of a GP letter to targeted patients.
6. The letter discussed the problems associated with long-term benzodiazepine use and invited patients to try and reduce their use and eventually stopAdequate social support, being able to attend regular reviews and no previous history of complicated drug withdrawal is desirable for successful benzodiazepine withdrawal.

Management of benzodiazepine withdrawal
Switching to diazepam

1. Diazepam is preferred because it possesses a long half-life, thus avoiding sharp fluctuations in plasma level.
2. It is also available in variable strengths and formulations. This facilitates stepwise dose substitution from other benzodiazepines and allows for small incremental reductions in dosage.
3. The National Health Service Clinical Knowledge Summaries recommend switching to diazepam for people using short acting benzodiazepines such as alprazolam and lorazepam, for preparations that do not allow for small reductions in dose (that is alprazolam, flurazepam, loprazolam and lormetazepam) and for some complex patients who may experience difficulty withdrawing directly from temazepam and nitrazepam due to a high degree of dependency

Management of benzodiazepine withdrawal
Gradual Dosage Reduction

1. It is generally recommended that the dosage should be tapered gradually in long-term benzodiazepine users such as a 5-10% reduction every 1-2 weeks.
2. Abrupt withdrawal, especially from high doses, can precipitate convulsions, acute psychotic or confusional states and panic reactions.
3. Benzodiazepines' enhancement of GABA's inhibitory activity reduces the brain's output of excitatory neurotransmitter such as norepinephrine, serotonin, dopamine and acetylcholine.
4. The abrupt withdrawal of benzodiazepines may be accompanied by uncontrolled release of dopamine, serotonin and other neurotransmitters which are linked to hallucinatory experiences similar to those in psychotic disorders.

The rate of withdrawal

1. The rate of withdrawal be tailored to the patient's individual needs and should take into account such factors as lifestyle, personality, environmental stressors, reasons for taking benzodiazepines and the amount of support available.
2. Various authors suggest optimal times of between 6-8 weeks to a few months for the duration of withdrawal, but some patients may take a year or more.
3. A personalised approach, empowering the patient by letting them guide their own reduction rate is likely to result in better outcomes.
4. Patients may develop numerous symptoms of anxiety despite careful dose reductions.

Anxiety - therapeutic principles

- drug therapy is adjunctive
- choice of drugs:

  among sedatives-hypnotics, **benzodiazepines are preferred**

  dosage:wide variations

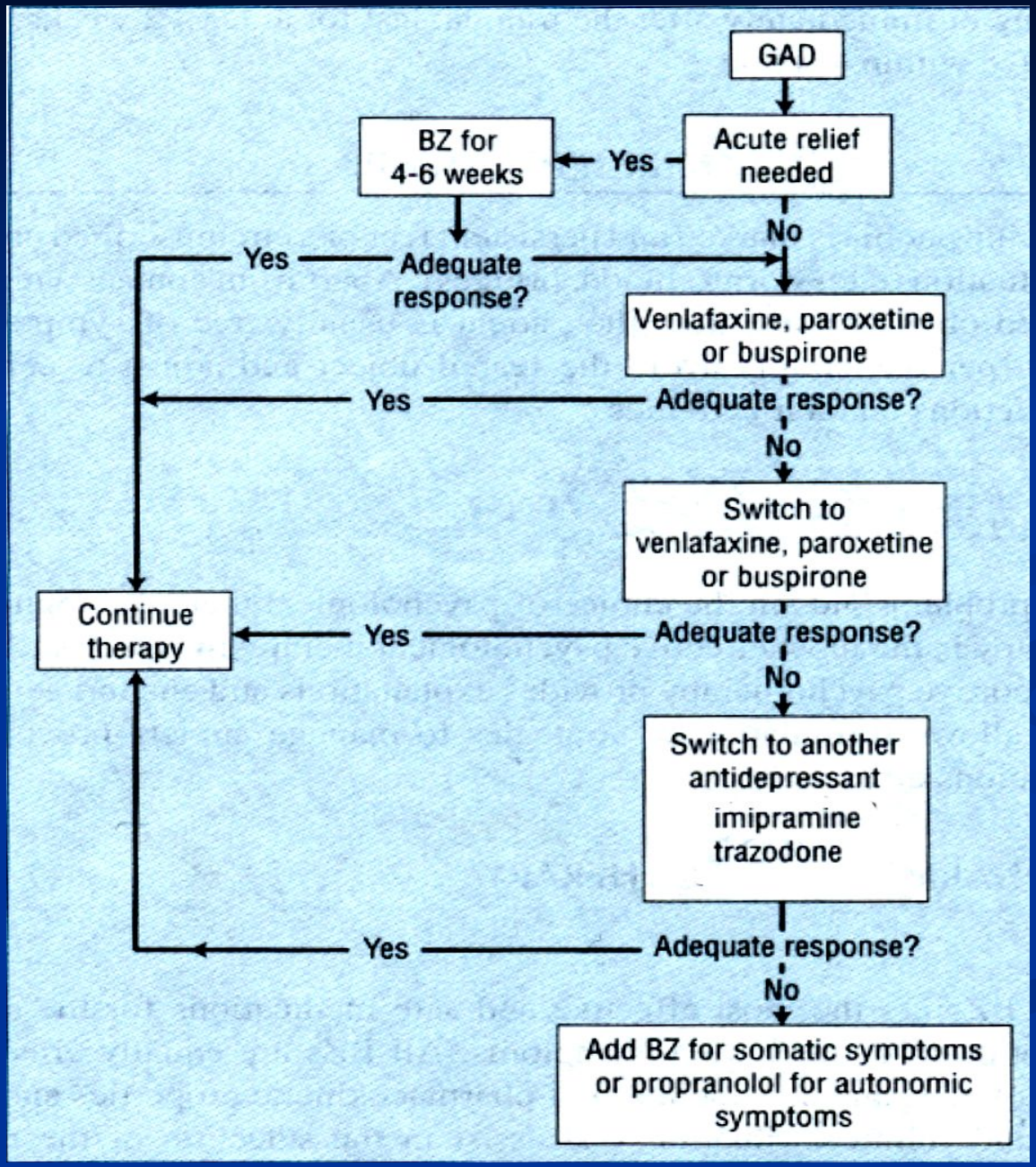
  adjust to symptoms

  limit duration

  antidepressants are the treatment of choice for GAD

  buspirone, β-adrenoceptor blockers

  in special circumstances


GAD
Acute relief needed
Yes
BZ for 4-6 weeks
No
Adequate response?
Yes
Venlafaxine, paroxetine or buspirone
Adequate response?
Yes
No
Switch to venlafaxine, paroxetine or buspirone
Adequate response?
Yes
No
Continue therapy
Switch to another antidepressant imipramine trazodone
Adequate response?
Yes
No
Add BZ for somatic symptoms or propranolol for autonomic symptoms

Drugs for anxiety

<u>Sedatives, hypnotics, anxiolytics, antianxiety drugs</u>

- Benzodiazepines:

  diazepam, oxazepam, lorazepam

- Barbiturates:

  phenobarbital, amobarbital

- Miscelaneous other anxiolytics, sedatives, hypnotics

  glutethimide, methaqualone

  buspirone

Drugs for anxiety

Antidepressants

venlafaxine, paroxetine

Miscellaneous

- β-adrenoceptor blockers:
  propranolol

- Sedative antihistaminics:
  diphenhydramine
- Sedative antipsychotics:
  phenothiazines

שם הרופא
תחום
מספר רשיון 16842
כתובת רח' צה"ל 52 חיפה
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פקס 04-8530178
מרפאה:בריאות הנפש - חיפה מחוז:חיפה

כללית 100 שנה
הכי טובה למשפחה

221713

סיכום ביקור

תאריך 11/06/2013

פרטי המטופל

שם משפחה ושם פרטי	מס זהות	גיל	מין	ת.לידה	שם האב
		56.00	נ	01/06/1957	יחזקאל

ישוב	רחוב	מס בית	טלפון	טלפון נוסף
חיפה	יהואש המלך	29 / 002	4 -8375906	52 - 2822504

לום רב,

תאריך הביקור: 11/06/2013

סוג ביקור: 0 ביקור רגיל

מהות הביקור: רגיל

תלונות/סיבת הפניה

היא כועסת כי " נבדקה בביטוח לאומי והושפלה " .
היא מתלוננת שהפיסטולה מקשה על חייה עד כדי כך ש"בלילות היא מתפללת כדי שלא תקום למחרת" . היא שוללת כוונות התאבדות כי לא רוצה לעשות בושות למשפחתה .
מתקשה לתפקד וגם צריכה להיות קרובה לשירותים . בתוך תיקה מלא פדים , שקיות ניילון , TISSUE , תחתונים.....
בבדיקה : ריכוז מעט ירות . זיכרון והתמצאות שמורים . לא נתגלו סימנים פסיכוטים חריפים . מצב רוח דיספורי . מתוחה ...
נערכה שיחת תמיכה . תרופות ללא שינוי.

אבחנה:

אבחנה	איפיון	קוד
PANIC DISORDER EPISODIC PAROXYSMAL ANXIETY		F410
PRESCRIPTION GIVEN WITHOUT NEED FOR INT.		V6801

רופות:

תרופה	כמות	מתן	פ	א. הגשה	D	T	יחידות	הופק	ר/ח	ק	נ	M
TRANXAL 15 MG	1	יחיד	1	יחידות	30	30	U	P		ק	נ	3
FLUOXETINE HCL 20MG	1	CAP	2	כמוסות	30	60	U	P		ק	נ	3
DIAZEPAM 5 MG TAB 5mg	1	TAB	3	טבליות	30	90	U	P		ק	ח	3
VABEN TAB 10MG	1	TAB	2	טבליות	30	60	U	P		ק	ח	3
BROTIZOLAM 0.25MG	1	TAB	1	טבליות	30	30	U	P		ק	ח	3

נ שהופקו דרך אלגוריתם: הפקת מרשמים לתרופות קבועות למשך:3 חודשים

פעולות:

פעולות	קוד	כמות
4 טיפול פרטני - פסיכותרפיה	4	1

BDZ practicalities

	The Drug	D	$T_{1/2}$
Hypnotics	Temazepam	10	14
	Nitrazepam	5	30
	Flunitrazepam*	1	35
	Zolpidem	10	3
	Zopiclone	7.5	4
Anxiolytics	Alprazolam	1	14
	Oxazepam*	30	8
	Lorazepam*	4	14
	Clonazepam	2	35
	Diazepam†	5	32+