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Drugs and Sleep: What the Cardiologist should know

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GRACE-PENN MEDICINE

ESH

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Before knowing if the patient has Sleep Disorders

Drugs adversely affecting OSA thus overstimating severity

- Benzodiazepines,
- Opioids,
- Muscle relaxants,
- Male hormones

- Testing could be done with (real life setting)
- Drugs can be weaned to improve symptoms

Before knowing if the patient has Sleep Disorders

Drugs that do not affect OSA and can even potentially improve respiratory function during sleep underestimating severity :

- anti-inflammatory drugs,
- diuretics,
- bronchodilators,
- acetylcholinesterase inhibitors,
- antiparkinsonian,
- decongestant drugs, drugs for intranasal use,
- topical soft tissue lubricant,
- female sex hormones.

Once diagnosis has been established

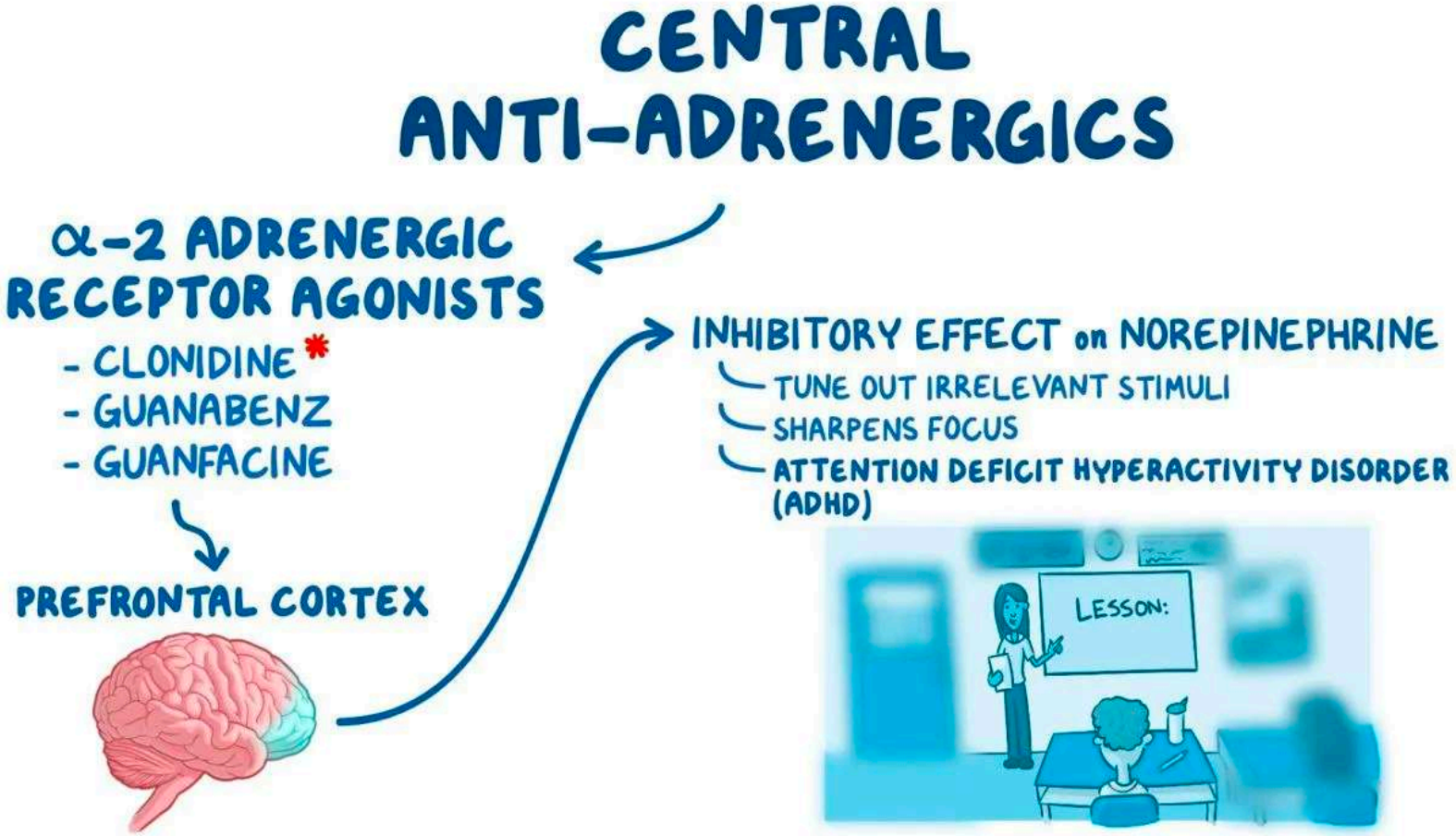
- Management of the disease can directly/ indirectly improve sleep pattern:
  - Central Sleep Apnea and HF
  - Body weight reduction in HTN or patient with Diabetes
- Management of the disease can sometimes avoid / post pone requirement for ventilation

EN FRANCAIS

- PEU IMPORTE LE SOMMEIL !!
- BENEFICE CV >> RISQUE SOMMEIL
- MAIS ADAPATATION POUR AMELIORER LE CONFORT , LES SYMPTOMES ET DONC ADHESION

Alpha Blocker:
IMPORTANCE OF CENTRAL EFFECT

Alpha Blocker (false)



ALPHA-2 ADRENERGIC AGONISTS

* OPPOSE EFFECTS of SYMPATHETIC NERVOUS SYSTEM

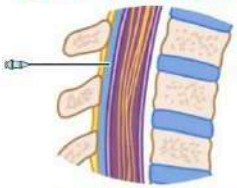
* ↓ SMOOTH MUSCLE CONTRACTION

ORALLY
↳ TREAT ADHD

* CLONIDINE
* GUANFACINE
* METHYLDOPA

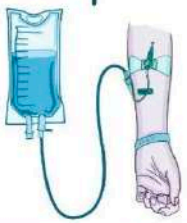
TRANSDERMALLY
↳ TREAT HYPERTENSION

LESS FREQUENTLY



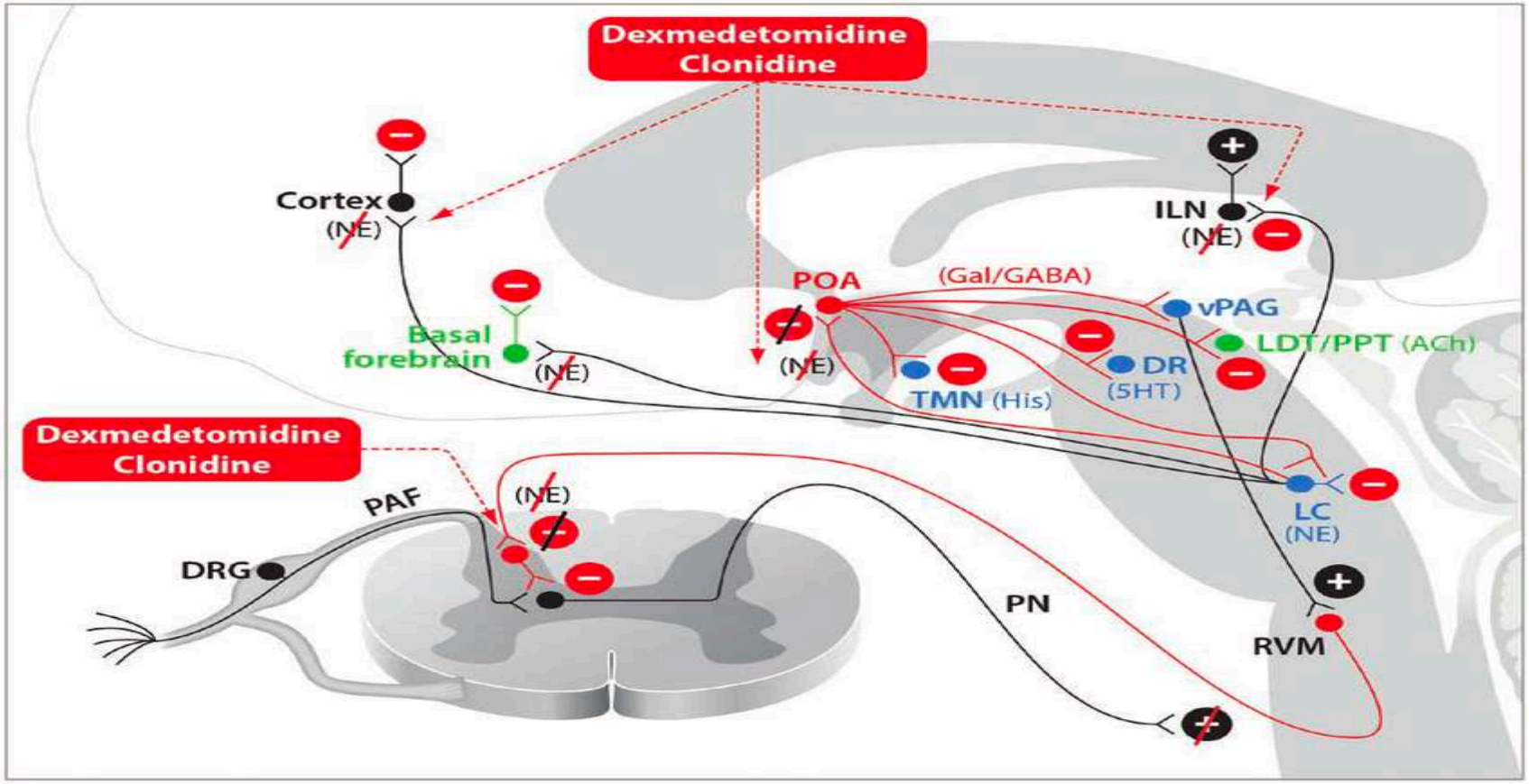
EPIDURAL
↳ PAIN MANAGEMENT in CANCER

ORALLY



INTRAVENOUSLY
↳ TREAT HYPERTENSIVE CRISES

Dexmedetomidine
cousin de la clonidine



Clondine et Dexmetomidine

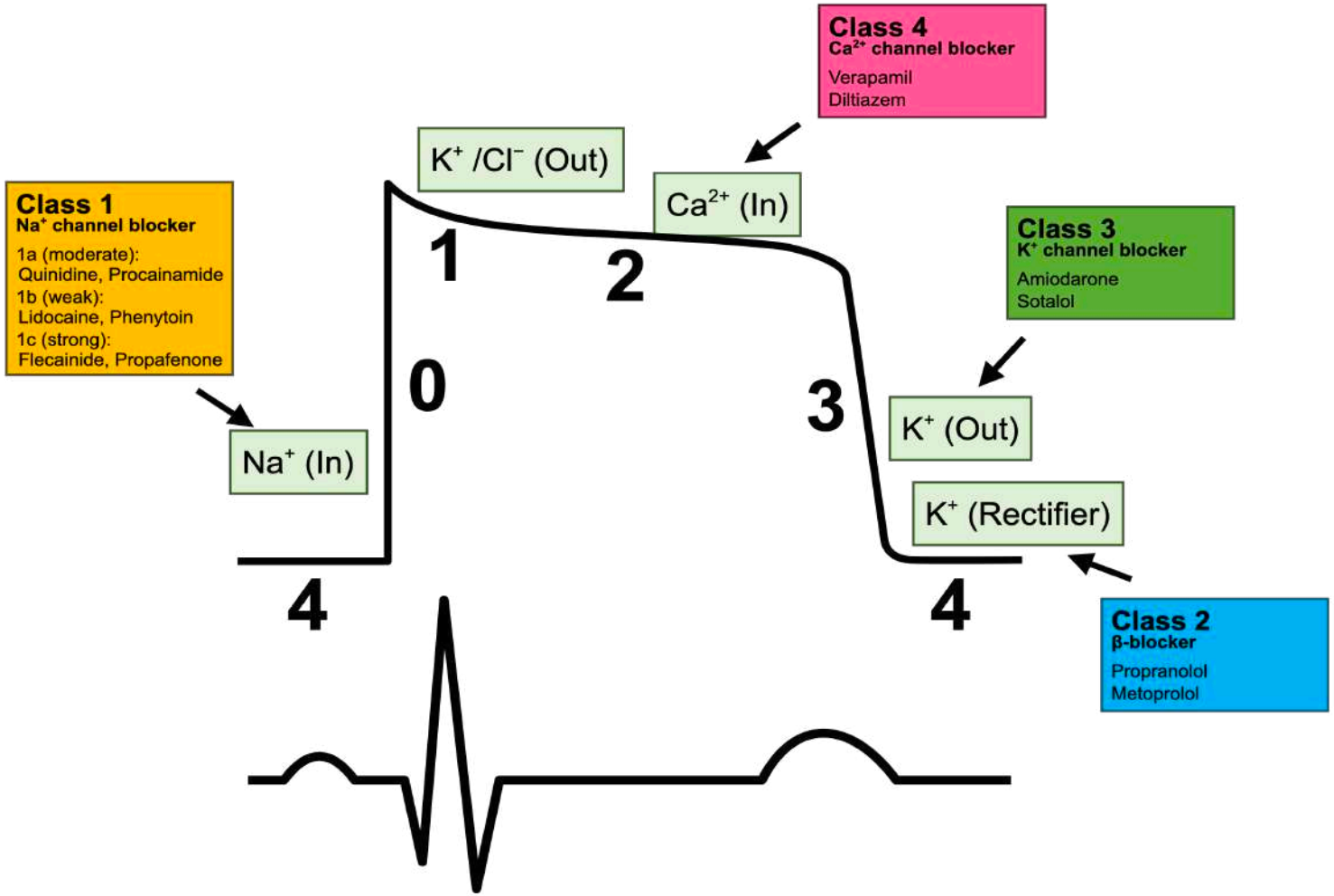
Authors	Study design	LOE	Diagnosis	Type of surgery	Pts N	Intervention	Medication requirement	Pain and emergence	Hemodynamics	Respiratory events	Hospital stay
Pawlik[27] 2005	RCT	1b	PSG	Septoplasty ± UPPP	30	Oral clonidine 2 ug/kg the evening before and 2 h before induction	↓ Propofol (P <0.05). ↓ Antihypertensives (P <0.001)	↓ mean VAS in PACU and 24h (P <0.001) in clonidine group; faster eye opening on command in clonidine group (P <0.05)	↓ MAP and HR during surgery and emergence in clonidine group (P <0.001)	↓ desaturation indices in perioperative period vs baseline values in both groups (P <0.05)	NA
Chawla [40] 2010	Chart review$	2c	Previous h/o OSA	Airway re-construction	Dex 125 Control 143	Dex 1 ug/kg and infusion of 0.1-0.2 ug/kg/hr	↓ Hydralazine (P <0.001) ↓ GTN (P = 0.005) ↓ Clonidine (P <0.001) ↓ Beta blockers (P <0.001)	↓ Morphine (P = 0.008)	Stable MAP	NA	NA
Olumuyiwa[42] 2009	Cohort$	2c	PSG	Laparoscopic bariatric	22 OSA pts	Dex 1 ug/kg and infusion at 0.4 ug/kg/hr	No intraoperative opioid needed	↓ Pain score in PACU; No postoperative opioid needed	Stable hemodynamics	NA	NA
Dhar[38] 2003	Case series	4	Previous h/o OSA	Laparoscopy; colostomy	2	Dex 1 ug/kg and infusion at 0.2 ug/kg/hr	NA	Smooth emergence	Stable hemodynamics	No adverse events	NA
Basem[41] 2007	Case series	4	Previous h/o OSA	Tracheos-tomy	5:2 OSA pts	Dex 1 ug/kg and infusion at 0.6 ug/kg/hr	NA	Patients comfortable	Transient ↓ BP	No adverse events	NA
Plunkett[36] 2009	Case report	4	Previous h/o OSA	Awake Thy-roidectomy	1	Dex 1 ug/kg and infusion at 0.2-1.0 ug/kg/hr	↓ Fentanyl	↓ Pain score in PACU	Stable intraop vital signs	No adverse events	NA
Ramsay[37] 2006	Case report	4	Previous h/o OSA	Tracheal resection	1	Dex 1ug/kg and infusion at 0.7-10 ug/kg/hr	No intraop or postop opioid	No pain Smooth emergence	↓ BP	SpO_2 >95% throughout the procedure	2 days
Hofer[44] 2004	Case report	4	Previous h/o OSA	Roux-en-Y gastric bypass	1	Dex 1.4 ug/kg and infusion at 0.7 ug/kg/hr	NA	↓ Morphine	NA	NA	NA
Huncke[36] 2008	Case report	4	Previous h/o OSA	Awake craniotomy	1	Dex 0.4ug/kg and infusion at 0.1-0.2 ug/kg/hr	Remifentanil infusion	Minimal pain; Mildly sedated; Verbally responded	NA	No adverse events	NA

RCT: Randomized double-blinded placebo-controlled trial; LOE: Level of evidence; Pts N: Number of patients; $: Retrospective; UVPP: Uvulo palato pharyngoplasty; PSG: Polysomnography; OSA: Obstructive sleep apnea; Dex: Dexmedetomidine; PACU: Post anesthesia care unit; NA: Not available; SpO_2: Oxygen saturation; VAS: Visual analog scale; MAP: Mean arterial pressure; HR: Heart rate

Inconsistent Data

- One study in hypertensive patients found that clonidine decreased total sleep time, however another study in healthy patients showed that clonidine increased total sleep time.
- Another study reported that clonidine suppressed rapid eye movement (REM) sleep and the apneas occurring during REM, which decreased nocturnal hypoxemia.
- Despite the inconsistent data on the effects of the alpha adrenergic agonists on sleep quality it is clear that the class exhibits a high degree of CNS effects.
- MESSAGE FOR CARDIOLOGIST :
  - As such, these agents probably should not be considered preferred agents for hypertension, particularly in the geriatric population and specially if OSA / Anesthesia.

AAR


Class 4
Ca2+ channel blocker
Verapamil
Diltiazem
K+ /Cl− (Out)
Ca2+ (In)
Class 1
Na+ channel blocker
1a (moderate):
Quinidine, Procainamide
1b (weak):
Lidocaine, Phenytoin
1c (strong):
Flecainide, Propafenone
Class 3
K+ channel blocker
Amiodarone
Sotalol
1
2
0
3
Na+ (In)
K+ (Out)
K+ (Rectifier)
4
4
Class 2
β-blocker
Propranolol
Metoprolol

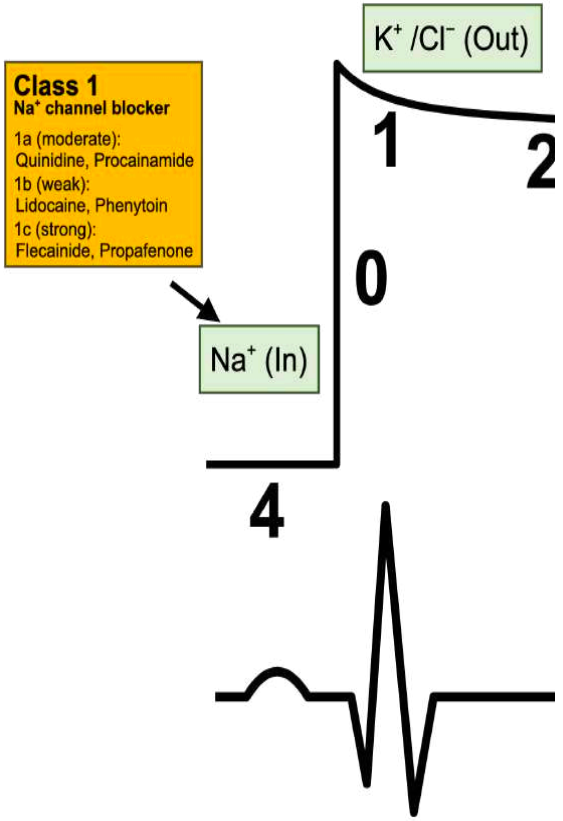
Class I AA: No Problem

Class I

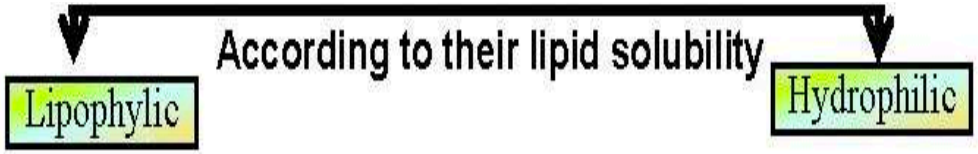
- Few studies showing any negative effects of the Class I antiarrhythmics on sleep quality.

- Propafenone states that insomnia occurs in 1-2% of patients, with fatigue occurring in 2-6% and drowsiness occurring in 1% of patients.

- Despite paucity of association it seems prudent to discuss these adverse reactions with patients and the geriatric subset of patients in particular



Class II: Beta Blockers all about PK



	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
$t_{1/2}$	Short	Long
CNS side effects	High	low
	Metoprolol Propranolol, Timolol Labetalol , Carvedilol	Atenolol, Bisprolol, Esmolol Sotalol

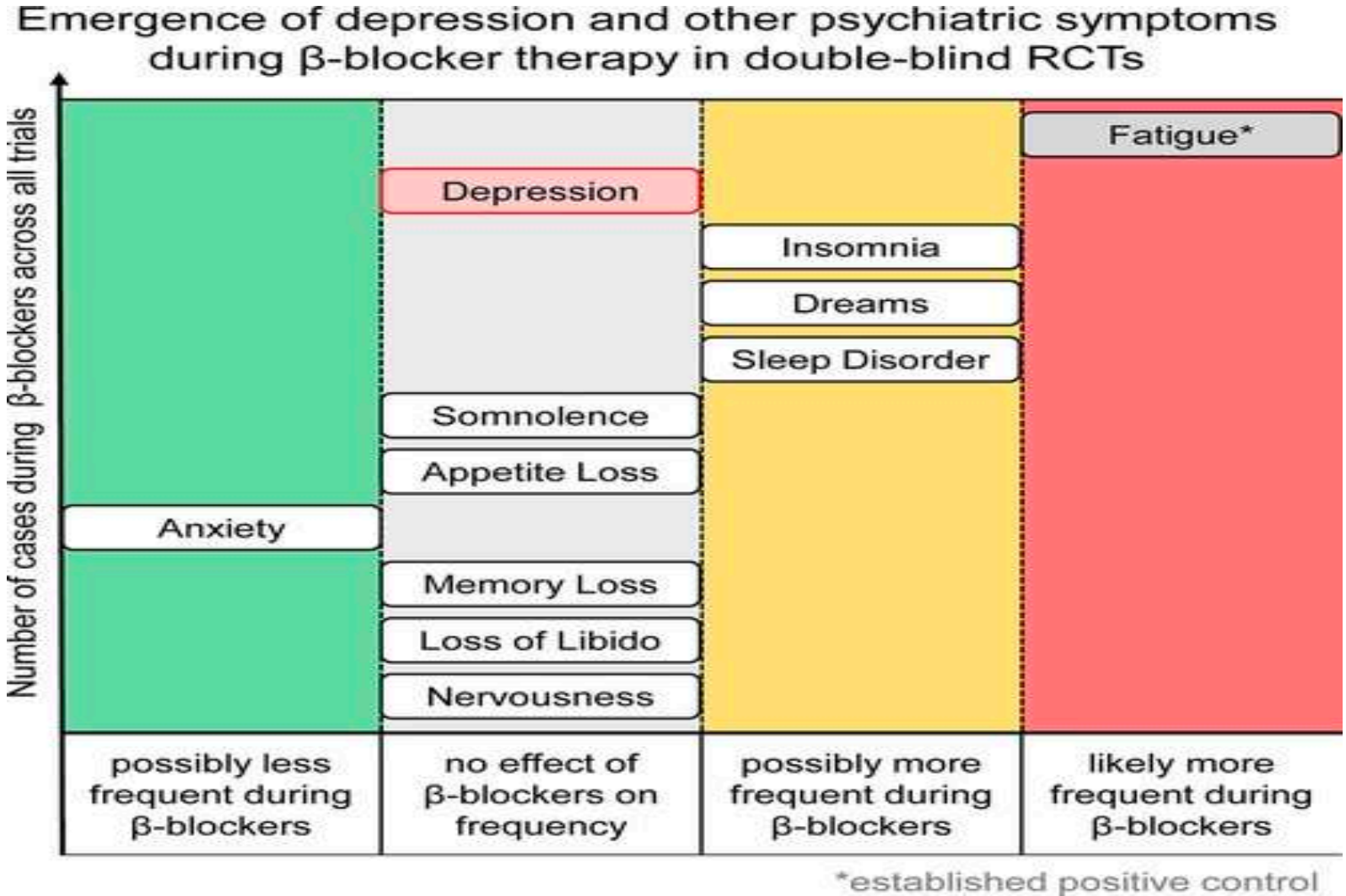
CNS depressant effects i.e. Sedative effect ⊘ Anxiety

Drug – Drug interaction

Polymorphism

Half life

Beyond sleep CNS side effects with impact on sleep (complex semiology)



AA Class III: No problem

- Amiodarone
  This agent is known to have a plethora of adverse reactions, many of them serious. CNS effects, including insomnia, fatigue and other sleep disturbances are described as occurring in 3% to 40% of patients in the package labeling and neurologic side effects were reported in the literature in 20-40% of patients.

Dronedarone
This is the newest agent of the class and while it has decreased efficacy over amiodarone, it also has decreased adverse reactions, including no known adverse effects on sleep quality or architecture.
Dofetilide
There are no published studies detailing any association between dofetilide and negative sleep quality; however, the package labeling states that insomnia occurs in 4% of treated patients.

- Sotalol
  8% occurrence of undefined sleep problems; however a very small published study which evaluated the effects of sotalol 320mg or 960mg on the CNS via sleep, EEG, and psychophysiological parameters showed no difference between the two treated groups.

- The Class III agents, although similarly classed, have vastly different associations with sleep disturbance and sleep quality.

Class IV:
Non-dihydropyridine Calcium Channel Blockers,
NO PROBLEM

- Diltiazem and Verapamil: no data indicating an association between diltiazem and sleep disturbance and although sleep disturbance is listed as a potential adverse effect in the product labeling of verapamil, it is not known to be a common side effect, occurring in less than 1% of patients treated.

- BUT VERAPAMIL inhibits CYP450 3A4 and can increase plasmatic concentration of drugs affecting sleep

RAS blocking agent

Angiotensin Converting Enzyme (ACE) Inhibitors / ARB

- ACE inhibitors are thought to negatively affect sleep in some patients by increasing the amount of circulating bradykinin.
- The associated cough and rhinopharyngeal inflammation induced by the bradykinin may worsen the AHI.
- Additionally, ACE inhibitors may affect potassium levels, potentially leading to leg cramps as well as painful joints and muscles in some patients.
- Since these side effects do not affect all patients, clinicians should discuss them with patients and adjust therapy accordingly if necessary, to avoid sleep disturbances.

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STUDY DESIGN

Impact of sacubitril–valsartan combination in patients with chronic heart failure and sleep apnoea syndrome: the ENTRESTO-SAS study design

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Abstract

Aims Sleep-disordered breathing (SDB) is a highly prevalent co-morbidity in patients with chronic heart failure (CHF) and can play a detrimental role in the pathophysiology course of CHF. However, the best way to manage SDB in CHF remains a matter of debate. Sacubitril–valsartan has been included in the 2016 European Society of Cardiology guidelines as an alternative to angiotensin-converting enzyme inhibitors to further reduce the risk of progression of CHF, CHF hospitalization, and death in ambulatory patients. Sacubitril and valsartan are good candidates for correcting SDB of CHF patients because their known mechanisms of action are likely to counteract the pathophysiology of SDB in CHF.

Methods and results The ENTRESTO-SAS trial is a 3-month, multicentric, prospective, open-label real-life cohort study. Patients eligible for sacubitril–valsartan treatment (i.e. adults with left ventricular ejection fraction ≤35%, who remain symptomatic despite optimal treatment with an angiotensin-converting enzyme inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist) will be evaluated before and after 3 months of treatment (nocturnal ventilatory polygraphy, echocardiography, laboratory testing, and quality-of-life and SDB questionnaires). The primary outcome is the change in the Apnoea–Hypopnoea Index, before and after 3 months of treatment. One hundred twenty patients are required to detect a significant 20% improvement of the Apnoea–Hypopnoea Index with a power of 90% at an alpha risk of 5%.

Conclusions In the context of the SERVE-HF study, physicians are waiting for new trials and alternative therapies. We sought to assess in the ENTRESTO-SAS trial whether sacubitril–valsartan could improve the outcome of SDB in CHF patients.

Keywords Heart failure; Sleep apnoea syndrome; Continuous positive airway pressure; Sacubitril–valsartan; Sleep-disordered breathing

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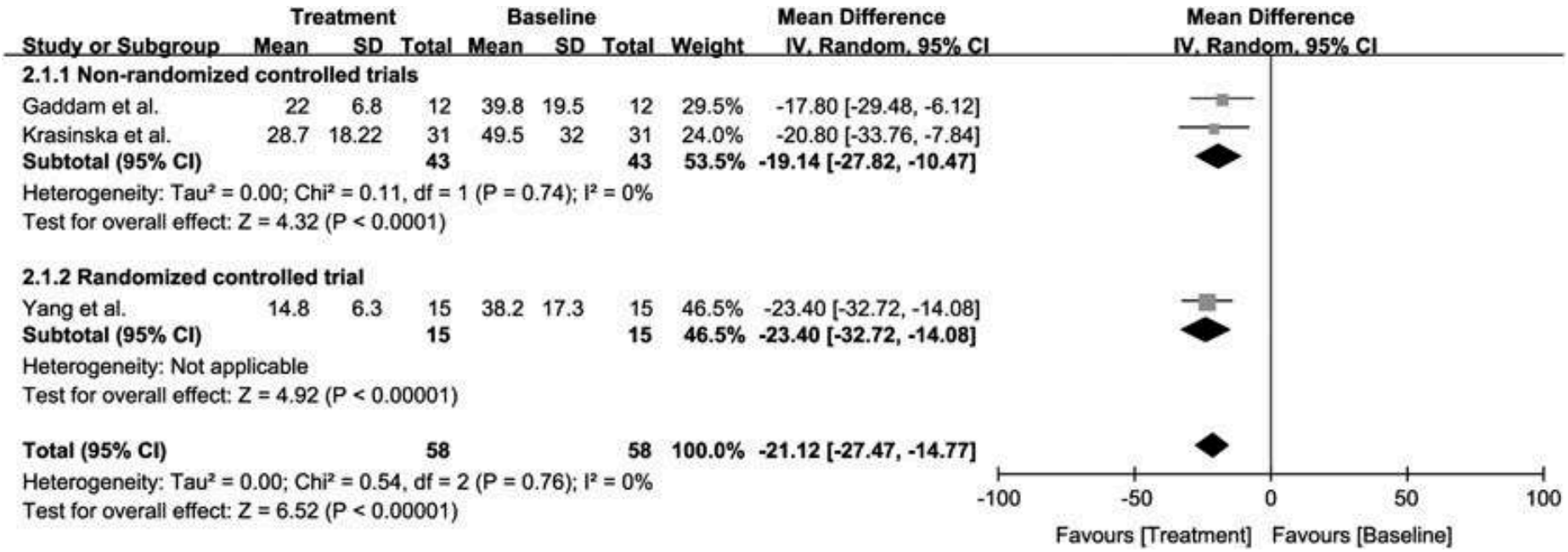
Introduction

Chronic heart failure (CHF) is a frequent pathology marked by significant morbidity and mortality.[1] Approximately 1–2% of the adult population in developed countries has CHF, with a prevalence rising to ≥10% among persons 70 years of age or older.[2] Despite progress in the medical management of CHF and a relative reduction in hospitalization in recent years by 30–50%,[3,4] the last European data (ESC-HF pilot study) demonstrated that 12-month hospitalization rates for hospitalized and stable/ambulatory CHF patients were 44% and 32%, respectively, and the 12-month all-cause mortality rates were 17% and 7%, respectively.[5] At 4.5 years, mortality remains high in developed countries, reported in 2011 as reaching over 70% in an American cohort study.[6]

In this trial , SV treatment for 3 months in SA patients is associated with a significant decrease in AHI. These results support the current guidelines that recommend first an optimization of the HFrEF treatment in patients with HFrEF and central SA. A potential positive airway pressure sparing effect merits further investigation.

MRA and OSA in refractory HTN



HMG Co-A Reductase Inhibitors: PK again

- These agents are known to cause muscle pain which may affect sleep quality by not allowing patients to fall asleep and stay asleep ? SAMSON study no !
- Lipophilic type HMG Co-A reductase inhibitors may cause a disturbance in sleep architecture and cause insomnia or nightmares via their increased penetration of the BBB.
- If difficulties with sleeping, it may be prudent to switch to a hydrophilic agent preferentially.

Lipophilic (fat loving) statins	Hydrophilic (water loving) statins
○ Lovastatin ○ Simvastatin ○ Atorvastatin ○ Fluvastatin ○ Pitavastatin	○ Pravastatin ○ Rosuvastatin

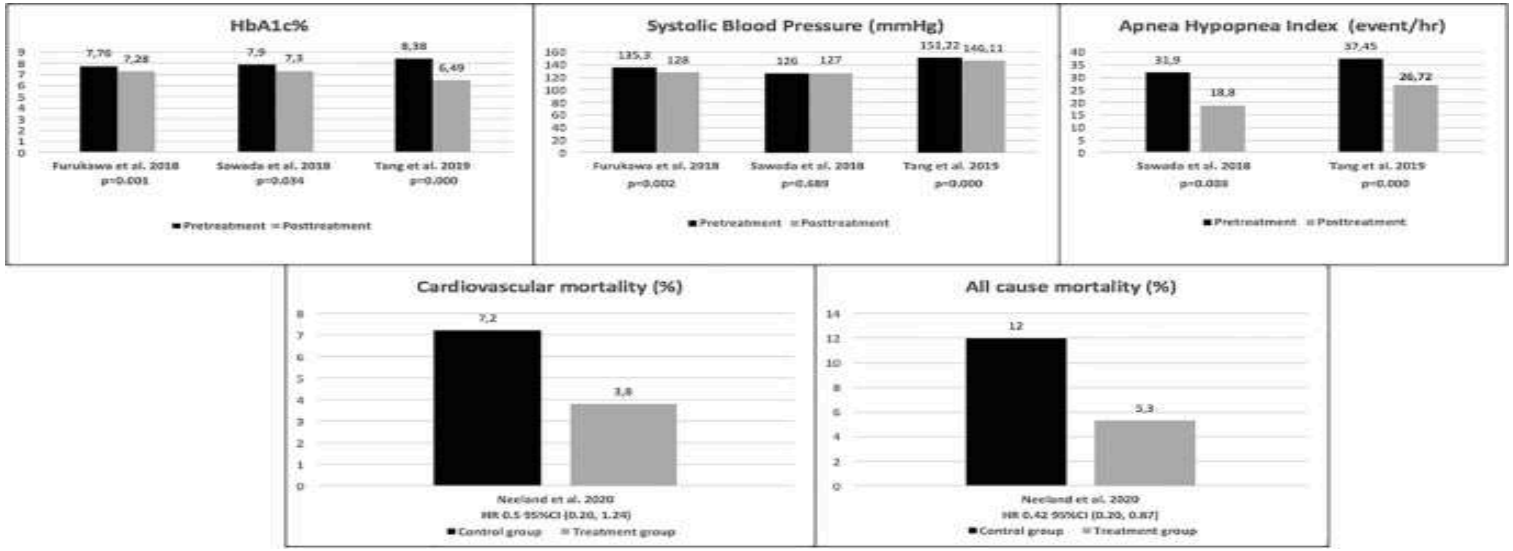
Tang et al. *Nutrition and Diabetes* (2019)9:32
https://doi.org/10.1038/s41387-019-0098-5

Nutrition & Diabetes

ARTICLE Open Access

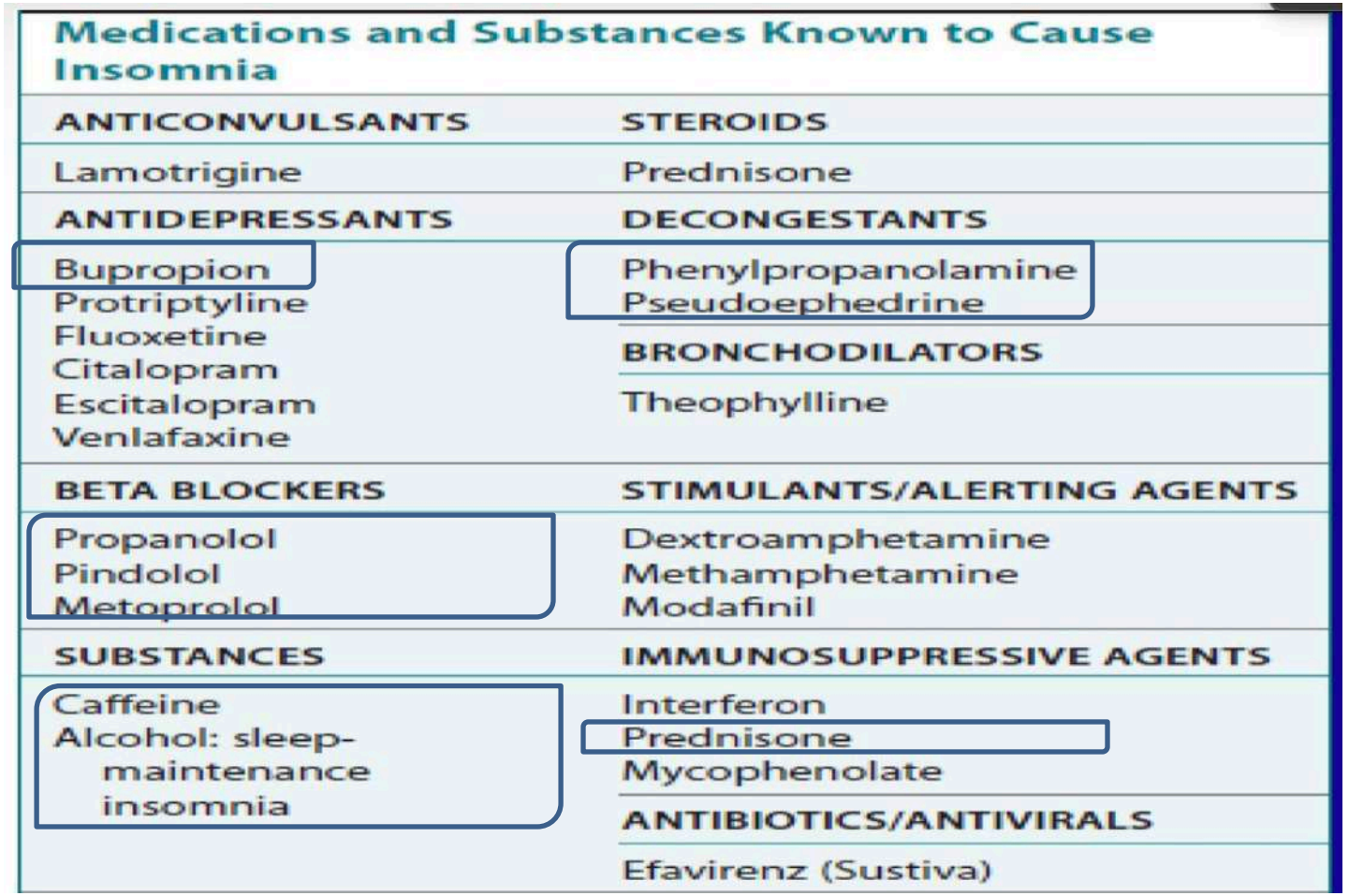
Effect of dapagliflozin on obstructive sleep apnea in patients with type 2 diabetes: a preliminary study

Yi Tang[1], Qin Sun[2], Xiao-Yan Bai[3], Yun-Fan Zhou[4], Qiong-Lan Zhou[5] and Min Zhang[2]



And beyond

Medication causing insomnia



Medications and Substances Known to Cause Insomnia	
ANTICONVULSANTS	**STEROIDS**
Lamotrigine	Prednisone
ANTIDEPRESSANTS	**DECONGESTANTS**
Bupropion Protriptyline Fluoxetine Citalopram Escitalopram Venlafaxine	Phenylpropanolamine Pseudoephedrine
	BRONCHODILATORS
	Theophylline
BETA BLOCKERS	**STIMULANTS/ALERTING AGENTS**
Propanolol Pindolol Metoprolol	Dextroamphetamine Methamphetamine Modafinil
SUBSTANCES	**IMMUNOSUPPRESSIVE AGENTS**
Caffeine Alcohol: sleep-maintenance insomnia	Interferon Prednisone Mycophenolate
	ANTIBIOTICS/ANTIVIRALS
	Efavirenz (Sustiva)

Drugs increasing weight and OSA symptoms/ severity

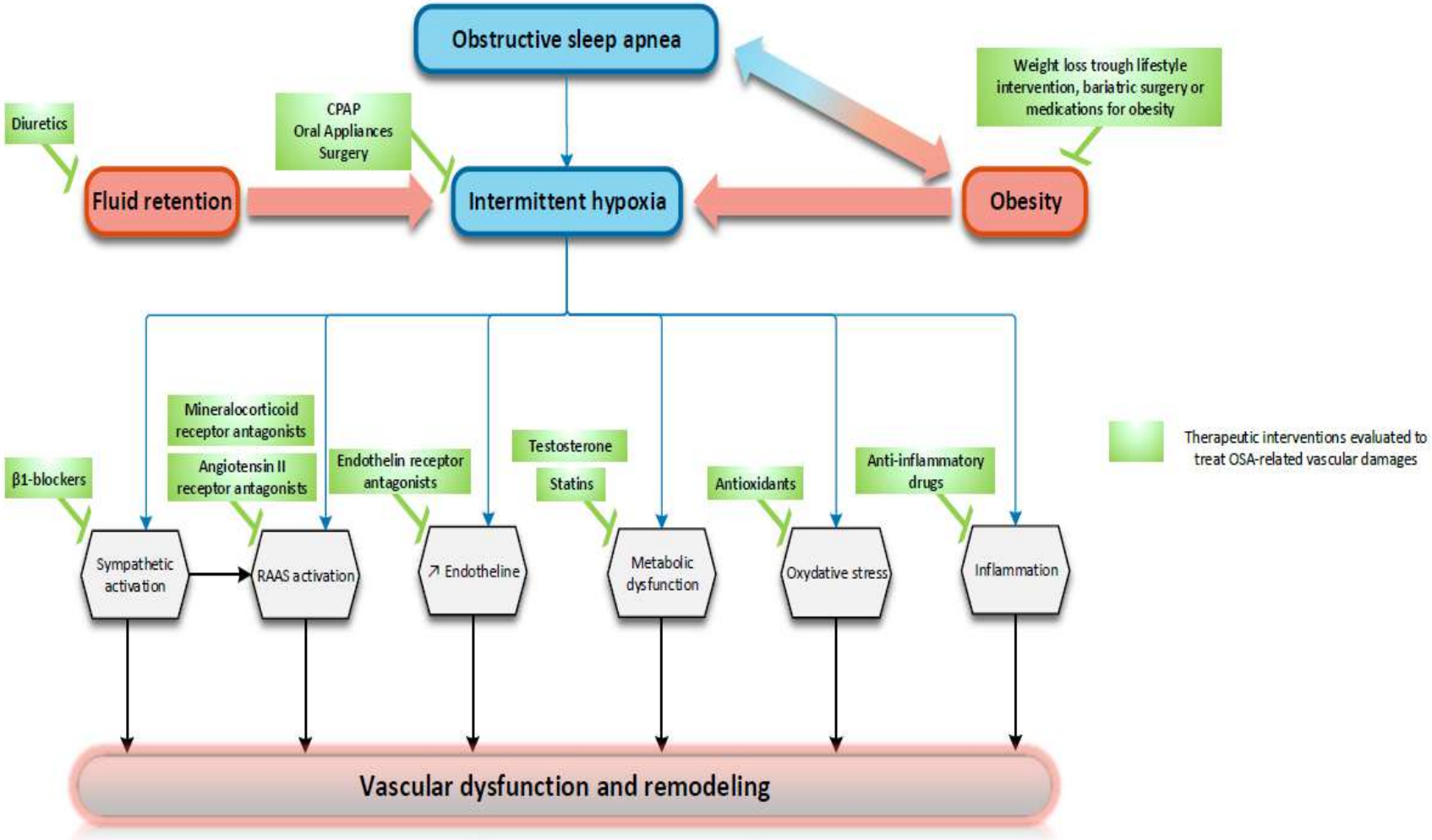
Category	Drugs that cause weight gain	Possible alternatives
Neuroleptics	Thioridazine, haloperidol, olanzapine, quetiapine, risperidone, clozapine	Ziprasidone, aripiprazole
Tricyclic antidepressants	Amitriptyline, nortriptyline, imipramine, doxepin	Protriptyline, bupropion, nefazodone
Monoamine oxidase inhibitors	Phenelzine	
Selective serotonin reuptake inhibitors	Paroxetine	Fluoxetine, sertraline
Other antidepressants	Mirtazapine	
Anticonvulsants	Valproate, carbamazepine, gabapentin	Topiramate[a], lamotrigine, zonisamide[a]
Antidiabetic drugs	Insulin, sulfonylureas, thiazolidinediones	Acarbose, sitagliptin, saxagliptin, canagliflozin, dapagliflozin, pramlintide, exenatide, liraglutide, miglitol, metformin, orlistat
Antihistamines	Cyproheptadine	Inhalers, decongestants
β- and α-adrenergic blockers	Propranolol, doxazosin	ACE inhibitors[b], calcium channel blockers
Steroid hormones	Contraceptives, glucocorticoids, progestational steroids	Barrier methods, nonsteroidal anti-inflammatory agents

Kushner et al. 2014

IMPORTANT FOR CARDIOLOGIST: Drugs for Residual Sleepiness

- Drugs for residual sleepiness:
- All sympathomimetic drugs
- Sympathomimetic effects
- Management of CV risk
- Management of target organ

CV drugs and SBD (cause / consequences)



Strategies to prevent Drug – induced sleep risk

BENEFIT RISK RATION MATTERS

Step 1: Identify patients at risk
Step 2: Modify treatment accordingly

- Review current drug therapy
  - Change in patient status
  - Indication no longer exists
  - Safer agent available
  - Drug interactions
  - Drug adverse effects
  - Simplification
- Discontinue unnecessary therapy
- Consider ADE as cause of any new symptom
- Consider non-pharmacologic approaches