The Association of Dementia and Mortality with Benzodiazepines

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Declaration of Interest in Relation to Benzodiazepines and Hypnotics

• No shares or ownership or part ownership or personal retainer from a company by myself or any close relatives

• Research grant application on benzodiazepines and hypnotics in preparation

• Sat on focus groups for market research for Britannia

• Received honoraria for speaking at industry supported symposia on benzodiazepines/hypnotics from Bristol-Myers-Squibb and Servier, and received hospitality at these meetings

• Written documents on Z-drugs for Alpharma, and the use of benzodiazepines/hypnotics for the NHS, Turning Point, British Association for Psychopharmacology, Clinical Knowledge Summaries, and SMMGP
Summary of Important Associations between Benzos & Dementia/Mortality

- Benzos used often/daily associated with:
  - Mortality HR 5.30 (95% CI 4.50-6.30) with a dose response relationship, & mortality in men > women (Kripke et al 2012)
  - Dementia HR 1.6 (95% CI 1.08-2.38) (de Gage et al 2012)
  - Cancer HR 1.35 (95% CI 1.18-1.55) (Kripke et al 2012)

- If a causal link between benzos use and these issues:
  - Major public health implications
  - Benzos should be used with caution or not at all
  - Or if do use them, Benzos not recommended if suspected or actual dementia, cancer or other mortality risk is present
Many Possible Associations Between BDZ/Hypnotic Use & Mortality

<table>
<thead>
<tr>
<th>Accidents &amp; Injuries</th>
<th>Mental Health</th>
<th>Drug &amp; Alcohol Use</th>
<th>Physical Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTAs/accidents</td>
<td>Suicide</td>
<td>Injecting use</td>
<td>Dementia</td>
</tr>
<tr>
<td>Falls &amp; broken hips</td>
<td>Depression</td>
<td>Smoking</td>
<td>Cancers</td>
</tr>
<tr>
<td>Hangover effects</td>
<td>Stress and anxiety</td>
<td>Alcohol and opiate use</td>
<td>Infections</td>
</tr>
<tr>
<td>Impaired motor skills</td>
<td>Short &amp; long sleep</td>
<td>Other risks of overdose</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>Poor judgement</td>
<td>Sleep apnea</td>
<td>Polydrug use</td>
<td>CVD</td>
</tr>
</tbody>
</table>
Important Types of Confounding Factors to Adjust for in the Studies

1. Demographics – age, sex, ethnicity, marital status, education attained, socioeconomic status
2. Physical health factors – BMI, diabetes, asthma, physical health medications, cardiovascular disease (CVD) e.g. High BP
3. Mental health factors – Sleep, anxiety, depression, stress or other emotional issues
4. Drug and alcohol use – Smoking, alcohol, drugs
5. Cognitive brain factors – MMSE, other tests (relevant to dementia and MCI studies only)
Theoretical Predictions About Effects of Confounding Factors - 1

• Hypnotic or other benzodiazepine use is:
  – Likely to be associated with mental health factors e.g. Sleep, anxiety, depression, stress or other emotional issues, and drug and alcohol use

• 3 possibilities if adjust for drug/alcohol and mental health factors in terms of HR related to mortality, cancer or dementia:
  – HR falls: Suggests these were mediating factors and benzos/hypnotics are on the causal pathway
  – HR rises: Suggests these were confounding factors, e.g. dementia is independent of hypnotic use, but also increases hypnotic use, i.e. hypnotic given for prodrome of dementia such as sleep problem, and is an indicator of presence of dementia rather than a cause of it
  – HR remains unaffected: There is no evidence for a relationship
Theoretical Predictions About Effects of Confounding Factors - 2

• Hypnotic or other benzodiazepine use is: 
  – Not likely to associated with the physical health risk factors or cognitive brain factors, unless a result of mental health factors or drug/alcohol use

• 3 possibilities if adjust for physical/cognitive brain factors in terms of HR related to mortality, cancer or dementia:
  – HR falls: Suggests these were mediating factors, and benzos/hypnotics are on the causal pathway
  – HR rises: Suggests these were confounding factors e.g. dementia is independent of hypnotic use, but also increases hypnotic use, i.e. hypnotic given for prodrome of dementia, and is an indicator of dementia rather than a cause of it
  – HR remains unaffected: There is no evidence for a relationship
Theoretical Predictions About Effects of Confounding Factors - 3

• Combining the effects of physical/cognitive brain factors and the mental health factors or drug/alcohol factors:
  – If hypnotic/benzo use not associated with physical/cognitive brain factors, then they will not affect the HR, so the HR will be easier to interpret (provided mental health & drug/alcohol factors taken into account)
  – If hypnotic/benzo use is associated with physical/cognitive brain factors (even if mental health & drug/alcohol factors taken into account), this will affect the HR, and the HR will be difficult to interpret – 3 possibilities:
    • Confounding has more effect than mediating factors on HR
    • Mediating has more effect than confounding factors on HR
    • Mediating and confounding effects on HR balance each other out
Looking at the HR in the Studies

• Studies typically do not distinguish between the two different types of factors:
  – Studies typically adjust for all types of confounding factors all together, rather than separating them out
  – It is not unreasonable to assume that any changes in HR are due to factors likely to be associated with change e.g. Mental health and drug/alcohol factors

• Studies not uncommonly fail to adjust for mental health factors:
  – If they do so, depression is the commonest factor adjusted for

• In this presentation, figures in grey type are not statistically significant, while figures in black are significant
A Hypothesis to Test and Evidence to Look out For to Support the Hypothesis

There is no causal relationship between Benzos use and cancer, dementia or mortality i.e. Benzo use is an ‘epiphenomena’

• Potential evidence to look out for:
  – Non-pharmacological effects e.g. Low doses of drug having much higher effects than expected
  – HR not being reduced (or even increasing) when taking account of confounding factors – not a causal effect
  – Plausible mechanisms that may account for the associations e.g. Hypnotic use associated with stress
  – If another mechanism does account for the strong association, all hypnotics should have a similar effect, independent of chemical class
Is usage of hypnotics associated with mortality?

Lena Mallon, Jan-Erik Broman, Jerker Hetta

Objective: To investigate the influence of hypnotic usage on all-cause and cause-specific mortality in a middle-aged population.

Methods: A cohort of 1750 men and 1773 women aged 30–65 years who responded to a postal questionnaire in 1983. The questionnaire included questions about hypnotic usage, sleep duration, sleep complaints, medical conditions, depression, demographic and life style variables. Mortality data for the period 1983–2003 were collected.

Results: Regular hypnotic usage was reported by 1.7% of men and 2.2% of women, and was associated with short sleep, sleeping difficulties, several health problems and depression. During the 20-year follow-up period 379 men (21.5%) and 278 women (15.5%) died. After adjustment for potential risk factors in multivariate analyses regular hypnotic usage was associated with significantly increased risk of all-cause mortality in men (Hazard ratios [HR], 4.54; 95% confidence interval [CI], 2.47–8.37) and in women 2.03 (95% CI, 1.07–3.86). With regard to cause-specific mortality, regular hypnotic usage in men was a risk factor for coronary artery disease death, cancer death, suicide and death from “all remaining causes.” In women it was a risk factor for suicide.

Conclusions: Our results show an increased risk of all-cause mortality and cause-specific mortality in regular users of hypnotics.
Postal Questionnaire Methodology
(Mallon et al. Sleep Medicine 2009, 10, 279-86)

- Questionnaires sent to 5102 subjects aged 30-65 years in 1983
- Subjects randomly selected from the general population of 2 towns in Sweden using the Central Population Registry (1/25th of each pop)
- 69.6% response rate, after one reminder
- 1750 men and 1773 women responded
- Mean age 46 ± 10 years
- 20 year follow up (1983-2003), with mortality data based on death certificates
- 18.5% died (21.6% men, 15.5% women)
Regular Hypnotic Use Strongest or 2\textsuperscript{nd} Strongest Predictor of All Cause Mortality
(Mallon et al. Sleep Medicine 2009, 10, 279-86)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR Men</th>
<th>HR Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular hypnotic use</td>
<td>3.51</td>
<td>2.29</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.75</td>
<td>5.16</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.98</td>
<td>1.92</td>
</tr>
<tr>
<td>Depression</td>
<td>1.92</td>
<td>1.41</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.89</td>
<td>1.52</td>
</tr>
<tr>
<td>Difficulty initiating sleep</td>
<td>1.84</td>
<td>1.52</td>
</tr>
<tr>
<td>Living alone</td>
<td>1.72</td>
<td>1.60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.53</td>
<td>1.45</td>
</tr>
<tr>
<td>Sleep latency &gt; 45 mins</td>
<td>1.44</td>
<td>1.27</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>1.42</td>
<td>1.70</td>
</tr>
</tbody>
</table>
Survival in Men Aged 30-65 Years Using Hypnotics Over 20 Year FU (Mallon et al. Sleep Medicine 2009, 10, 279-86)

- Regular hypnotic use by 1.7% men, 63.3% died
- Sometimes use hypnotics
- No hypnotic use 20.9% died
- Mean age of death in men 68 ± 11 years
Survival in Women Aged 30-65 Years Using Hypnotics Over 20 Year FU
(Mallon et al. Sleep Medicine 2009, 10, 279-86)

- No hypnotic use: 14.7% died
- Sometimes use hypnotics
- Regular hypnotic use by 2.2% women, 46.2% died

Mean age of death in women: 70 ± 10 years
Types of Confounding & Other Factors Measured in the Mallon Study
(Mallon et al. Sleep Medicine 2009, 10, 279-86)

1. Demographics: Age, living alone
2. Physical health factors: BMI ≥ 30, heart disease, hypertension, asthma, diabetes
3. Mental health factors measured: depression, sleep onset, middle insomnia, total sleep < 6 hrs, sleep latency > 45 mins, habitual snoring
4. Drug and alcohol use: Smoking
5. Cognitive brain factors: N/A
Effects of Adjustment for Variables on All Cause Mortality and Regular Hypnotic Use in 20 Year FU Study
(Mallon et al. Sleep Medicine 2009, 10, 279-86)

• Men
  – HR 3.51 (95% CI 2.21-5.57) adjusted for age only
  – HR 4.54 (95% CI 2.47-8.37) adjusted for 14 variables

• Women
  – HR 2.29 (95% CI 1.42-3.71) adjusted for age only
  – HR 2.03 (95% CI 1.07-3.86) adjusted for 14 variables
Hypnotics’ association with mortality or cancer: a matched cohort study

Daniel F Kripke,¹ Robert D Langer,² Lawrence E Kline¹

• 2½ yr FU study of the largest rural integrated health system in Pennsylvania, USA (Geisinger Health System)
  – Examined primary care OP visits in 2002-2006 in all patients aged ≥ 18 yrs with a sleep related indication for a hypnotic
  – Matched those who received ≥ 1 order for a hypnotic with 2 controls who didn’t (matched for age ± 5 yrs, sex, smoking status, and period of observation)
  – Death ascertained from the Social Security Death Index
  – Cancer ascertained from the Cancer Registry

## Characteristics of Study Population

*Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850*

<table>
<thead>
<tr>
<th></th>
<th>Non hypnotic users</th>
<th>Hypnotic users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>23,674</td>
<td>10,531</td>
</tr>
<tr>
<td>Female sex</td>
<td>62.7%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Age</td>
<td>53.6 ± 16.6</td>
<td>54.0 ± 16.9</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>93.5%</td>
<td>97.0%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>42.9%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Years of observation</td>
<td>2.50 ± 1.43</td>
<td>2.49 ± 1.39</td>
</tr>
<tr>
<td>Died during FU</td>
<td>1.2%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>
Numbers of Hypnotics Used, When Dividing the Population into Thirds
(based on numbers of hypnotics used in last 12 months)
(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)

<table>
<thead>
<tr>
<th></th>
<th>Any Hypnotic pills/yr (mean)</th>
<th>Zolpiden Only mg/year (mean)</th>
<th>Temazepam Only mg/year (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Third</td>
<td>0.4-18 (8)</td>
<td>5-130 (60)</td>
<td>1-240 (98)</td>
</tr>
<tr>
<td>2nd Third</td>
<td>18-132 (57)</td>
<td>130-800 (360)</td>
<td>240-1640 (683)</td>
</tr>
<tr>
<td>3rd Third</td>
<td>&gt; 132 (469)</td>
<td>&gt; 800 (3600)</td>
<td>&gt; 1640 (7777)</td>
</tr>
</tbody>
</table>

Zolpidem was the most frequently prescribed hypnotic
Types of Confounding & Other Factors Measured in the Kripke Study

(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)

1. Demographics: Age, sex, ethnicity, marital status
2. Physical health factors: Body mass index, and matching of 10 classes of co-morbid diagnoses
3. Mental health (MH) factors: None as Pennsylvania laws protect the confidentiality of MH diagnoses
4. Drug and alcohol use: Self-reported alcohol use, smoking status
5. Cognitive brain factors: N/A
<table>
<thead>
<tr>
<th></th>
<th>Any Hypnotic</th>
<th>Zolpiden Only</th>
<th>Temazepam Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR any hypnotic vs No hypnotic (95% CI)</td>
<td>HR zopiclone vs No hypnotic (95% CI)</td>
<td>HR temazepam vs No hypnotic (95% CI)</td>
</tr>
<tr>
<td>1st Third</td>
<td>3.60 (2.92-4.44)</td>
<td>3.93 (2.98-5.17)</td>
<td>3.71 (2.55-5.38)</td>
</tr>
<tr>
<td>2nd Third</td>
<td>4.43 (3.67-5.36)</td>
<td>4.54 (3.46-5.95)</td>
<td>4.15 (2.88-5.99)</td>
</tr>
<tr>
<td>3rd Third</td>
<td>5.32 (4.50-6.30)</td>
<td>5.69 (4.58-7.07)</td>
<td>6.56 (5.03-8.55)</td>
</tr>
</tbody>
</table>
Hypnotic Use, Age and Survival

Blue = no hypnotic; Red = had hypnotic

- 18-55 yrs: HR 9.71
- 55-65 yrs: HR 4.18
- 65-75 yrs: HR 4.68
- 75+ yrs: HR 4.08

(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)
Unique Use of Benzos and Non-Benzo Hypnotics and Association with Death
(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)

<table>
<thead>
<tr>
<th>Hypnotic Class</th>
<th>Subtype of Hypnotic</th>
<th>No. Who Died (no. who uniquely used the drug)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>No hypnotic use</td>
<td>285 (2,3671)</td>
<td>Reference</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Temazepam</td>
<td>143 (2,076)</td>
<td>4.98 (4.05-6.14)</td>
</tr>
<tr>
<td></td>
<td>Triazolam</td>
<td>5 (64)</td>
<td>4.50 (1.83-11.10)</td>
</tr>
<tr>
<td></td>
<td>Flurazepam</td>
<td>6 (133)</td>
<td>2.21 (0.98-4.98) NS</td>
</tr>
<tr>
<td>Z-drugs</td>
<td>Zolpidem</td>
<td>265 (4,336)</td>
<td>4.82 (4.06-5.74)</td>
</tr>
<tr>
<td></td>
<td>Eszopiclone</td>
<td>6 (266)</td>
<td>30.6 (12.9-72.7)</td>
</tr>
<tr>
<td></td>
<td>Zaleplon</td>
<td>18 (331)</td>
<td>3.75 (2.29-6.12)</td>
</tr>
<tr>
<td>Other hypnotics</td>
<td>Barbiturates</td>
<td>13 (228)</td>
<td>2.78 (1.57-4.92)</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>26 (495)</td>
<td>4.57 (3.01-6.94)</td>
</tr>
</tbody>
</table>
# Hazard Ratios for Cancers Associated with Hypnotic Use

(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)

<table>
<thead>
<tr>
<th></th>
<th>Any Hypnotic</th>
<th>Zolpiden only</th>
<th>Temazepam only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR vs No Hypnotic (95% CI)</td>
<td>HR vs No type of Hypnotic (95% CI)</td>
<td>HR vs No type of Hypnotic (95% CI)</td>
</tr>
<tr>
<td><strong>1st Tertile</strong></td>
<td>0.86 (0.72-1.02) NS</td>
<td>0.79 (0.60-1.04) NS</td>
<td>0.48 (0.30-0.77)</td>
</tr>
<tr>
<td><strong>2nd Tertile</strong></td>
<td>1.20 (1.03-1.40)</td>
<td>1.07 (0.83-1.39) NS</td>
<td>1.44 (1.05-1.98)</td>
</tr>
<tr>
<td><strong>3rd Tertile</strong></td>
<td>1.35 (1.18-1.55)</td>
<td>1.28 (1.03-1.59)</td>
<td>1.99 (1.57-2.52)</td>
</tr>
</tbody>
</table>
Hypnotic Use, Age and Cancer Incidence

(Blue = no hypnotic; Red = had hypnotic)

Hypnotic Use, Age and Cancer Incidence

(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)
### Subtypes of Cancer Associated with Hypnotic Use (*higher risk than smoking*)

(Kripke et al BMJ Open 2012;2:e000850. doi:10.1136/bmjopen-2012-000850)

<table>
<thead>
<tr>
<th>Cancer Type Associated with Hypnotic Use (number of cases)</th>
<th>HR for Use of Any Hypnotic (95% CI)</th>
<th>Cancer Type Not Associated with Hypnotic Use (number of cases)</th>
<th>HR for Use of Any Hypnotic (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Lymphoma (N=135)</td>
<td>2.99 (2.11-4.25)</td>
<td>Leukaemia (N=78)</td>
<td>1.14 (0.70-1.85)</td>
</tr>
<tr>
<td>*Lung (N=189)</td>
<td>2.97 (2.20-4.01)</td>
<td>Breast (N=400)</td>
<td>1.13 (0.91-1.39)</td>
</tr>
<tr>
<td>Oesophagus (N=20)</td>
<td>2.51 (1.01-6.25)</td>
<td>Uterus/cervix (N=175)</td>
<td>0.83 (0.59-1.16)</td>
</tr>
<tr>
<td>*Colon (N=213)</td>
<td>1.61 (1.21-2.13)</td>
<td>Melanoma (N=121)</td>
<td>0.83 (0.59-1.16)</td>
</tr>
<tr>
<td>*Prostate (N=320)</td>
<td>1.39 (1.09-1.76)</td>
<td>Bladder (N=111)</td>
<td>0.68 (0.40-1.14)</td>
</tr>
<tr>
<td>*All other major cancers (N=443)</td>
<td>1.67 (1.38-2.03)</td>
<td>Non-melanoma skin cancers (N=934)</td>
<td>1.05 (0.91-1.22)</td>
</tr>
</tbody>
</table>

*Significant association*
Consistency with Other Published Studies

• Hypnotics associated with mortality:
  – 18 of 24 other studies reported significantly increased mortality associated with hypnotic use (reviewed in Kripke et al 2012 online suppl.)

• Hypnotics associated with cancer:

• Benzos are typically not carcinogenic:
  – But possibility that they may cause chromosomal damage in skin and increased cancer rates in RCTs of hypnotics (kripke 2008)
What About Other Explanations?

• Study excluded 23.7% subjects:
  – Only included subjects if had an explicit sleep related indication and night time use was intended

• 7 potential confounders controlled for:
  – Demographic, drug/alcohol and physical health
  – Matching for comorbid diagnoses suggests presence of physical illness’s do not account for the association

• Study did not control for sleep or mental health variables (depression, anxiety etc):
  – But association still found in other studies that have controlled for mental health factors (Althuis et al 1998, Mallon et al 2009, Gallacher 2012)
  – Other sleep variables not controlled for – see below
The U Shaped Mortality Curve with Hours of Sleep in 480,841 Men
(Kripke et al Arch Gen Psychiatry 2002;59:131-6)

• HR adjusted for 32 variables including sleep, physical health, medications, demographics, but not depression

• HR increased only to a small degree when insomnia or hypnotic use was removed from the adjustment
Sleep Problems Associated with Mortality

• Sleep duration linked to mortality, measured objectively or subjectively in 2 meta-analyses (Gallicchio and Kalesan 2009, Cappuccio et al 2010):
  – 10% increased mortality for short sleep (<7 hours)
  – 20-30% increase for long sleep (>8 hours)

• Subjective insomnia not very linked to mortality:
  – Only 6 of 18 studies found a link, of which 3 controlled for appropriate confounders – hypnotics, sleep duration, OSA, somatic/psychiatric symptoms (Mallon et al 2002, Hublin et al 2011, Sivertsen et al 2014)
  – Stronger link for men, and if short sleep duration and if more objectively measured (Mallon et al 2002, Vgontzas et al 2010, Sivertsen et al 2014)
Cautions Required in Interpreting Sleep and Mortality Data
(Kurina et al Ann Epidemiol 2003;23(6):361-70)

• U shaped mortality curve in the 2 meta-analyses not consistently found:
  – Heterogeneity found between studies, and method used under-estimates heterogeneity
  – Only ¼ studies support U shaped curve, and only found in studies asking about usual sleep duration
  – No association of short sleep and mortality found in any studies asking about usual bed times & wake times
  – People who have mortality risk factors report shorter sleep, even when have same level of objective sleep
  – Careful attention needed to be paid to measurement bias, confounding and reverse causation
Benzodiazepine use and risk of dementia: prospective population based study

Sophie Billioti de Gage PhD student\textsuperscript{12}, Bernard Bégaud professor\textsuperscript{123}, Fabienne Bazin researcher\textsuperscript{12}, Hélène Verdoux professor\textsuperscript{124}, Jean-François Dartigues professor\textsuperscript{153}, Karine Pérès researcher\textsuperscript{15}, Tobias Kurth director of research\textsuperscript{167}, Antoine Pariente associate professor\textsuperscript{123}

Abstract

Objective To evaluate the association between use of benzodiazepines and incident dementia.

Design Prospective, population based study.

Setting PAQUID study, France.

Participants 1063 men and women (mean age 78.2 years) who were free of dementia and did not start taking benzodiazepines until at least the third year of follow-up.

Main outcome measures Incident dementia, confirmed by a neurologist.

Results During a 15 year follow-up, 253 incident cases of dementia were confirmed. New use of benzodiazepines was associated with an increased risk of dementia (multivariable adjusted hazard ratio 1.60, 95% confidence interval 1.08 to 2.38). Sensitivity analysis considering the existence of depressive symptoms showed a similar association (hazard ratio 1.62, 1.08 to 2.43). A secondary analysis pooled cohorts of participants who started benzodiazepines during follow-up and evaluated the association with incident dementia. The pooled hazard ratio across the five cohorts of new benzodiazepine users was 1.46 (1.10 to 1.94). Results of a complementary nested case-control study showed that ever use of benzodiazepines was associated with an approximately 50% increase in the risk of dementia (adjusted odds ratio 1.55, 1.24 to 1.95) compared with never users. The results were similar in past users (odds ratio 1.56, 1.23 to 1.98) and recent users (1.48, 0.83 to 2.63) but reached significance only for past users.

Conclusions In this prospective population based study, new use of benzodiazepines was associated with increased risk of dementia. The result was robust in pooled analyses across cohorts of new users of benzodiazepines throughout the study and in a complementary case-control study. Considering the extent to which benzodiazepines are prescribed and the number of potential adverse effects of this drug class in the general population, indiscriminate widespread use should be cautioned against.
Do BDZ Cause Dementia?

• 4 positive studies, 2 negative studies
• Best study is de Gage et al from France (2012):
  – 1st time use of BDZ at 68-70 yrs of age
  – Large study N=1063 men and women
  – Followed up 15 years (median 6.2 yrs)
  – Three studies of the data:
    • Main cohort study had a run in time of ≥ 3 yrs to control for factors associated with starting of BDZ
    • Secondary cohort study to look at effects of time
    • A nested case controlled study with up to 4 controls for each case matched for age ± 2 years & sex
Rates of Dementia Development
(de Gage et al BMJ 2012, 345: e6231 doi: 0.1136/bmj.e6231)

• Dementia assessed by trained psychologists using DSM-III-R, and confirmed by a neurologist
• 8.9% developed dementia within 2 years
• 23.8% developed dementia over 15 years:
  – 32% in BDZ users
  – 23% in non-BDZ users
• Incident rate of dementia during 15 year FU:
  – 4.8 per 100 person years in BDZ users
  – 3.2 per 100 person years in non-BDZ users
15 Year Dementia-Free Survival in New Benzodiazepine Users and Non-Users
(de Gage et al BMJ 2012, 345: e6231 doi: 0.1136/bmj.e6231)

HR 1.60 (95% CI 1.08-2.38)
Outcomes for BDZ Use and Dementia
(de Gage et al BMJ 2012, 345: e6231 doi: 1136/bmj.e6231)

• Main cohort study:
  – HR: 1.60 (95% CI 1.08-2.38)

• Secondary cohort study:
  – HR: 1.46 (95% CI 1.10-1.94)

• Case controlled study:
  – HR: 1.55 (95% CI 1.24-1.95)
Types of Confounding & Other Factors Measured in the de Cage Study
(de Gage et al BMJ 2012, 345: e6231 doi: 1136/bmj.e6231)

1. Demographics: Age, sex, educational level, marital status
2. Physical health factors: Use of anti-diabetic drugs, anti-hypertensives, statins, platelet inhibitors, oral anticoagulants
3. Mental health (MH) factors measured: Depression included in sensitivity analysis
4. Drug and alcohol use: Regular wine use
5. Cognitive brain factors measured: MMSE score, Benton visual retention test, Isaac set test
Could these Findings be Due to Confounding Factors Not Measured?
(de Gage et al BMJ 2012, 345: e6231 doi: 1136/bmj.e6231)

• Study did not measure sleep or anxiety, both of which are prodromes for dementia:
  – Anxiety in middle age is associated with an increased risk of dementia (Johansson et al 2010)

• Brain changes associated with Alzheimer's disease may develop 20-30 years before the development of the clinical manifestations:
Dementia and New Use of Benzo – Effects of Adjustment on Hazard Ratio
(de Gage et al BMJ 2012, 345: e6231 doi: 1136/bmj.e6231)

• Adjustment for age at baseline only:
  – HR 1.59 (95% CI 1.09-2.34)

• Adjusted for many variables (age, sex, schooling, singleness, wine, statins/ DM/ BP etc drugs, MMSE change over first 3 years of run-in time before outcomes were assessed):
  – HR 1.60 (95% CI 1.08-2.38)

• Adjusted for many variables and significant depression at baseline (CES-D scale):
  – HR 1.62 (95% CI 1.08-2.43)
Ever Use, Recent Use and Past Use of Benzos in Case-Controlled Study
(de Gage et al BMJ 2012, 345: e6231 doi: 1136/bmj.e6231)

• Ever use (recent+past) of BDZ vs BDZ non-users:
  – HR 1.54 (95% CI 1.24-1.93) matched age/sex
  – HR 1.55 (95% CI 1.24-1.95) adjusted for all

• Recent use of BDZ vs BDZ non-users:
  – HR 1.58 (95% CI 0.90-2.78) matched age/sex
  – HR 1.56 (95% CI 1.23-1.98) adjusted for all

• Past use of BDZ vs BDZ non-users:
  – HR 1.54 (95% CI 1.23-1.93) matched age/sex
  – HR 1.56 (95% CI 1.23-1.98) adjusted for all
Cognitive Decline or Dementia is Known to be Associated with Other Conditions

• Stressful life-events and PTSD:
  – Dementia (Persson and Skoog 1986)

• ‘High neuroticism’ (stress-prone personality factor):
  – Cognitive decline (Wilson et al 2007)
Midlife psychological stress and risk of dementia: a 35-year longitudinal population study

Lena Johansson, Xinxin Guo, Margda Waern, Svante Östling, Deborah Gustafson, Calle Bengtsson and Ingmar Skoog

During the 35-year follow-up, 161 females developed dementia (105 Alzheimer’s disease, 40 vascular dementia and 16 other dementias). We found that the risk of dementia (hazard ratios, 95% confidence intervals) was increased in females reporting frequent/constant stress in 1968 (1.60, 1.10–2.34), in 1974 (1.65, 1.12–2.41) and in 1980 (1.60, 1.01–2.52). Frequent/constant stress reported in 1968 and 1974 was associated with Alzheimer’s disease. Reporting stress at one, two or three examinations was related to a sequentially higher dementia risk. Compared to females reporting no stress, hazard ratios (95% confidence intervals) for incident dementia were 1.10 (0.71–1.71) for females reporting frequent/constant stress at one examination, 1.73 (1.01–2.95) for those reporting stress at two examinations and 2.51 (1.33–4.77) at three examinations. To conclude, we found an association between psychological stress in middle-aged women and development of dementia, especially Alzheimer’s disease. More studies are needed to confirm our findings and to study potential neurobiological mechanisms of these associations.
Midlife Stress and Dementia

• Prospective population study of women in Gothenburg, Sweden (N=1415):
  – Asked stress question which predicts ↑ BP, cancer, myocardial infarction, and psychosomatic diseases
  – Dementia assessed by psychiatrists and experienced psychiatric nurses, cognitive tests, and informant interviews
  – 11.4% developed dementia over 35 year FU
  – Adjustment for 11 potential confounders: demographic, drug/alcohol use, and physical health
Physician Administered Stress Question

• ‘Have you experienced any period of stress (one month or longer) in relation to circumstances in everyday life, such as work, health or family situation? Stress referred to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances’

• Asked to chose from 6 possible responses:

<table>
<thead>
<tr>
<th>Response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stress</td>
</tr>
<tr>
<td>1</td>
<td>Previous stress &gt; 5 yrs ago</td>
</tr>
<tr>
<td>2</td>
<td>One period of stress in last 5 yrs</td>
</tr>
<tr>
<td>3</td>
<td>Several periods of stress in last 5 yrs</td>
</tr>
<tr>
<td>4</td>
<td>Constant stress in last year</td>
</tr>
<tr>
<td>5</td>
<td>Constant stress in last 5 yrs</td>
</tr>
</tbody>
</table>

Frequent or constant stress over last 5 yrs
Occasional stress
Previous stress
No stress
Outcomes From Mid-life Stress Study

• Association with dementia found for:
  – ‘frequent/constant stress’ associated with increased risk of dementia HR 1.60 (95% CI 1.10-2.34)
  – ‘frequent/constant stress’ reported by 15-20% of people at different time points (1968, 1974, 1980)

• Association with dementia not found for:
  – Previous stress (HR 0.87, 95% CI 0.51-1.47)
  – Occasional stress (HR 0.89, 95% CI 0.55-1.46)

• Results consistent over 3 different examinations (1968, 1974, 1980), early or late onset dementia and if early onset dementia excluded
Types of Confounding & Other Factors Measured in the Johansson Study


1. Demographics: Age, marital status, education, socioeconomic status, having children
2. Physical health factors: Physical activity, coronary heart disease, hypertension, anti-hypertensive medication use, waist and hip circumference
3. Mental health factors measured: Psychological stress question (includes irritability and sleep)
4. Drug and alcohol use: Smoking, wine consumption
5. Cognitive brain factors measured: Dementia assessed by experts, cognitive tests, and informant interviews
Dementia & Frequent/Chronic Stress
– Effects of Adjustment for Confounders

• 1968 examination:
  – HR 1.74 (95% CI 1.20-2.51) adjusting for age
  – HR 1.60 (95% CI 1.10-2.34) adjusting for 11 variables

• 1974 examination:
  – HR 1.65 (95% CI 1.14-2.39) adjusting for age
  – HR 1.65 (95% CI 1.12-2.41) adjusting for 11 variables

• 1980 examination:
  – HR 1.73 (95% CI 1.10-2.71) adjusting for age
  – HR 1.60 (95% CI 1.01-2.52) adjusting for 10 variables
Cumulative Exposure to Frequent/Chronic Stress Increases Dementia Risk  

<table>
<thead>
<tr>
<th></th>
<th>HR adjusted for age</th>
<th>HR adjusted for 11 variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>At no examination</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>At 1 examination</td>
<td>1.09 (0.71-1.69)</td>
<td>1.10 (0.71-1.71)</td>
</tr>
<tr>
<td>At 2 examinations</td>
<td>1.82 (1.07-3.09)</td>
<td>1.73 (1.01-2.95)</td>
</tr>
<tr>
<td>At 3 examinations</td>
<td>2.83 (1.53-5.23)</td>
<td>2.51 (1.33-4.77)</td>
</tr>
</tbody>
</table>
Dementia Subtypes & Frequent/Chronic Stress in Women at ≥ 2 Examinations (dementia sub-typed on clinical grounds only) (Johansson et al Brain Advance Access May 20, 2010, 1-8)

- **Alzheimer’s without CVD:**
  - HR 2.10 (95% CI 1.13-3.89) adjusting for age
  - HR 2.20 (95% CI 1.07-3.80) adjusting for 11 variables

- **Alzheimer’s with CVD:**
  - HR 4.07 (95% CI 1.80-9.20) adjusting for age
  - HR 3.28 (95% CI 1.40-7.71) adjusting for 11 variables

- **Pure vascular dementia:**
  - HR 1.45 (95% CI 0.55-3.79) adjusting for age
  - HR 1.20 (95% CI 0.45-3.23) adjusting for 11 variables
Review of Evidence Against Benzos Causing Dementia, Cancer & Mortality

• Non-pharmacology effects:
  – Kripke et al 2012: An average of 8 pills a year is associated with a HR of 3.60 for mortality for any hypnotic

• All hypnotics independent of chemical class have a similar HR:
  – Kripke et al 2012: Mortality associated with Z-drugs, barbiturates and antihistamines, as well as benzos - although 2 exceptions stand out:
    • Temazepam in 1st tertile had reduced risk HR 0.48 (0.30-0.77)
    • Eszopiclone had much higher risks HR 30.6 (12.9-72.7)
Review of Evidence Against Benzos Causing Dementia, Cancer & Mortality 2

• Lack of evidence of causality for mortality:
  – Mallon et al 2009: HR 3.5 → 4.5 (men), HR 2.3 → 2.0 (women) adjusting for 14 variables including depression and sleep
  – Kripke et al 2012: Demonstrates mortality not due to physical health issues, but doesn’t exclude mental health factors

• Lack of evidence of causality for dementia:
  – De Gage et al 2012: HR 1.59 → 1.62 adjusting for many variables including depression
Interpretation of Evidence Against Benzos Causing Dementia, Cancer & Mortality

• Physical health factors vs mental health factors:
  – Kripke et al 2012 have demonstrated that matching for physical health factors did not account for the HR
  – The studies overall did not take account of many mental health factors, except depression and sleep, which may not be the best indicators to have used
  – The interpretation of the sleep data in particular is fraught with difficulties
  – It remains possible that if chronic stress as a confounder were taken into account, the associations may have weakened or disappeared
Possible Reasons for the Associations Found and their Implications

• Cognitive impairment not meeting criteria for dementia, which is not an early sign of dementia
• Develops very gradually over a number of years, affects about 15% of elderly people
• A risk factor for Alzheimer’s disease and mortality, but is not associated with cognitive decline once dementia is clinically evident
• Distress proneness/neuroticism associated with more rapid decline in episodic memory
• Distress proneness/neuroticism not associated with dementia like lesions e.g. tangles/plaques
Mild Cognitive Impairment FU Study

• 1256 people with av. age 77 years at baseline
• Dementia and MCI at baseline excluded, diagnosed by experienced clinician
• 38% developed MCI over 12 years of FU
• MCI more common in men than women
• Neuroticism score predicted MCI, after controlling for age, sex and education
• Association not changed by adjusting for baseline depressive symptoms (CES-D)
Depression, Distress Proneness and Mild Cognitive Impairment (MCI)  

- Association between distress proneness and MCI not changed by adjusting for baseline depressive symptoms
- Association of depressive symptoms and MCI is however eliminated by controlling for distress proneness
- This indicates that depressive symptoms are a proxy for distress proneness – for the enduring tendency to experience negative emotions
Mild Cognitive Impairment (MCI) Developing Over a 12 Year Period

Study Year

Cumulative Risk

High trait anxiety

Low trait anxiety

0 2 4 6 8 10 12
0.0
0.5
1.0
Types of Confounding & Other Factors Measured in the Study

1. Demographics: Age, sex, education
2. Physical health factors: None
3. Mental health (MH) factors measured: Distress proneness (NEO PI), depression (CES-D)
4. Drug and alcohol use: None
5. Cognitive brain factors measured: MMSE, Complex Ideational Material and 17 other tests of 5 cognitive domains (episodic, semantic & working memory, perceptual speed, visuospatial ability)

1. Distress proneness/neuroticism trait
2. Increased level of chronic stress over the life span
3. Limbic structures compromised e.g. Hippocampus
4. Learning and memory mediated by Hippocampus are selectively affected e.g. Episodic memory
5. Mild Cognitive impairment (but not dementia)
Physiological Effects of Acute Stress

Acute stress – environmental or psychological

CRF neurones in corticolimbic areas of brain

↑CRF

Hypothalamus → CRF/AVP

↑ACTH

Anterior pituitary

Adrenal cortex → Transient cortisol & DHEA release

↑NA and ↓ Adrenaline

Locus Coeruleus

↑tone in Sympathetic NS

↑physiological arousal/anxiety/attention

↑Interleukin-6 etc

Negative Feedback means that cortisol release is switched off when the stress finishes
Physiological Effects of Chronic Stress

Chronic stress – environmental or psychological

CRF hypersecretion

CRF neurones in corticolimbic areas of brain

Hypothalamus

↑CRF/AVP

↑ACTH

Hypersecretion of cortisol

Anterior pituitary

↑ACTH

Adrenal cortex

↑tone in sympathetic NS

↑NA and Adrenaline

Locus Coeruleus

High interleukin-6 etc

Reduced sensitivity to negative feedback means cortisol release is no longer switched off as the stress continues

↑physiological arousal/anxiety/attention
Downstream Effects of Elevated Cortisol & Sympathetic System Arousal

High Cortisol Levels

- Immune suppression: 
  - Increased infections and increased cancers
- Hormonal effects: 
  - ↓GH, ↓LH/testosterone, reduced menstrual periods
  - ↓ bone mass - osteoporosis
- Memory damage: 
  - Hippocampal atrophy
- Reduced inflammation

High interleukin-6 and SNS Stimulation

- Flight and fight response: 
  - ↑HR, ↑RR, ↑cardiac output, perfusion of brain, heart, muscles
- Increased arousal: 
  - Reduced sleep + daytime tiredness
  - Reduced appetite for food/sex
- Increased gluconeogenesis, fat and protein mobilisation 
  - Central fat & metabolic syndrome
- Increased inflammation
CRF and endogenous opioids have opposing effects on locus coeruleus and interact to co-regulate it.

An imbalance in this regulation as a result of prior stress include increased risk of opiate use.

Like chronic stress, opiate tolerance may result in an imbalance of influence on the LC–NE system in favour of CRF-induced activation.

Repeated opiate use could increase the risk of developing stress-related disorders, including psychiatric disorders e.g. anxiety, depression, PTSD.
Effects of Opioids on the HPA Limb of the Stress Pathways

- Opiate agonists and antagonists release ACTH through an unknown central mechanisms
- Endogenous opioids tonically inhibit the release of CRF, so opioid antagonists will increase CRF
- Opioid \( \mu \)-agonists release ACTH by acting through CRF-independent mechanisms
- Opioid \( k \)-agonists stimulate the release of CRF, which is abolish by opioid antagonists
Disorders Associated with HPA Axis Hyperfunction (Increased Activity)

• During chronic stress
  – Melancholic depression
  – OCD
  – Panic disorder
  – Functional gastrointestinal disease
  – Anorexia Nervosa
  – Malnutrition

• Addictive disorders and behaviours
  – Chronic active alcoholism
  – Alcohol/narcotic withdrawal
  – Excessive exercise (obligate athleticism)

• Childhood/developmental disorders
  – Childhood sexual abuse
  – PTSD in childhood
  – Attachment disorder of infancy
  – Truncal/central obesity (metabolic syndrome)
  – Psychosocial short stature

• Hormonal states/Physical disorders:
  – Diabetes Mellitus
  – Hyperthyroidism
  – Cushing’s syndrome
  – Pregnancy (last trimester)
Income Inequality and Stress Effects
(Wilkinson and Pickett, The Spirit Level, 2nd Ed. 2010, pp.68, 85-87)

• Income inequality (rather than absolute income) in a county or region is related to the percentage of many social problems including:
  – Illicit drug use and mental illness, especially anxiety disorders, impulse-control disorders and severe mental illness, but mood disorders less so

• Issues related to income inequality have steep social gradients:
  – Issues more common lower down the social ladder

• The biology of chronic stress may explain why unequal societies are usually unhealthy societies
Income Inequality Correlates with the Percent of Mental Illness in Countries

(Who World Mental Health Survey Consortium data, Wilkinson and Pickett, The Spirit Level, 2nd Ed. 2010, p.66-68, 287,310)

$r = 0.73$

$P < 0.01$

www.equalitytrust.org.uk
Income Inequality Correlates with the Illicit Drug Use Within a Country


r = 0.63
P < 0.01

www.equalitytrust.org.uk
Model for Stress, Mortality & Dementia

Factors causing frequent or constant stress

Chronic (frequent/constant) physiological stress

Chronic activation of HPA axis and SNS

↑ glucocorticoids & ↑ NA

↑ Immune suppression

↑ Cancers & infections

Hippocampal atrophy & ↑ deposits β-amyloid peptide & tau-protein

↑ Alzheimer’s disease

↑ CVD – BP, MI’s, strokes

↑ Vascular dementia
Principles of Treatment of the Chronically Activated Stress Response

• Reduce HPA axis stressors and effects:
  – Promote regular & deep sleep, healthy living
  – Enhance HPA axis signal sensitivity feedback, i.e. Reduce resistance to cortisol etc
  – Support brain systems being damaged by high cortisol e.g. Hippocampal memory

• Psychology: Use lifestyle management, where patient understanding & participation is vital

• Medication: Combine lifestyle management with medication, where there is major distress
Chronic stress – environmental or psychological → CRF neurones in corticolimbic areas of brain →

- Hypothalamus: ↑CRF/AVP → Hypothalamus → ↑ACTH → Adrenal cortex → Hypersecretion of cortisol
- Locus Coeruleus: CRF hypersecretion → ↑NA and ↓Adrenaline → ↑tissue in sympathetic NS → ↑physiological arousal/anxiety/attention → High interleukin-6

Reduced sensitivity to negative feedback means cortisol release is no longer switched off as the stress continues.
Some Potential Treatment of Hyperstimulation of Stress Pathways

Chronic stress – environmental or psychological

CRF neurones in corticolimbic areas of brain

Hypothalamus
- CRF hypersecretion
- ↑CRF/AVP
- ↓ACTH
- Adrenal cortex
  - Hypersecretion of cortisol

Anterior pituitary
- ↑ACTH
- Adrenal cortex

CRF hypersecretion
- Reduced sensitivity to negative feedback means cortisol release is no longer switched off as the stress continues

Locus Coeruleus
- ↑tone in sympathetic NS
- ↑NA and ↓Adrenaline
- ↑physiological arousal/anxiety/attention
- High interleukin-6

Antidepressants (possibly CRF antagonists)
- Lofexidine
- Vagal nerve stimulation
- Hypnotics & sedatives
- NSAID

Change environmental stressors

Change perception of or psychological stressors

Antidepressants
- Antidepressants (possibly CRF antagonists)
- Change environmental stressors

Hyperstimulation of Stress Pathways
Psychological Interventions to Tackle the Chronic Activation of the Stress Pathways

• Management of environmental stressors:
  – Adjust work or home environment

• Management of emotional arousal:
  – Use stress management techniques to manage emotions more effectively
  – Learn to perceive and respond to stressful situations in ways that don’t stimulate the HPA axis

• Diet and exercise:
  – Eating patterns, lifestyle balance, moderate non-competitive exercise, regular daily/weekly relaxation

• Sleep:
  – Improve quality and quantity of sleep - Deep sleep has an inhibitory effect on stress system
Pharmacological Interventions to Tackle Chronic Activation of the Stress Pathways - CRF Receptor Antagonists

- Ideal agent to reverse underlying cause on common pathway of the different limbs of the stress system i.e. CRF receptor antagonists:
  - Antalarmin is a CRF type 1 antagonist, originally described by Chen (1994), and investigated by Lundkvist et al (1996) and Chen (1996, 1997), reviewed by Elenkov (1999)
  - Tested in rats and shown to block pituitary CRH receptors (Webster et al 1996)
  - Tested in adult male rhesus monkeys reducing fear, anxiety, and the response to stress (Habib et al 2000)
  - Not tested in humans, but expected benefits in psychiatric, reproductive and cardiovascular disorders (Habib et al 2000)
Pharmacological Interventions to Tackle Chronic Activation of the Stress Pathways - Antidepressants

• Antidepressants down regulate the HPA axis, reducing cortisol levels:
  – Some depressed patients have elevated cortisol, esp. patients with melancholic and atypical depression
  – Cortisol reduces in depressed patients with high cortisol, but not others (Inder et al 2001), and may in fact increase in healthy controls
  – Depressed and primarily insomnia patients with raised cortisol who recover with antidepressants have reduce cortisol (Rodenbeck et al 2003)

• Antidepressants long term (not acutely) reduce CRF secretion, so down regulate the entire stress response, including reducing inflammation:
  – Imipramine has been shown to do this in humans (Michelson et al 1997)
Pharmacological Interventions to Tackle Chronic Activation of the Stress Pathways
- Other Interventions

• Lofexidine: Alpha-2 adrenergic agonists reduce SNS activation (Shinla et al 2007 in humans, Highfield et al 2001 in rats)

• Vagal nerve stimulation (VNS) via external ear: Rebalances the autonomic nervous system, which may be effective in cardiac failure (Clancy et al 2013, 2014)

• NSAID (prostaglandin inhibitors): Improve sleep & reduce fatigue, reducing low grade inflammation
Do Hypnotics Help or Harm?

- High associations suggest that hypnotics:
  - Do not reverse underlying psychopathology i.e. They are symptomatic treatments only
  - Increase sleep, but fail to reverse underlying stress response e.g. They don’t reduce the SNS arousal

- However, it is likely that hypnotics:
  - Do reverse underlying psychopathology to some extent so that the strong associations are still found
  - May reverse some sleep disruption which would further increase in cortisol, but doesn’t switch off the cortisol production or SNS activation
  - May act primarily to prevent the aggravating factor of poor sleep making matters worse by increasing interleukin 6 and more inflammation
Conclusions on BDZ & Physical Illness

• Robust findings for:
  – Hypnotic use associated with increase in all cause mortality (and lesser evidence for some cancers)
  – Benzodiazepine use associated with dementia
  – Midlife constant or frequent subjective stress associated with later dementia

• Important to know if non-hypnotic benzo use is also associated with morbidity/mortality:
  – If not a causal effect of benzo hypnotics, then strong association may not exist for non-hypnotic use of benzos
  – If a causal effect of benzo hypnotics, then strong association will still exist for non-hypnotic use of benzos
Hypnotic vs Non-Hypnotic Benzo Use
Review of Current Studies

• Studies of hypnotic use only:
  – Mortality studies show a strong association, and a less strong association with cancer (Kripke et al 2012, Mallon et al 2009)

• Studies of both hypnotic & non-hypnotic use:
  – Dementia studies show a robust and significant association (de Gage et al 2012)
  – In France 30% of the over 65 yrs use Benzos
  – Main use of benzos is probably as hypnotics

• Studies of non-hypnotic use only:
  – No major studies
Testing the Hypothesis that Associations Found are Due to the Stress Pathways

- Either need an RCT of benzo use versus placebo:
  - Expensive and may be difficult to get through ethics
- Or a cohort follow up study of non-hypnotic benzo use in a population (similar to current studies):
  - Using benzos for anxiety or other indications
  - Low levels of co-morbidity
  - Not associated with significant chronic activation of stress pathways (including HPA axis)
- Outcomes to be measured similar to current studies:
  - Development of mortality, cancer and dementia
Testing the Chronic Stress Hypothesis

• Stress levels in societies are related to social gradients and in particular income inequality (Wilkinson and Pickett 2\textsuperscript{nd} Ed. 2010)

• If stress causes increased mortality, dementia and cancers, then they should be correlated (r) to income inequality:
  – Income inequality correlated with mortality in adults aged 25-64 (r=0.53), less so with elderly 65+ (r=0.20)
  – Income inequality correlated weakly with prostate cancer (r=0.12), but not for breast cancer (r=0.01), consistent with Kripke et al 2012. However subjective stress did predict breast cancer in another study (Helgesson et al 2003)
  – Not tested for dementia or hypnotic use
Suggestion that Social Deprivation Associated with Higher Rates of Prescribed Benzos in Different NHS Regions of England
Implication for Research Studies

• Studies need to have a measure of chronic stress e.g. stress question used by Johansson 2010

• A question to measure **perceived** chronic stress:
  – May be more predictive than an objective measure of the HPA axis or SNS system, as this only gives a snapshot in time
  – Depression or anxiety measures may not be broad enough concepts, but can be used as proxy measures

• This measure should be used to adjust for confounding in studies of mortality, cancer and dementia
Other Research Studies to Consider
(in addition to the ones specified above)

• Is hypnotic use correlated with indices of social status, such as income inequality or deprivation?

• Are different types of cancer correlated with hypnotic use, to the extent that social gradients exist for that subtype of cancer?

• Is dementia and its subtypes correlated with hypnotic use, to the extent that social gradients exist for that subtype of dementia?

• etc
Suggested Features to Identify Chronic Activation of Stress Response System

• Evidence of physiological hyperarousal both day and night for ≥ 4 weeks:
  – Insomnia associated with daytime fatigue (but difficulty falling asleep during the day, even if an opportunity arises)
  – Physical symptoms of hyperarousal or anxiety, not due to any other physical or psychiatric disorder

• With/without evidence of psychological/emotional hyperarousal both day and night ≥ 4 weeks:
  – Difficulty relaxing, switching off mind/thoughts
  – Distress that is difficult to bear
Abnormalities of the Central Stress System as a Psychiatric Disorder

• Many patients will meet criteria for a specific psychiatric disorder, e.g. Chronic PTSD or GAD
• Some patients with have stress related psychiatric symptoms, but not meet criteria for a specific psychiatric disorder e.g. Chronic abuse
• Some may have no obvious psychiatric symptoms, but still have abnormal cortisol stress response e.g. Prior to the development of the disorder – an opportunity for prevention
Implications for Changing Our Practice

• If high arousal state, consider antidepressants:
  – Expect high arousal to be associated with high cortisol

• If not highly aroused, may have a normal or other abnormal cortisol state:
  – Antidepressants may not be of benefit or may make their state worse (by suppressing CRF further)

• Identify highly aroused patients by asking about:
  – Primary sleep problem with insomnia and daytime tiredness (unable to fall asleep in day)
  – Physiological symptoms of anxiety ± cognitive symptoms of arousal
Conclusions 1

• Robust associations exist, but causality not proven
• Evidence that associations are unlikely to be causal
• Taking account of physical and demographic confounders typically makes little difference and may increase the association
• Plausible mechanisms exist to explain the findings:
  - The stress pathways and chronic stress in particular
• It remains perfectly possible that the associations found are:
  – Due to unmeasured confounders such as chronic stress
  – Would largely or completely disappear for cancer and dementia, and be significantly reduced for mortality
Conclusions 2

• Doctors should take chronic physiological arousal states more seriously, as they are strongly associated with morbidity and mortality

• Treatment of chronic stress states involve:
  – Psychological or environmental changes
  – Drug treatments, e.g. antidepressants treatment

• The chronic stress hypothesis can be tested by:
  – looking at non-hypnotic benzos
  – Other associations with issues with a social gradient
  – Other predictions about disorders not yet investigated