Insomnia, Anxiety and Depression in the Geriatric Population

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DECLARATION OF CONFLICTS OF INTEREST

- No financial interests to declare
- I will discuss some off-label use of medications (trazodone, mirtazapine, quetiapine and pregabalin)

OBJECTIVES

- Outline a new hypothesis of anxiety and depression
- Discuss insomnia in the elderly
- Review safety concerns regarding anxiolytics, antidepressants & HS sedatives
- Discuss treatment recommendations

CASE: VC

- 82 yo female comes to you with c/o poor sleep, worry re: her health, and depressed mood
- Physical exam, lytes, TSH , B12, CT scan are normal
- HDRS = 18 ; PHQ 9 = 10 (≥ 10 positive MDD)
- Current Rx:
  - zopiclone 7.5 mg po at HS
  - lorazepam 1 mg in am
  - citalopram 40 mg
- What do you do?

INTRODUCTION

- There appears to be a ***virtuous cycle***[1] that maintains brain health

[1]Nehls M. Journal of Molecular Psychiatry (2016) 4:3

THE VIRTUOUS CYCLE

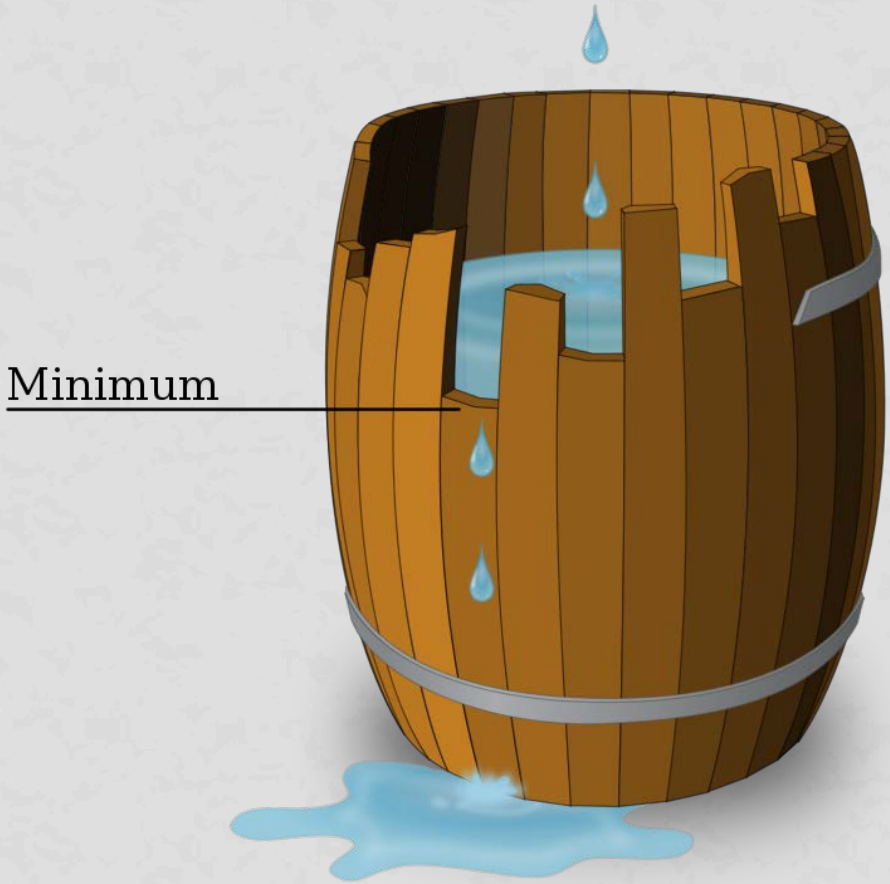
- "What did our ancestors do?"
  - ***Switch Metabolic Gears*** (hunger)
  - ***Exercise*** (hunting)
  - ***Socializing*** (hunt in a group)
  - ***Bright light*** (went in daytime)
  - ***Novel stimuli*** (where is the food?)
  - Adequate ***sleep*** (rest)

THE LAW OF THE MINIMUM

- The Law of the Minimum dictates that the ***scarcest factor*** limits growth

Nehls M. Journal of Molecular Psychiatry (2016) 4:3

Liebig's Law of The Minimum



By DooFi - Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=6627159

A HYPOTHESIS

- Is that depression and anxiety represent some break in the ***virtuous cycle***
- A persistent ***lack of one element (eg sleep)*** may cause depressive symptoms to begin
- What we call *depression* or *anxiety* might signal inadequate hippocampal renewal

WHY PILLS HAVE LIMITED BENEFITS

- Sleeping pills and antidepressants are both only ***modestly effective,***
- They do not correct deficiencies in the Law of the Minimum
- If a factor is missing, it becomes the rate limiting step

Mattson MP. Trends in Cognitive Sciences, March 2019, Vol. 23, No. 3

HIPPOCAMPAL NEUROGENESIS

- ~700 neurons are added in the hippocampus each day
- there is an annual turnover of ~1.8 % of the neurons, with a modest decline during aging.

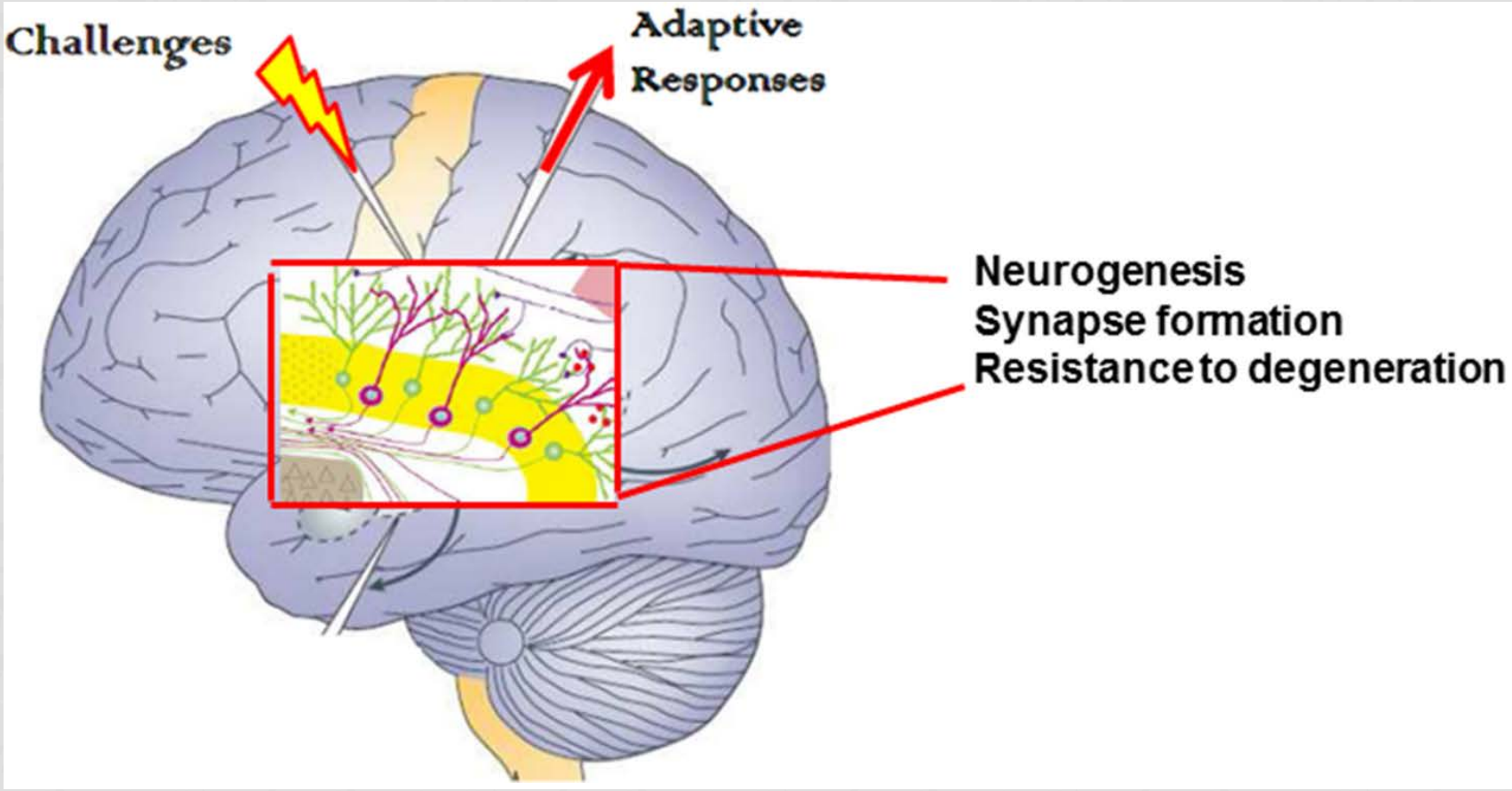
Horgusluoglu E. Am J Med Genet B Neuropsychiatr Genet. 2017 January ; 174(1): 93–112.

NEUROGENESIS

- New hippocampal neurons are necessary for:
  - spatial navigation (useful in hunting),
  - episodic learning and memory retrieval
  - **regulation of mood**
  - **psychological resilience (resistance to stress)**
  - **reduction in anxiety**

Nehls M. Journal of Molecular Psychiatry (2016) 4:3

EUSTRESS



Mattson MP. *Dose-Response*, 12:600–618, 2014

ADULT NEUROGENESIS

- Senescent mice maintained in enriched environments show ***a fivefold increase in*** AHN.

Kempermann G. Ann Neurol. 2002;52(2):135–43.

AHN IN DEPRESSION

- SSRI's lose their antidepressant effect when neurogenesis is prevented.

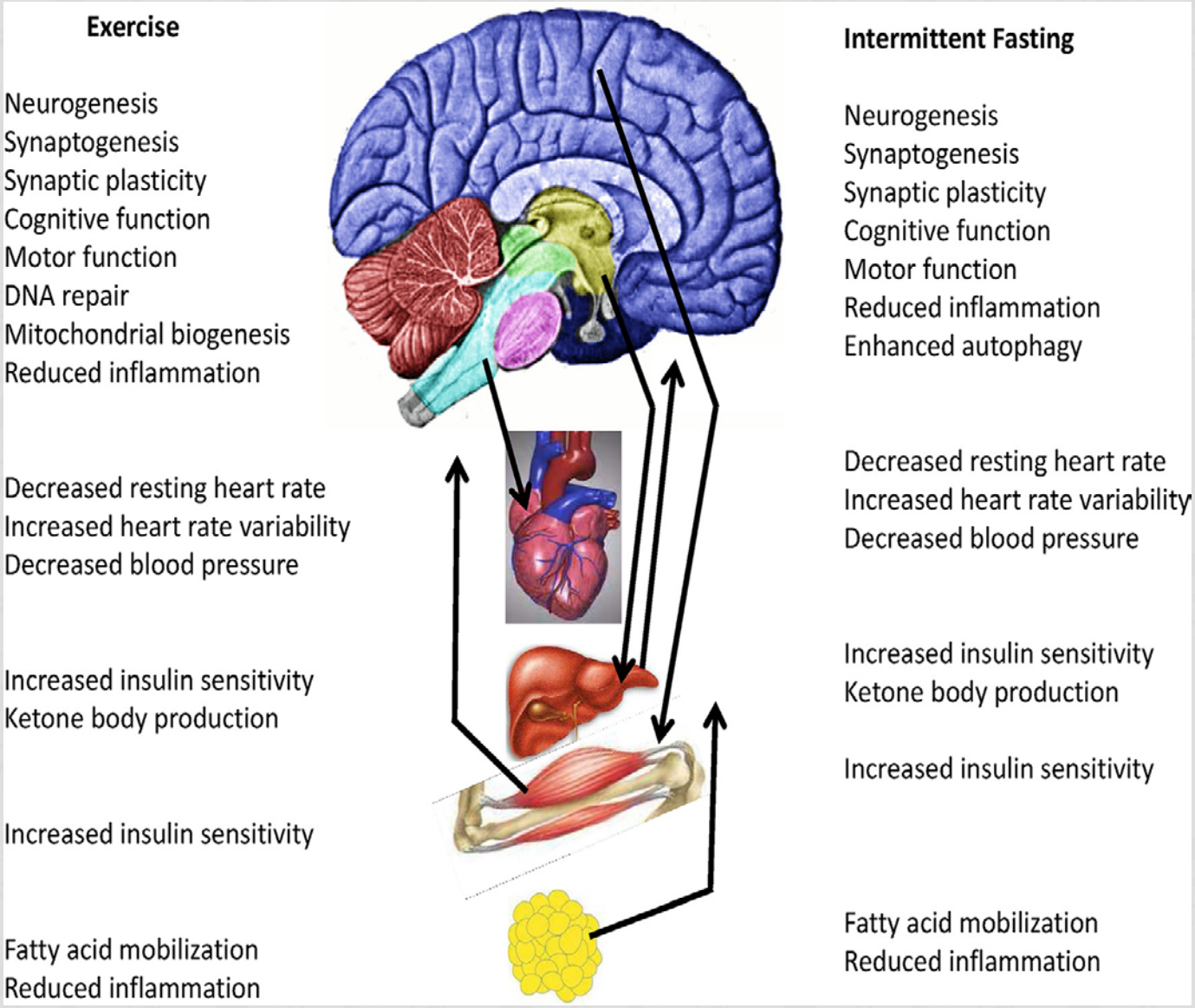
Peng L. Am J Pathol 2018, 188:

EXERCISE & HIPPOCAMPAL VOLUME

- After 1 year , an aerobic exercise group showed an **increase** in hippocampal volume of ~ 2 %,

- A stretching (yoga) control group demonstrated a 1.4 % **decline in volume** over the one-year interval,

Nehls Journal of Molecular Psychiatry (2016) 4:3


Exercise
Neurogenesis
Synaptogenesis
Synaptic plasticity
Cognitive function
Motor function
DNA repair
Mitochondrial biogenesis
Reduced inflammation
Decreased resting heart rate
Increased heart rate variability
Decreased blood pressure
Increased insulin sensitivity
Ketone body production
Increased insulin sensitivity
Fatty acid mobilization
Reduced inflammation
Intermittent Fasting
Neurogenesis
Synaptogenesis
Synaptic plasticity
Cognitive function
Motor function
Reduced inflammation
Enhanced autophagy
Decreased resting heart rate
Increased heart rate variability
Decreased blood pressure
Increased insulin sensitivity
Ketone body production
Increased insulin sensitivity
Fatty acid mobilization
Reduced inflammation

STRATEGIES PROMOTING BRAIN HEALTH

- Treat hypertension
- Maintain low BMI in middle age
- Avoid hyperglycemia (↓ insulin resistance)
- Physical exercise
- Social activity
- New challenges (eustress)
- Sufficient deep sleep

should be promoted as critical factors in brain health

Nehls Journal of Molecular Psychiatry (2016) 4:3

ANXIETY

AUDIENCE Q'S

- What is the typical age of onset for anxiety disorders?
- What does the American Geriatrics Society recommend?
- What is the risk of hip fracture in benzodiazepine vs antidepressant users?

ANXIETY IS LIFELONG

- Average age of onset of symptoms is ~11yrs of age
- Anxiety does *not* first present in older age (< 1% after age 54)
- When it does, suspect organicity or cognitive impairment

Wolitzky-Taylor K. DEPRESSION AND ANXIETY 2010; 27 :190–211

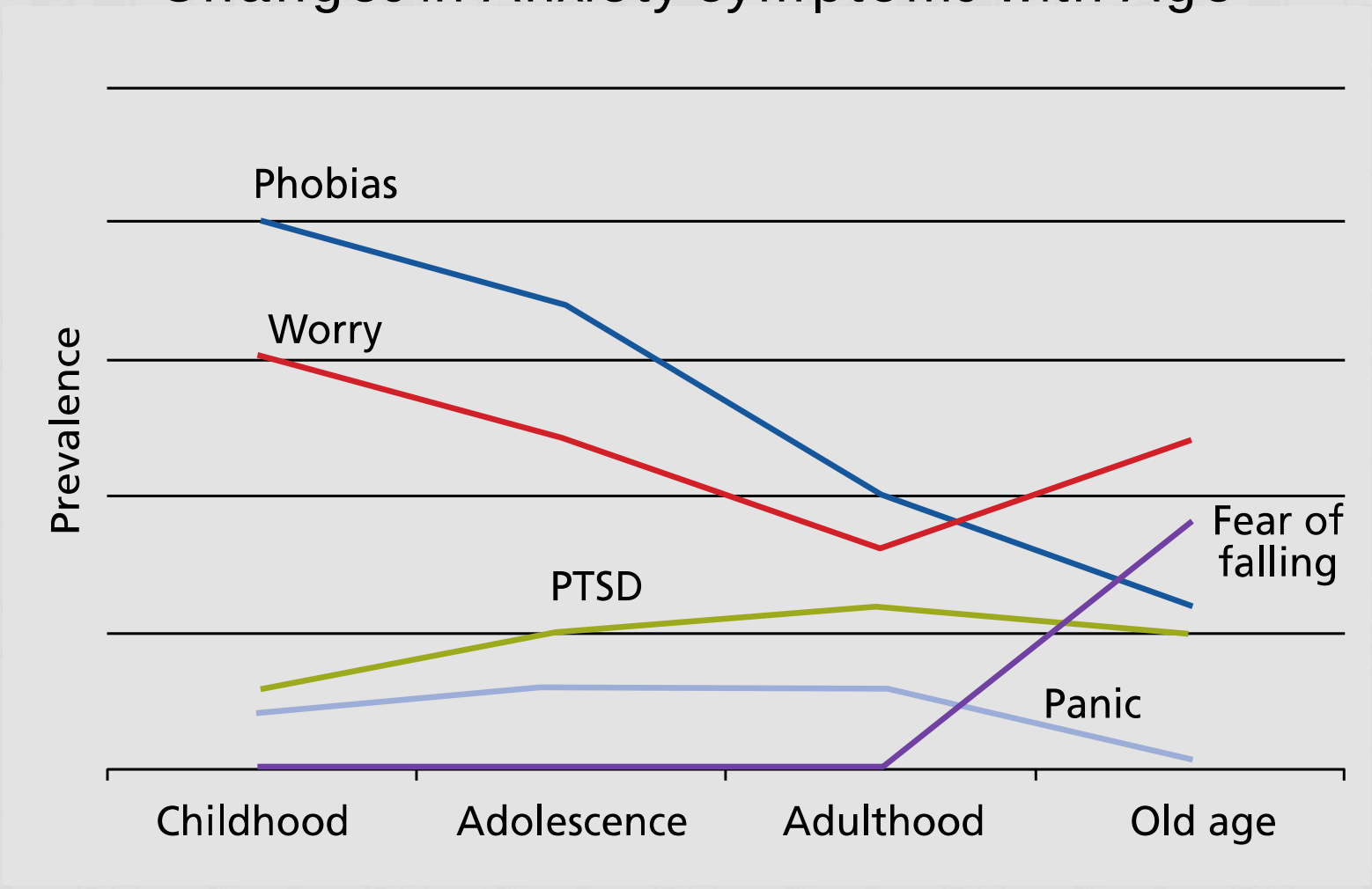


Figure 1. Changes in anxiety disorder presentation across the lifespan. PTSD, post-traumatic stress disorder

GENERALIZED ANXIETY DISORDER (GAD)

- Most studies in older adults have been on ***GAD***,
- Drug studies in people > 65 show they respond to treatment similarly to those aged < 65.

GAD **Diagnostic Criteria** **300.02**

- **Excessive anxiety and worry** for ≥ 6 months,
- The individual finds it difficult to control the worry.
- ≥ 3 of the following :
  - **Restlessness**.
  - **Fatigue.**
  - **Difficulty concentrating**.
  - **Irritability.**
  - **Muscle tension**.
  - **Sleep disturbance**
- The anxiety or worry causes distress or impairment in functioning.

DRUG TX OF ANXIETY IN LATE LIFE

- There is evidence for:
  - citalopram
  - sertraline &
  - venlafaxine ER
- in the treatment of GAD and Panic Disorder in older populations

Wolitzky-Taylor K. DEPRESSION AND ANXIETY 2010; 27 :190–211

DRUG TX OF ANXIETY IN LATE LIFE

- Sertraline was compared to **CBT** for older patients with anxiety
- both treatments led to improved anxiety and worry symptoms
- Sertraline had a greater effect than CBT.

Wolitzky-Taylor K. DEPRESSION AND ANXIETY 2010; 27 :190–211

EVIDENCE BASED TX ANXIETY

- A meta-analysis of CBT for anxiety in elderly patients showed a **small benefit in favor of CBT** at 6 months,
- The *least benefit* seen where the control was permitted pharmacotherapy.

EVIDENCE BASED TX ANXIETY

- Compared to younger adults, CBT ***may be less effective for anxiety in older adults***.
- There is some evidence that older adults can also benefit from internet-based CBT.
  - ***e.g MindShift*** at http://www.anxietycanada.ca/

BENZODIAZEPINES

- The American Geriatrics Society recommends that **benzodiazepines be avoided in people > 65** .

Pary R. POSTGRADUATE MEDICINE 2019, VOL. 131, NO. 5, 330–332

BENZODIAZEPINES

- Both benzodiazepines, and Z-drugs are significantly associated with an ↑'d risk of hip fracture
- (BZ RR = **1.52**, 95% CI 1.37–1.68)
- (Z drugs RR = **1.90**, 95% CI 1.68 – 2.13)

Donnelly K, et al PLoS ONE (2017) 12(4): e0174730.

BUT ARE SSRI'S SAFER?

- Relative risk of fractures with SSRI use in elderly patients is similar:
  - (RR) = **1.60** (95% CI 1.38 - 1.86)

(?)FASTING

- The production of **ketone bodies** appears to lead to enhancement of mood and neuroprotection.
- Amin et al. found reduced depression and anxiety scores after Ramadan fasting.

Ika Fidianingsih Journal of Complementary and Integrative Medicine. 2019; 20170172

(?)CBD

- Cannabinoids appear to demonstrate moderate efficacy in pain and chemotherapy-related nausea;
- there are limited data to suggest benefits in the treatment of anxiety.

Beedham W. Geriatrics 2020, 5, 2; doi:10.3390/geriatrics5010002

AUDIENCE Q'S

- What is the typical age of onset for anxiety disorders?
- What does *the American Geriatrics Society recommend*?
- What is the risk of hip fracture in benzodiazepine vs SSRI users?

WHAT I DO

- If MMSE ≥ 26, consider CBT or longer term pool with residents
- Consider sertraline (25 mg initially) or mirtazapine (7.5-15 mg at HS)
- Occasionally use quetiapine (RCT target dose 168 mg daily) or pregabalin (RCT target dose 270 mg daily) but lowest effective dose is best

DEPRESSION

AUDIENCE Q'S

- What is the typical improvement on the Hamilton Depression Rating Scale seen with antidepressants?
- What *serious* adverse events may be seen with SSRI's?
- What nonpharmacological interventions have evidence for efficacy in depression?

AUDIENCE Q'S

- Which drugs have RCT evidence in late life depression?
- Which drug may work faster in depression?

EPIDEMIOLOGY

- Depression is the most common *mental health* problem for older adults

Canadian Coalition for Seniors' Mental Health National Guidelines 2006.

MDD occurs in ~ 5% of community-dwelling older adults

NEJM 371;13 nejm.org September 25, 2014

LATE LIFE DEPRESSION

- ***Late-life depression*** is defined as MDD in people ≥ 60 years of age

NEJM 371;13 nejm.org September 25, 2014

LLD: EPIDEMIOLOGY

- Depressive *symptoms* affect 15% of community living elderly

CCSMH, 2006

- Rates increase with other morbidity:
  - 5 - 10% in primary care
  - 37% in critical care hospitalizations

CIHI 2010

.

LATE LIFE DEPRESSION

- LLD doubles the risk of *dementia*

Cherbuin N. BMJ Open 2015;5 doi:10.1136

LATE LIFE DEPRESSION

- This cohort may be more comfortable with seeing a doctor for *physical* reasons.
  - can present with bodily symptoms (pain, bowel complaints).

Table 1. Presentation of depression in the elderly: X *indicates the symptom is prominent;* XX *indicates the symptom is very prominent.*

TYPICAL SYMPTOMS	PROMINENT IN ELDERLY PATIENTS	PROMINENT IN YOUNGER PATIENTS
SIG E CAPS		
• Sleep (insomnia or excess sleep)	XX	X
• Interest (anhedonia)	X	X
• Guilt	X (often feeling a burden to family)	XX
• Energy	XX	X
• Concentration	X	X
• Affect (dysphoria)		XX
• Psychomotor changes	XX	X
• Suicide	X (higher rate, especially for older men)	X
Other		
• Anxiety	XX	X
• Decreased appetite or weight loss	X	X
• Complaints of memory loss	XX	
• Pain	X	
• Fatigue	XX	X

Data from the Canadian Coalition for Seniors' Mental Health.[1]

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(Use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3

Over the last 2 weeks, how often have you been bothered by any of the following problems?
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5. Poor appetite or overeating	0	1	2	3

PHARMACOTHERAPY OF LLD

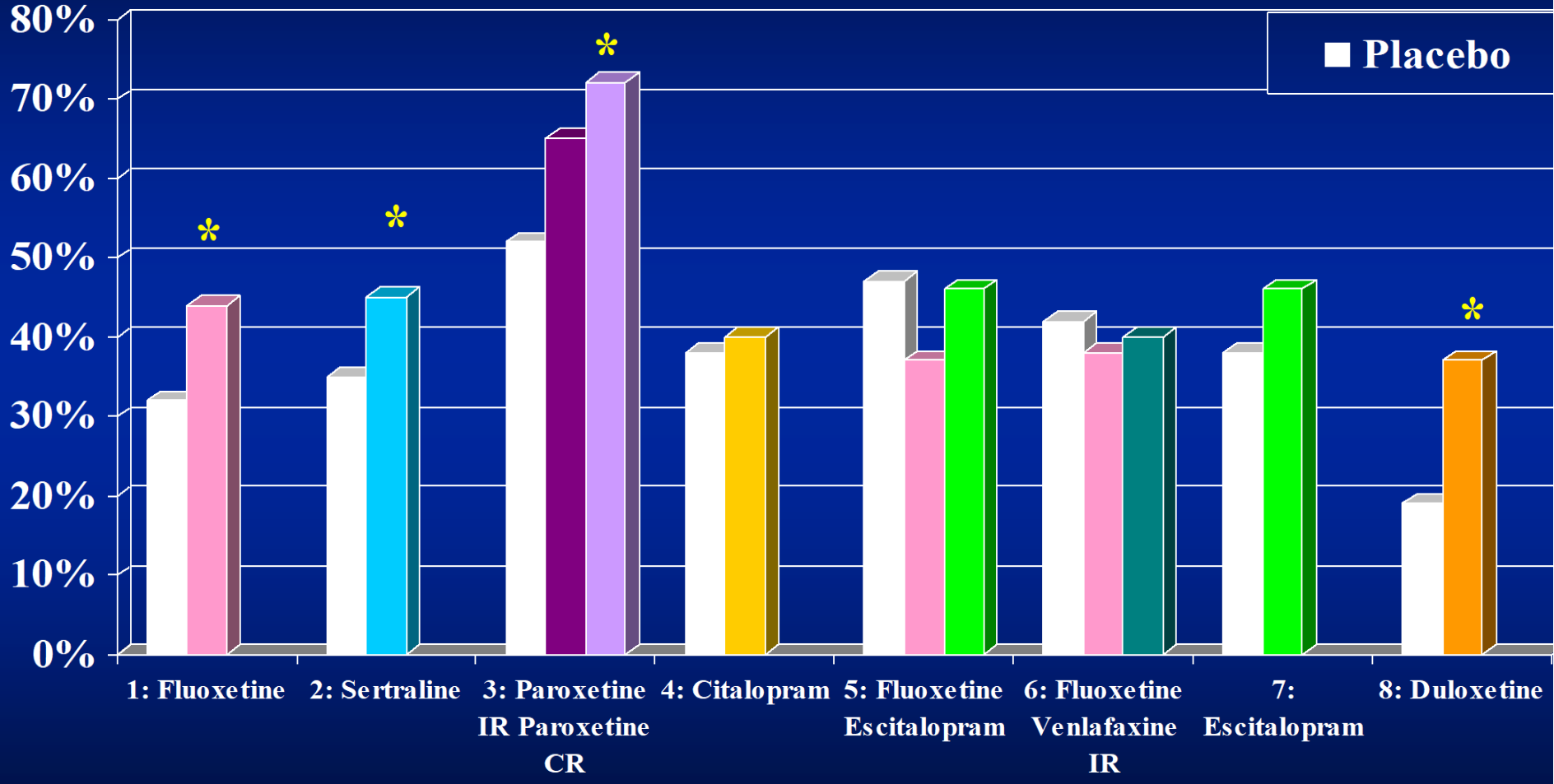
Ideal drugs	Real drugs
Large benefits	Modest benefits
Harmless	Some potential for harm
Well tolerated	Generally well-tolerated
Linear pharmacokinetics	Some are non-linear
Predictable half-life	Variable: short - long t / 2
Few drug-drug interactions (DDI)	Frequent DDI

TX OF LLD

- ~14% of older adults are on an antidepressant

Mojtabai R. J Clin Psychiatry 2014;75(2):169–77.

Response Rates (%) in Eight Published Randomized Placebo-Controlled Trials



1. Tollefson et al (1995) Int Psychogeriatrics; 7:89–104 – 2. Schneider et al (2003) Am J Psych; 160:1277-85 – 3. Rapaport et al (2003) J Clin Psych; 64:1065–74 – 4. Roose et al (2004) Am J Psych; 161:2050-9 – 5. Kasper et al (2005) Am J Geri Psych; 13:884-91 – 6. Schatzberg & Roose (2006) Am J Geri Psych; 14:361-70 – 7. Bose et al. (2008) Am J Geri Psych; 16:14-20 – 8. Raskin et al (2007) Am J Psychiatry; 164:900-9

Source: Benoit H. Mulsant, MD

DRUGS WITH EVIDENCE IN LLD

- **Sertraline (✔)**
- **Duloxetine (?)**
- **Fluoxetine (X)**
- **Paroxetine (X)**
- **Quetiapine (X)**
- *Not citalopram or escitalopram*
- *Not venlafaxine*
- *Not mirtazapine*

But Do SSRI's *Work*?

- Meta-analyses suggest that antidepressants are only ***marginally more effective than placebo.***
- ***average HDRS change is ≈ 1.9-2.7 pts*** depending on the study
- ***NICE criteria for min clin sig. Δ is 3 points***
- ?an example of the Law of the Minimum?

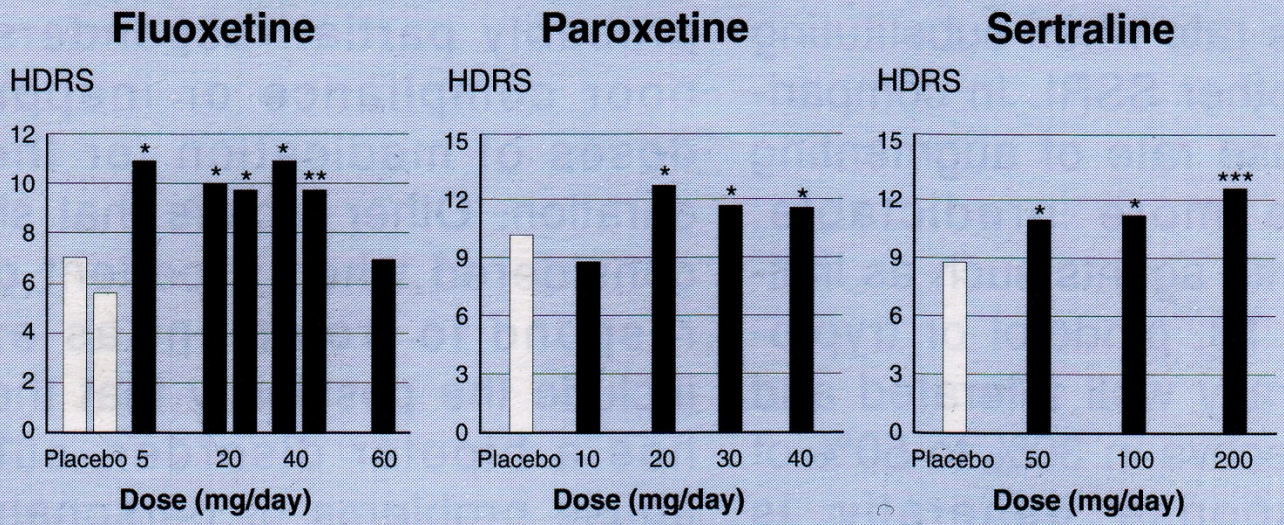
MIRTAZAPINE IS FASTER?

- Evidence from 7 trials comparing mirtazapine to fluoxetine, citalopram, paroxetine and sertraline showed:
- ***mirtazapine has a faster onset of action***

IS MORE BETTER?

Figure 1

Efficacy of Antidepressants as a Function of the Dosage



Wernicke JF et al. 1987, 1988

Dunner D, Dunbar G et al. 1992

Fabre LF et al. 1995

HDRS = Hamilton Depression Rating Scale

*p < 0,05 **p< 0,01 ***p < 0,001 vs. placebo

Reesal R. Can J Diagnosis 1996;19-22

MAINTENANCE TX

- Rates of relapse after discontinuation of treatment may be higher in older patients

Rost K. *BMJ* 2002;325(7370):934.

- Treatment should be continued for **12 months** *from the time of remission* (and up to 2 years)

CCSMH, 2006

NON PHARM TREATMENT OF LLD

NON PHARM TX OF LLD

- Psychotherapy:
  - ***Cognitive behavioral therapy(CBT)***
  - Problem solving therapy
  - Brief dynamic therapy
  - Interpersonal therapy (IPT)
  - Reminiscence therapy

NON PHARM TX OF LLD

- There is evidence that:
  - improved socializing
  - life review
  - music therapy, &
  - exercise

  can prevent and improve depression (Grade A recommendation)

Canadian Coalition for Seniors' Mental Health. National guidelines for seniors' mental health. 2006.

LIGHT THERAPY

- Light therapy can be added to medication for *nonseasonal* mild to mod MDD.
- Most effective when given during the first week of antidepressant treatment.
  - 10,000 lux /30 mins/ day in early am.
  - 12–18 inches from the unit with their eyes open.

McMaster PBSG EDUCATIONAL MODULE Vol. 22 (2), February 2014

LIGHT THERAPY

- One RCT found a standard course of light therapy **as effective as fluoxetine** 20 mg
  - 67% response rates (for each)
  - 50% & 54% remission rates (respectively).
- Light treatment showed an **earlier response** onset and **lower rate of side effects** compared with fluoxetine.

EXERCISE

- Exercise may be a useful second line adjunct to medication for mild to mod MDD.
- involved 3 sessions/week for 30–60 minutes for an average of 12 weeks.
- Improvement may be seen in 7–10 days.

McMaster PBSG EDUCATIONAL MODULE Vol. 22 (2), February 2014

ELECTROCONVULSIVE THERAPY (ECT)

- Very effective modality of tx
- May work when other tx is ineffective
- Particularly helpful with psychotic features

rTMS

- Repetitive transcranial magnetic stimulation
- Trial underway locally for dementia
- No evidence for efficacy in LLD

ADVERSE EFFECTS OF RX

CONCERNS WITH A/D IN ELDERLY

- Efficacy (?)
- Risk of bleeding (2)
- Anticholinergic effects
- SIADH picture (dilutional hyponatremia)
- Effects on bone
- Falls & orthostatic hypotension(1)
- Suicidality (?)
- Changes in sleep architecture
- Stroke (?)
- QT prolongation/ cardiotoxicity
- Increased mortality (?)

(1) Sterke CS. Br J Clin Pharmacol 2012;73:812-820

(2) Andrade C. J Clin Psch 2010;71(12) 1565-1575

Risk of Bleeding with SSRI's

Table 4 | Risk of upper gastrointestinal bleeding as a function of current use of SSRIs, aspirin, and other NSAIDs.

Medications used	Adjusted odds ratio (95% CI)
SSRI alone	1.7 (1.01–2.8)
Aspirin alone	2.4 (1.72–3.3)
Other NSAIDs alone	4.3 (3.7–5.1)
SSRI and aspirin, no other NSAIDs	3.0 (0.96–9.2)
Aspirin and other NSAIDs, no SSRI	13 (8.7–20)
SSRI and other NSAIDs, no aspirin	8.0 (4.8–13)
SSRI, aspirin, and other NSAIDs	28 (7.6–103)

Adapted from Dall et al. (2009).

Andrews PA. Frontiers in Psychology 2012;3(117):1-19

ANTICHOLINERGIC SIDE EFFECTS

- Avoid 3° amines (amitriptyline, imipramine)
  - also cause orthostatic hypotension
  - Use 2° amines (nortriptyline, desipramine)
  - 30 mg paroxetine is more anticholinergic than 50 mg nortriptylinre

Chew ML. Am Geriatr Soc 56:1333–1341, 2008.

HYPONATREMIA

- SIADH picture (dilutional hyponatremia)
  - > frequent in elderly
  - ~ 8% of those starting SSRI's
  - Often occurs 7-14 days into tx
  - May be mild and subclinical but occ'lly persistent

Frank C. *Can Fam Physician* 2014;60:121-6

FALLS

- Fall risk increases with antidepressant use.
  - dose-related for TCA's , not for SSRI's
  - **RR 1.9** for SSRI's

Thapa NEJM 1998

HPB WARNING JAN 2012

- A thorough QT study, conducted according to international standards, assessing the effects of citalopram 20 mg per day and 60 mg per day on the QT interval has shown that citalopram causes dose-dependent QT prolongation.

- Celexa® (citalopram hydrobromide) should no longer be prescribed at doses greater than 40 mg per day.

- 20 mg per day is the maximum recommended dose for patients with hepatic impairment, patients who are 65 years of age or older, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor.

- Celexa® (citalopram hydrobromide) is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation.

OTHER DRUGS TO AVOID

- **Fluoxetine** (long metabolite half life, activating, unfavorable pharmacokinetics with age)

ANTIDEPRESSANT TAKE HOME POINTS

- Consider non-pharmacologic modalities
- Avoid anticholinergic antidepressants
- Avoid high doses
- Check sodium in 10-14 days (to rule out ↓)
- Monitor QTc
- Monitor for risk of bleeding
- Watch for possible increased suicidality
- Think about bone fragility fractures

AUDIENCE Q'S

- What is the typical improvement seen with antidepressant medication?
- What serious adverse events may be seen with SSRI's?
- What alternative interventions have evidence for efficacy?

AUDIENCE Q'S

- Which drugs have evidence in late life depression?
- Which drug might work faster?

WHAT I DO

- Recommend behavioral activation, increased socializing and exercise
- Encourage exposure to bright light
- If required, recommend sertraline **(✔)** and mirtazapine **(X)** (no RCT evidence)

INSOMNIA

AUDIENCE Q'S

- On average, how much *faster* does a person fall asleep on a sleeping pill?
- How much *longer* does a person typically sleep with a sleeping pill?
- What are the risks of serious A/E's on sleeping pills?

Audience Q's

- Before electric light, what was the pattern of sleep like?
- What should be the first line intervention in insomnia?

INSOMNIA

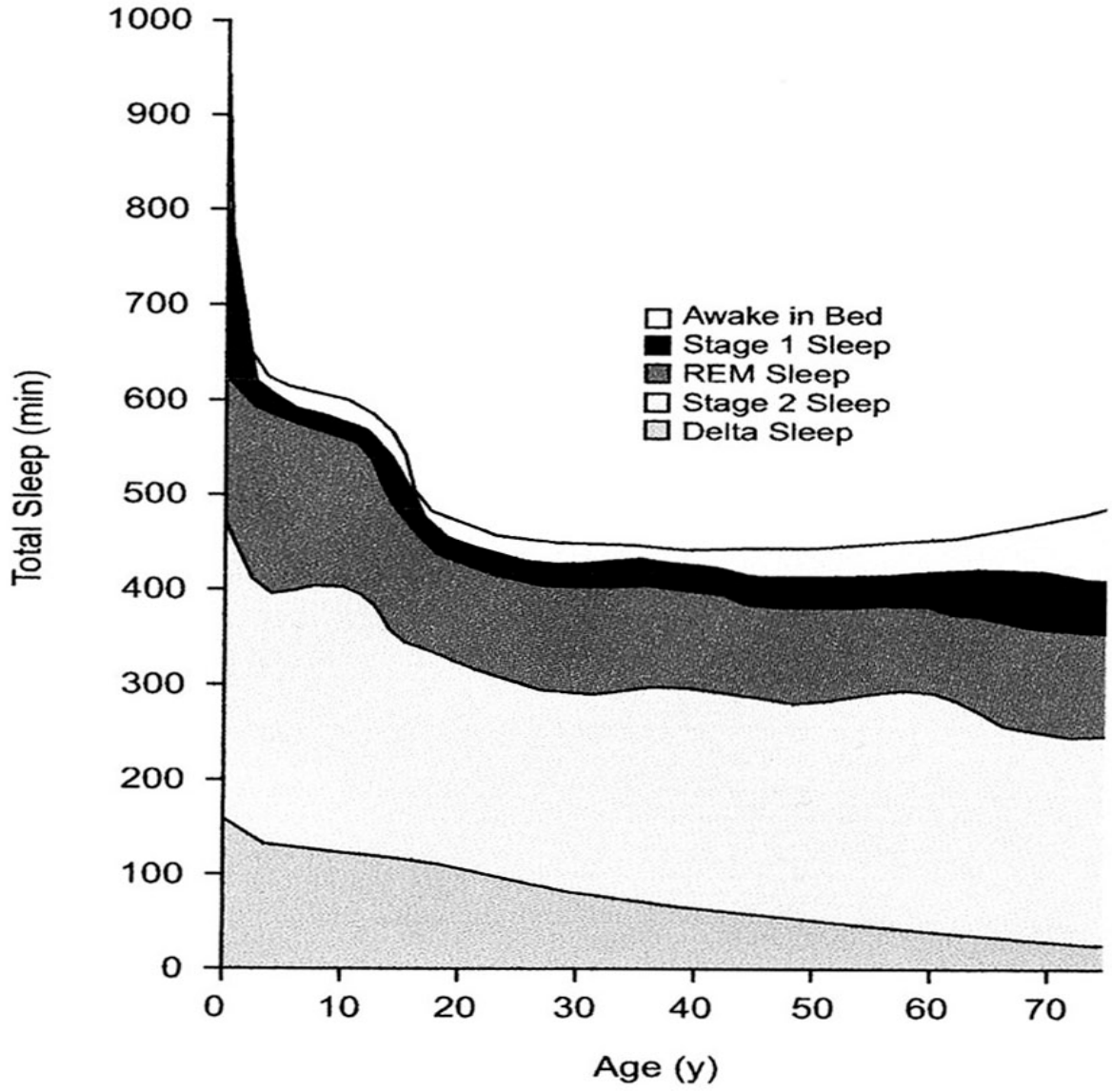
- Insomnia is broadly defined as "dissatisfaction with sleep"

  Gooneratne N. *Clin Geriatr Med*. 2014 August ; 30(3): 591–627.

- Incidence of insomnia increases with age

Foley DJ. Sleep 1999;22(2): S366-372

Figure 4. Development of Sleep Over a Lifetime



Ermin MK. J Clin Psych 2001;62(Suppl 10) 9-17

DSM 5 INSOMNIA

- **Dissatisfaction with sleep quantity or quality, associated with ≥ 1of** :
  - **Difficulty *initiating* sleep**.
  - **Difficulty *maintaining* sleep**, characterized by **frequent awakenings** or **problems returning to sleep after awakenings**.
  - **Early-morning awakening** with inability to return to sleep.
- This causes **clinically significant distress** or **impairment**.
  - **at least 3 nights per week.**
  - The sleep difficulty is **present for at least 3 months**.

Source: DSM 5 APA 2013

EPIDEMIOLOGY

- The overall prevalence of insomnia depends on how it is defined.
- Prevalence is commonly quoted as 20–40% for nocturnal sleep *complaints*
- When *diagnostic criteria* are applied, the prevalence is approximately ***2–5%***.

Gooneratne N. *Clin Geriatr Med*. 2014 August ; 30(3): 591–627

SUBJECTIVE SLEEP QUALITY

- Despite these physiological changes, *healthy* elderly ***may report less disrupted sleep*** as they age

Grandner MA.Sleep 2012;35(3): 395-406

- Older adults ***may actually be more tolerant of sleep deprivation*** than younger age groups.

Gooneratne N. *Clin Geriatr Med*. 2014 August ; 30(3): 591–627.

SLEEP & NEUROGENESIS

- An important function of sleep is to provide time for neurogenesis

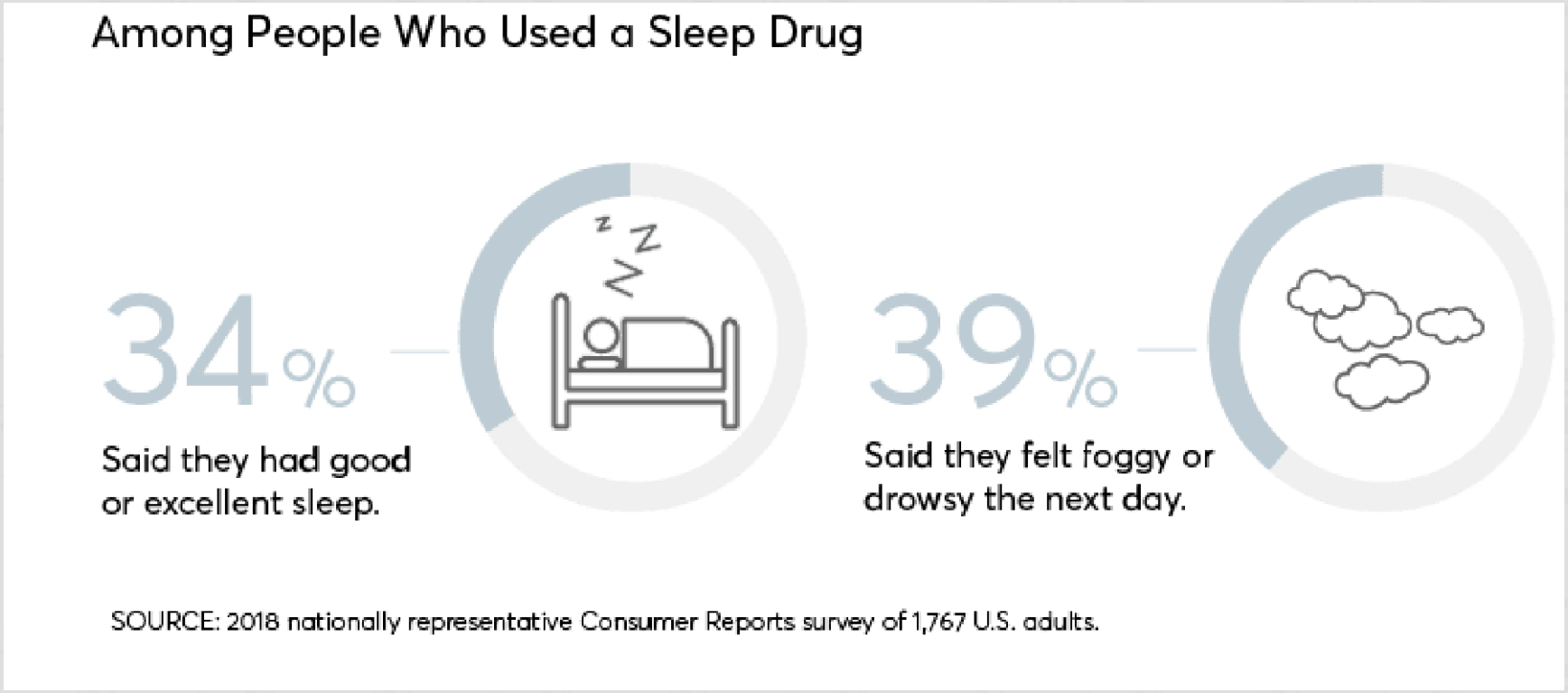
Nehls Journal of Molecular Psychiatry (2016) 4:3

SLEEP IN HISTORY

- In the preindustrial age there was a **first** and **second** sleep.
- "The most effective remedy for middle-of-the- night wakefulness... (is) ***history***."
- "Many people wake up at night and panic. I tell them that what they are experiencing is a throwback to the **bi-modal sleep pattern**."

Ekirch AR. Sleep Health 4 (2018) 515–518

HS SEDATIVES



Medications Authorized by Health Canada (e-CPS) for Insomnia (or sedation) (equivalency is approximate)

(Benzodiazepine receptor agonists (Z-drugs)	*T_{max}* (hours)*	*Half-life (hours)[a]*	*Single dose*	*Dose range*	*Approx. equivalency*
Zolpidem	~30+ min (1.4 hr)	2.5–3	5 and 10 mg disintegrating tablets	5 mg women and over age 65 5–10 mg men	20 mg
Zopiclone	~30+ min (< 2hrs)	5–6	5 and 10 mg tablets At least 12 hours before driving or operating machinery Does not accumulate	3.75–7.5 mg at bedtime 5 mg in elderly patients, in patients with hepatic or renal impairment or being treating with CYP3A4 inhibitors	15 mg
Benzodiazepine anxiolytics (and recommended use)					
Long-acting					
Diazepam (sedation)	0.5–1.5	20–100#	2 mg, 5mg, 10 mg tablets	2–10 mg bid-qid	5 mg
Flurazepam[b] (insomnia)	0.5–1		15 mg, 30 mg capsule	15–30 mg hs	15 mg
Intermediate-acting					
Alprazolam **	1–2	6–15	0.25, 0.5 mg, 1 & 2mg,		0.5 mg
(anxiety disorders)				0.25–0.5 tid	
(panic disorder)				0.5 mg tid	
Lorazepam (sedation) †	1–5	10-20‡	0.5 mg, 1 mg, 2 mg tablets	0.5–1 mg hs	0.5–1 mg
Nitrazepam[b] (insomnia)	2–3	16–55	5 mg, 10 mg tablet	5–10 mg hs	5–10 mg
Temazepam (insomnia)†	0.5–1	8–30	15 mg, 30 mg tablets	15–30 mg hs (for 5–7 days); 5–15 mg hs recommended for elderly patients	10–15 mg
Short-acting					
Triazolam** (insomnia)	1–2	1.5–5	0.125 mg, 0.25 mg tablet	0.125–0.25 mg hs	0.25 mg

Medications Authorized by Health Canada (e-CPS) for Insomnia (or sedation) (equivalency is approximate)

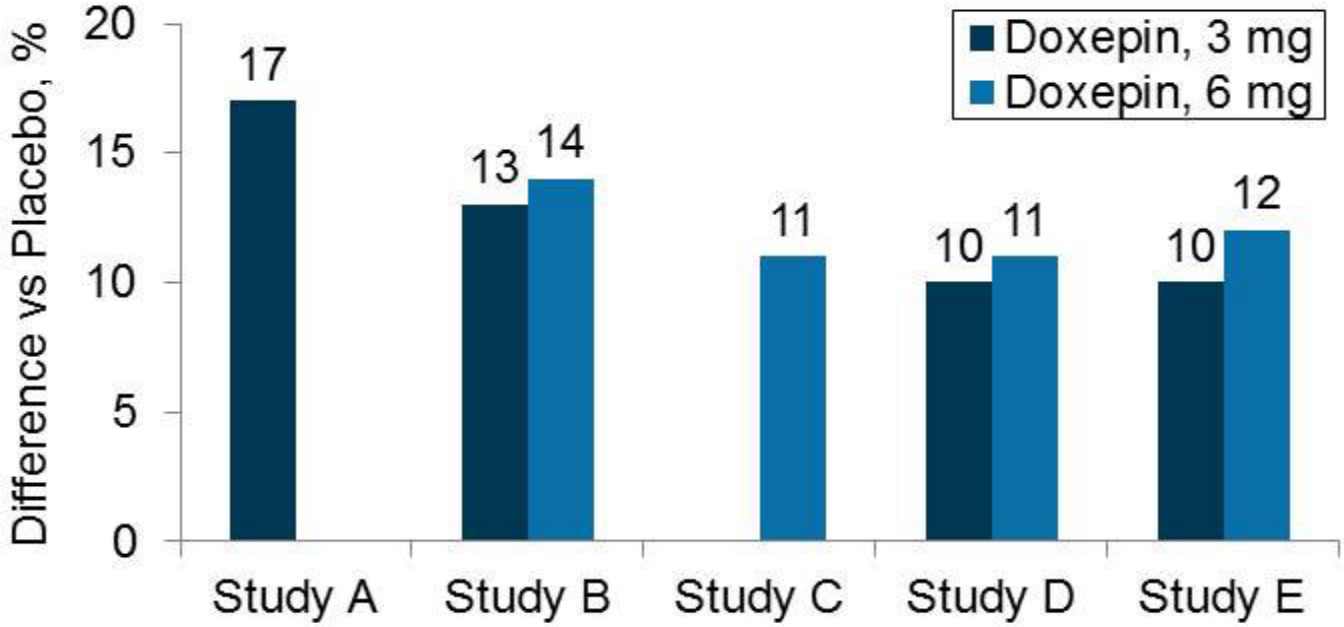
(Benzodiazepine receptor agonists (Z-drugs)	*T_{max}* (hours)*	*Half-life (hours)[a]*	*Single dose*	*Dose range*	*Approx. equivalency*
Zolpidem XXXXXX	~30+ min (1.4 hr)	2.5–3	5 and 10 mg disintegrating tablets	5 mg women and over age 65 5–10 mg men	20 mg
Zopiclone XXXXXX	~30+ min (< 2hrs)	5–6	5 and 10 mg tablets At least 12 hours before driving or operating machinery Does not accumulate	3.75–7.5 mg at bedtime 5 mg in elderly patients, in patients with hepatic or renal impairment or being treating with CYP3A4 inhibitors	15 mg
Benzodiazepine anxiolytics (and recommended use)					
Long-acting					
Diazepam (sedation) XXXXXX	0.5–1.5	20–100#	2 mg, 5mg, 10 mg tablets	2–10 mg bid-qid	5 mg
Flurazepam[b] (insomnia) XXXXXX	0.5–1		15 mg, 30 mg capsule	15–30 mg hs	15 mg
Intermediate-acting					
Alprazolam** XXXXXX	1–2	6–15	0.25, 0.5 mg, 1 & 2mg,		0.5 mg
(anxiety disorders)				0.25–0.5 tid	
(panic disorder)				0.5 mg tid	
Lorazepam (sedation) † XXXXXX	1–5	10-20‡	0.5 mg, 1 mg, 2 mg tablets	0.5–1 mg hs	0.5–1 mg
Nitrazepam[b] (insomnia) XXXXXX	2–3	16–55	5 mg, 10 mg tablet	5–10 mg hs	5–10 mg
Temazepam (insomnia)† XXXXXX	0.5–1	8–30	15 mg, 30 mg tablets	15–30 mg hs (for 5–7 days); 5–15 mg hs recommended for elderly patients	10–15 mg
Short-acting					
Triazolam** (insomnia) XXXXXX	1–2	1.5–5	0.125 mg, 0.25 mg tablet	0.125–0.25 mg hs	0.25 mg

OTHER AGENTS

- Doxepin (Silenor) approved in Canada
- (Trazodone) not indicated
- (Mirtazapine) not indicated
- Suvorexant (Belsomra) n/a in Canada
- Melatonin

Low-Dose Doxepin (3 and/or 6 mg): Review of 5 Clinical Trials

Difference in sleep efficiency during hour 8, doxepin vs placebo



- Low-dose doxepin improved sleep efficiency during the last quarter and the final hour of the night, measured by polysomnography
- Well-tolerated; associated with no clinically significant residual effects the next morning

Durrance H. Sleep 2012;35:A224

TRAZODONE

- *In depressed* pts with insomnia (n=12) :
  - 100mg x 7 days improved PSG measures of sleep (total sleep, sleep efficiency, and SWS)
  - subjective sleep quality:

    trazodone = placebo

Ware JC. J Clin Psychiatry1990;51:suppl. 238

EXERCISE

- 3 RCT's showed improvement in sleep in older adults who exercised in:
  - depth & duration
  - continuity & quality
  - quality by self-report
  - onset latency

King AC. JAMA 1997;277(1):32-37

Li F. J Am Ger Soc 2004;52 (6):892-900 (Tai Chi)

King AC. Biol Sci Med Sci 2008;63(9):997-1004

EFFICACY OF HYPNOTICS

- 2000 metaanalysis in CMAJ showed:
  - average self-report sleep latency improvement of **11.7 mins**
  - 48.4 mins of increased sleep duration
  - ≈ same effect size as exercise

Holbrook AM. CMAJ 2000;162(2):225-233

EFFECTIVENESS OF HYPNOTICS

- A meta analysis looked at 24 studies in pts > 60
- Sleep quality ↑'d (effect size 0.14 p<0.05)
- Sleep duration ↑'d (by **25.2 mins** p<0.001)
- Nocturnal awakenings ↓d (0.63 p<0.001)

Glass J. BMJ 2005

HYPNOTIC SIDE EFFECTS

However:

- Adverse cognitive effects **4.78x** more common
- Adverse psychomotor effects **2.61x** more common
- Daytime fatigue **3.82** x more common

Glass J. BMJ 2005

HYPNOTICS AND MORTALITY

- Kripke in 2012 highlighted the possible risks of even **periodic** use of HS sedatives in the elderly (≥18 times/yr)
- In addition to impaired cognition, mobility, and hip fracture,
- Results showed 3 fold to 5 fold increased mortality, depending on frequency of use

Kripke DF. BMJ 2012: 2

HYPNOTICS AND MORTALITY

- Other studies have shown more modest mortality risk associated with HS sedative use
- HR **1.14**, 95% (CI 1.12–1.1.6)

Choi JW. Journal of Clinical Sleep Medicine 2018 Vol. 14, No. 10

HYPNOTICS AND MORTALITY

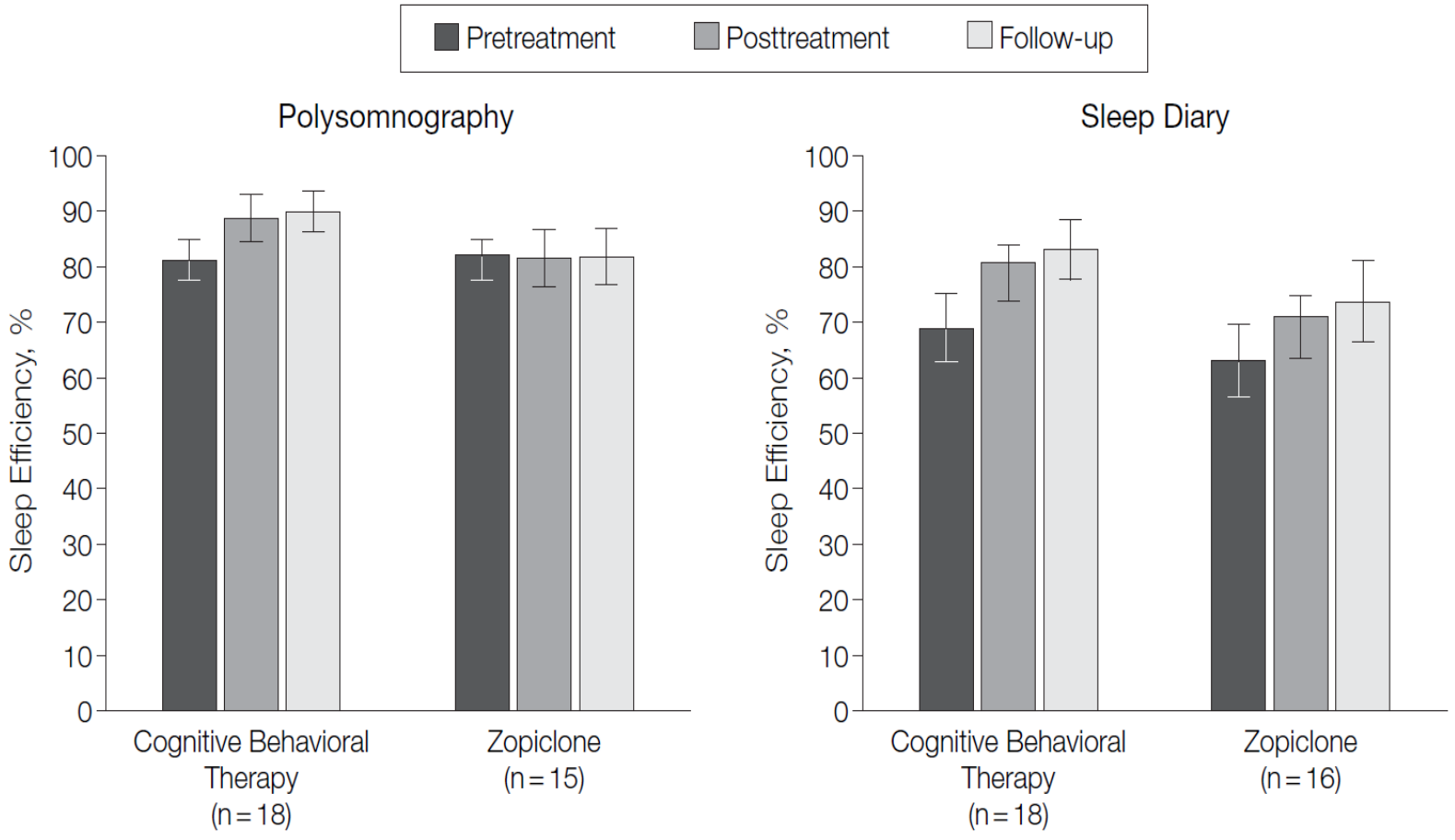
- Based on only modest benefits, and significant apparent risks:
- Even ***short-term or occasional use of HS sedatives may be unacceptable in the elderly***

CBT FOR INSOMNIA (CBT-I)

- A meta analysis of CBT-I concluded it was *as effective as hypnotics* with more durable results
- Suggested CBT-I should be considered as ***first line therapy*** for insomnia
- Goal is to achieve 85-90% sleep *efficiency* (total time asleep ÷ time in bed)

Mitchell MD BMC Family Practice 2012;13:40

Figure 2. Sleep Efficiency at Pretreatment, Posttreatment, and Follow-up as Measured With Polysomnography and Sleep Diary



Sivertsen B. JAMA 2006; 295(24):2851-2858

TURN OFF THE LIGHTS

- Light acts as a stimulant, promoting alertness and reducing the ability to fall asleep.
- It suppresses melatonin, the biochemical signal of darkness .
- Ordinary room light (i.e., 100 lux or less) can induce these effects.
- These effects of light are most apparent with blue light (λmax 480 nm).

Rahman SA. Physiol Behav. 2017 August 01; 177: 221–229

CBT PRINCIPLES

- To address:
  - Unrealistic sleep expectations ("I must have 9 hours of sleep per night"),
  - Maladaptive beliefs about sleep
  - Mistaken beliefs about the causes of insomnia ("I have a chemical imbalance);
  - Getting worked up sleep ("I am useless after a bad night's sleep");
  - Concern about losing control over sleep

THE LAST WORD?

- "The risks of....hypnotics outweigh any benefits".
- "These drugs **should not be prescribed** except in further clinical trials and hospice situations".
- "CBT for insomnia and bright light treatment for circadian rhythm disorders are ***the safest and probably the most effective*** treatments for insomnia".

Kripke D. Drug Saf (2016) 39:93–107

THE LAST WORD

- **CBT** for insomnia or **bright light**, often used in combination, should be the first choice.
- For trazodone, doxepin, and melatonin, there are no adequate data to estimate whether long-term risks outweigh benefits.

Kripke D. Drug Saf (2016) 39:93–107

THE LAST WORD

- If some Rx for insomnia must be risked, it appears
- **trazodone** in minimal doses,
- **doxepin** (in low dosage, e.g., 6 mg), or
- **melatonin**

would be the least-risky options available,

- these drugs should *generally be combined with CBT* or bright light treatment.

Kripke D. Drug Saf (2016) 39:93–107

AUDIENCE Q'S

- What is the typical improvement in sleep duration with a sleeping pill?
- On average, how much faster does a person taking a sleeping pill fall asleep?
- What are the risks of serious A/E's on sleeping pills?

Audience Q's

- Before electric light, what was the pattern of sleep like?
- What should be the first line intervention in insomnia?

TAKE HOME POINTS

- Think of the virtuous cycle!
- ***Psychoeducation*** re:
  - Trivial "benefits" of HS sedatives on sleep
  - Potential harms of sleeping pills
  - Biphasic sleep being a historical norm
  - Benefits of bright light exposure
  - Provide a sleep hygiene handout
  - Recommend a sleep log
  - Effects of exercise

CASE: VC

- 82 yof with anxiety, depression & c/o poor sleep
- D-E-P-R-E-S-C-R-I-B-E !
- Recommend reducing citalopram, ↓ and d/c zopiclone
- Aim for zero lorazepam
- Encourage behavioral activation
- Consider alt pharmacotherapy if req

WHAT I DO

- Handout on sleep hygiene
- Suggest avoid caffeine esp. >1400hrs
- Last liquid by 2000hrs
- Try melatonin 0.3-3 mg 2 hrs pre-retiring, *combined with daytime bright light*
- In institutions, low dose trazodone, or occasionally mirtazapine

Useful Websites

These sites contain a wide-variety of sleep information for both practitioners and patients:

American Academy of Sleep Medicine: www.aasmnet.org
American Insomnia Association: www.americaninsomniaassociation.org
National Sleep Foundation: www.sleepfoundation.org
National Heart, Lung, and Blood Institute: www.nhlbi.nih.gov/health/public/sleep/insomnia.htm
National Institute of Neurological Disorders and Stroke: www.ninds.nih.gov
Sepracor: www.getsomesleep.com
Help Guide: http://www.helpguide.org/aging/sleep_disorders.htm

McCrae CS. Insomnia in Practitioner's Guide to Evidence –Based Psychotherapy 2006 324-334

Q's

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