

The Relationship Between Psychotropic Medications and Sleep

Alberta Sleep Forum

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Dr. Atul Khullar

MD MSc FRCPC DABSM DABPN (Cert. Sleep Medicine)

Medical Director: Northern Alberta Sleep Clinic

Assistant Clinical Professor, University of Alberta

Consultant - Sleep & Mood Disorders Clinic, Edmonton, AB

Medsleep Canada

Objectives

1. Gain an overview of the major types of psychotropic medications where they are used
1. Learn the effects of psychotropic medications on sleep/wake cycles and the expression of sleep problems, both positively and negatively
1. Appreciate how certain types of psychoactive medications should drive certain clinical decisions in referral/treatment of sleep medicine patients

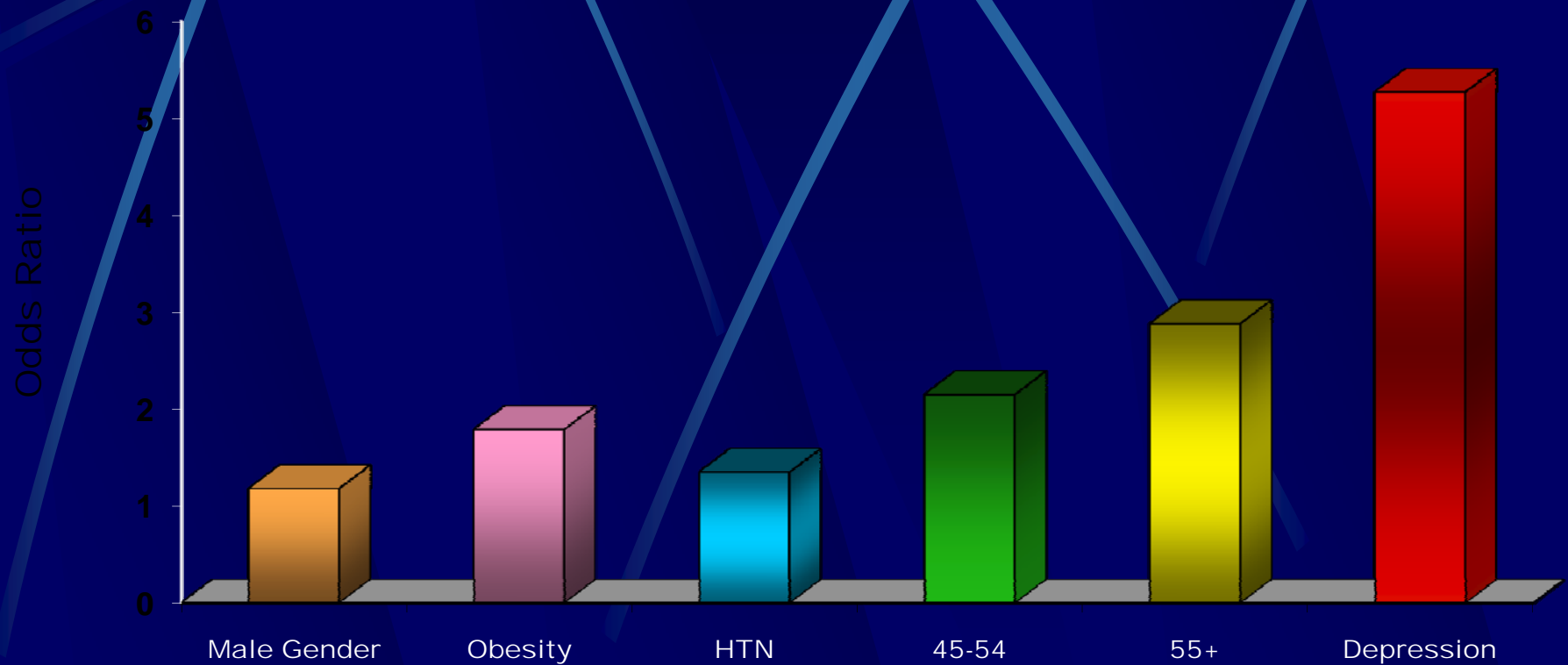
Mr. Met takes his post lunch nap



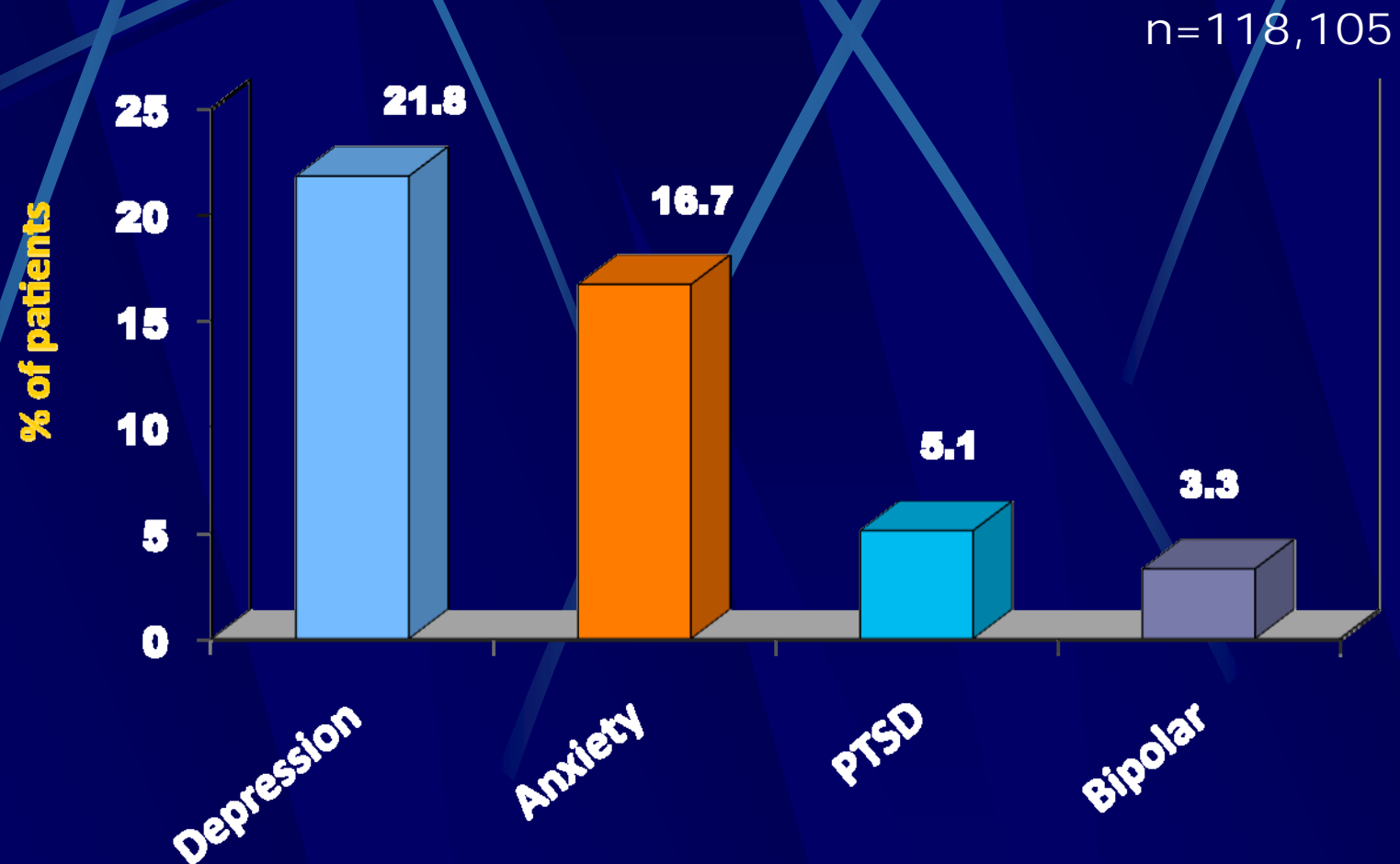
Psychotropic medications can...

- Promote sleep OR wakefulness
 - Alter the timing/amount of sleep stages
- Affect airway dynamics
 - Directly or indirectly (ie. causing weight gain)
- Cause restless leg syndrome/PLM
- Often the real reason patient is not sleeping
 - Or sleeping too much
- Change accuracy of both types of sleep studies
 - Also can determine which type of study to send for
 - Reviewing medications is key for anyone who deals patients with sleep problems

Risk Factors for Obstructive Sleep Apnea



Patients With Sleep Apnea Have High Rates of Mental Illness

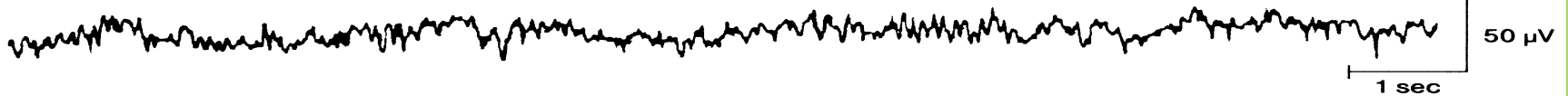


Sleep Stages



- Sleep is split into two types:
- 1. NREM
 - Stage N1 and N2
 - Stage N3 (deep or “slow wave” sleep)
- 2. REM (rapid eye movement)
 - “dream sleep”
- These rotate in a cyclical manner at night

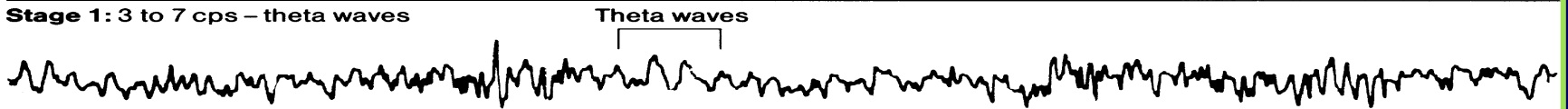
Awake: low voltage – random, fast



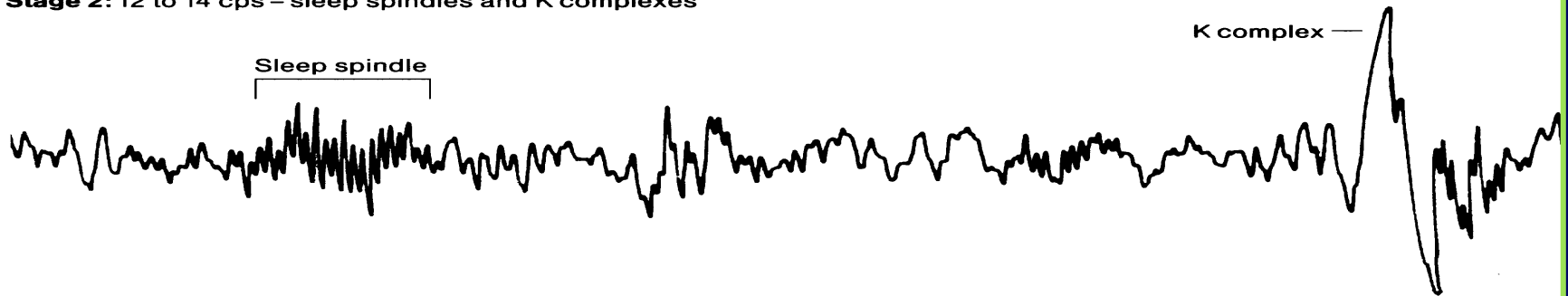
Drowsy: 8 to 12 cps – alpha waves



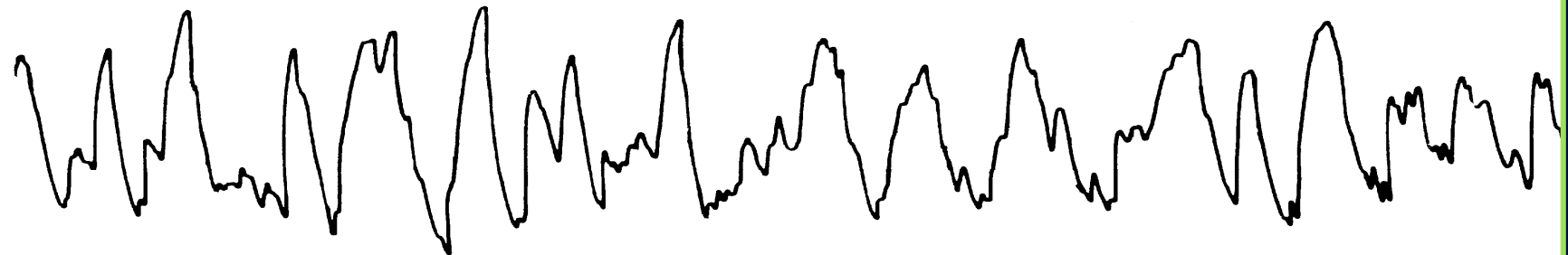
Stage 1: 3 to 7 cps – theta waves



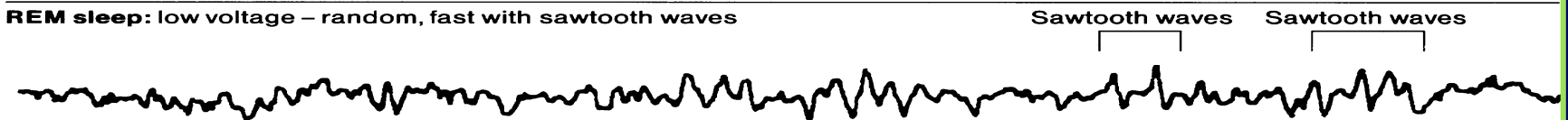
Stage 2: 12 to 14 cps – sleep spindles and K complexes



Delta sleep: (stages 3 and 4) 1/2 to 2 cps – delta waves $>75 \mu$ V

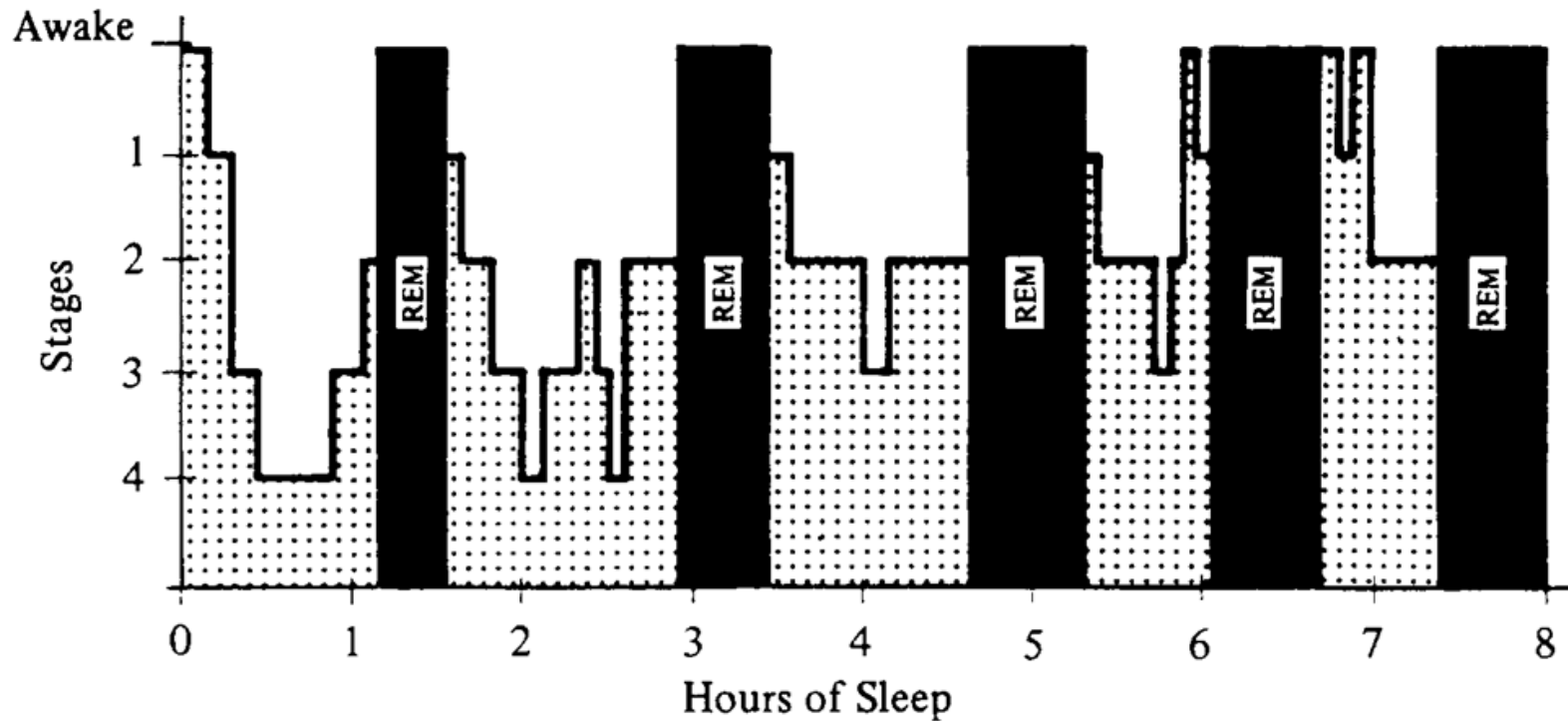


REM sleep: low voltage – random, fast with sawtooth waves



Normal Sleep Histogram

SEQUENCES OF STATES AND STAGES OF SLEEP ON A TYPICAL NIGHT



Drugs in Psychiatry Made Ridiculously Simple

- 1. Antidepressants (AD)
- 2. Antipsychotics (AP)
- 3. Anti-epileptic drugs (AED)
 - Used for bipolar/behavior control
- 4. Other
 - A. Hypnotics
 - B. Benzodiazepines
 - C. Lithium
 - D. Stimulants
 - E. Opiates/Cannabinoids



Caution!

- There are few absolute truths about psychotropic medications/sleep
- Often trends for each medication with substantial individual variation
- Effect of a medication can depend on
 - Dose
 - Context of use/illness being treated
 - Timing (when in circadian rhythm drug is given)
- Usually a cost-benefit ratio for each medication with regards to sleep

Sometimes the medication is not really helping



Other limitations to this data

- **Studies vary widely in methodology**
 - Sleep variables measured (subjective/objective)
 - Healthy vs. ill patients
 - Length of time patient was on drug
 - Studies often last for only a few days
 - Style of objective sleep monitoring
 - Dose
 - Control of other medication

Antidepressants 2009

TCA

Amitriptyline
Imipramine
Clomipramine
Trimipramine
Maprotiline
Amoxapine
Nortriptyline
Desipramine

MAOI

Phenelzine
Tranylcypromine

SSRI

Citalopram [Celexa]
Escitalopram [Cipralex]
Fluoxetine [Prozac]
Fluvoxamine [Luvox]
Sertraline [Zoloft]
Paroxetine [Paxil]

SARI

Trazodone
{Nefazodone}

NDRI

Bupropion-SR/XL [Wellbutrin]

SNRI

Duloxetine [Cymbalta]
Venlafaxine-XR [Effexor]
O-desmethylvenlafaxine
[Pristiq]

NaSSA

Mirtazapine [Remeron]

RIMA

Moclobemide [Manerix]

Development of Antidepressant Treatments

Improved Safety and Tolerability

TCA

Non-selective
Tricyclic AD
Effects on Multiple
Neurotransmitter
Systems

SSRI

Selective 5-HT
Re-uptake inhibitor
Primary Effect on the
5-HT System

SNRI

Serotonin and
Norepinephrine
Reuptake Inhibitor
Effects on 5-HT and
NA

ASRI

Allosteric Serotonin
Reuptake Inhibitor
Serotonin Dual Action
5-HT and Allosteric Site

1950s

1960s

1980s

1990s

2002

MAOI

Mono-amine
oxidase inhibitor
Effect on Monoamines

NDRI

Norepinephrine and
Dopamine Reuptake Inhibitor
Effect on NE and DA

NaSSA

Noradrenergic and specific
serotonergic antidepressant
Effect on NA and 5-HT specific

Improved Safety and Tolerability

Other Uses of Antidepressants

- Anxiety disorders
 - Include panic attacks, obsessive compulsive disorder, social anxiety, PTSD
- Behavior problems
- Menopausal symptoms
- Sleeping pills
- Migraine prophylaxis
- Anti-pain medications



PSG in Depressed Patients

Decreased

- Sleep efficiency
- Sleep continuity
- Total sleep time
- REM Latency
- Slow wave sleep (SWS)

Increased

- Time to sleep onset
- Stage 1
 - Sometimes Stage 2
- First REM stage
- Total REM time
- Density of eye movements during REM

Older Antidepressants - TCA

- Most common one seen is Amitriptyline (Elavil)
 - Also Nortriptyline (Aventyl), Desipramine, Doxepin (Sinequan), Trimipramine (Surmontil)
 - Raise many neurotransmitters in the brain
- Used occasionally at low doses as sleeping pills, migraine prophylaxis and for chronic pain
 - Higher doses for resistant depression (rare)
- Cause sedation, weight gain, dizziness
- Tend to increase slow wave sleep/suppress REM
 - Possibly lead to RLS/PLM, but not as much as other AD

Older antidepressants - MAOI

- Rarely used
 - Irreversible: Phenelzine (Nardil), Tranylcypromine (Parnate) Reversible: Manerix (Moclobemide)
 - Also raise many neurotransmitters in the brain
- Very potent REM suppressants¹
 - Marked REM rebound when stopped
 - Can lead to nightmares, RLS/PLMD, parasomnia
- Objective effects of older AD on sleep appear to correlate with clinical/subjective effects²

Consensus of Sleep Effects of Older AD

	SC	SWS	REM supp	Sedation	NE	5-HT	H1	Anti- ACH
3e Tricyclics								
Amitriptyline	+++	+	+++	++++	+	++	++++	++++
Doxepin	+++	++	++	++++	++	+	+++	++
Imipramine	0	++	++	++	+	+	+	++
Clomipramine	0	+	++++	++	+	+++	+	++
2e Tricyclics								
Desipramine	0	+	++	+/-	+++	0	0	+
Nortryptiline	+	+	++	+	++	+/-	+	++
MAOI								
Phe nelzine	--	0	++++	--	+++	+++	0	0
Tranlycypromine	--	0	++++	--	+++	+++	0	0

+ = increases, - decreases, +/- conflicting evidence, 0- minimal or no effect

SC = sleep continuity, SWS = slow wave sleep, H1 = histaminic receptor blockade, Anti-Ach - anticholinergic effect mediated through muscarinic receptors.

Serotonin Reuptake Inhibitors (SRI)

- Fluoxetine (Prozac), Paroxetine (Paxil), Fluvoxamine (Luvox) Sertraline (Zoloft), Citalopram (Celexa) Escitalopram (Cipralex)
- First line treatment, best studied
 - Don't work any better, but much lower toxicity
- Many low-grade side effects
 - GI, sleep disruption, sexual dysfunction
- Some general effects with each
 - Marked variability between patients
 - Many have effects on other neurotransmitter systems
- Often trial and error to find right one

Clinical Sleep Effects of SRI

- Very idiosyncratic
 - Most likely to have insomnia/agitation (5-20%)¹
 - 35-60% of depressed patients on SRI are also on a hypnotic²
 - Any individual can be either sedated or stimulated
 - Subjective measures of sleep on SRI correlate poorly with objective findings^{3,4}
- Appear to be some trends and variability
 - More sedating: Luvox, Paxil
 - More stimulating: Prozac
 - Neutral: Zoloft, Celexa, Cipralex
 - Usually best to take in late afternoon (not Prozac – am)

Objective Effects on Sleep of SRI

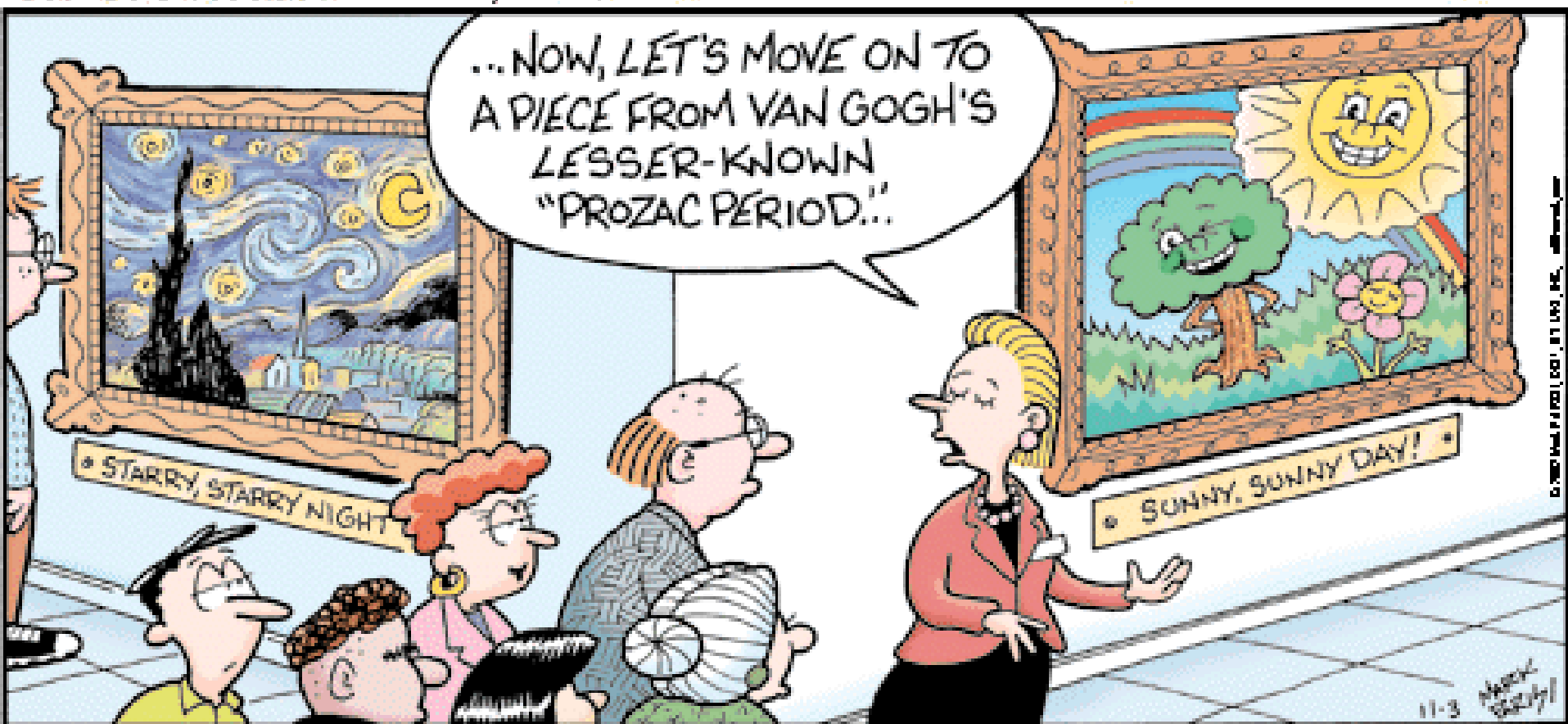
- In class variation in objective sleep measures
 - Possibly due to receptor profile differences¹
 - Can also be due to half-life (ie withdrawal with paroxetine towards end of night if patient took AD previous morning)
- Objectively SRI tend to:
 - Increase REM latency/REM suppression
 - Partial tolerance to this effect has been seen over a few weeks
 - Increased # of awakenings/stage 1 sleep
 - Decreased sleep efficiency/REM periods
 - Overall appear to “lighten sleep”
 - Raising serotonin can make airway less likely to collapse
 - In rats, not seen clinically in humans

Objective Effects on Sleep of SRI - 2

- SRI increase extraocular movements, worsen both RLS and periodic limb movements
 - Best evidence for fluoxetine^{1,2}
 - SRI is factor that increased RLS in recent large epidemiologic study³
 - SRI drugs make polysomnograms difficult to interpret
 - Sleep wake transitions and REM determination become fuzzy
 - SNRI, MAOI appear to have these difficulties as well
 - Can cause REM behavior disorder and nightmares
- Patients note that subjective sleep improves
 - Unclear if this continues longer term

SRI- from a sleep point of view

- Prozac: potentially stimulating and disruptive to sleep
- Paxil: potentially sedating, weight gain, anticholinergic effects and withdrawal agitation symptoms
 - All can effect sleep negatively
- Luvox – sedating
- Cipralex, Zoloft and possibly Celexa appear to clinically preserve sleep more often than the other ones
 - Possibly less EOM, RLS, PLMD
- Cipralex/Zoloft were shown to be slightly superior on tolerability and efficacy in a large meta-analysis of newer antidepressants in depression¹



Non SRI in common use

- Venlafaxine (Effexor), Duloxetine (Cymbalta)
 - Very common, blocks re-uptake of both serotonin and norepinephrine (SNRI)
- Bupropion (Wellbutrin)
 - Stimulating, blocks norepinephrine and dopamine uptake
- Mirtazapine (Remeron)
 - Sedating, weight gain, multiple chemical actions
- Trazodone (Desyrel)
 - ⚠ Older, used more as hypnotic at low doses

Venlafaxine (Effexor)

- Clinically tends to be activating
 - At low to medium doses is much like an activating SRI
 - Occasional sedation is also seen
 - Withdrawal is common and can disrupt sleep
 - Causes lots of nightmares, night sweats, parasomnias
 - Global objective sleep changes similar to SRIs^{1,2}
 - Also worsens RLS/PLM/EOM
- New cleaner version of venlafaxine (Pristiq)
 - May be less disruptive to sleep in all of above factors
 - May not work as well either

Duloxetine (Cymbalta)

- Duloxetine is in similar class to venlafaxine
 - More dual action effect
 - Much higher increase of norepinephrine
 - Appears to be more activating
 - Withdrawal is less likely
- Similar objective sleep changes to older ADs¹
 - Sleep is worse on higher dose
- Has anti-pain effects which may help sleep by itself

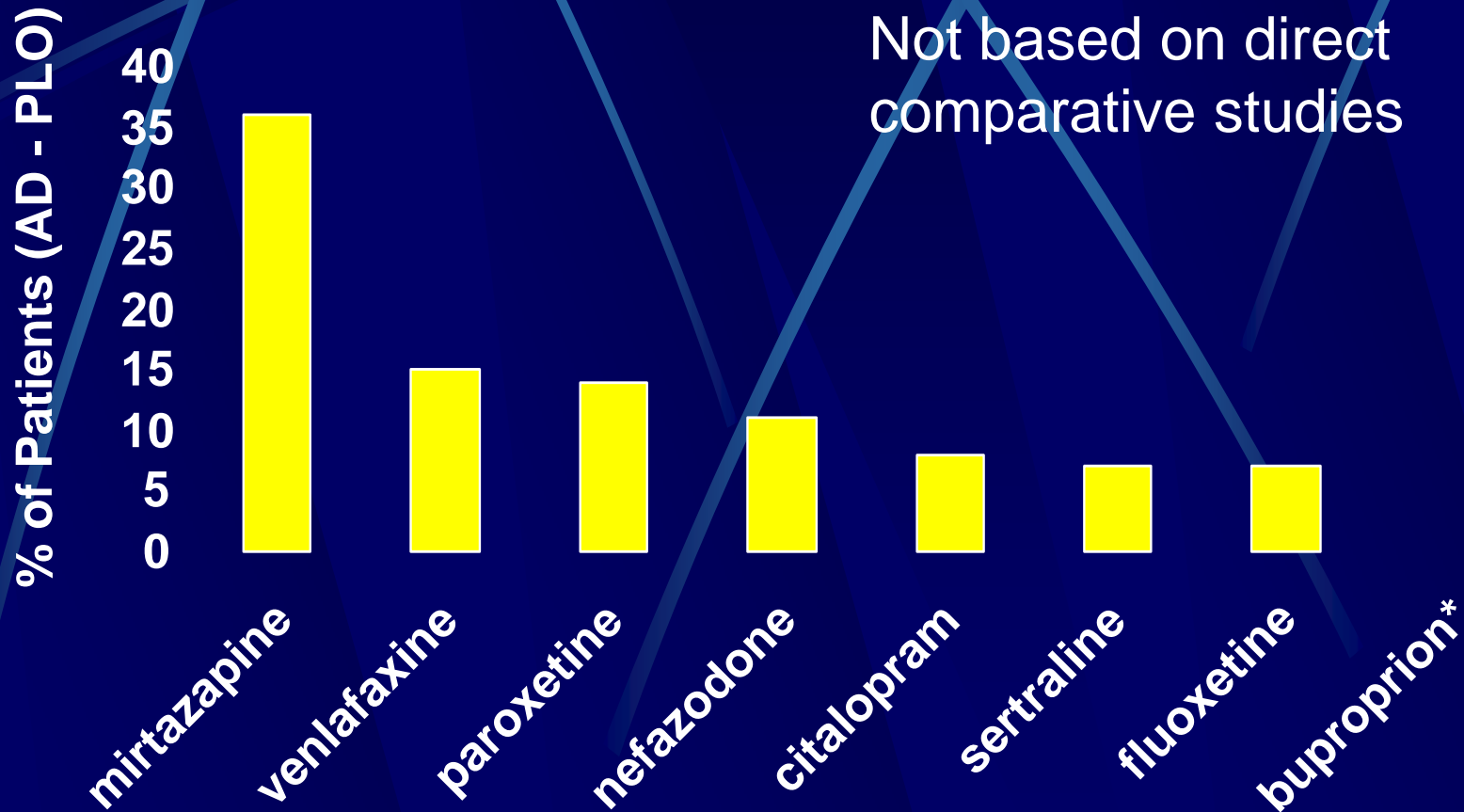
Mirtazapine (Remeron)

- Different profile in sleep from other agents
 - Increased sleep continuity/efficiency, SWS & REM^{1,2,3}
 - Somnolence/daytime impairment in performance⁴
 - Seen on driving simulators compared to other antidepressants
 - Thought to be related to histaminic antagonism
 - Fairly significant for prompting RLS symptoms
- Weight gain can be a problem
 - (2-5kg in some 8 week trials)⁵
- The subjective improvement in sleep doesn't really correlate to the patients overall improvement

Bupropion (Wellbutrin)

- Almost universally activating clinically
 - Doesn't suppress REM like most other antidepressants
 - Improved PLMs in depressed patients¹
 - Possibly due to increased dopamine
- Weight loss has been noted²
- Used occasionally for fatigue and hypersomnolence
 - Reasonable choice for a depressed, sleepy patient
- Clearly different effects on sleep than other AD

Incidence of Somnolence/Sedation on Antidepressants Compared to Placebo



PDR 2001: Incidence on Active (AD) – Incidence on Placebo (PLO);

*No difference for bupropion

Drugs for Sleep –Hypnotics

Zopiclone (Imovane, Rhovane)

- Isomer is eszopiclone or Lunesta in US
- Probably the best choice for most people for pure sleep issues
- Doesn't really treat anything else
- Increases sleep efficiency, may change staging
- Minimal affect on airway dynamics

Antihistamines

- Very effective for getting hours of sleep
- Many effective sleep medications have histamine blockade
- Often in OTC (i.e. Tylenol PM, Benadryl, Gravol)
- Pure antihistamines not usually good long term, especially in older people; causes mental dulling, confusion

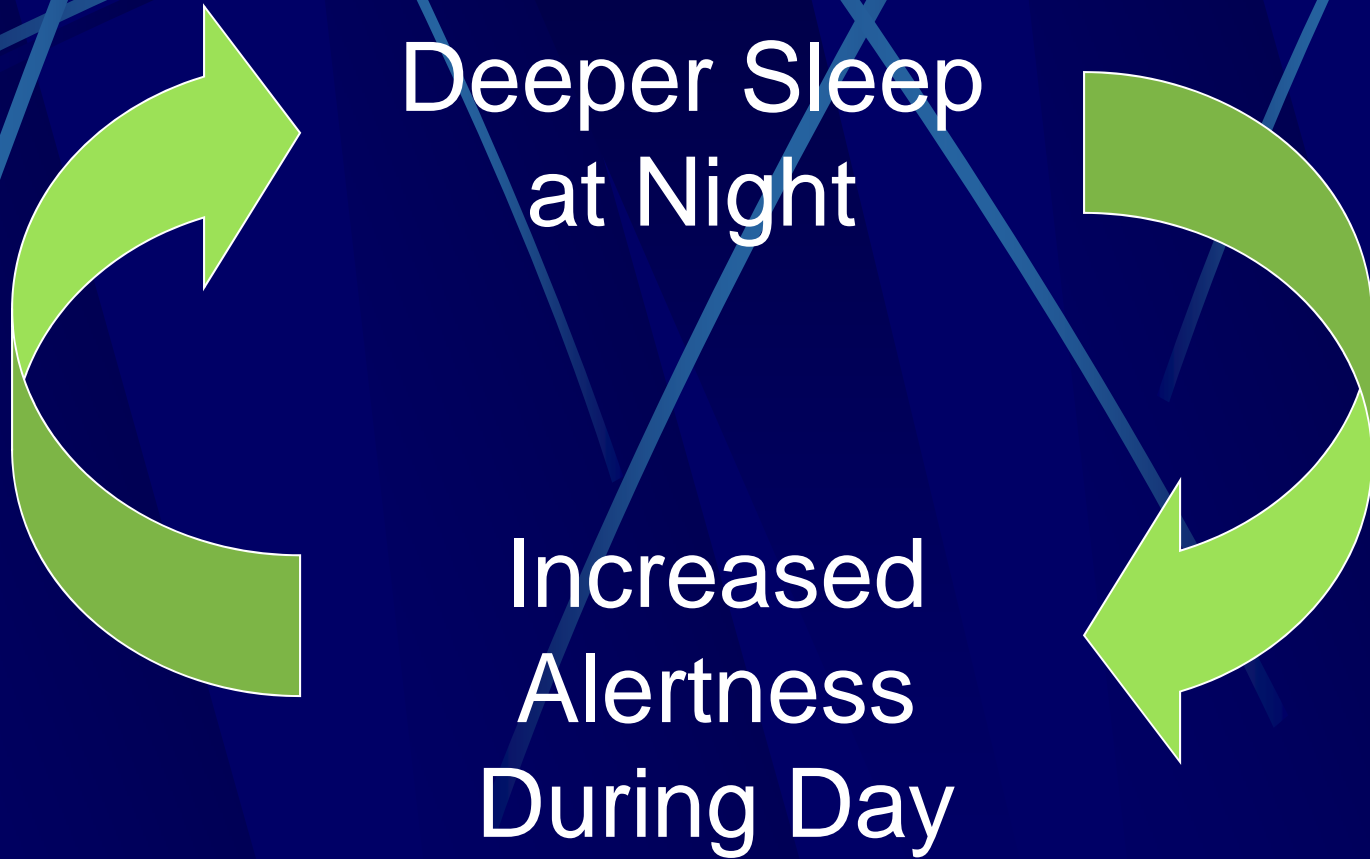
Hypnotics - continued

- **Sedating Antidepressants**
 - Already discussed
- **Natural products**
 - Melatonin can be useful (doses 1-5mg at night)
 - Valerian very weak, but can be used
 - Tryptophan is option (wide dose range)
- **Opiate Pain medications**
 - Milder: Tylenol #3/4, Codeine
 - Stronger: Morphine (MS Contin), Oxycodone (OxyContin), Methadone
 - Can help sleep by reducing pain
 - Long term often increase sleep/sedation, fragmentation
 - Paradoxically feel less restful especially at medium to high doses
- **Benzodiazepines**

Benzodiazepines

- **Common ones**
 - **Medium half-life:** Clonazepam (Rivotril), Temazepam (Restoril),
 - **Short half-life:** Alprazolam (Xanax), Ativan (lorazepam)
 - **Long half-life:** Diazepam (Valium) Chlordiazepoxide (Librium)
- **Medium range are best for promoting sleep**
- **Also used for RLS/PLMD, parasomnias and anxiety**
 - **Avoid long and short acting ones for sleep**
 - **Sleep is still not “natural”**
 - **Less slow wave, REM and increased sleep spindles**
 - **Lower abuse potential/Less rebound**
 - **Short acting ones better for anxiety during the day**
 - **Often get rebound when used at night**
- **Avoid in elderly people/substance abusers**
- **Higher doses can cause airway collapse/relaxation**

Understand Treatment Goal





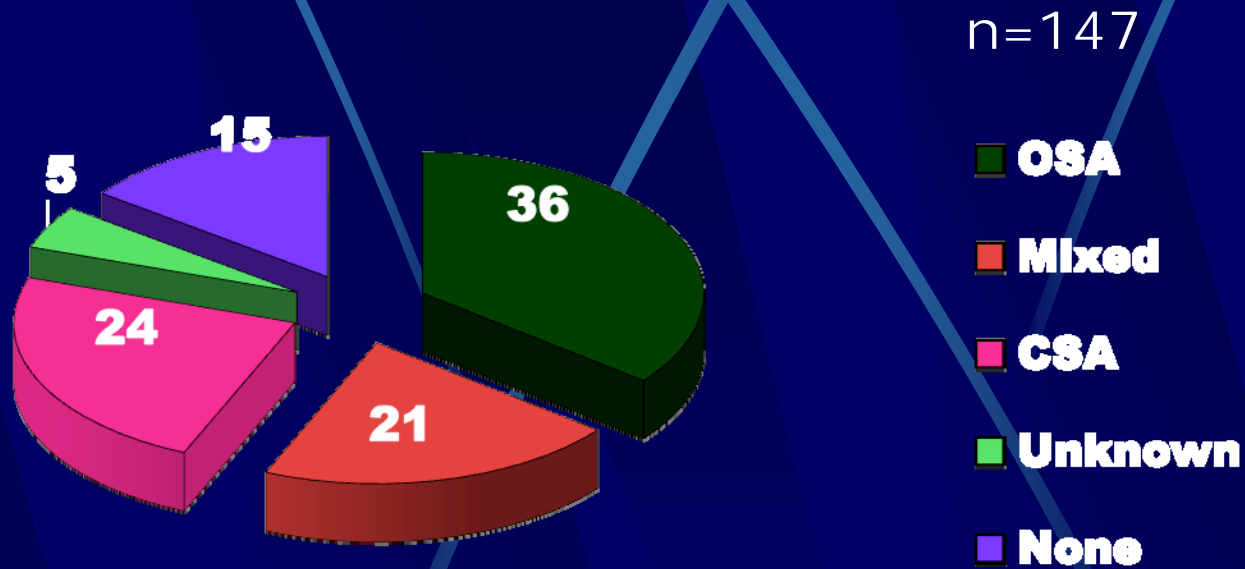
Opiates and Sleep

- **Acute opiate dosing: shortened sleep latency**
 - Paradoxically reduces sleep time/efficiency, REM/SWS sleep
- **Chronic use usually leads to partial tolerance**
 - Increased fatigue, sedation and sleep fragmentation often persists
- **Opioids also cause relaxation of the airway**
 - Depress internal drive to breathe
 - Possibly cause airway collapse
- **Can aggravate/cause OSA**
- **Lead to CSA by lowering drive to breathe**
 - People also become very hypoxic in gradual fashion
 - Aggravated by smoking
 - 30-40% of methadone patients have significant sleep apnea

Opiates & Sleep Apnea

- **Often dose dependent**
 - In vulnerable individuals even low dose can cause
 - Especially if on other sedatives or using too much
- **High rates of central/mixed sleep apnea**
 - Cannot auto-pap these people!!
 - Unsafe and also will lead to poor compliance
 - They need full sleep studies and observed titrations
 - Often only titrate a low pressure to treat obstructives
 - ASV may be useful
 - Even when on straight pressure, download can be misleading
- **Educate pt about effects of opiates on sleep/breathing**

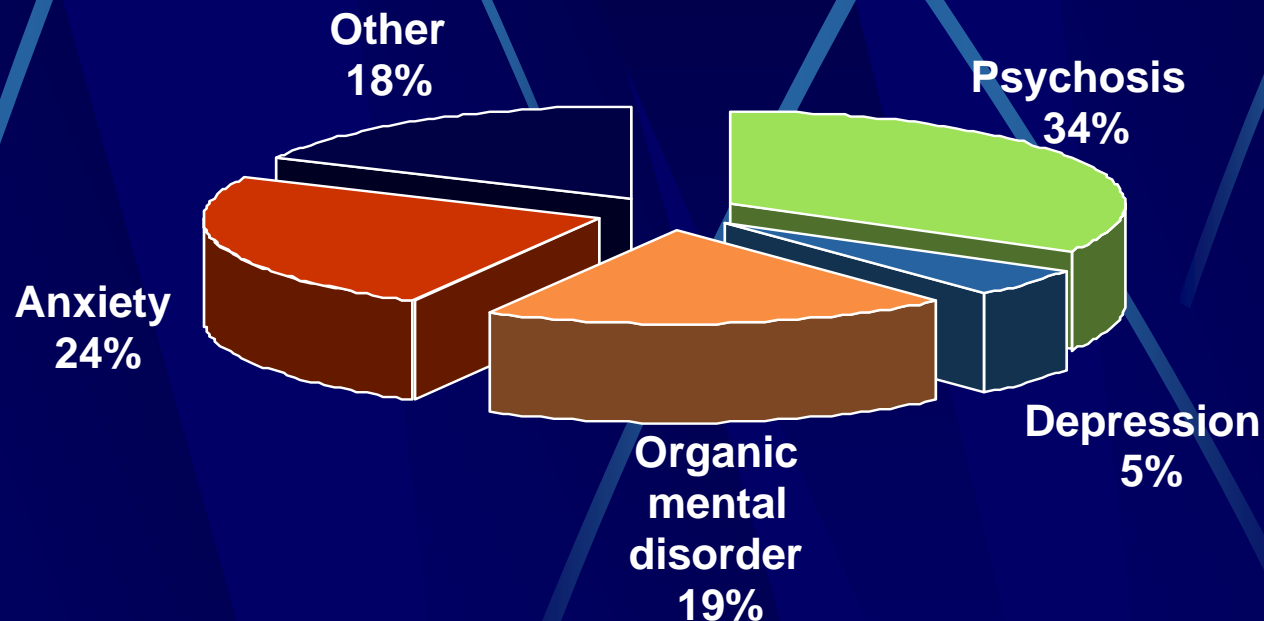
Sleep Apnea in Patients With Opioids



Anti-Psychotics

- Initially called major tranquilizers
- Older ones (typicals) mostly used for schizophrenia and heavy sedation
 - Haldol, Nozinan, Chlorpromazine are some examples
- Newer medications for psychosis (atypicals) share many effects on the brain with AD/mood stabilizers
 - Aripiprazole (Abilify), Quetiapine (Seroquel), Ziprasidone (Zeldox), Olanzapine (Zyprexa), Risperidone (Risperidal), Clozaril (Clozapine) are ones in Canada
- Atypicals more often used in non-psychotic patients

Most anti-psychotics aren't being used for psychosis



New areas of use of atypical antipsychotics

- **Low dose:** Sleep, Anxiety, Depression, Behavior Control (Dementia patients)
- **Medium dose:** Bipolar disorder
- **High dose:** Antipsychotic effect (least common use for some of them)
- All except Abilify and Zeldox can cause significant sedation, weight gain and metabolic disturbance
 - All may cause sleep apnea independent of weight gain

Sleep effects of typical anti-psychotics

- SZ itself has marked effects on sleep
 - Decreased TST, SE, SWS¹
 - Increased Stage 1²
- Typical antipsychotics (TAP) tend to be
 - Sedating, increase SE, SWS, REM suppression
- TAP can produce akathisia that can mimic RLS
 - Distinguished from RLS, by location (global), incomplete resolution with movement and timing (all day)
 - Risperidone and Abilify can do this too

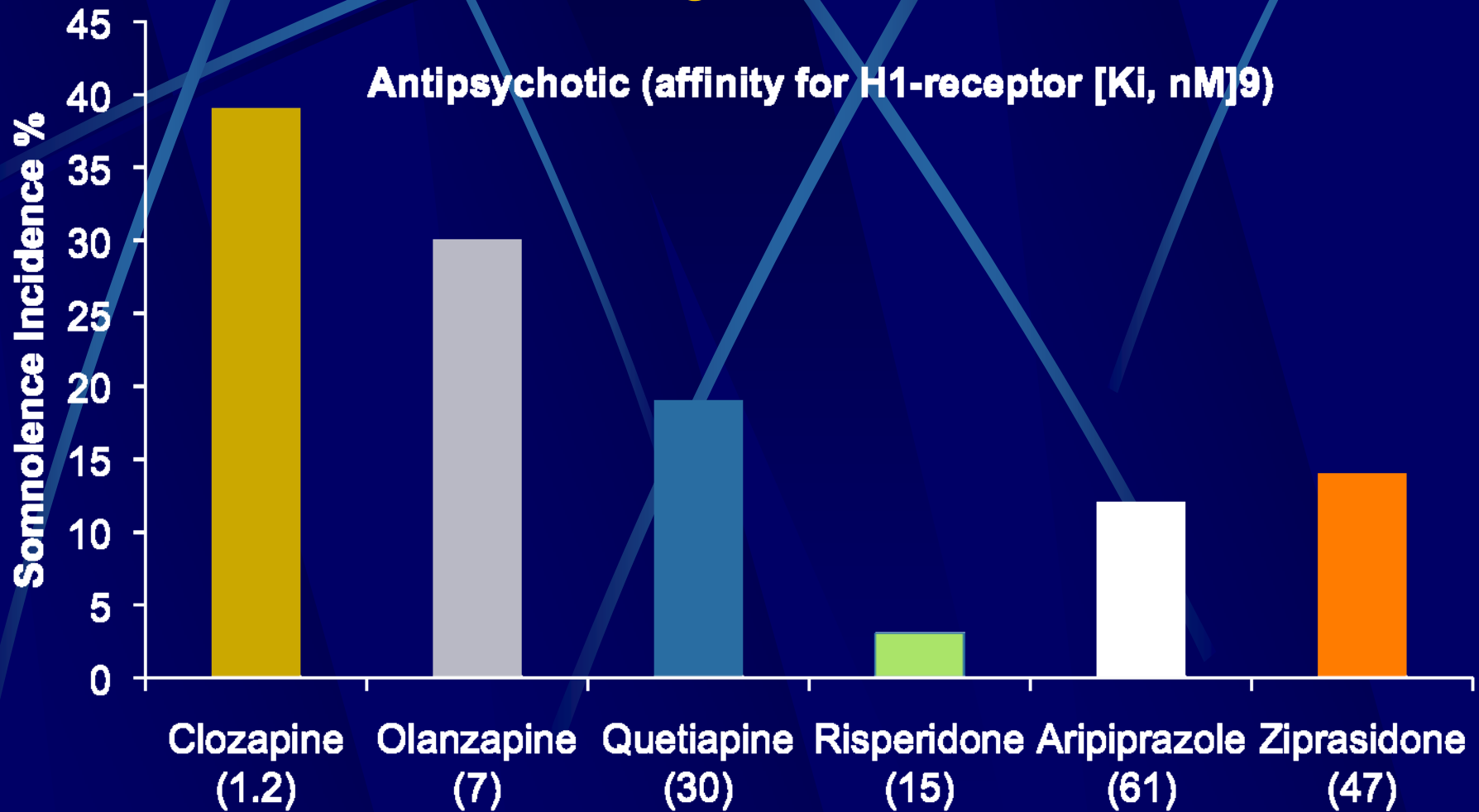
Effects* of new antipsychotics

*This represents an approximation from both consensus of clinicians and evidence from placebo-controlled and comparison trials ^{1,2}

Most ↓ Least	Sedation	Weight gain
	Clozapine Quetiapine (Hi) Olanzapine Quetiapine (Lo) Risperidone Aripipazole** Ziprasidone**	Clozapine Olanzapine Quetiapine (Hi) Risperidone Quetiapine (Lo) Aripipazole Ziprasidone

** - At higher doses these can be sedating, lower doses tend to be activating

Sleepiness and H₁-Receptor Affinity of AAP



Atypical Antipsychotics and Sleep

- Improve sleep continuity compared to older antipsychotics
 - May be due to better treatment of mood symptoms
- Have similar effects on REM as antidepressants
 - Likely due to shared receptor profile
- Most tend to increase slow wave sleep
- Seroquel can cause restless legs/PLMs
 - Has a metabolite that has antidepressant effects on brain
- Context of use can influence changes in sleep
 - Depends on severity of illness being treated

The Spiral of Weight Gain

Mental Illness

Unhealthy Diet
Lack of Physical Activity
Smoking



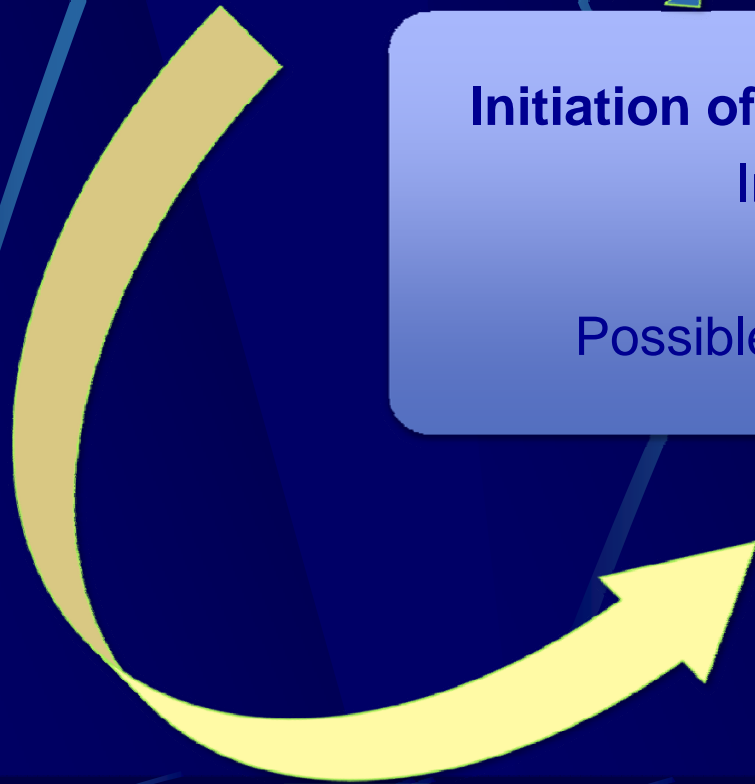
Initiation of weight gaining medication

Increased appetite
Weight gain
Possible direct metabolic effects



Metabolic dysregulation

Diabetes mellitus
Dyslipidemia
Sleep apnea/Hypertension
Increased cardiovascular risk



Potential Weight Change/Year	Wt Loss (0 to -5 lb)	Wt Neutral (0 lb)	Slight Wt Gain (1-5 lb)	Moderate Wt Gain (6-10 lb)	Mod-Sev Wt Gain (11-15 lb)	Severe Wt Gain (>15 lb)
Anti depressants	Bupropion Fluoxetine	Citalopram Duloxetine Escitalopram Sertraline Trazodone Venlafaxine Desvenlafaxine	Desipramine Nortriptyline Paroxetine	Amitriptyline Doxepin Imipramine Mirtazapine MAOI		
Anti psychotics		Aripiprazole Ziprasidone	Low dose quetiapine Fluphenazine Haloperidol Paliperidone	High dose quetiapine Risperidone		Clozapine Olanzapine
Mood Stabilizers	Topiramate	Lamotrigine Oxcarbazepine	Carbamazepine Pregabalin	Gabapentin	Lithium Valproate	
Stimulants	Amphetamine Atomoxetine Methylphenidate	Modafinil				
Sedative-Hypnotics		Benzodiazepine Buspirone Zopiclone			Vieweg et al 2006	

Medication Management When Considering Metabolic Effects

AVOID USING	CAUTION IF USING	CONSIDER USING
Paroxetine Mirtazapine Tertiary Tricyclic Valproic Acid Olanzapine	Lithium Quetiapine Risperidone Pregabalin Gabapentin Secondary Tricyclic	Bupropion Lamotrigine Ziprasidone Aripiprazole Duloxetine Topiramate

Always be aware of idiosyncratic weight gain with other SSRI medications

Lithium and Anti-Convulsants

- Try to dose **all at night** if tolerated & effective
- Mostly for bipolar, bipolar-like disorder
- **Lithium**
 - Sedating, causes daytime fatigue, leg twitches
- **Epival (Valproic Acid)**
 - Can be quite sedating and often causes mental slowness
 - Lithium and Epival can have significant weight gain
- **Tegretol (Carbamazepine)**
 - Somewhat sedating, usually causes fatigue
- **Lamictal (Lamotrigine)**
 - Excellent mild mood stabilizer
 - Can be activating or sedating
 - Often improves sleep by stabilizing mood

Anti-Convulsants

- **Topamax (Topiramate)**
 - More problems with mental slowness, but can be fatiguing
 - Used for migraines, can cause weight loss
- **Gabpentin (Lyrica)/Pregabalin (Lyrica)**
 - Can be good for insomnia/RLS, anxiety
 - Have benzodiazepine type effects, without the tolerance
 - Often unnecessarily given in day, causing sleep problems
 - Very useful for vague pain states, RLS and anxiety
 - Both appear to increase sleep continuity, slow wave sleep
 - Weight gain is possible

What are Stimulants Used For?

- Fatigue, sleepiness, narcolepsy, attention deficit disorder, improving depression
- Common ones Ritalin, Dexedrine, Modafinil (Alertec)
 - Different formulations of Dexedrine/Modafinil (short, medium, long acting)
- Can fragment sleep, especially long acting
 - Individual variation
- Often given to tired patients where sleep apnea or other sleep problem is not ruled out
 - This or a sleeping pill that isn't working may be a red flag for further evaluation

Conclusions

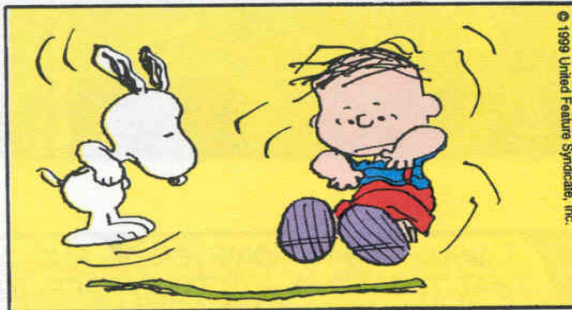
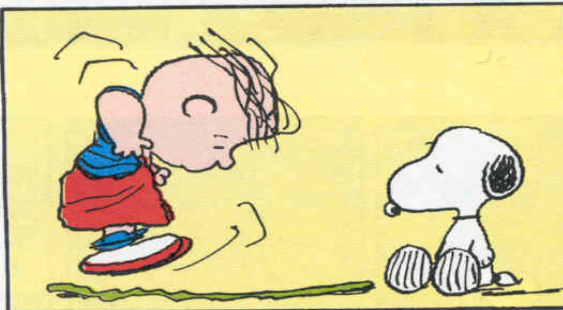
- **Increased use for newer psychoactive agents**
 - Because of lower level of toxicity
 - Effects on sleep difficult to interpret at times
 - Limited data on the sleep effects
- **Can have significant disruption of sleep/wake due to side effects of psychoactive agents**
 - Timing or type of medication dosing can create/solve many cases of “hypersomnolence” or “insomnia”
 - Consolidated dosing is needed
 - Very few global rules, each patient is different

Conclusions - 2

- **People on psychotropic medications at increased risk for weight gain/sleep apnea**
 - Must be more judicious about use of auto-pap/home testing with patients on many psychoactive medications
 - Safety issues with CPAP treatment on patients with opiates and high dose sedatives
- **Review of psychoactive meds is part of the job of anyone who works sleep disorders patients**
 - Often first/next step for the patient who is not responding
 - It will improve the care you give to patients significantly

PEANUTS

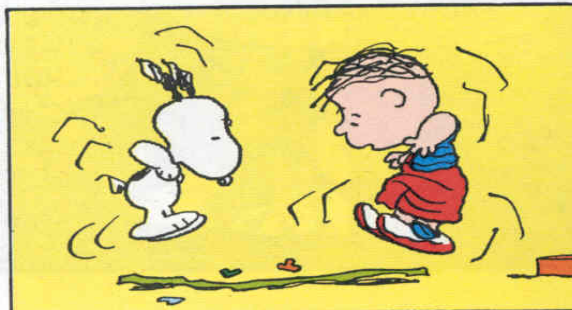
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