

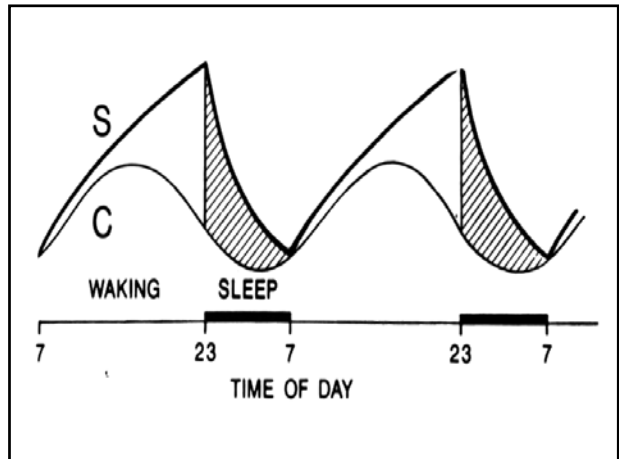
Updates in Sleep Medicine

Professor Y.K. Wing
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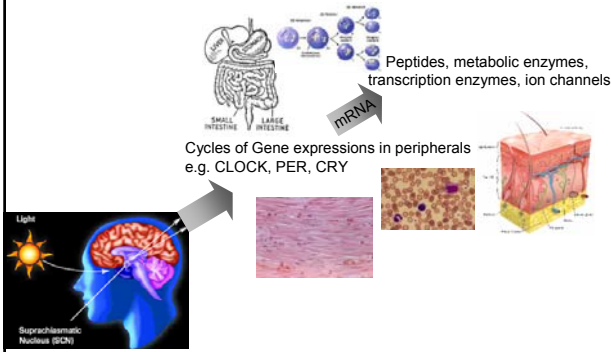
Outline

- Introduction
- Sleep disorders
 - Insomnia
 - Sleep deprivation
 - Narcolepsy
 - Parasomnia
 - Restless leg syndrome
 - Sleep disordered breathing

Introduction



The circadian rhythm: not only sleep & wake control!



Clock genes & diseases

- Sleep disorders:
 - Delay sleep phase
 - Advance sleep phase
 - Jet-lag
- Physical illnesses:
 - Cancer
- Mental illnesses:
 - Affective disorders

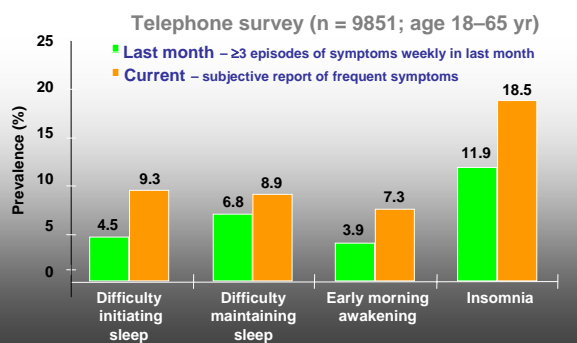
Lamont et al, Sleep medicine 2007

Sleep Disorders

Insomnia

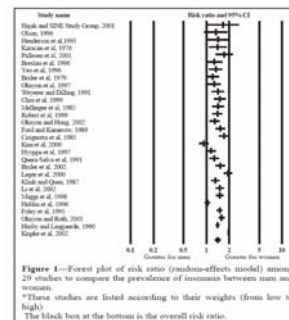
- Types of insomnia:
 - Difficult in initiating sleep (DIS)
 - sleep latency >30mins
 - Difficult in maintaining sleep (DMS)
 - nocturnal awakenings with great difficulty in resuming sleep
 - Early morning awakenings (EMA)
 - abnormal awakening >1.5hr prior to the desired wake-up time
 - Non-restorative sleep (NRS)
 - normal duration of sleep but complain of tiredness at awakening
- DSM-IV criteria:
 - DIS/ DMS/ EMA/ NRS
 - ≥3 times a week for ≥1 month
 - Marked personal distress or interferes with personal functioning in daily living

Prevalence of Insomnia in Hong Kong (1998)



Li & Wing et al. 2002

Sex Differences in Insomnia

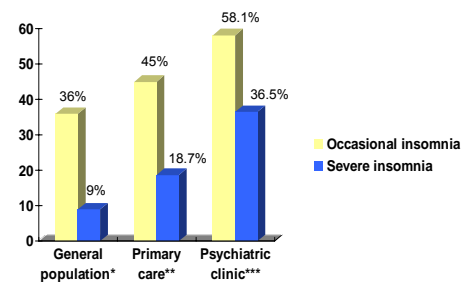


Zhang & Wing 2006

Female & Insomnia – Why more?

- Increase underlying depression & anxiety
- Increase complaint & bodily awareness?
- More stress?
- Sex steroid

Insomnia & clinical population

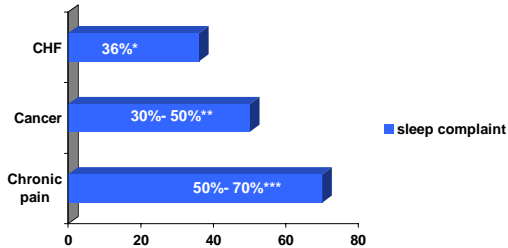


* National sleep foundation 1991;

** Hohagen F, et al. 1993;

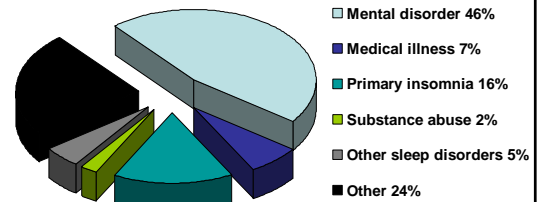
*** Local data, treated psychiatric population 2006

Insomnia & Medical illnesses



* Brostrom A, et al. 2005
 ** Savard J, et al. 2001
 *** Stiefel F, et al. 2006

Common co-morbidities of insomnia



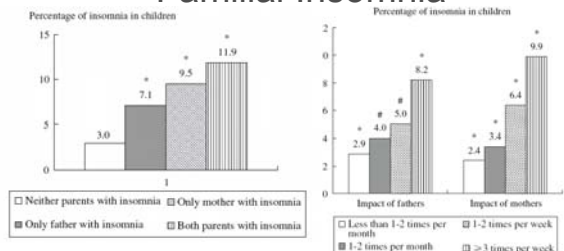
Ohayon MM. 2002

Concept of insomnia as co-morbidities

- Insomnia as
 - Symptoms
 - Co-morbid disorder
 - Predictors of future psychiatric illnesses* e.g. depression, anxiety, alcohol abuse
- Emphasis on management of **both** insomnia and the physical/ psychiatric illnesses

* Breslau et al, 1996; Ford et al, 1989; Fong & Wing et al 2007

Familial Insomnia



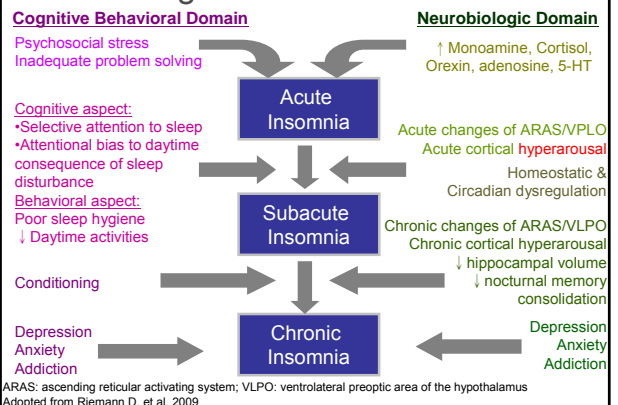
- Strong familial aggregation of insomnia
- Dose response effect

Zhang & Wing et al, 2009

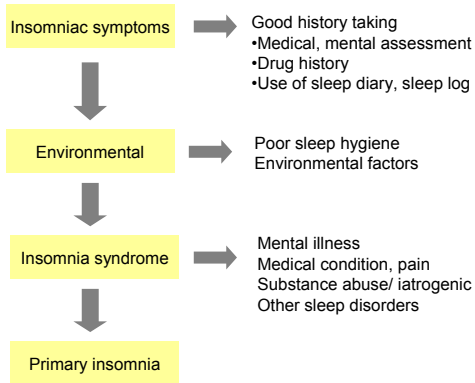
Consequences of insomnia

- Significant morbidities
 - ↑ rate of accidents
 - ↓ performance & productivity
 - ↓ quality of life
 - ↑ risk of depression & other psychiatric disorders
 - ↑ disability
 - ↑ healthcare utilization
 - ↑ BP & mortality

Neuro-cognitive Model of Insomnia



Management of insomnia: Start with Good Assessment!



Insomnia Treatment

- Pharmacotherapy
- Non-pharmacological treatment:
 - Sleep hygiene
 - Behavioral modification:
 - Sleep restriction
 - Relaxation
 - Cognitive behavioral therapy

Pharmacological Tx of insomnia: the Principle

- Treat co-morbid medical & psychiatric illnesses
- Short term use of hypnotics
- “Ideal Hypnotics”:
 - Short acting
 - No hangover effect
 - No dependence

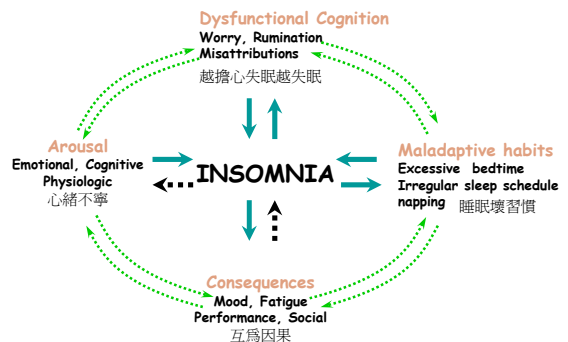
Commonly used drugs for insomnia

	Usual therapeutic dosage (mg/ day)
Non-Benzodiazepine hypnotics	
– Zopiclone (Imovane)	3.75- 7.5
– Zolpidem (Stilnox)	5-10
Short-acting Benzodiazepine	
Lorazepam (Ativan)	0.5-1.5
Long-acting Benzodiazepine	
– Diazepam (Valium)	2-30
– Clonazepam	0.5-6
Other off-label use sedative drugs:	
– Antihistamine	
– Sedative antidepressants (low dose)	
– Sedative neuroleptics (low dose)	

Newer hypnotics

- Melatonin related:
 - Ramelteon: MT1/ MT2 receptor agonist
 - Agomelatine: MT1/ MT2 receptor agonist with 5-HT2c antagonism
- Other investigational products:
 - 5HT2A receptor antagonist
 - Orexin/Hypocretin antagonist

A Microanalytic Model of Insomnia



Morin C.M. (1993) Insomnia: Psychological Assessment and Management. The Guilford Press. P57

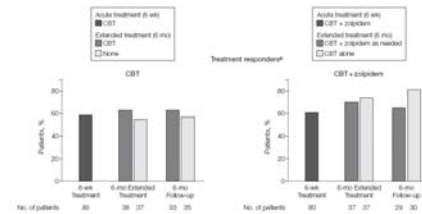
Cognitive Therapy for Insomnia

- Some dysfunctional belief in insomniacs:
 - Unrealistic expectation about sleep
“ I *must* sleep 8 hours a day”
 - Magnification of consequence of insomnia
“ I *cannot function at all* after a bad night”
- Therapy:
 - To identify these dysfunctional belief
 - Build up correct attitude about sleep

*Morin CM et al. 2009

CBT vs Combined therapy

- CBT achieved high remission rate in both acute & chronic phases

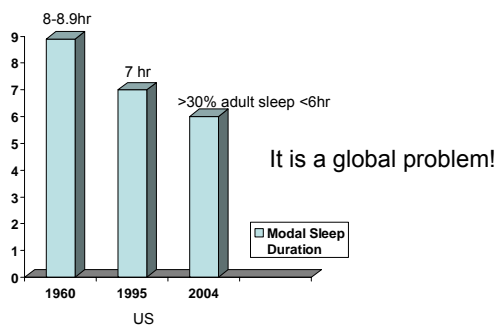


Sleep Deprivation

How much sleep do we need?

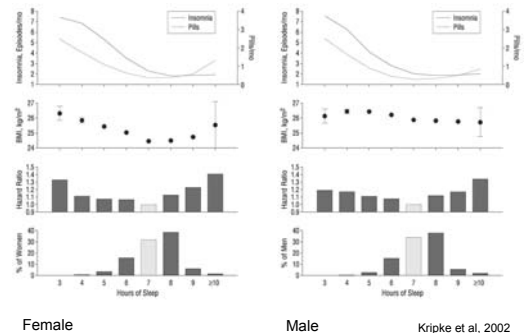
- Individual variation
- 8 hrs rule may not apply
- Sleep as essential vs. luxury (cf. food)
- Are we sleep deprived in modern era?

We are sleeping less!



Knutson KL, et al. 2008

Sleep duration & Mortality

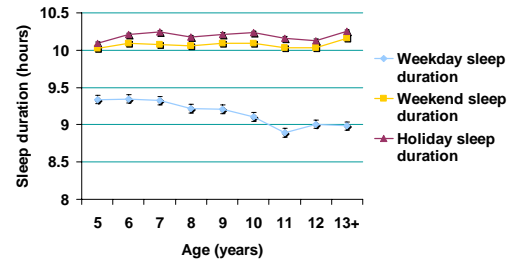


Kripke et al. 2002

Sleep duration & Mortality

- The best survival was found among those who slept 7 hrs (6.5-7.4hrs) per night
- U-shaped curve
 - ↑ mortality hazard in those sleeping > 8 hr or < 6 hr

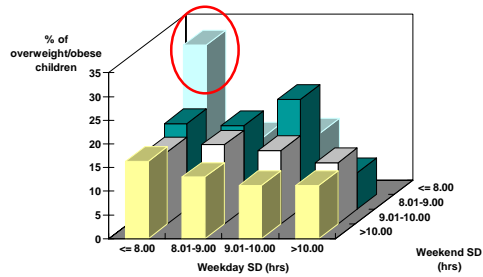
Hong Kong Epidemiological study (2003) Sleep durations in school age children



Wing et al. 2009

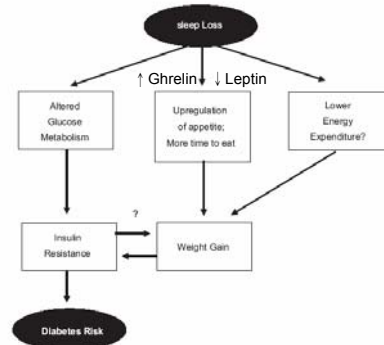
Sleep durations - Interaction effect

Percentages of overweight/obesity as a function of weekday and weekend sleep durations



Wing et al. 2009

Metabolic consequence of sleep deprivation



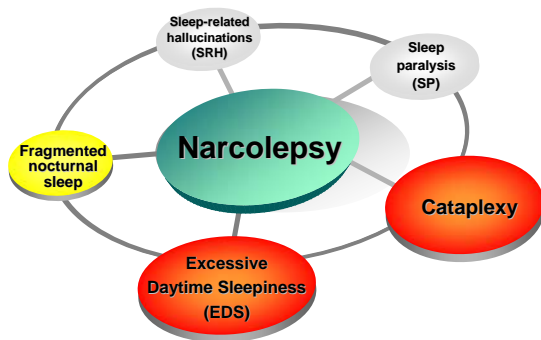
Knutson KL, et al. 2007

Treasure your sleep, Treasure your health!

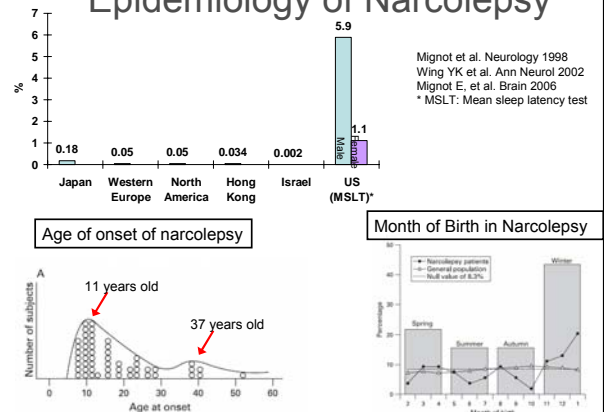
- All start with better management of:
 - Priority – sleep is essential and important!
 - Time allocation
 - Sleep hygiene
 - Stress coping

Narcolepsy

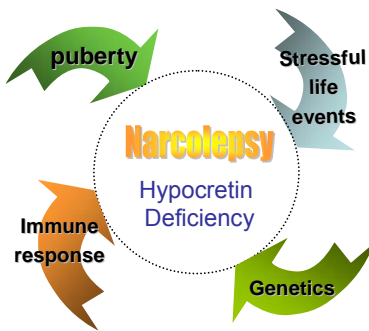
Symptoms of Narcolepsy



Epidemiology of Narcolepsy



Etiologic Risk Factors for Narcolepsy



Impact of Narcolepsy

- Stigmatization
- Crippling effect on academic and work performance
- Increased accident rates



Treatment of narcolepsy

- Sleep hygiene!
- Regular naps if needed
- Pharmacological options:
 - EDS: stimulants (methylphenidate, modafinil)
 - Cataplexy, sleep paralysis: antidepressants

Pharmacological treatment for EDS

Types	Classification/ Mechanism of Action
Caffeine	Stimulant
Methylphenidate	Stimulant Block reuptake of monoamines (mainly dopamine)
Modafinil	Non-stimulant wake promoting agent Mechanism unknown
Sodium oxybate	Na-salt of GHB CNS suppressant, acting on GABA
Selegine	MAO-B inhibitor Metabolized to amphetamine & methylamphetamine
Reboxetine	Selective noradrenaline reuptake inhibitor
Ritanserin	5-HT2 antagonist

Clinical Experience in HK

Medication	Usual Dosage	
Methylphenidate (Ritalin)	10-40mg	Lower cost Short acting Multi-dosage
Modafinil	100-400mg	Longer-acting Once daily/BD Well tolerability
Sodium Oxybate	30-45g	Consolidate nocturnal sleep Restricted usage Abuse potential

Pharmacological consideration

- To optimize control of EDS:
 - Time of dosage according to individual basis
 - Multi-dosage, particularly for short acting stimulant
 - Combination therapy:
 - Use of both short & long acting drugs e.g. modafinil & methylphenidate
 - Emphasize on sleep hygiene!
 - Management of nocturnal symptoms

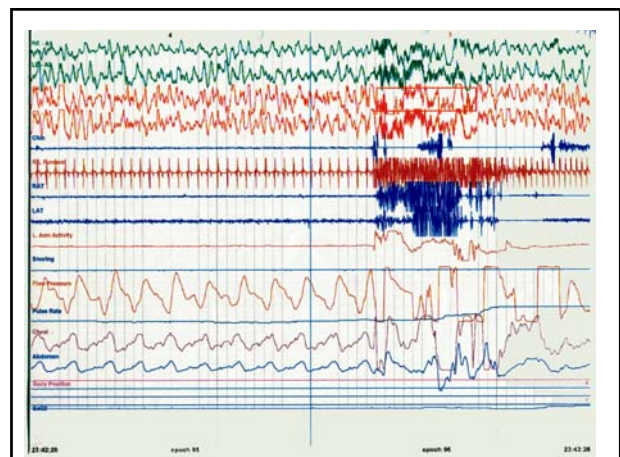
Parasomnia

Parasomnia

- Undesirable events during sleep
- Manifested as sleep-related movement, perception, autonomic functionings
- Examples:
 - Sleepwalking (Somnambulism)
 - Night terror

Sleepwalking

- Ambulation during sleep, arising at slow wave sleep
- Characterized by:
 - Ambulation under altered consciousness
 - Difficult to be aroused during the event
 - Amnesia about the event



Sleepwalking

- More common in children:
 - 10-20% of healthy children have had at least one episode of sleepwalking
 - Subsided with increasing age
 - Equal distribution in both sexes
 - Recurrence of sleepwalking: look for co-morbid sleep apnea
- Adult onset sleepwalking is rare:
 - Prevalence ~1%
 - More likely to be associated with psychopathology, medical illnesses, drug usage esp. hypnotics

Prevalence of parasomnia in Psychiatric clinic*: Clinical epidemiological study in HK

	<u>Sleepwalking</u>	<u>Sleep-related eating disorder (SRED)</u>	<u>General population (Sleepwalking)</u>
Lifetime prevalence	8.5%	4.0%	2-3.9%
1-year prevalence	2.9%	2.4%	

Association with psychotropic usage (Polypharmacy):

- Sleepwalking:
 - Sedative antidepressants OR 2.4 (1.1- 5.8)
 - Non-benzodiazepine hypnotics OR 6.8 (3.0- 15.1)
- SRED:
 - Zopiclone usage OR 22.1 (8.2- 59.8)
 - Sedative antidepressants OR 4.7 (1.4-15.9)
 - SSRIs OR 5.1 (1.6- 16.6)

* Lam et al. 2008

Management of sleepwalking

General:

- Home safety
- Management of potential triggers:
 - Avoid sleep deprivation
 - Early management of febrile condition
- Stress management
- Avoid alcohol

Adult sleepwalkers:

- Work up for underlying aetiology
- Treat psychopathology, co-morbid sleep disorders e.g. OSAS
- ? Hypnotics related

Pharmacological options

- Reserved for subjects:
 - Refractory to non-pharmacological treatment
 - Frequent sleepwalkers with potential danger
- Drug options:
 - No well conducted control trials
 - Common choice: benzodiazepine

Another sleep walking?

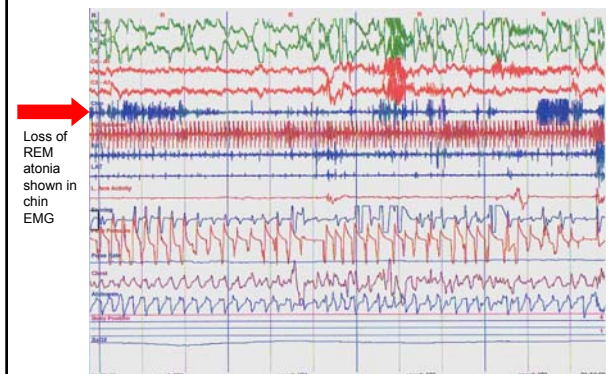
Case

- Male, 81 yrs
- Duration: 10 yrs
- Injuries during sleep: bruises over limbs/head; frequent falls from bed: used mattress on floor for protection; punched wife several times
- No significant physical illness
- Frequent dreams and acting out

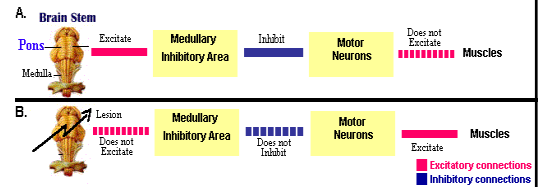
REM Sleep Behavior Disorder

- Symptoms
 - violent behaviors during sleep
 - attempt to enact dream
 - injury to self or bed-partner
- Epidemiology
 - 0.38%-1% of the elderly population
 - male, elderly

PSG showing loss of REM atonia



Anatomical Mechanism of RBD



A. Normal REM sleep

B. RBD REM sleep

RBD & Neurodegenerative diseases

- RBD was found to be early precursor of:
 - Parkinson's disease
 - Lewy body dementia
 - Other synucleinopathy
- Pathophysiology:
 - Neurodegenerative process

RBD & Psychiatry

- Atypical RBD in psychiatric patients:*
 - Younger age
 - Female predominance
 - Associated with:
 - Antidepressant usage esp. SSRI
 - Depression
- Aetiology:**
 - more complex than a mere drug induced condition

Lam & Wing et al. 2008
Lam & Wing et al. Submitted

Management

- Work up:
 - PSG for ascertainment of diagnosis
 - Look out for co-morbid neurodegenerative diseases
 - Drug related?
- Home safety
- Drug treatment:
 - Clonazepam: effective for 90% of cases
 - Melatonin

Restless leg syndrome

Restless leg syndrome (RLS)

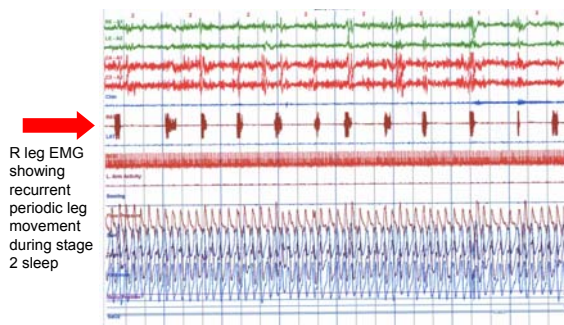
- Uncomfortable dysesthesias or paresthesias, mostly in the lower limbs
- Motor restlessness
- Occurring primarily at rest in the night and alleviated by movement

RLS

- Worsen by:
 - Caffeinated drinks
 - Pregnancy
 - Prolonged exposure to cold
 - Iron deficiency
 - Uremia
- Commonly associated with periodic leg movement syndrome (PLMS)

*Karatas M. The Neurologist 2007

PLMS Polysomnography



PLMS

- Condition characterized by:
 - Repetitive stereotypic movements during sleep, mostly affecting the lower limbs
 - PSG features, subjects may not have active complaints
- Prevalence: 3.9%- 11% in general population
- ↑ with advancing age
- Pathophysiology:
 - Hypodopaminergic
 - Genetic: 63% 1st degree relative of PLMS proband have PLMS*

*Montplaisir et al., 1996; Ondo et al, 1996; Walters et al., 1996

PLMS & HT in Children

- PLMS as a risk factor for HT

Night BP parameters	PLMS N=17	Non-PLMS N=297	Crude OR	Adjusted OR [#]
Systolic BP mean (mmHg)	103±12	100±8		
Diastolic BP mean (mmHg)	61±8	59±5		
Systolic BP z score	0.63±1.46	0.24±1.03		
Diastolic BP z score	0.85±1.46	0.24±1.03		
Mean arterial pressure z score	0.86±1.29	0.71±0.78		
Systolic pre-HT, N (%)	5(29.4)	45(15.2)	2.33(0.78-6.94)	2.71(0.88-8.39)
Diastolic pre-HT, N (%)	7(41.2)	65(21.9)	2.50(0.92-6.82)	2.55(0.90-7.22)
Systolic HT, N (%)	5(29.4)	27(9.1)	4.2(1.4-12.7)*	6.3(1.8-20.9)*
Diastolic HT, N (%)	7(41.2)	38(12.8)	4.8(1.7-13.4)*	4.8(1.7-14.1)*
Systolic and diastolic HT, N (%)	5(29.4)	11(3.7)	10.8(3.3-36.1)*	18.5(4.6-74.3)*
Systolic or diastolic HT, N(%)	7(41.2)	53(17.8)	3.2(1.2-8.9)*	3.3(1.2-10.0)*

Adjusted for age, gender, risk for OSA and birth history
*p<0,05

Wing et al. In press

Management of RLS

- Work up:
 - Clinical history + PSG for PLMS
 - Blood taking for iron deficiency
 - Drug related condition?
- Treatment options:
 - Clonazepam
 - Dopamine agonist

Sleep Disordered Breathing

Adult vs. Childhood OSAS

	Adult	Child
Snoring	+++	++
Daytime Sleepiness	>90%	30%
Behavioral & Learning	+	+++
Gender	3:1	1:1 (?more boys)
Obesity	++	+
Adenoid and Tonsils	Some	+++
Treatment	CPAP	Adenotonsillectomy

Ferber et al 'Principles and Practice of Sleep Medicine in the Child'
Wing et al, 2003

Childhood OSAS

- Habitual snoring (88%)
- Struggle to breathe during sleep (74%)
- Restless sleep (74%)
- ↑ night sweats (58%)
- Witnessed apnoea (24%)
- Enuresis (8%)

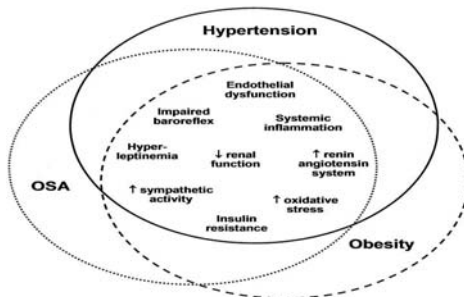
Li et al, 2001

Consequence of OSA in Childhood

- Neurobehavioral morbidity
- Hypertension
- Cardiovascular morbidity
- Poor growth



HT & OSAS



Thromb 2008;63:803-808. doi:10.1136/thx.2007.091132

Sleep-disordered breathing

Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study

A M Liu,¹ C T Au,¹ R Y T Sung,¹ C Ho,² P C Ng,¹ T F Fok,¹ Y K Wing²

Subjects aged 6-13 from local primary school N=466

Exclusion:
• Primary snorer
• Previous Tx of OSA
• Facial Dysmorphology & neurological disease

Control group

AHI ≤ 1

N=127

Mild OSAS

1 < AHI ≤ 5

N=133

OSAS

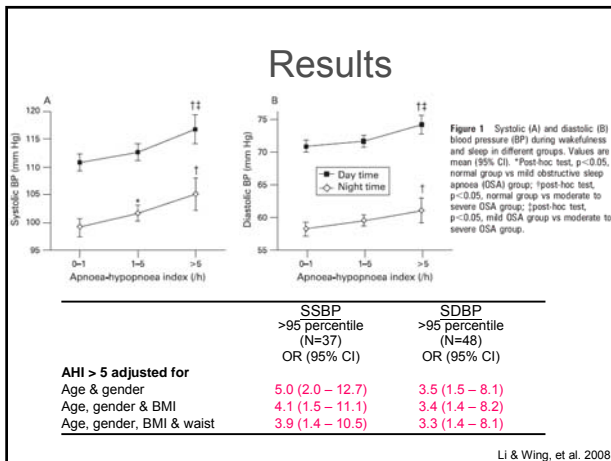
AHI > 5

N=46

Overnight PSG

BP Measurement (Day: Q30min; Night: Q1hr)

HT definition: 1) mean SBP/SDP >95th percentile 2) Z score



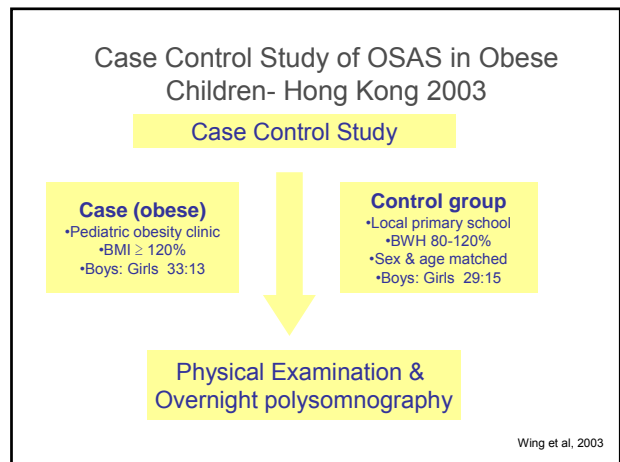
HT & OSAS: Local study conclusion

- BP levels ↑ with severity of childhood OSAS
- Effect independent of obesity
- AHI > 5 had significantly higher risk for nocturnal systolic & diastolic HT

Cardiac remodeling in Childhood OSAS

- AHI ≥ 5 is associated with:
 - Sub-clinical RV & LV dysfunction
 - Effect independent of obesity
- Treatment with resultant > 50% ↓ in AHI is associated with reversibility of the cardiac dysfunction

Chan & Wing et al. 2008



Results

		Obese	Control
AI	1	14 (30.4)	10 (22.7)
	5	7 (15.2)	1 (2.3)
OAI	1	12 (26.1)	1 (2.3)**
	5	7 (15.2)	1 (2.3)
AHI	1	36 (78.3)	31 (70.5)
	5	15 (32.6)	2 (4.5)**
ODI 1.4		28 (39.1)	12 (27.3)**

** p<0.01

- Obese children have ↑ risk of childhood OSAS, predominantly obstructive type
- Obesity is an independent risk factor for childhood OSAS

Adenotonsillectomy for Childhood OSAS

- ↓ pulmonary hypertension
- Improved growth
- Improve neurocognitive function
- ↓ nocturnal enuresis

- Need further clarification for:
 - Childhood OSAS cut-off for intervention
 - Guideline for surgical treatment

Leiberman A, et al. 2006

Adult OSAS in commercial drivers

- Prevalence of OSAS & OSAS symptoms in commercial bus drivers: (Phase 1 N= 1016, home PSG N= 211)
 - Sleepiness at work: 69%
 - Fallen asleep while driving: 24%
 - Snoring > 3nights/ week: 23.9%
 - Witnessed apnea: 3.7%
 - RDI \geq 5: 40.3%
 - RDI \geq 15: 17.5%
- Acceptance of CPAP treatment is low

Hui DS et al. 2006

Adult OSAS: Vascular risk factors

Table 2—Metabolic Parameters in the OSA Group and Control Group*

Serum Concentration	OSA Subjects (n = 30)	Control Subjects (n = 30)	p Value
Leptin, ng/mL	9.18 \pm 4.24	6.54 \pm 3.51	0.001
Glucose, mmol/L	5.7 \pm 1.7	5.3 \pm 0.7	NS
Insulin, ng/mL	0.39 \pm 0.17	0.26 \pm 0.13	0.003
Hemoglobin A1c	0.07 \pm 0.04	0.05 \pm 0.03	0.01
Cholesterol, mmol/L	5.2 \pm 0.9	4.5 \pm 1.0	NS
\geq 5.2 mmol/L	14 (47)	11 (37)	NS
LDL cholesterol, mmol/L	3.4 \pm 0.7	3.1 \pm 0.9	NS
\geq 3.4 mmol/L	14 (47)	10 (33)	NS
HDL cholesterol, mmol/L	1.30 \pm 0.35	1.12 \pm 0.29	NS
\leq 0.9 mmol/L	19 (63)	22 (73)	NS
TC/HDL cholesterol ratio	5.1 \pm 1.6	4.5 \pm 1.3	NS
\geq 5.0	15 (50)	7 (23)	0.032
Triglyceride, mmol/L	1.6 \pm 0.6	1.2 \pm 0.6	0.026
\geq 2 mmol/L	10 (33)	2 (7)	0.01

*Values are given as mean \pm SD or No. (%) unless otherwise indicated. NS = not significant.

- \uparrow serum leptin in OSAS group with control of BMI
- Normalization of serum leptin with CPAP treatment
- Possible mechanism:
 - \uparrow fat mass
 - \uparrow leptin resistance

Ip M et al 2000

Treatment of sleep apnea

- Obstructive SAS (OSAS)
 - General
 - Weight reduction
 - Sleep hygiene
 - Avoid alcohol/sedative drug
 - Sleep position training
 - Specific
 - CPAP
 - Surgery
 - Dental appliance
- Central SAS
 - Respiratory stimulants