

# The Development of New Benzodiazepine (BDZ) and Other Sedative-Anxiolytic-Hypnotic (SAH) Guidelines Suitable for Use by General Adult Psychiatrists

Fergus Law<sup>1</sup>, Sue Wilson<sup>2</sup>, Judy Myles<sup>3</sup> and David Nutt<sup>2</sup>

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Anxiety Module Workshop ([www.bap.org.uk](http://www.bap.org.uk))

<sup>1</sup>Bristol Specialist Drug Service, Cedar House, Blackberry Hill Hospital, Manor Road, Fishponds, Bristol, BS8 1TD, UK; <sup>2</sup>Psychopharmacology Unit, Dorothy Hodgkin Building, Whitson St, Bristol, BS1 3NY, UK; and <sup>3</sup>St George's Medical School, London

[Fergus.Law@awp.nhs.uk](mailto:Fergus.Law@awp.nhs.uk)

# BDZ Guidelines By August Bodies

- Committee on Review of Medicines (1980)
- Quality Assurance Project (1985)
- Committee on Safety of Medicines (1988)
- American Psychiatric Association (1990)
- Consensus conference on GAD (1992)
- Royal Society of Medicine (1992)
- Mental Health Foundation (1993)
- National Medical Advisory Committee (1994)
- World Health Organisation (1996)
- Royal College of Psychiatrists (1997)
- Academy of Sleep Medicine (1999)
- Many others: BNF, Maudsley, DOH, DVLA, Nasdahl et al (1985), Nicholson (1986), Tyrer (1989), Salzman & Watsky (1993), Ashton (1994) etc etc.

# Why is There a Need for New BDZ/Hypnotic Guidelines?

- Conformation of BDZ prescribing to guidelines is being used to assess performance at a national level (NSF for Mental Health 1999)
- Audits reveal an enormous divergence between BDZ guidelines and psychiatric practice
- BDZ guidelines for psychiatrists (e.g. WHO 1996, RCPsych 1997) specify a number of principles similar to other guidelines & then provide so many exceptions to them, they seriously undermine themselves
- Guidelines should be evidence based: Current guidelines have more to do with policy than evidence
- Calls for improvement (e.g. Williams & McBride 1998)

# Typical BDZ/Hypnotic Guidelines

- Use lowest BDZ/hypnotic dose for briefest time
  - 2-4 weeks for hypnotics
  - Up to 4 weeks for anxiolytics
- Use only one BDZ (give long-acting one at night if need both a hypnotic and an anxiolytic effect)
- Dose used should be in therapeutic range (i.e. within BNF limits)
- Reduce gradually after both short term (> 2 weeks) and long term use
- Only use in acute self-limiting situations/conditions
- Only use for severe symptoms (never mild symptoms)
- Do not use in those with a history of addiction

# Results of Local Audit of Guidelines in an Inpatient Psychiatric Unit

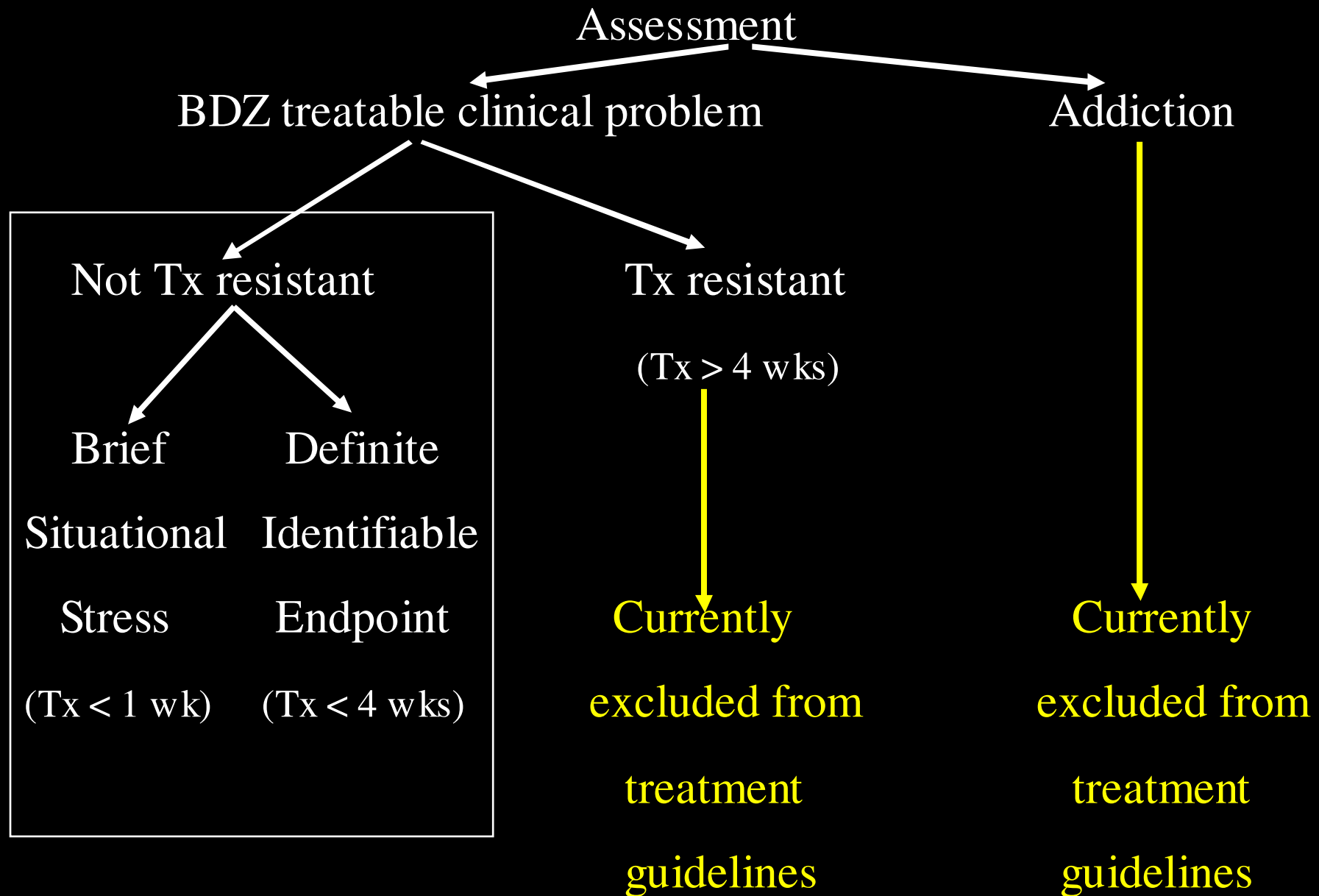
(showing percent NOT fulfilling audit criteria)

- Use lowest BDZ/hypnotic dose for briefest time
  - 2-4 weeks for hypnotics
  - Up to 4 weeks for anxiolytics } **64%**
- Use only one BDZ (give long-acting one at night if need both a hypnotic and an anxiolytic effect) **43%**
- Dose used should be in therapeutic range (i.e. BNF limits) **31%**
- Reduce gradually after both short term (> 2 weeks) and long term use **100%**
- Only use in acute self-limiting situations/conditions **90%**
- Only use for severe symptoms (not mild symptoms) **??%**
- Do not use in those with a history of addiction **89%**

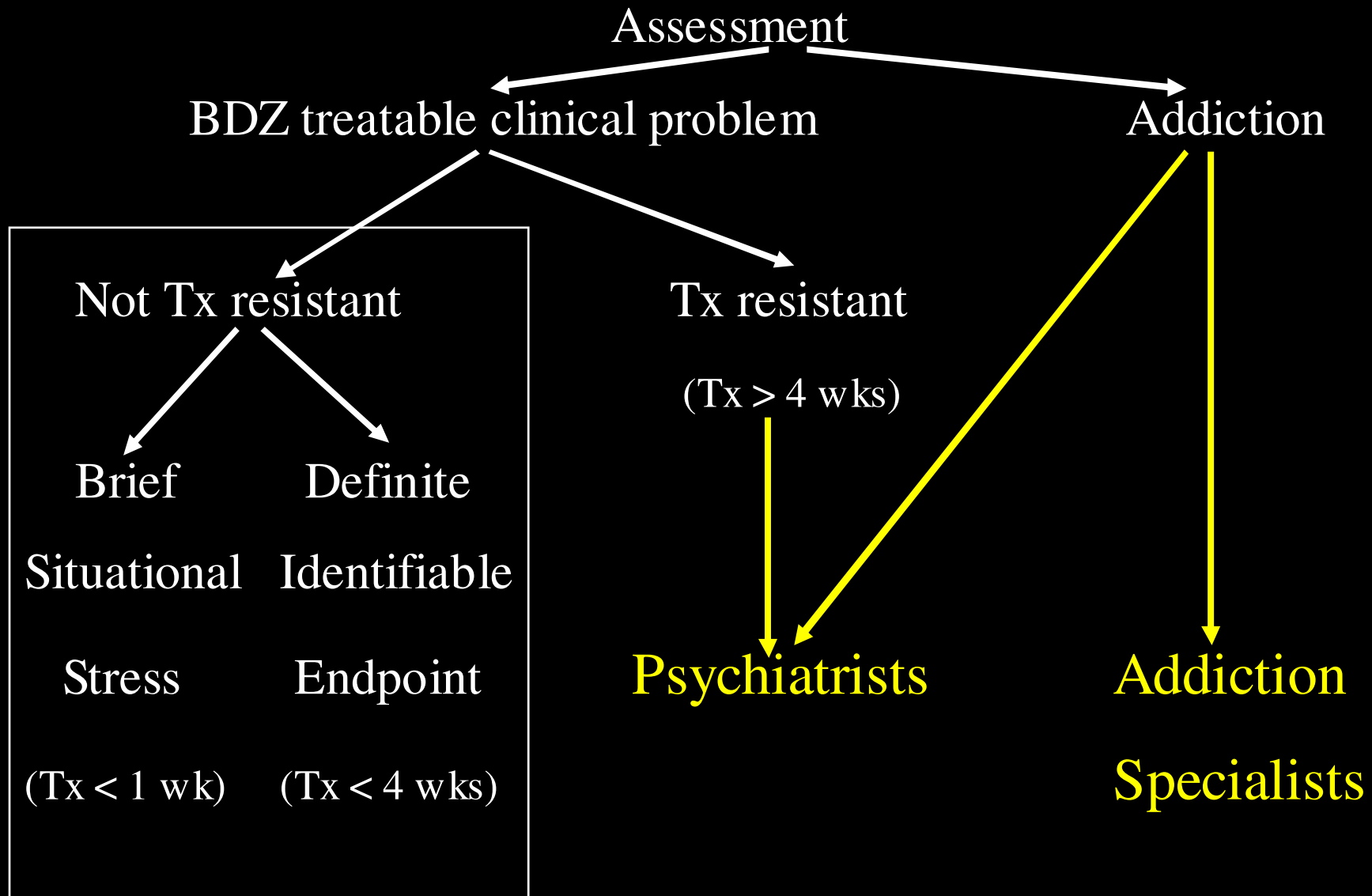
# Problems With Current Guidelines

- Exclude the very conditions where BDZ most useful (e.g. chronic anxiety)
- Need to reduce the dose almost as soon as the therapeutic dose is reached or even before!
- No guidance on treatment of:
  - Moderate symptoms
  - Treatment resistance (to non-BDZ drugs)
  - Treatment in the presence of comorbidity
- The evidence base for the time limits doesn't stand up to scrutiny (early misuse of EBM !!!)

# Current BDZ Guidelines: Only for GP's?



# BDZ Guidelines: Specialists Ignored



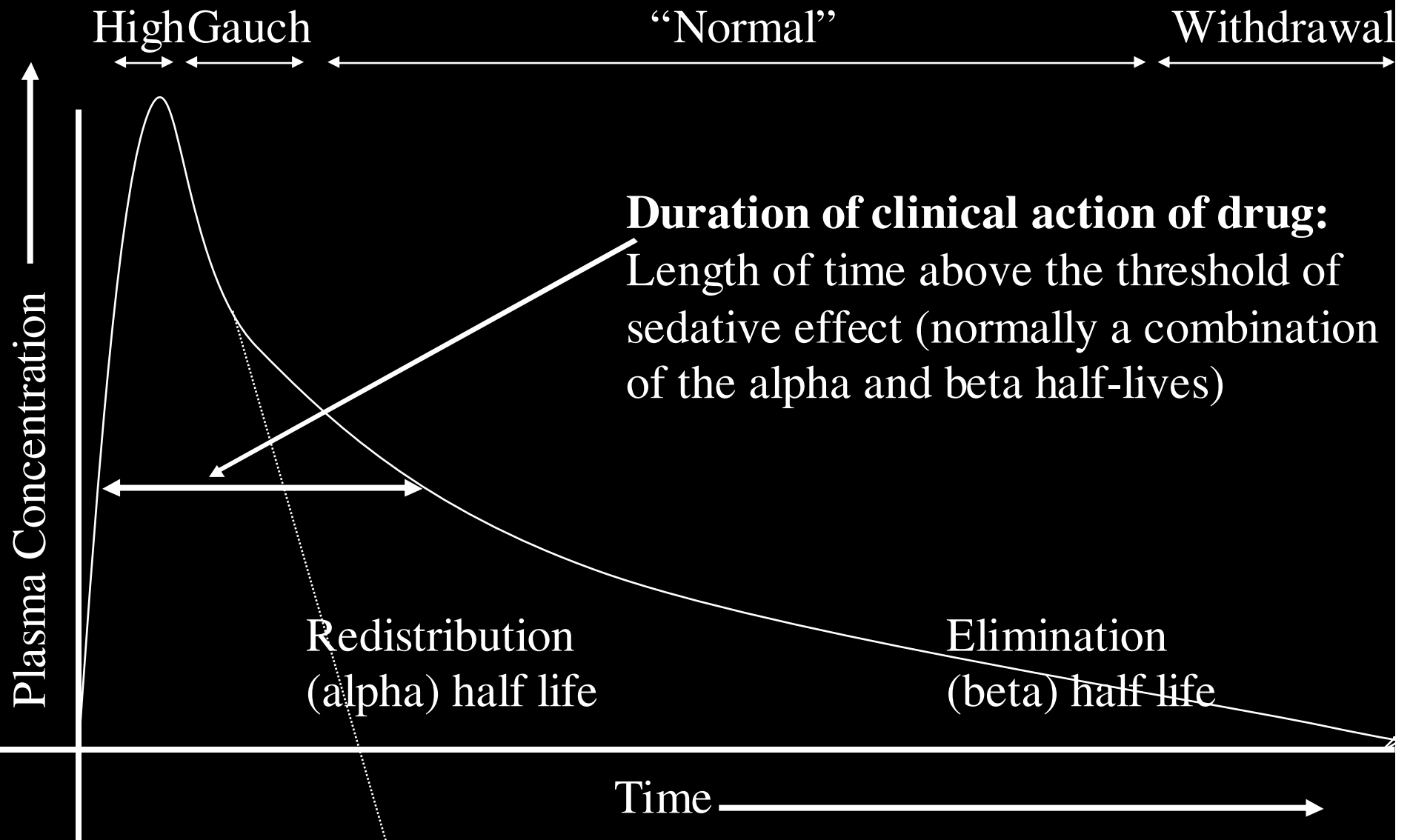
# First New Additional Principle Building on Current Guidelines

- Treat the patient as a whole person and according to his/her needs (while retaining the principle of only using BDZ for severe distress)
- Extend criteria for use from 1, to all 3 below:
  1. Severe primary or secondary insomnia or anxiety
  2. Moderate insomnia/anxiety secondary to another cause associated with moderate or severe distress
  3. Mild insomnia/anxiety secondary to another cause associated with severe distress

# Rationale for the Insomnia Time Limit

- Evidence base (claimed):
  - Sleep EEG measures returned to normal within 2-4 weeks of BDZ treatment (Kales et al 1977, Kales & Kales 1983 review)
- Critique of this statement:
  - True for 6 older non-BDZ (choral hydrate, secobarbital etc)
  - True for Triazolam (short acting BDZ, 3 studies at 2-3 week FU) & Temazepam hard gelatin capsules (intermediate acting BDZ with slow onset, 3 studies at 4-5 weeks FU)
  - False for Flurazepam (long acting BDZ): Slight loss of efficacy over 2 (5 studies) & 4 week FU (4 studies)
    - Subjective sleep quality is not strongly related to the objective (sleep EEG) measures, partially because hypnotics have anxiolytic-relaxants effects, to which minimal tolerance develops (i.e. effect is long lasting)
    - The general idea is surely to treat the patient as a whole person rather than the sleep EEG!!

# Two Compartment Pharmacokinetics of BDZ (after Dettli 1986)

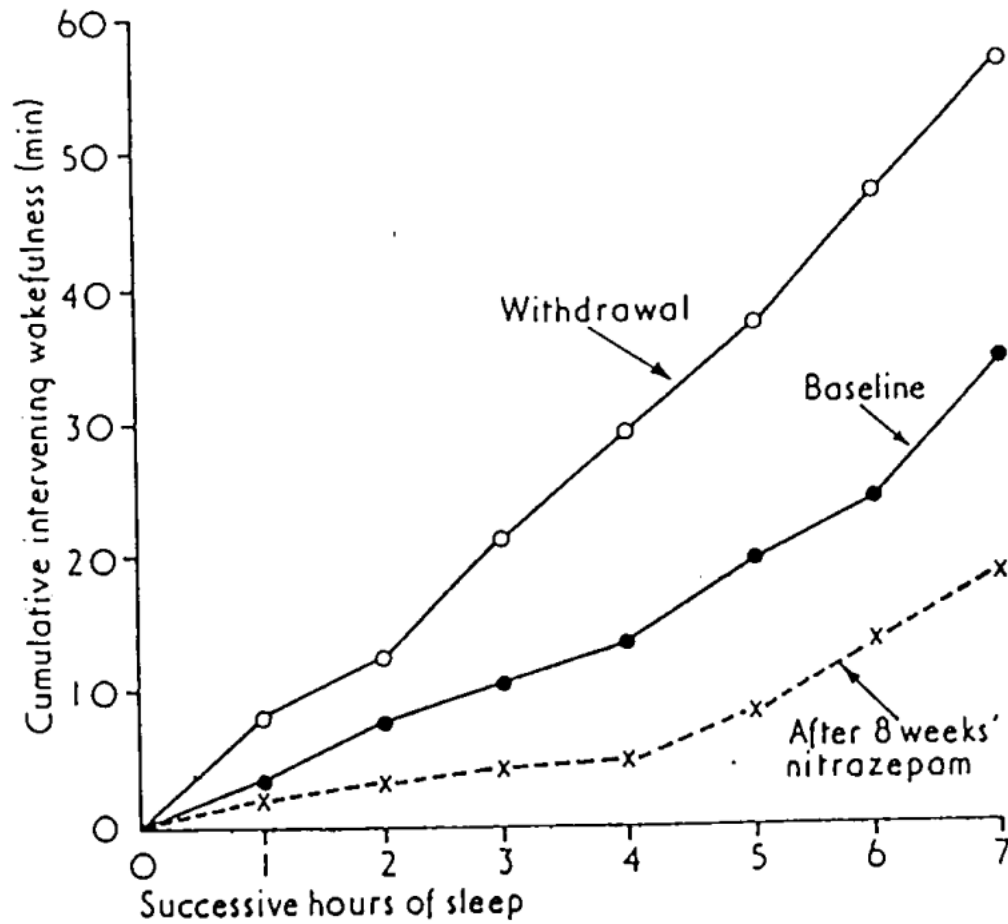


# Other Evidence for the Irrationality of the Insomnia Time Limit (cont.)

(EEG = sleep EEG study; Subj. = sleep study with subjective measures)

- Efficacy maintained long term (until study ends) for BDZ used nightly in many studies:
  - **Flurazepam 30mg:** 4 weeks EEG (4 studies, Kales & Kales 1983 review)
  - **Nitrazepam 5mg:** 6 weeks subj. (Tamminen and Hansen 1987), 8 weeks EEG (Adam et al 1976)
  - **Estazolam 2mg:** 6 weeks EEG (Lamphere et al 1986)
  - **Triazolam 0.5mg:** 3 weeks EEG (Pegram et al 1980), 5 weeks (Mitler et al 1984)
  - **Midazolam 15mg:** 5 weeks EEG (Lamphere et al 1990)
- Lack of long term studies probably because these are older drugs and there is therefore little incentive for the pharmaceutical industry to study the longer term effects

## Partial Tolerance to 5mg Nitrazepam after 8 Weeks Therapy (Adam et al 1976)



# Other Evidence for the Irrationality of the Insomnia Time Limit

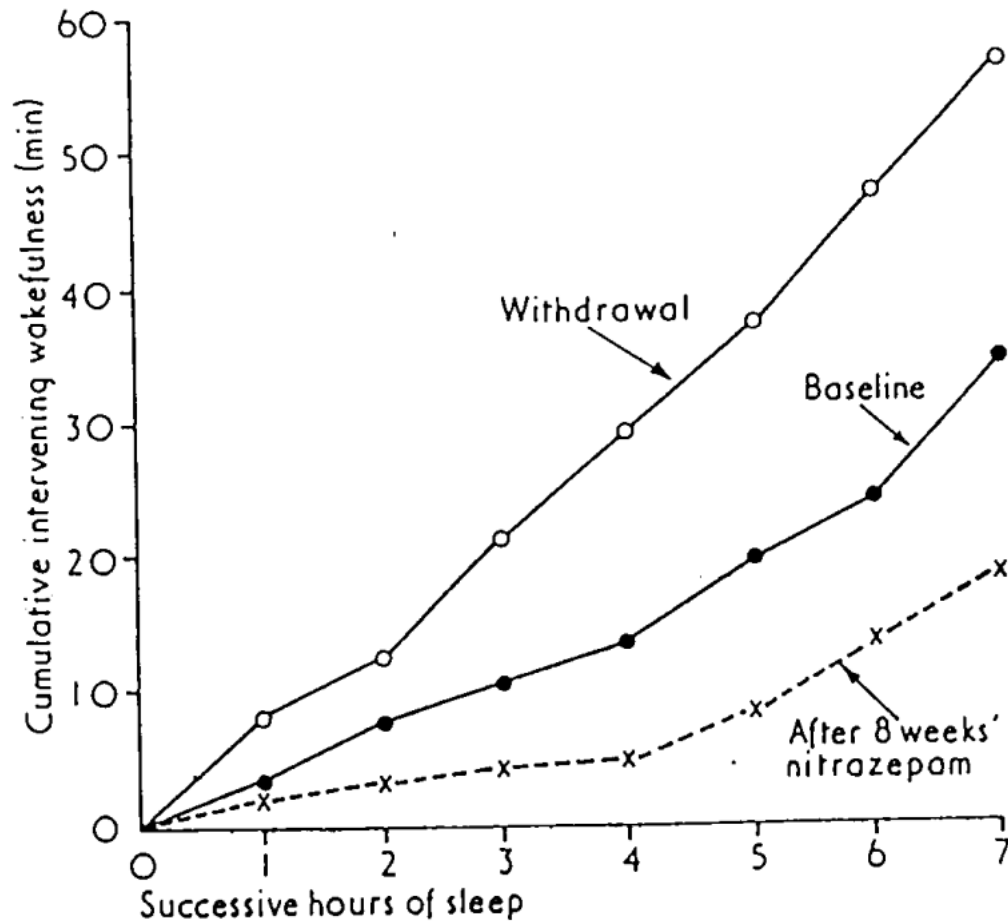
(EEG = sleep EEG study; Subj. = sleep study with subjective measures)

- Efficacy maintained long term (until study ends) for regular nightly non-BDZ:
  - **Zopiclone 7.5mg:** 6 weeks subj. (Tamminen and Hansen 1987), 8 weeks EEG (Pecknold et al 1990), 17 weeks EEG (Flemming et al 1990)
  - **Zolpidem 10-20mg:** 4 weeks DB RCT EEG (Monti et al 1996), 5 weeks EEG (Scharf et al 1994), 12 weeks DB RCT subj. (Scharf et al 1994), 6 months EEG (Kummer et al 1993), 6 months subj. (Schlich et al 1991), 1 year subj. (Maarek et al 1992) etc
  - **Zaleplon 5-10mg:** all 1 year subj. (Hedner et al 1999, Scharf 1999, 1999)

# Rationale for the Anxiolytic Time Limit

- Evidence Base:
  - Withdrawal reactions gradually become more common and significant as time passes (e.g. after 4 weeks)
- Reinterpreting the evidence:
  - Most withdrawal reactions are not problematic:
    - Rebound phenomena
    - Pseudowithdrawal (i.e. expectations)
    - Physiological withdrawal
    - Return of original symptoms - Tx by continuing BDZ
    - Actual (ICD-10) dependence - only problematic one
- Fear of withdrawal reactions seems to be largely a fear that doctors have, rather than a problem that the Pt experiences!

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# BDZ Typically Remain Effective in Panic Anxiety Long Term (i.e. Over Whole Period of Study)

- Tx studies: Efficacy for panic maintained without need for dose escalation to control symptoms (Davidson 1990 review):
  - 8 mths (alprazolam, Schweizer et al 1993), 2.5-10 mths (Ladewig and Schwartz 1979), 1 yr (clonazepam, Pollack et al 1986), 1 yr (alprazolam, Sheehan 1987, Rickels et al 1993)
- FU studies: Doses typically reduce but less so if Tx resistant:
  - 7% higher dose at some time due to panic without clear precipitant. At F/U on av. 2.5 yrs: 5% more, 60% less, 5% same dose, 30% off. Improvement sustained if off or on less (alprazolam, Nagy et al 1989)
  - Tx resistant sample 1 yr F/U: 26% more, 13% less, 26% same dose, 35% off (clonazepam, Pollack et al 1986). FU 2 yrs: 33% more, 50% less, 17% same dose (clonazepam, Worthington et al 1998)

# BDZ Typically Remain Effective in GAD ± Chronic Anxiety Long Term (i.e. Over Whole Period of Study)

- Tx studies: Efficacy for GAD ± chronic anxiety maintained without dose escalation and without deterioration in symptoms:
  - 6 months (clorazepate, Rickels et al 1988), 4 months (alprazolam, lorazepam, Cohn & Wilcox 1984), 3.5-5.5 months (diazepam, Rickels et al 1983), 3 months (diazepam, Murphy et al 1989), But efficacy not maintained in one 2.5 month study (Power et al 1988)
- FU studies:
  - Continued efficacy seen on switch to placebo: 50% experienced slow return of original anxiety symptoms. 50% maintained improvement for 18 weeks after only 6 weeks treatment (diazepam, Rickels et al 1983)

# BDZ Typically Effective Long Term in Non Well Defined Anxiety Disorders (i.e. Over Whole Period of Study)

- Efficacy maintained until end of treatment study:
  - 6 months for diazepam and lorazepam (Siassi et al 1975 in moderate to severe anxiety, Gross 1977 in anxiety neurosis)
  - 6 months for diazepam and ketazolam (Fabre et al 1981 in chronic psychoneurotic patients)
  - 3 months for diazepam and clobazam (Schjonsby et al 1979 in anxiety neurosis)

# The Basis of Dose Escalation & Abuse

- Dose escalation occurs for two main reasons:
  - To improve treatment of the symptoms (i.e. Pt was not getting enough medication anyway)
  - Pt seeking the buzz/rush/high or sedation/gauch. As tolerance occurs rapidly to these effects, the Pt continually increases the dose 'to chase' the effect
- Pt not seeking the buzz/sedation (e.g. using to treat symptoms) do not escalate or get tolerant
- Drugs with rapid onset of effects cause the buzz or sedation, and this includes most BDZ. Slow onset BDZ include oxazepam, which has a very low risk of abuse

# Second New Additional Principle Building on Current Guidelines

- Time limits in any new BDZ guidelines should be evidence based:
  - Take account of the evidence for continuing efficacy of both hypnotic and anxiolytic use
  - Remove the absoluteness of the 2-4 weeks limit for treatment to allow longer treatment for conditions clinically requiring longer term treatment, or conditions resistant to other non-BDZ treatments

# Why Has The Evidence Been Ignored in Current Guidelines?

- Drive to reduce inappropriate prescribing of BDZ, e.g. use in depression still unacceptably high in Europe (Lepine et al 1997)
- Historically BDZ raised our awareness (and fears) of withdrawal and dependency, at a time that we understood very little about the phenomena involved and how best to manage them
- Problems produced by BDZ are mainly iatrogenic
- Adoption of the issue by pressure groups & the media

# Unusual Use of Term 'Dependency' in BDZ Literature

- Extrapolation from proxy measures is virtually universal:
  - Chronic use: e.g. difficulty stopping in 25-38%. Only if efficacy lost in 2-4 wks, would chronic use possibly indicate dependence. Most chronic (non-addict) users are using BDZ because they are still effective for their problems, and most addicts using BDZ chronically are not dependent on them (but using for the effects)
  - Pt resistance: If clinician wants to withdraw BDZ and Pt refuses
  - Other types of discontinuation syndromes (rebound, pseudowithdrawal, recurrence, physiological withdrawal)
  - Others: rate of relapse, escalating dose, illicit or inappropriate use
- Assumption: factors increasing the risk of chronic use or physiological withdrawal will also increase dependence risk
- No good evidence for this (Romach et al 1995, WHO 1981). If analogy with opiates holds, very unlikely to be true)

# ICD-10 Criteria for BDZ Dependence

Need  $\geq 3$  of 6 criteria in last 12 months:

- 2 drug related criteria:
  - Compulsion/cravings to take BDZ
  - Difficulties in controlling BDZ use
- 2 consequences of use criteria:
  - Progressive neglect of alternative pleasures/interests due to BDZ use
  - Persistent BDZ use despite harmful consequences
- 2 physiological criteria:
  - Characteristic BDZ withdrawal state
  - Evidence of tolerance to BDZ

Note: No mention of frequency or amount or chronicity of BDZ use. Can be dependent without having withdrawal or tolerance

# Factors Increasing Risk of BDZ Withdrawal Reactions

- Related to physiological withdrawal:
  - Longer term (e.g. > 4 months)
  - Higher than therapeutic dose use
  - High potency short/intermediate half-life BDZ (e.g. alprazolam, lorazepam)
- Related to diagnoses:
  - Chronic psychiatric problems: Chronic dysthymia or dysphoria  $\pm$  BPD or dependent PD, panic disorder, chronic psychosis, neuroleptic side-effects
  - Chronic physical problems: Esp. elderly, esp if in pain or chronic sleep difficulties
- Related to personality factors / addiction proneness:
  - FH or current/past alcohol or other sedative-hypnotic dependence

# Biological Aspects of BDZ Use

- BDZ reduce DA release in the Nuc. Accumbens (Finlay et al 92) unlike any other major drug of abuse, but DA is still involved in the reinforcing properties of BDZ (Spyraki & Fibiger 88)
- BDZ are not reinforcing (in animals) unless there is a past history of sedative-hypnotic exposure
- BDZ withdrawal reactions take a long time to develop:
  - 4 weeks                      very low risk
  - 4 months                     5-10%
  - 2 years                        25-45%
  - 6-8 years                      75%

# Prevalence Rates of BDZ Use in UK

- Balter et al 1984 cross national study (USA and 10 Western European Countries):
    - 11.2% (15.3% females, 6.7% males, N=2018) used for 1 day or more in last 12 months. Range in the different countries: 7.4% (Netherlands) to 17.6% (Belgium)
    - Daily use of BDZ (sedative/anxiolytic drugs):
      - 4.2% used for < 1 month
      - 2.7% for 1-3 months
      - 0.9% for 4-11 months
      - 3.1% for  $\geq 12$  months
      - 88.4% no daily use
- 6.7% for > 4 weeks

# Rates of BDZ Abuse & Dependence

- National surveys: Ladewig 1983 Swiss study of Physicians (73% response rate):
  - 0.6 cases of reported BDZ abuse per  $10^5$  population (incidence 0.0006 per year, exposure risk per script 0.00002), but low rates of BDZ use in Switzerland
- Psychiatric patients using DSM III criteria:
  - 1.5% BDZ dependence, 70% on BDZ (N=10,861 retrospective case records 1978-1981, Fleischhacker et al 1986, Innsbruck, Austria)
  - 0.5% (0.1-1.2%) BDZ dependence (N=32,762 retrospective case register study 1974-1983, Laux & König 1987, Weinberg, West Germany)

# Rates of BDZ Dependence by Length of Use in Pts Using BDZ Daily in Primary Care (De las Cuevas et al 2003, Canary Islands, N=1048)

47% Pop BDZ dependent as defined by SDS score of  $\geq 7$ :

Length of BDZ use	% Dependent	% Pop used this long
1-5 months	15%	14%
6-10 months	36%	16%
11-15 months	41%	17%
16-24 months	52%	16%
2-4 years	62%	10%
> 4 years	71%	17%

Validity of SDS wrt CIDI: 99% correctly classified by SDS,  
97.9% sensitivity, 94.2% specificity (De las Cuevas et al 00)

# High Rates of BDZ Dependence by Dose Used in Pts Using BDZ Daily in Primary Care (De las Cuevas et al 2003, Canary Islands, N=1048)

47% Pop BDZ dependent as defined by SDS score of  $\geq 7$ :

Diazepam equiv	% Dependent	% Pop on this dose
< 5 mg	19%	6%
5-9 mg	32%	27%
10-14 mg	43%	27%
15-20 mg	61%	24%
21-30 mg	71%	8%
31-40 mg	75%	3%
> 40 mg	87%	5%

Note: No relationship between length of use & dose found.  
i.e. dependence identified in low dose short duration users

# BDZ Dependency and Concurrent Dependency

- Most dependent on BDZ also dependent on other drugs:
  - 81% concurrent dependence. Of other 19% over half (57%) had been alcoholics (N=10,861, Fleishhacker et al 1986, DSM-III criteria)
  - 66% concurrent dependence. Of other 34% over half (60%) had history of another dependency. (N=9408, Wolf et al 1989, Munich, WHO criteria). Two patterns:
    - If only dependent on BDZ: esp women iatrogenically exposed
    - If dependent on BNZ and other drugs: esp younger men with alcohol problem

# Third New Additional Principle Building on Current Guidelines

- Establish evidence based risk categories (i.e. based on data on risk of dependence & risk of withdrawal):
  - Less than 4 weeks (old guidelines)
  - 4 weeks to 4 months
  - More than 4 months
- 4 months is the time when withdrawal reactions may become 'severe enough to cause additional suffering to the patient' (APA 1990 review, p.28)
- If treatment stopped within 4 months for long half life BDZ, then withdrawal reactions are rare. Evidence less clear for shorter acting BDZ (Peturrson and Lader 1984)

# Fourth New Additional Principle Building on Current Guidelines

- Periods of use of > 4 weeks be reserved for patients resistant to treatment by non-BDZ:
  - Use BDZ for > 4 weeks only when all other drug & psychological Tx have been tried and failed
  - Use BDZ for > 4 months only when continued use is clinically justified (i.e. accept higher level of risk of withdrawal reactions & dependence)
- This principle extends use to Pts often seen by psychiatrists and treated by them for > 4 weeks

# Risk of Long Term BDZ Prescribing

- Increased risk of withdrawal reactions and BDZ dependence syndrome
- The BDZ becomes the problem: Underlying issues avoided & BDZ seen as the solution. Anxiety may reduce if BDZ stopped (Rickels et al 90, 91, Schweizer et al 90)
- Subtle but definite cognitive deficits:
  - Anterograde amnesia (impaired delayed recall) occurs for a few hours after drug taken – to avoid give at night & not in divided doses (Lucki & Rickels 1986, 1988)
  - Emotional suppression leading to a cumulative effect on emotional coping and a learning deficit
- Possibly loss of driving license (see DVLA guidance)

# Benzodiazepines and Car Driving

- Acceptable to DVLA for licensing purposes:
  - Prescribed use within BNF limits even if BDZ dependence syndrome or physical dependence, provided none of the 3 criteria below are met
- Unacceptable to DVLA for licensing purposes:
  - Non-prescribed use
  - Prescribed use above BNF limits
  - Prescribed use within BNF limits if impairment
- License refusal or revocation until a minimum of one year period free of such use

# Fifth New Additional Principle

- It is defensible to expose patients to the risk of developing dependency by long term or indefinite use of BDZ when:
  - Alternative Tx's have failed (i.e. Tx resistance)
  - Benefits of Tx outweigh risks (i.e. alternatives worse or benefits better)
  - Decision taken in conjunction with patient
  - Tx is strictly individualised
  - Need for Tx reviewed periodically (to ensure efficacy is maintained)

# Six 'Withdrawal Risk' Categories

- **Contraindicated:** Too dangerous to use
- $\leq 1$  week: Based on idea that some conditions need only one dose or just a few doses
- $> 1$  week but  $\leq 4$  weeks: very low risk of BDZ withdrawal reactions & dependence after 4 weeks
- $> 4$  weeks but  $\leq 4$  months: e.g. less than 5-15% risk of withdrawal reactions & dependence (rare with long acting BDZ)
- $> 4$  months: A lengthy period of Tx required, but not needing indefinite Tx e.g. 25-50% after 2 years
- **Indefinite:** BDZ provide only effective Tx, and no hope of stopping without recurrence in foreseeable future e.g. 70-75% after 4-8 years

# The Analogy of Pain Treatment in Those with Opiate Addiction Problems

- We accept it is right to treat moderate or severe pain with opiates, in a patient who is treatment resistant to non-opiates
- We also accept that it is right to treat an opiate dependent person in such pain in exactly the same way (i.e. as clinically indicated by their disorder)
- Precautions: We would monitor them carefully and review them regularly to ensure the treatment is still clinically indicated (e.g. opiate dose is reduced as pain reduces, even in those demanding more opiates)

# Sixth New Additional Principle

- BDZ Addicts should be treated by BDZ like anyone else, i.e as clinically indicated (Applies primarily to Tx for disorders other than BDZ abuse or dependence):
  - Following a careful assessment of risks & benefits
  - If sufficient or clear evidence of treatment resistance to other non-BDZ treatments
- Precautions: Monitor them carefully and review them regularly to ensure the treatment is still clinically indicated (cf. analogy with pain Tx)

# Implications of The Six New Principles

- **Patients should not be excluded from treatment simply because:**

- They are in a high risk category
- They are treatment resistant
- They may develop a dependency

(although these factors must be taken into account in the assessment and clinically appropriate treatment given)

- Not recommending an “opening of the floodgates”, but more sophisticated assessments of the risks and benefits of benzodiazepine treatment in individual patients, with no automatic exclusions

# The Risk Formuli Model for Assessing Risks & Benefits in Individual Patients

Overall = Drug + Person + Treatment Strategy  
Risk Risk Risk Risk

Drug risk = Type of drug used + Dose & length of drug use + Other drugs used

(Type of drug: Z drugs < slow onset BDZ < rapid onset BDZ < older non-BDZ)

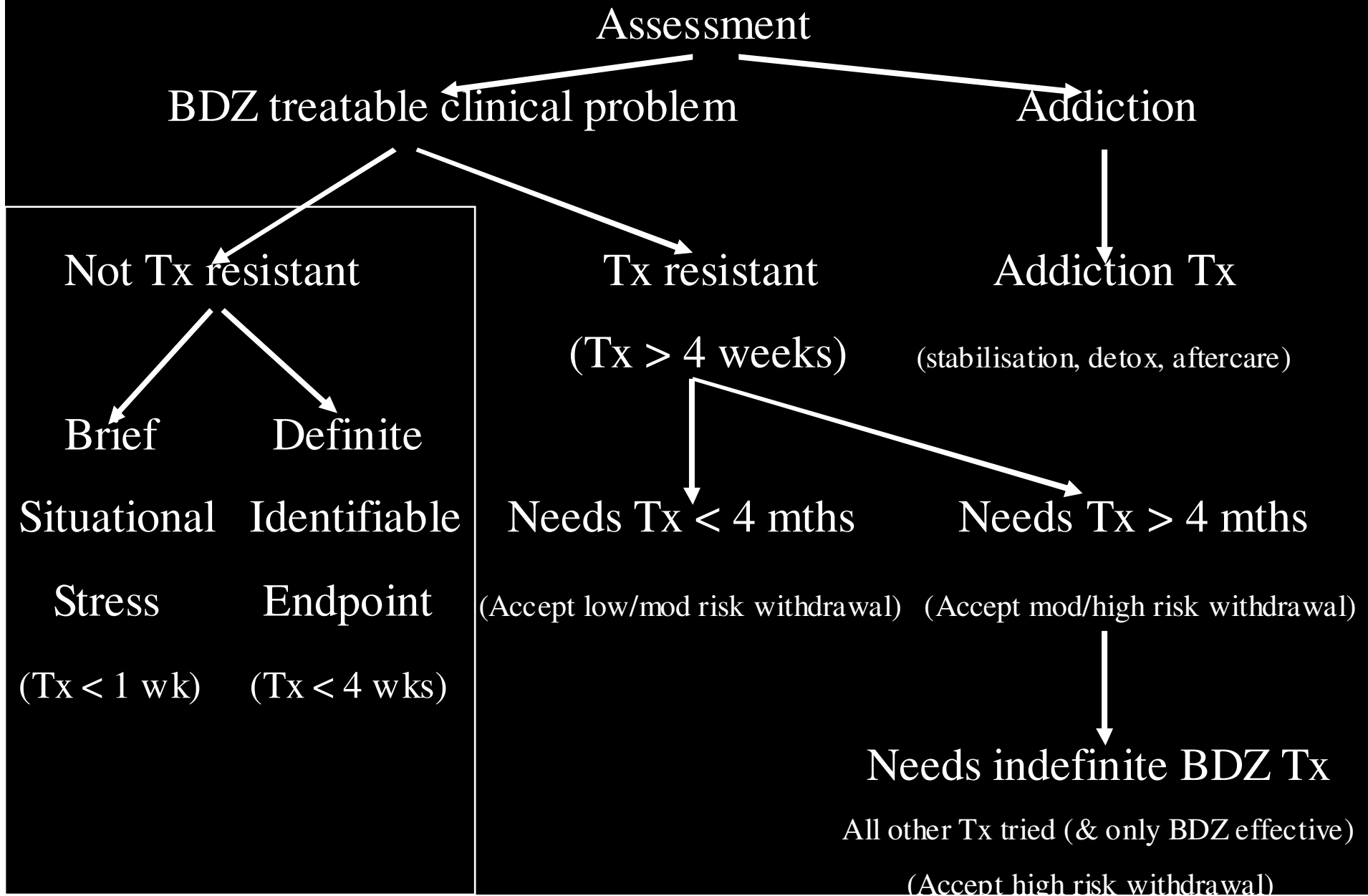
Person = H/O alcohol or sed/hypn abuse + Fun seeking vs self-medication + Axis 1 & 2 disorders

Tx strategy = Engagement in treatment + Goal focused therapy/use + Degree of monitoring

# Summary of the Six Principles Extending Current BDZ Guidelines (& Closing the Gap with Practice)

1. Allow treatment for mild/mod insomnia/anxiety where severe/mod comorbid distress is present
2. Time limits in any new BDZ guidelines should be evidence based (unlike the 2-4 week limit)
3. Introduce a 4 month risk boundary above which significant additional risk of problems is accepted
4. Reserve use for > 4 weeks for Tx resistant patients
5. Indefinite BDZ Tx is occasionally justified
6. Addicts with clinical problems justifying use of BDZ should be treated as clinically indicated

# Flowchart for BDZ Prescribing



# Summary of New BDZ Guidelines

- Use lowest dose for briefest time
- Use for > 4 weeks should be reserved for cases who are resistant to non-BDZ treatments
- Use only one BDZ (give more at night if need hypnotic + anxiolytic). Use the minimum number of BDZ if more than one is needed to fulfil a variety of roles
- Dose used should be in therapeutic range (i.e. BNF limits)
- Reduce gradually after long term use. There is only a need to reduce gradually after short term use (>2/52) if it has been shown that withdrawal will be problematic
- Only use for severe symptoms, or where the patients total distress from comorbid conditions warrants use for mild or moderate symptoms
- Indefinite BDZ treatment is occasionally justified
- Addicts should be treated as clinically indicated

# References for Further Reading

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