ZOLPIDEM IN BRAIN DAMAGE

Ralf Clauss MD, FRCP
Consultant Nuclear Medicine Physician
Royal Surrey County Hospital

Zolpidem and "Neurodormancy"

Unexpected effect of zolpidem in a patient with severely impaired consciousness

Exploration of Zolpidem effect in fully conscious patients with brain damage

Animal studies

Neurodormancy mechanism

Additional clinical observations

Patient L

- 28 years, male. RTA in 1996.
- Initial coma due to haemorrhage left lentiform nucleus, thalamus, brainstem, cerebellar peduncles.
- Discharged from hospital in 1996 with PVS.
- Maximum GCS score in 1999 was 9/15.
- Zolpidem: Spasticity decreased. Interacted spontaneously with comprehending answers to simple questions. Performed simple calculations. Fed himself. Wrote words. Max GCS score increased to a normal 15/15.
- 8 years on daily zolpidem therapy now.

Glasgow Coma Scale Pre-zolpidem

	Best Eye Response	Best Verbal Response	Best Motor Response
1	None	None	None
2	Open to pain	Incompre hensible sounds	Extension to pain
3	Verbal command	Inappro priate words	Flexion to pain
4	Spontaneo us	Confused	Withdraw from pain
5		Orientated	Localises pain
6			Obeys commands

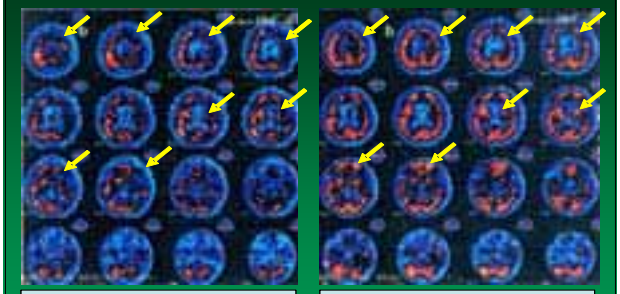
Total Score = 9/15

Glasgow Coma Scale Post-zolpidem

	Best Eye Response	Best Verbal Response	Best Motor Response
1	None	None	None
2	Open to pain	Incompreh ensible sounds	Extension to pain
3	Verbal command	Inappro priate words	Flexion to pain
4	Spontaneo us	Confused	Withdraw from pain
5		Orientated	Localises pain
6			Obeys commands

Total Score = 15/15

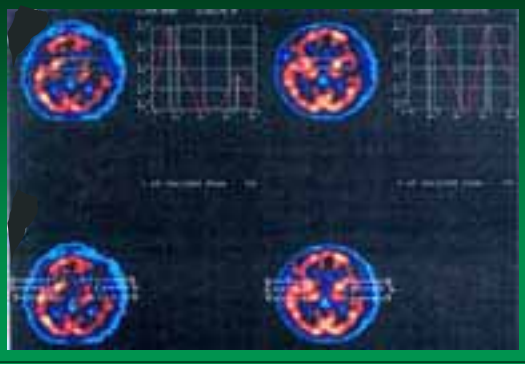
Patient L SPECT Scans 1999



Before Zolpidem
First row shows decreased perfusion in Left fronto parietal brain region (arrows).
Second row shows decreased perfusion in the left lentiform region (arrows)
Third row shows decreased perfusion in the left frontal region (arrows)

After Zolpidem
First row shows improved perfusion in Left fronto parietal brain region (arrows).
Second row shows improved perfusion in the left lentiform region (arrows)
Third row shows improved perfusion in the left frontal region (arrows)

Patient L Spect Scan Analysis



L's SPECT scan showed

re-activation

of inactive brain tissue

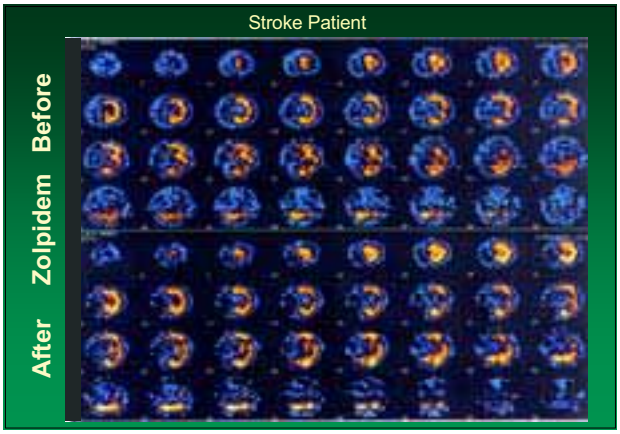
Zolpidem in disabled, conscious patients

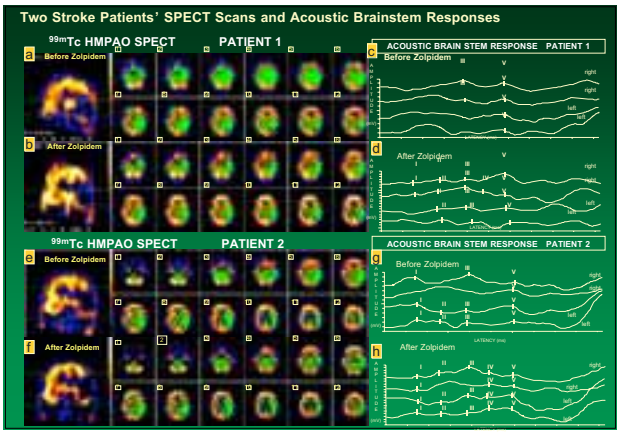
Birth Injury

Stroke

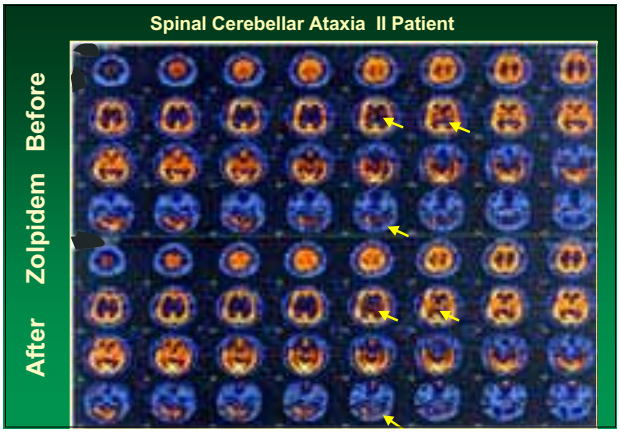
Traumatic Brain Injury

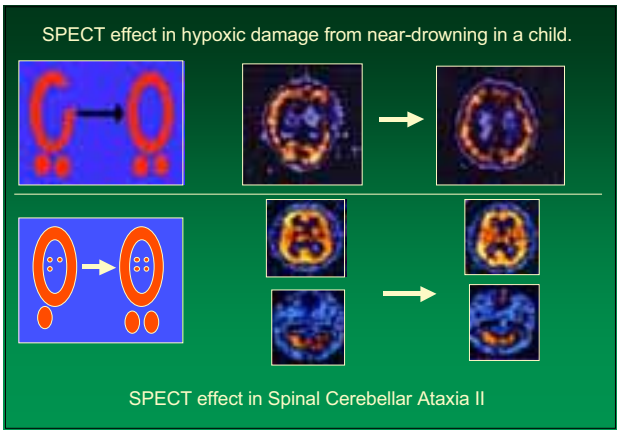
Stroke Patient

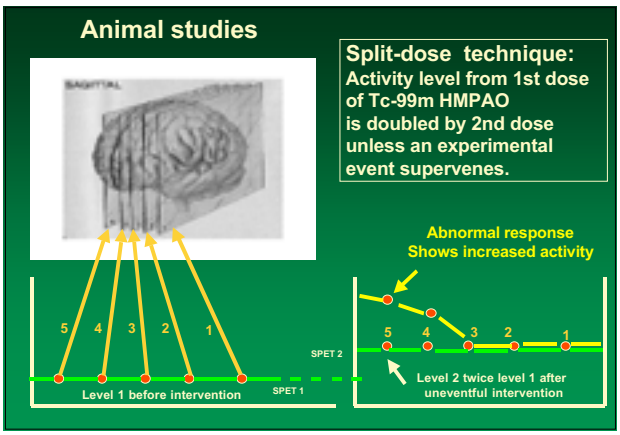


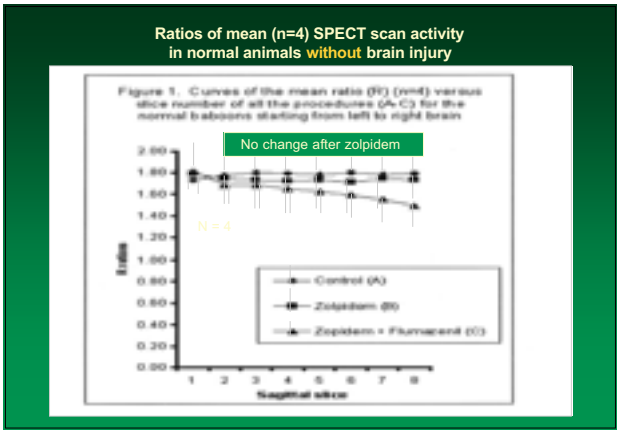

Two Stroke Patients' SPECT Scans and Acoustic Brainstem Responses
99mTc HMPAO SPECT PATIENT 1
Before Zolpidem
After Zolpidem
ACOUSTIC BRAIN STEM RESPONSE PATIENT 1
Before Zolpidem
After Zolpidem
99mTc HMPAO SPECT PATIENT 2
Before Zolpidem
After Zolpidem
ACOUSTIC BRAIN STEM RESPONSE PATIENT 2
Before Zolpidem
After Zolpidem


Bell's Palsy
(after surgical removal of acoustic neuroma)
Before zolpidem
After zolpidem
Site of scar over right ear

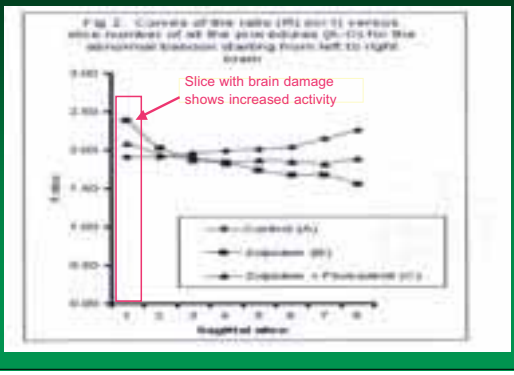

Spinal Cerebellar Ataxia II Patient
Before Zolpidem
After Zolpidem


SPECT effect in hypoxic damage from near-drowning in a child.
SPECT effect in Spinal Cerebellar Ataxia II

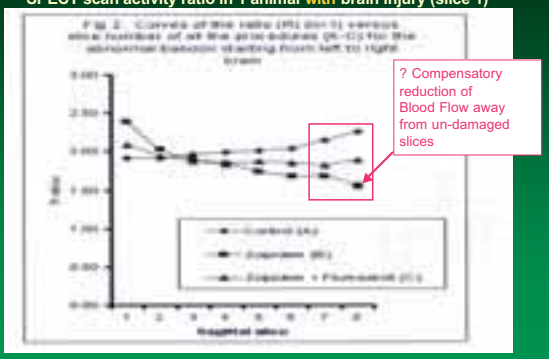

Animal studies
Split-dose technique:
Activity level from 1st dose of Tc-99m HMPAO is doubled by 2nd dose unless an experimental event supervenes.
Abnormal response
Shows increased activity
5 4 3 2 1
SPET 2
SPET 1
Level 1 before intervention
Level 2 twice level 1 after uneventful intervention


Ratios of mean (n=4) SPECT scan activity in normal animals without brain injury
No change after zolpidem
N = 4
Control (A)
Zolpidem (B)
Zolpidem + Flumazenil (C)

SPECT scan activity ratio in 1 animal with brain injury (slice 1)



SPECT scan activity ratio in 1 animal with brain injury (slice 1)



Zolpidem

Chemically distinct imidazopiridine

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GABA(A) receptor agonist with preferential omega 1 binding at alpha subunit

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Commonly prescribed for insomnia due to an exceptional safety profile including in overdose

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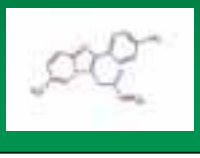
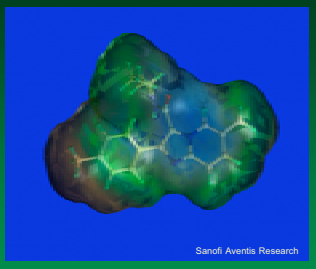
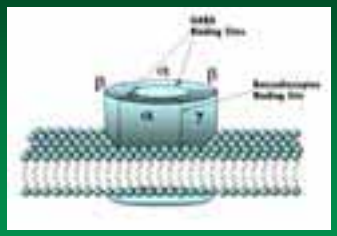
The zolpidem molecule

https://www.insilicostudios.com/xcart/skin1/images/freeStuff/rofec22-raysbkorig.jpg





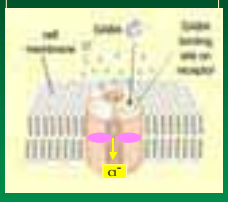
GABA receptor structure



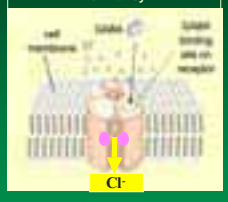
In normal receptors zolpidem increases the GABA effect via stimulation of the benzodiazepine 1 (omega 1) specific sub receptor

Dormancy pathway

Normal Receptor shape

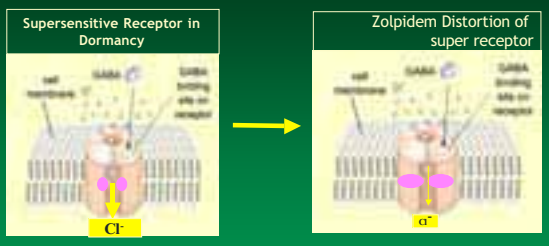


Supersensitive Receptor in Dormancy



Post hypoxia after GABA depletion, the GABA receptor becomes super efficient increasing GABA-ergic, inhibitory tone. This has a transmitter- and energy-saving effect.

Zolpidem action on the Dormant receptor

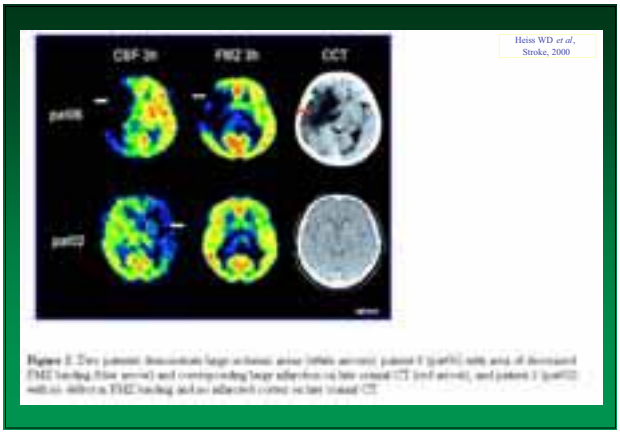


In supersensitive receptors, zolpidem does not increase GABAergic tone but instead interferes with GABA efficiency, so having an 'unlocking' effect

Rôle of GABA after injury

Two pathways after brain injury

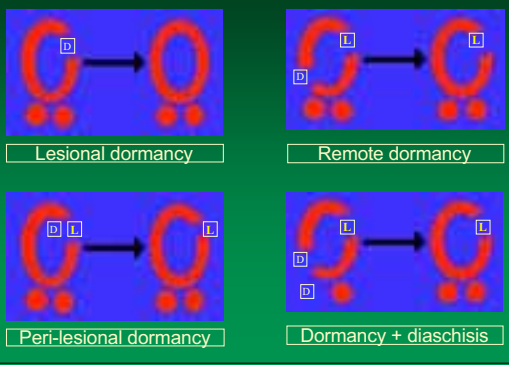
Neuro-Dormancy	Apoptosis
GABA-induced shutdown	Glutamate-induced excito-toxicity
Cellular survival	Cellular death



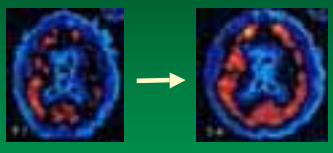
Reversal of neuro-dormancy

- Co-incident with clinical benefit
- Consistent with pharmacokinetics of zolpidem
- Location varies from patient to patient
- Activation of areas in SPECT and PET Scans compatible with clinical changes

Dormancy reversal patterns after zolpidem



Dormancy reversal in Patient L



Characteristics of the neuro-dormancy pathway

- Occurs after different types of brain damage
- Present after many years
- Intra and extra-lesional location
- Response to zolpidem suggests GABA -induced mechanism

Neurodormancy	Diaschisis
Remote or intra-lesional	Remote
Multiple locations	Usually single location
Unpredictable location	Predictable location
Late effect	Early or late
GABA depletion phenomenon ?	Neuro-physiological response

Identification of responders

Observe zolpidem effect for up to two weeks as one patient responded only after 8 days

SPECT or PET before and after zolpidem

SPECT or PET combined with CT or MRI

Zolpidem dosing

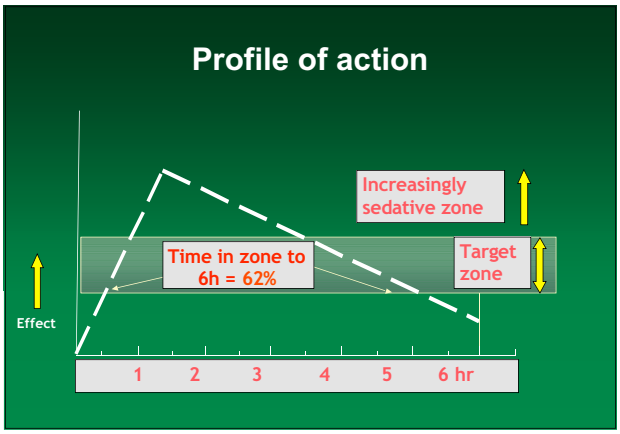
1. Usual UK sedative dose is 10mg at night
2. For brain damage a 10 mg morning dose often necessary
3. but use divided doses if too sedative
4. Response usually about 20-30 minutes, peaks by 1 hour and lasts 3-4 hours
5. Initial responses may be subtle. Eg: eye contact, constructing sentences, or a change in behaviour at home
6. More difficult to detect if masked by sedation

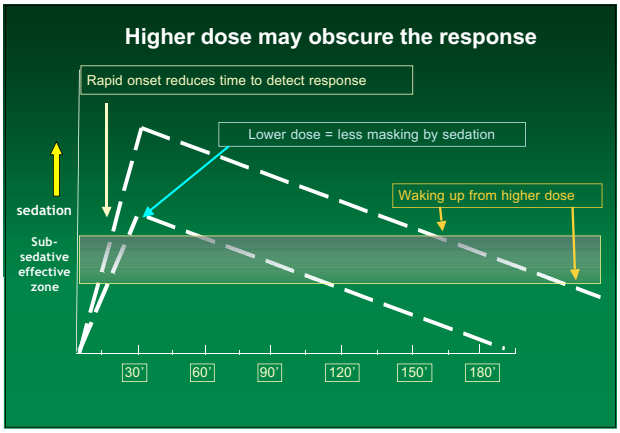
Observed immediate responses to zolpidem in impaired consciousness patients (minutes after oral application)

1. Facial blush	10-15	Early features
2. Eye blinking	10-15	
3. Yawn, cough, swallow	10-15	
4. Lifting tongue and licking lips	10-15	
5. Decreased strabismus, salivation	15-20	
6. Increased awareness/cognition/focussing	15-30	
7. Speech	20-30	
8. Smiling	20-30	
9. Relaxation of muscle spasms	20-30	

Reasons for under-estimating response rate

1. Some patients only respond after several days so are missed if only one day dosing is used
2. Generics have poorer response rates and some patients report no response.
3. Subtle changes can be easily missed or masked by sedation
4. Absorption profiles are important. Fast absorption may mask response due to rapid onset of sedation effect.





Louis after 8 years, September 2007

Now permanently conscious even off zolpidem

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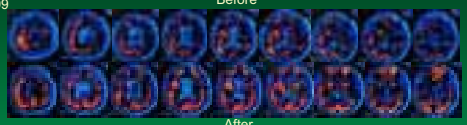
Obtains transient IQ improvement of 70-90 after zolpidem

Improvement in SPECT scans in 1999 and 2006

Louis 1999

Before



After

Louis 2006

Before

After

?

Is Louis

More **cognitive** now **because he is more conscious**

or is he

More **conscious** now **because he is more cognitive**

?

Summary of Zolpidem effect

Observed in wide variety of brain damage

In 2 - 80+ yrs age range

Some birth injuries responded after 20 to 30 years

Appears after dosing with zolpidem and disappears when zolpidem is eliminated (n= 1 validation)

SPECT/PET evidence of brain activation

Areas of further research

On zolpidem

Placebo-controlled validation of effect
Characteristics of responders
Methods of assessing response
Methods of assessing long term recovery
Formulations that minimise sedation

Neurophysiology

Neurodormancy hypothesis : GABA receptor studies
Link between activation in scans and clinical effect

Acknowledgement

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