

Opioids-associated sleep apnea, an update

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Arkansas Sleep meeting, 2024



Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and the Sleep Professionals of Arkansas & Washington Regional Center for Sleep Disorders. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Conflict of Interest Disclosures for Speakers

Shahrokh Javaheri, MD disclosed a financial relationship with ResMed and Phillips (received honorarium within the prior 24-months), and Eli Lilly (consultant).

The relevant financial relationships listed for this individual have been mitigated.

Learning Objectives

Identify a unified mechanism linking how opioids and other medications cause CSA

Gain an understanding in the role of Ticagrelor and CSA

Understand the prevalence of CSA associated with opioids

1. Javaheri S, Malik A, Smith J and Chung J. Adaptive pressure support servo-ventilation: a novel treatment for sleep apnea associated with use of opioids. *J Clin Sleep Med* 2008; 4:305-310.
2. Javaheri S, Harris N, Howard J, Chung E. Adaptive servo-ventilation for treatment of opioids-associated central sleep apnea. *J Clin Sleep Med* 2014; 10: 637-643.
3. Cao M, Javaheri S. Chronic opioid use: Effects on respiration and sleep. In, *Opioids Pharmacology, Clinical Uses and Adverse Effects*, Edited by Tvildiani D and Gegechkori K, Nova Science Publishers, Inc. New York, 2012; 1-13.
4. Javaheri S, Cao M. Opioid Induced Central Sleep Apnea. In *Proceedings of the X World Congress on Sleep Apnea, Section: Respiratory Disorders and Snoring*. Ed. Mario Fabiani. Edizioni Minerva Medica, Turin. 2012; pp 133-137
5. Javaheri S, Randerath WJ. Opioids-Induced Central Sleep Apnea: Mechanisms and Therapies. *Sleep Med Clin* 2014; 9:49-56
6. Arora N, Cao M, Javaheri S. Opioids, sedatives, and sleep hypoventilation. *Sleep Med Clin* 2014; 9: 391-398
7. Chowdhuri S, Javaheri S. Sleep Disordered Breathing Due to Chronic Opioid Use: Diverse Manifestations and Their Management. *Sleep Medicine Clinics* (2017)
8. Javaheri S, Patel S. Opioids Cause Central and Complex Sleep Apnea in Humans: Reversal with Discontinuation: A Plea for Detoxification. *J Clin Sleep Med* (2017)
9. Javaheri S. Badr S. Central Sleep Apnea: Pathophysiological Classification. *SLEEPJ*, 2023
10. Javaheri et al. Medications-Induced CSA. *SLEEPJ* (In Press)
11. Insights on Opioid-Induced Central Sleep Apnea (In Press)

Papever somniferum

somnus, “sleep”, and ferre, “bring”



No relevant COI

Papever somniferum somnus, “sleep”, and ferre, “bring”



FIG. 100. THE GOD OF SLEEP

The God of Sleep
Somnus (Latin)
Hypnos (Greek)



Hypnos/Somnus



□ Hypnos

- Hypnos was the Greek god of sleep
- His parents were Erebus (the god of darkness) and Nyx (the goddess of night)
- He was married to Pasithea (the goddess of hallucinations)
- His children were Morpheus (god of dreams), Phobetor (god of nightmares), Phantasus, and Ikelos.
- He lived in the underworld

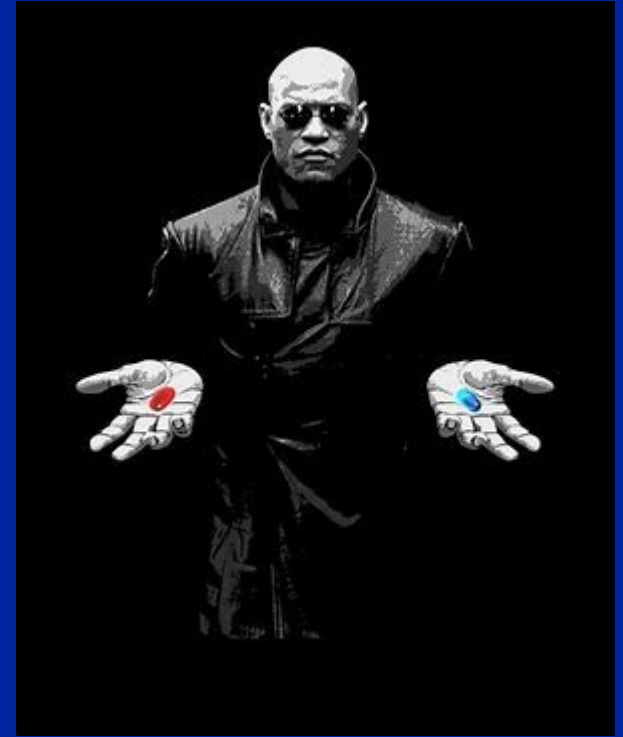
□ Somnus

- Somnus was the Roman god of sleep
- He was the brother of death and the son of night
- It was said that he had a thousand children (all gods/goddess of dreams).

Gods of Dreams



Phobetor (Frightener)

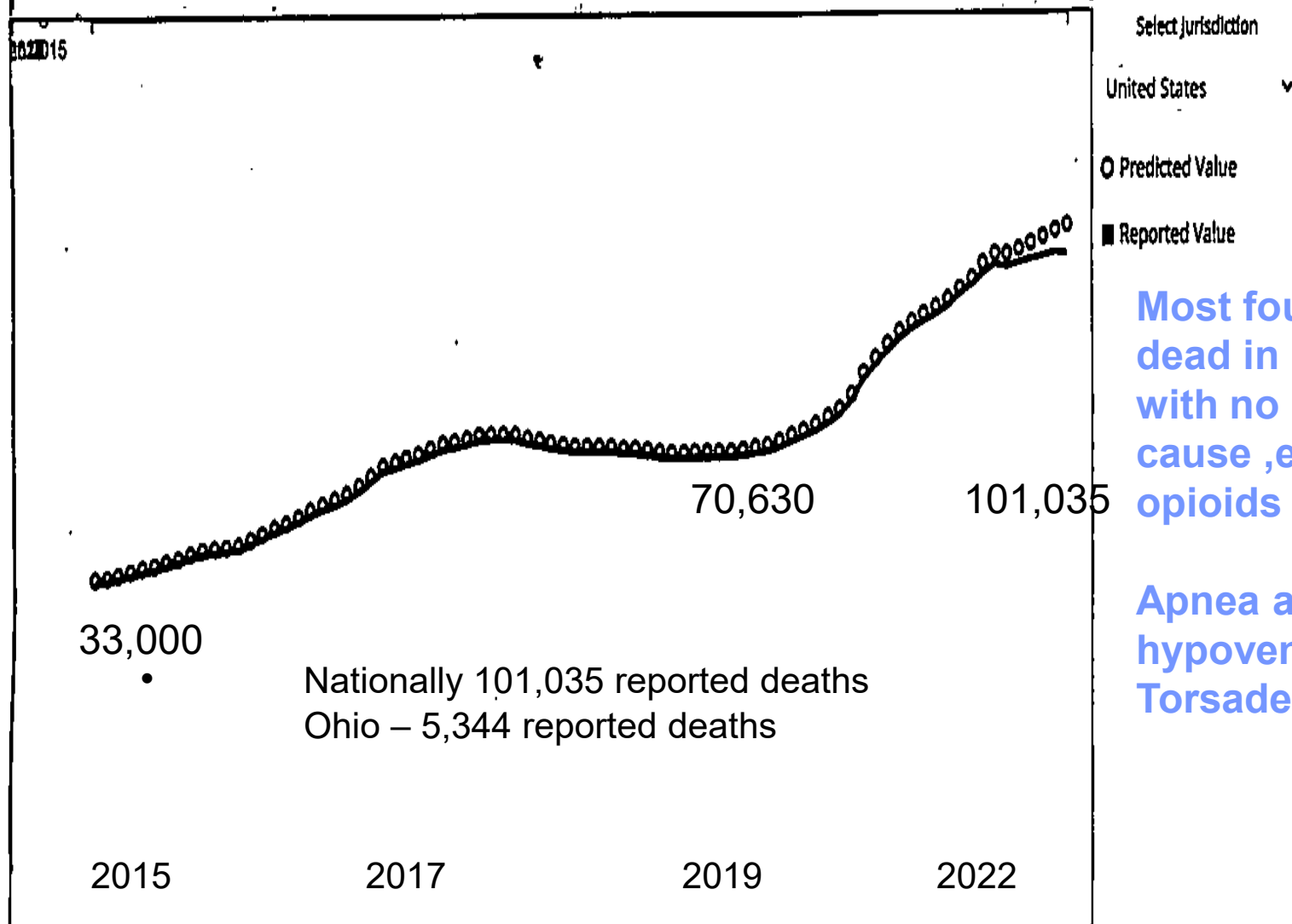


Morpheus

by zacky7avenged on DeviantArtMorpheus

12 Month-ending Provisional Counts of Drug Overdose Deaths: United States

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States

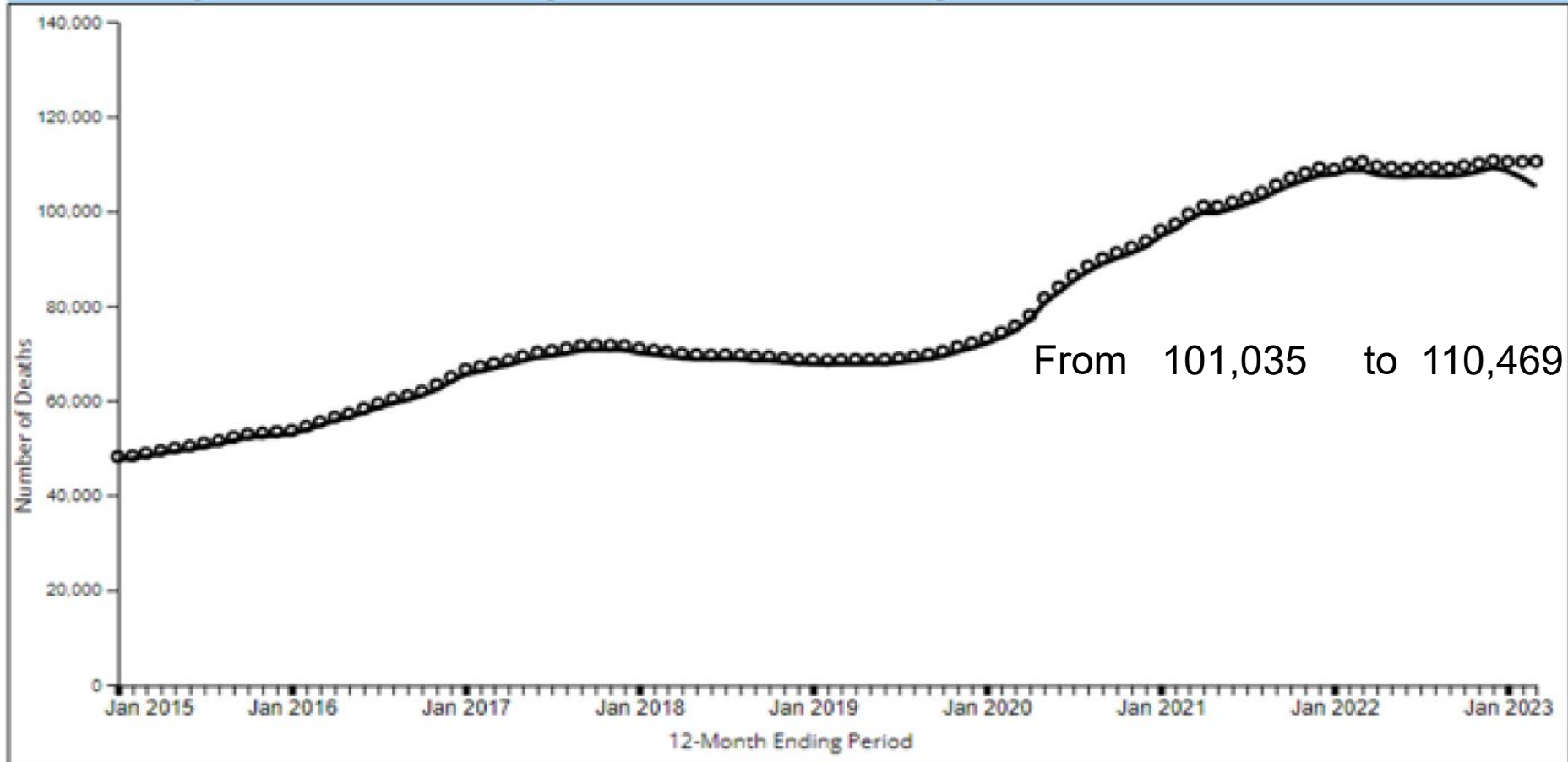


Most found dead in bed, with no known cause, except opioids in blood

Apnea and hypoventilation
Torsade

The plaque

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States





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□ Somnus **Had a brother Thanatos, the personified spirit of the god of non-violent death. ...**

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Cause of Death

Terminal Apnea/Hypoventilation/Hypoxia

Cardiac Arrest (Torsade de pointe)

Polymorphic ventricular tachycardia (PVT) is a form of ventricular tachycardia in which there are multiple ventricular foci with the resultant QRS complexes varying in amplitude, axis and duration



Torsades de pointes (TdP) is a specific form of polymorphic ventricular tachycardia occurring in the context of QT prolongation

Tdp has a characteristic morphology in which the QRS complexes “twist” around the isoelectric line.

For TdP to be diagnosed, the patient has to have evidence of both PVT and QT prolongation.

Current Prevalence of Sleep Apnea in USA

Age (years)	1988-1994 Young NEJM, 1994	2007-2010 Peppard Am J Epidemiol, 2013
Men (%)		
AHI > 5/hr (30-70)	26	34
AHI > 15/hr (30-70)	9	13
Women (%)		
AHI > 5/hr (30-70)	13	17
AHI > 15/hr (30-70)	4	6

ORD: Wakefulness vs Sleep

- While awake opioids decrease MV, TV and BR and increases PaCO₂
- While asleep , ORD takes the the form of sleep apneas and hypopneas, both obstructive and central, hypoventilation and desaturation
- Hypoventilation is expected to occur and be more severe in sleep than while awake, but no systematic studies have been done.

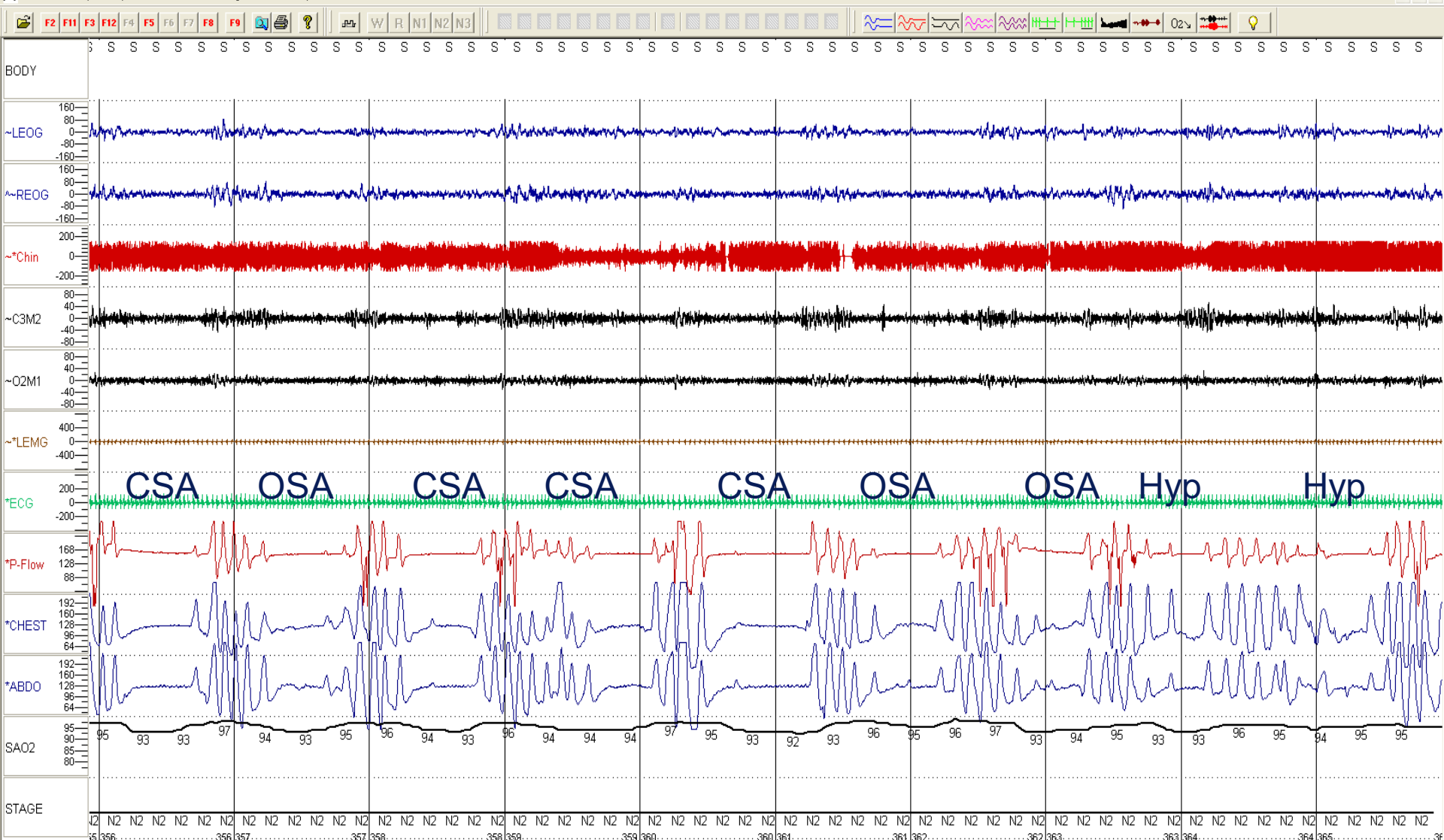
Sleep apnea in patients on opioids

Compared to general population

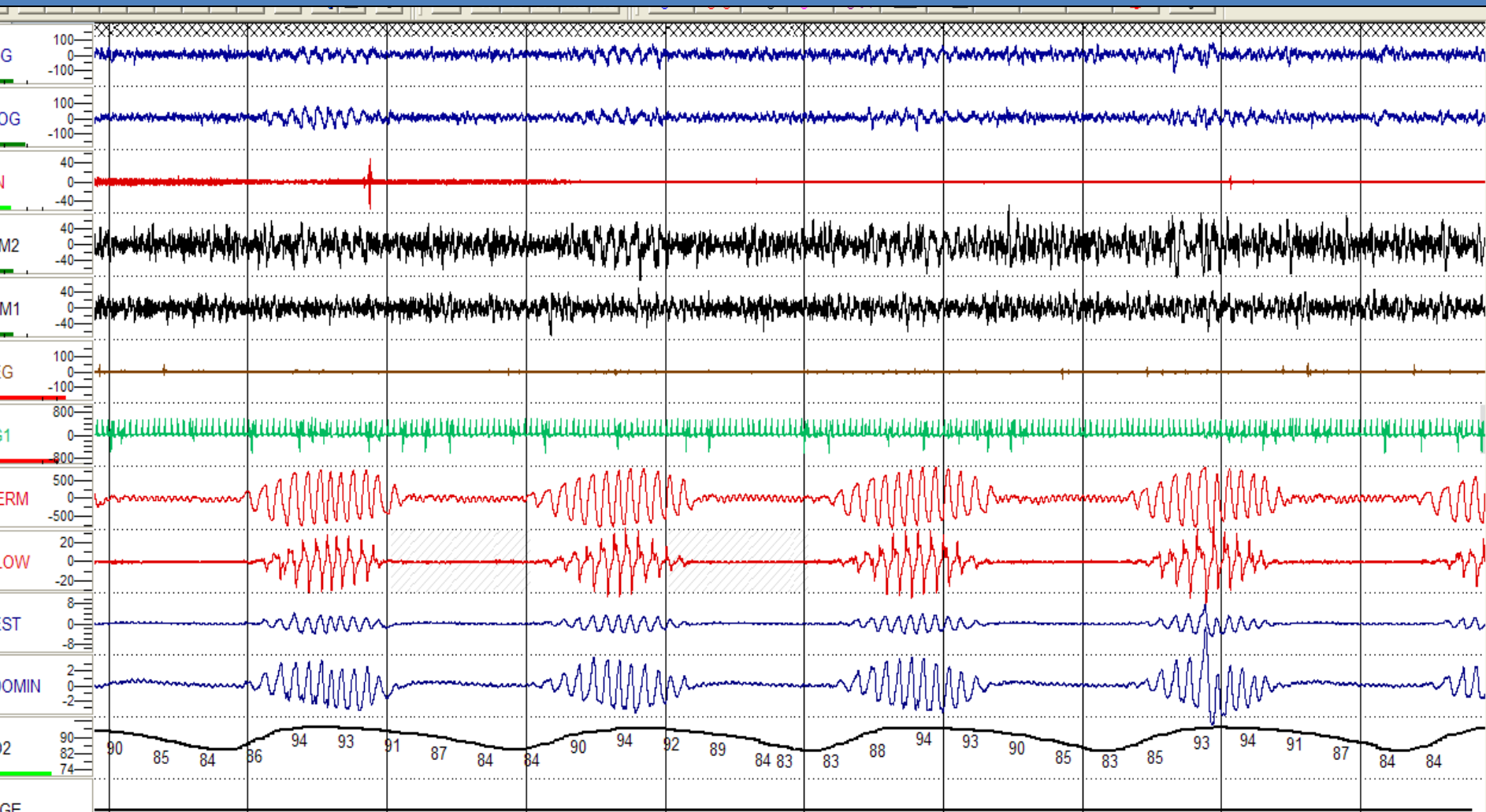
1. More prevalent
2. More severe
3. CSA is common
4. No gender predilection
5. Thin OSA common
6. Age not an issue
7. No dose of opioid is safe

Opioids and sleep apnea

Javaheri et al, JCSM,2014



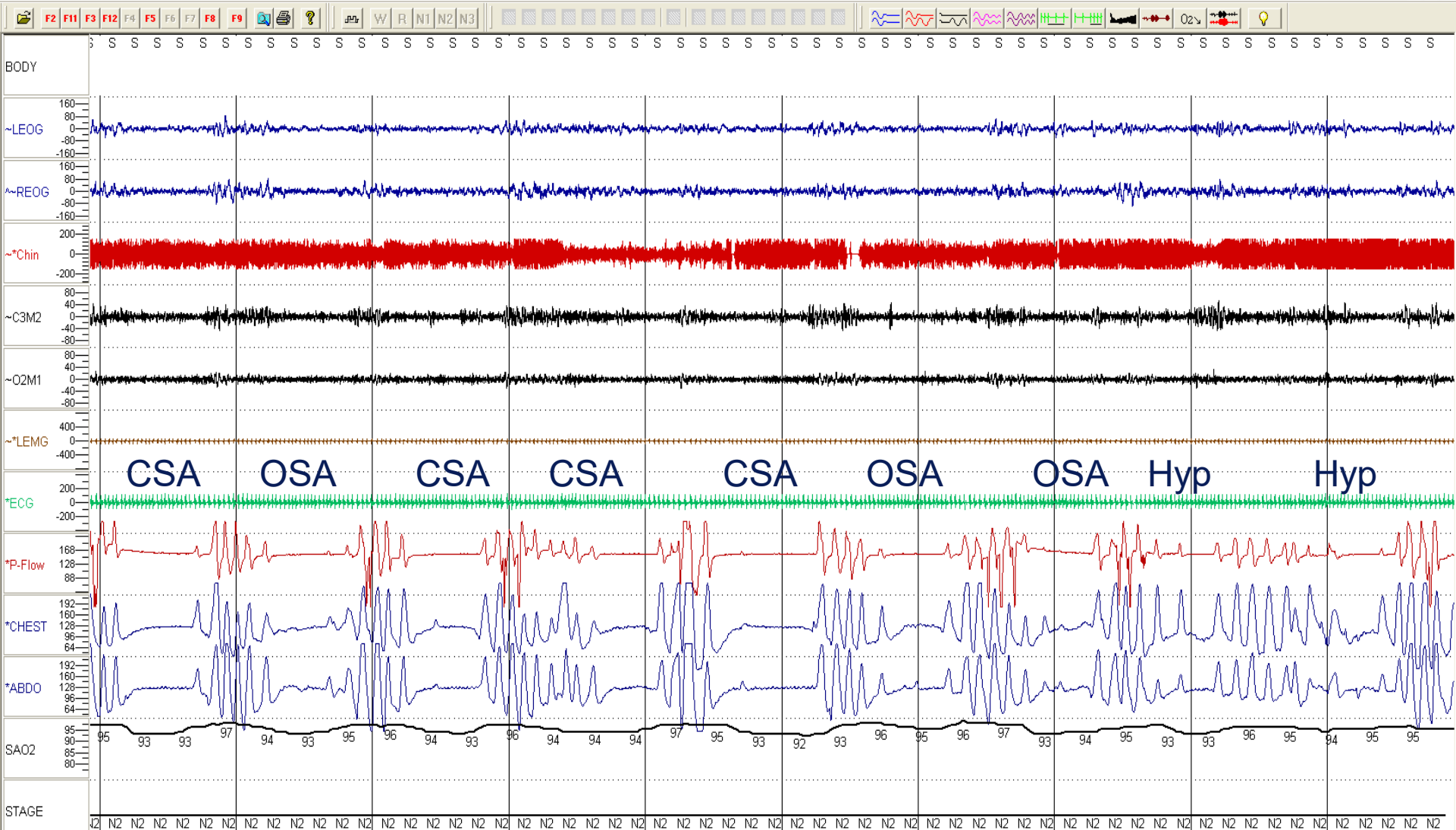
Hyperventilation-related increases in end-expiratory lung volume, intrinsic positive airway pressure, assistance to stroke volume



Opioids and sleep apnea

Javaheri et al, JCSM,2014

F4 File View Report Options Multimedia Scoring Window Help



Second degree heart block

Mobitz Type 2

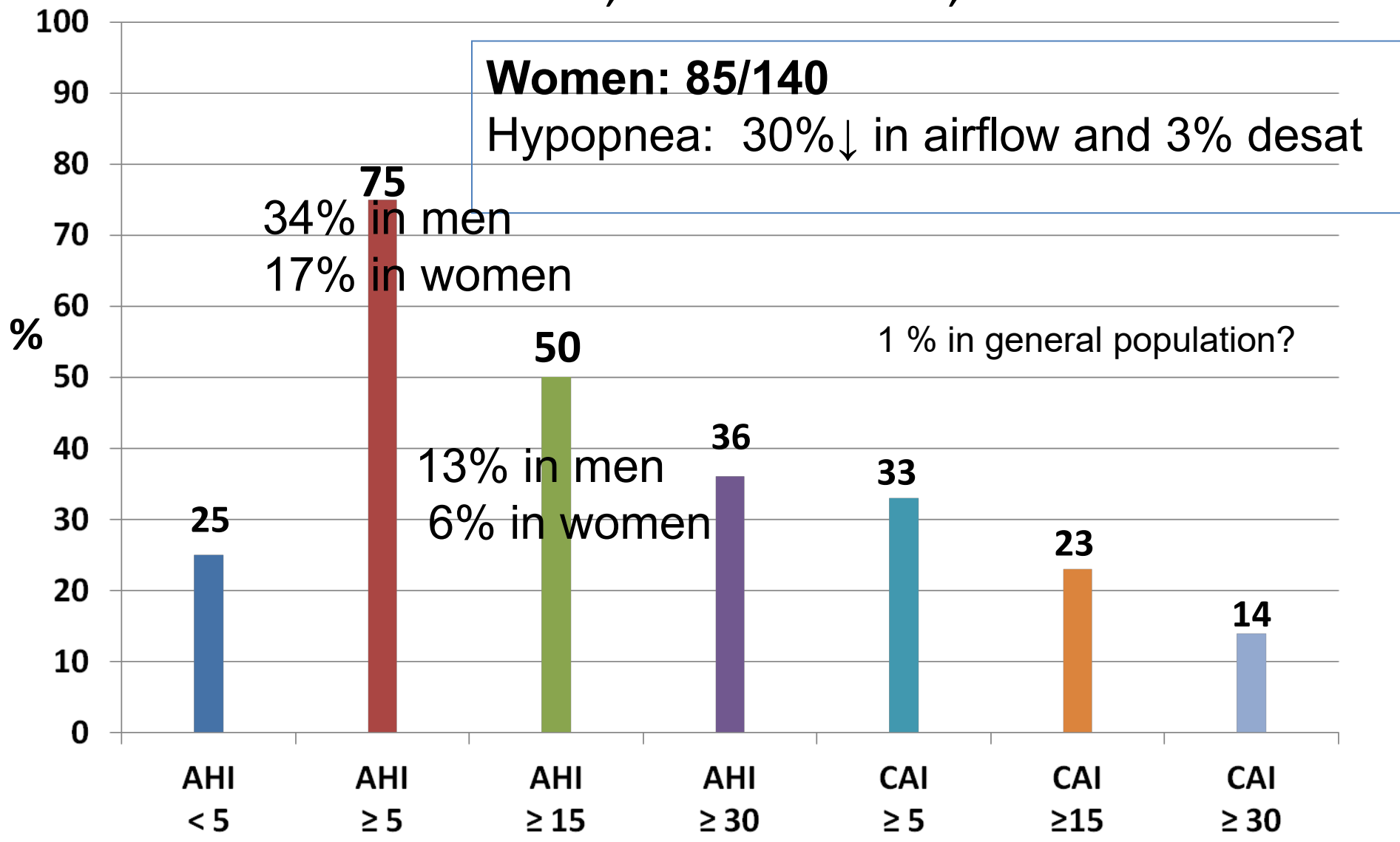


Please note :

- 1. conducted and non-conducted P waves**
- 2. PP intervals are always the same duration**
- 3. DRS complexes the same shape**

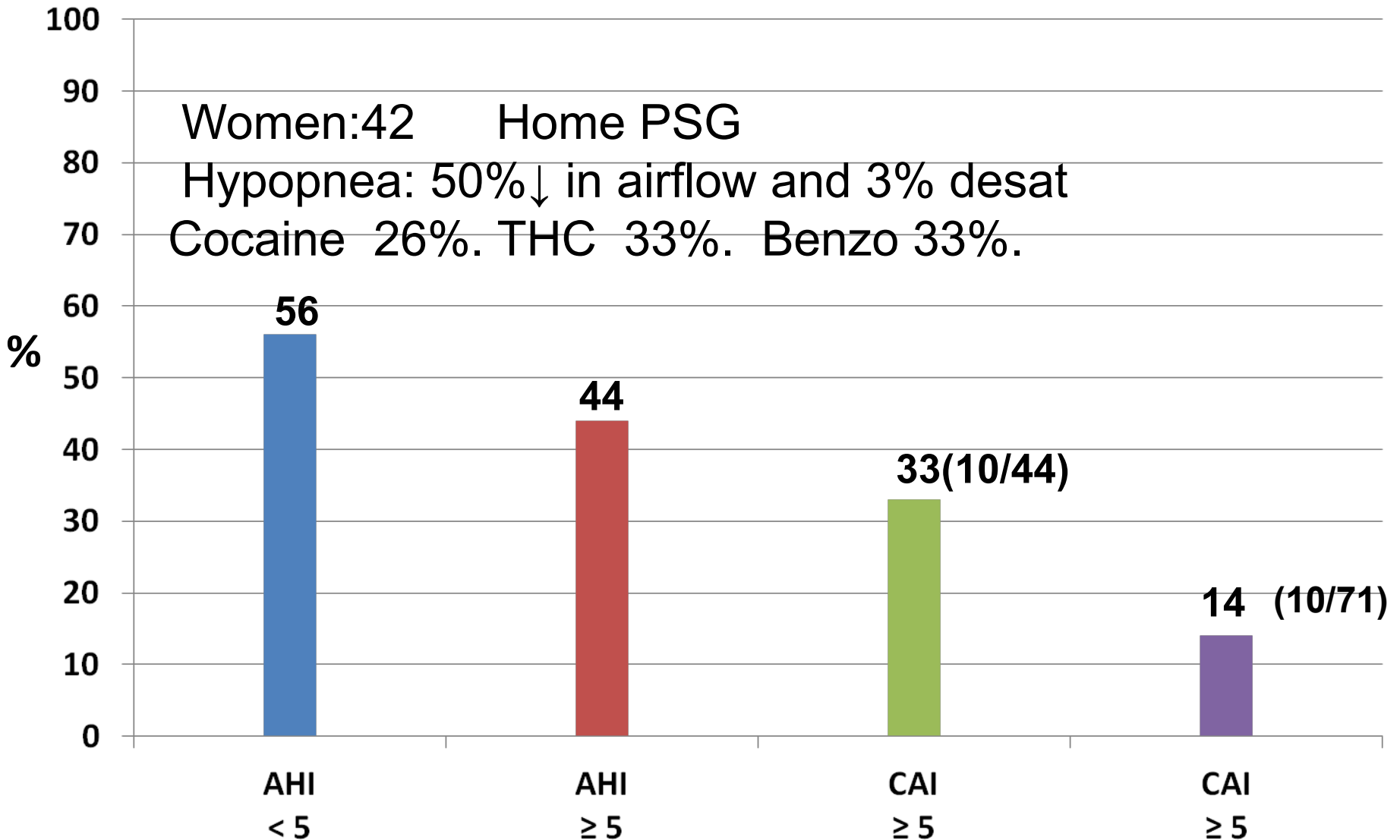
Prevalence of SA in patients on chronic opioids in pain clinic (140/392 consecutive patients)

Webster et al, Pain Medicine, 2008



Prevalence of SA in 71 patients in MMT

Sharkley et al, Drug and Alcohol Dep, 2010



Buprenorphine and SA

Buprenorphine: a semisynthetic μ -agonist
used for opioids dependency

N=70 consecutive patients on Suboxone

Mean age = 32

Mean BMI = 25

Female 60%

Mean values: AHI = 20

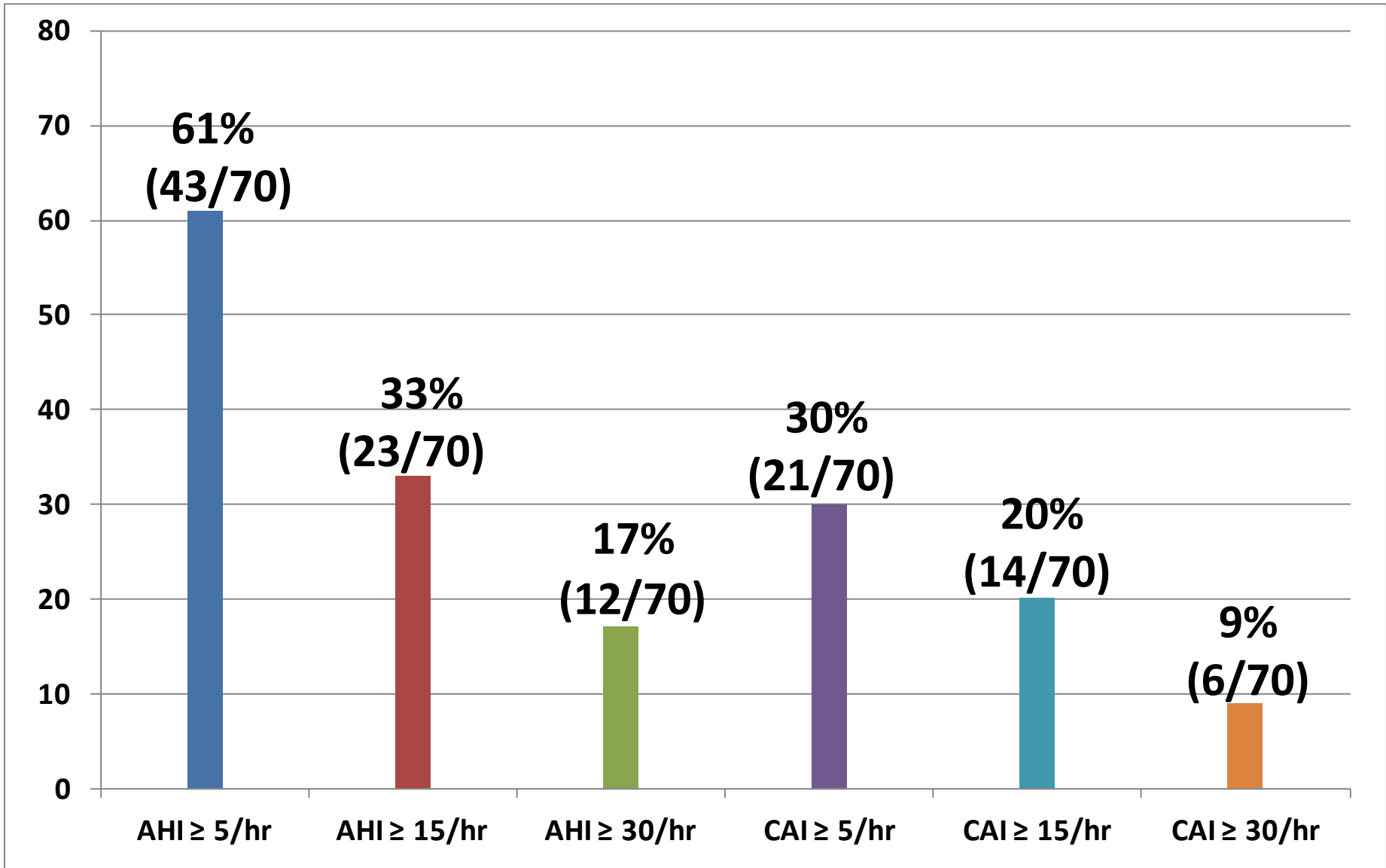
CAI = 11

OAI = 2

% time TST, $\text{SaO}_2 < 90\% = 23$

Buprenorphine and SA

Farney et al, Eur Respir J 2013; 42: 394–403



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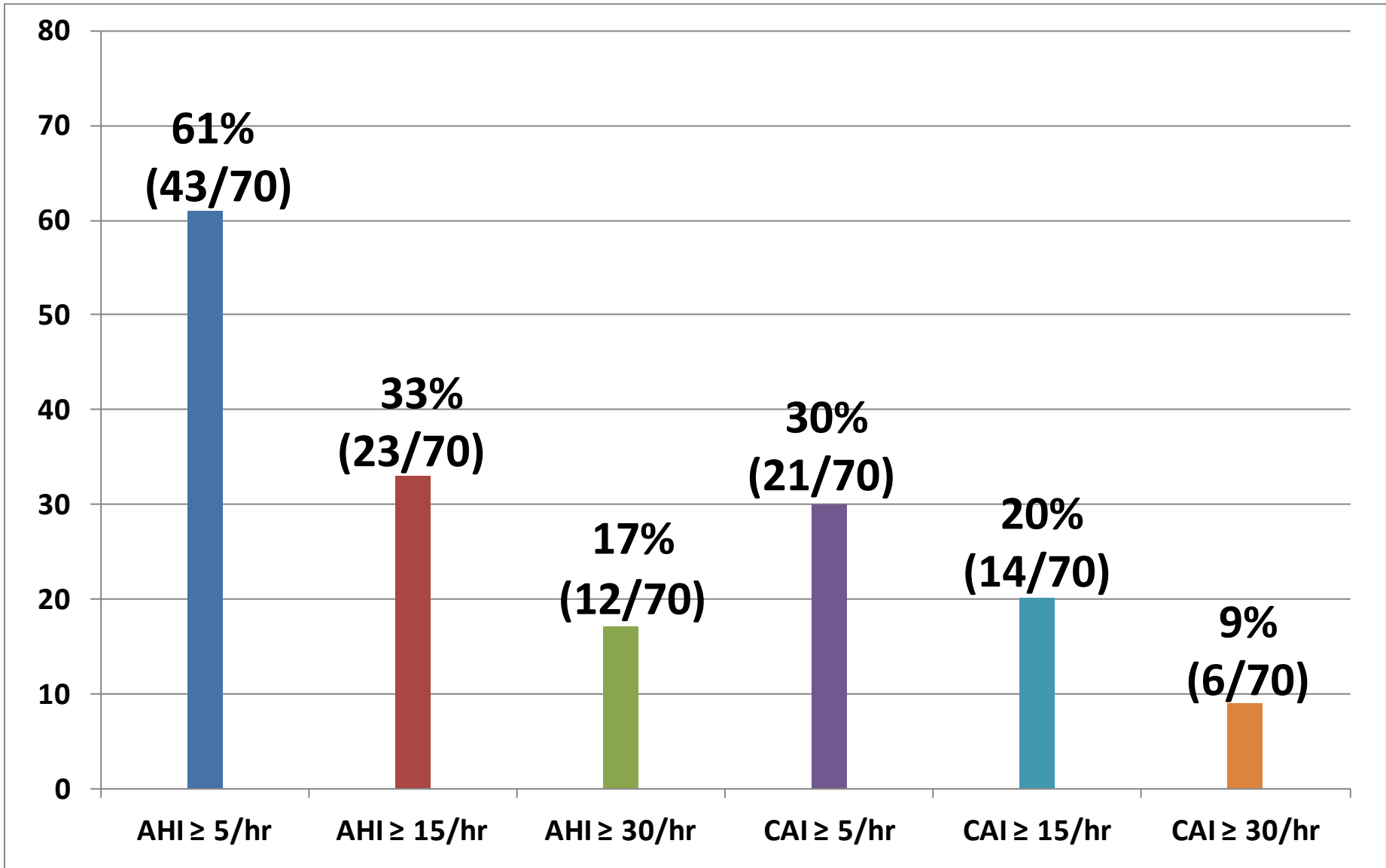
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Buprenorphine and SA

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Opioids receptors are abundant in respiratory system

Opioids receptor are present in brain stem inspiratory centers:

The pre-Botzinger Complex and KF/PB neurons
but absent in retrotrapezoid/parafacial nucleus
(RTN/pFRG) which is active during expiration

Opioid receptors are also present

carotid bodies

vagal nerves, and

mechanosensory receptors

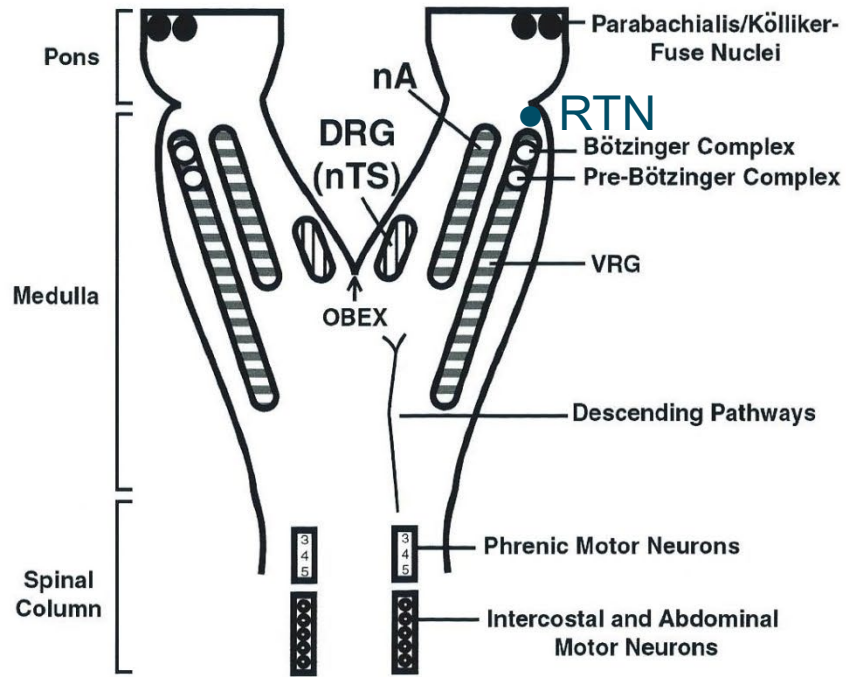
in the epithelial,

submucosal and

muscular layers of the airways

Opioids and the control of respiration. Pattinson. BJA 2008; 100 747-758

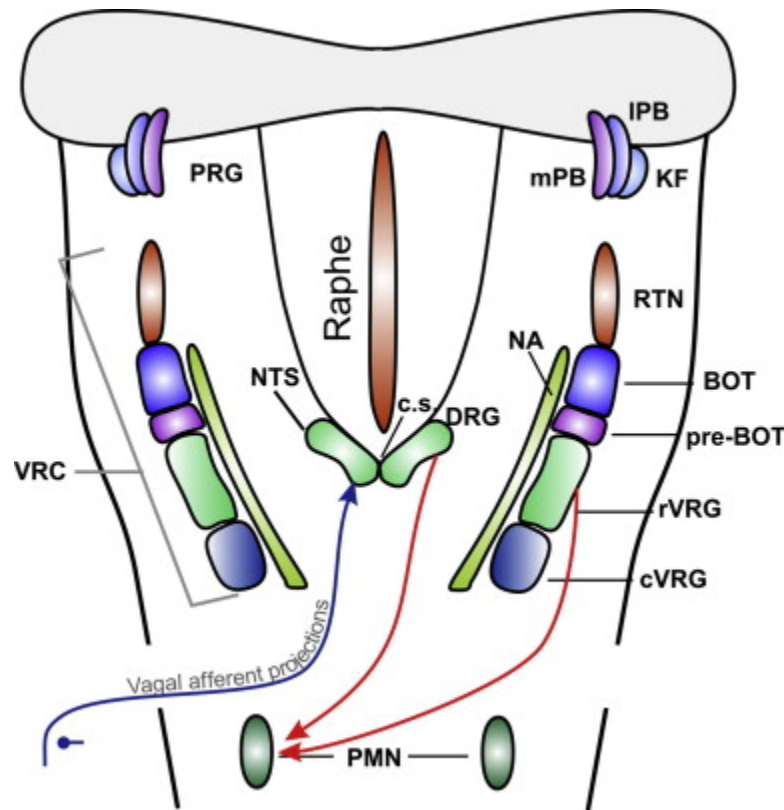
Schematic Organization of Brainstem Respiratory Centers



Modified from
Javaheri Determinants of carbon dioxide tension
In: Acid-Base Disorders and Their Treatment
2005; 47-77

The Brainstem Respiratory Network

Bautista T G, Pitts TE, Pilowsky PM, Morris KF

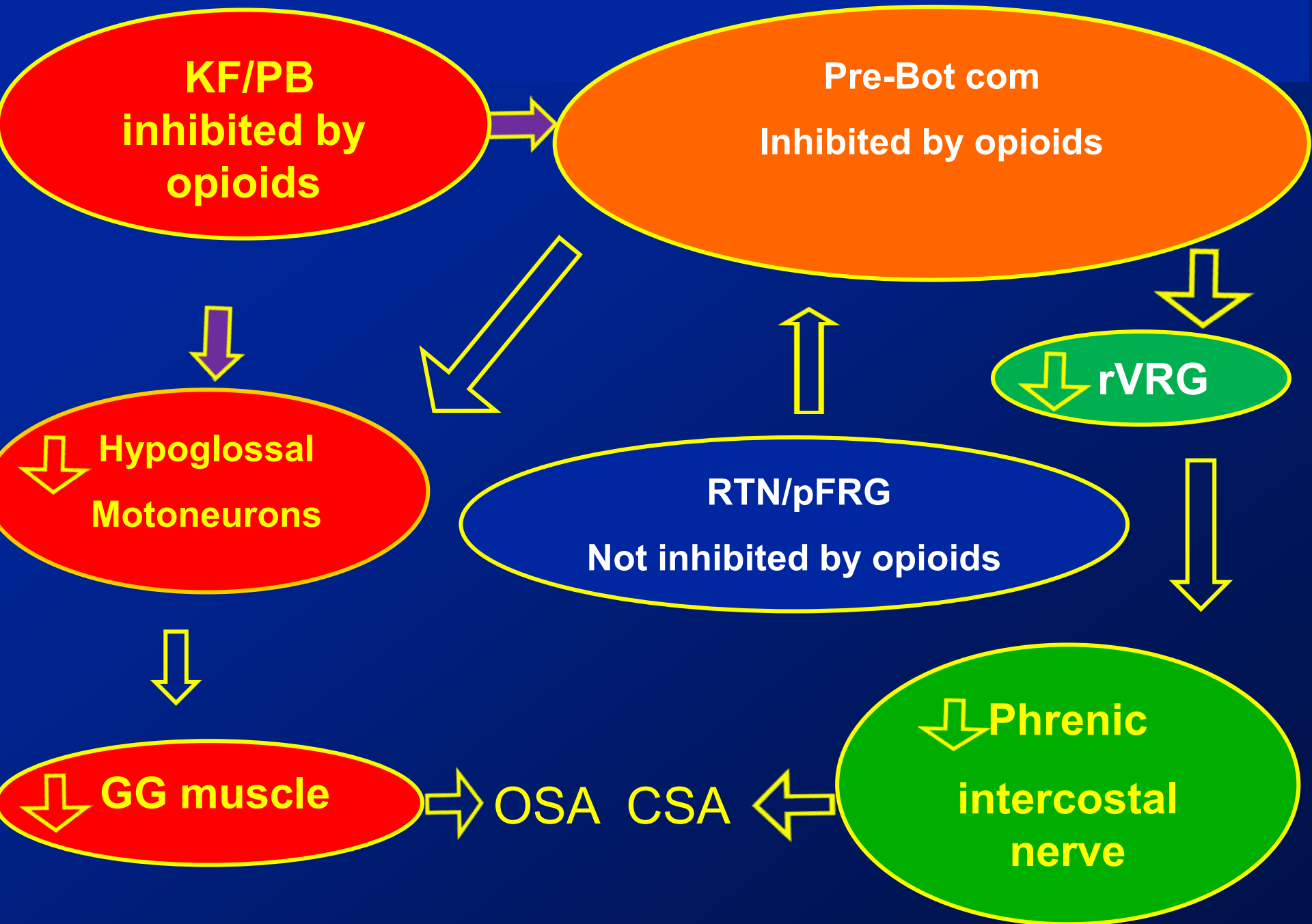


. The Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia

Neurochemistry of Pre Botz C KF neurons

Multiple receptors including mu-opioid receptors are prevalent in Pre Botz C neurons as well as KF-PB nuclei which send descending output to Pre Botz C

Opioids and Rhythm Generation



Destruction of preBötC

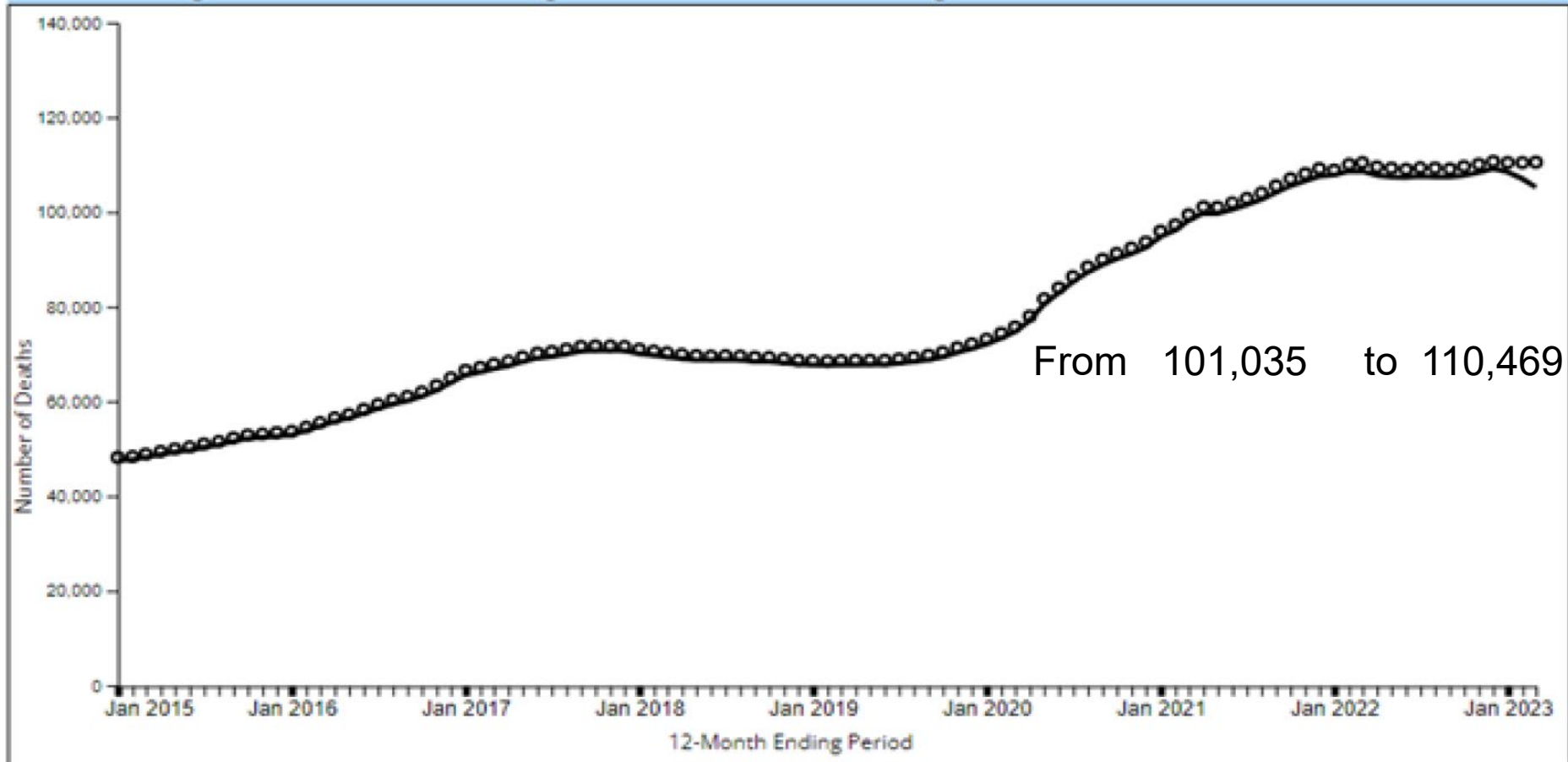
Neurochemically, preBötC neurons contain NK1 receptor and substance P is the endogenous agonist

In adult rats, selective destruction of preBötC neurons containing NK1 receptor causes disruption of breathing eventually to increased mortality during sleep

This latter finding in animals is relevant to opioids associated mortality in human as many individuals on opioids are found dead in bed, during sleep with no cause found at autopsy except opioids in the blood

The plaque

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



Treatment of OSA and CSA Associated with the Use of Opioids

- **Withdrawal of opioids**
- **PAP devices**
 - CPAP/bilevel : not recommended**
 - Bi-level with back up rate**
 - ASV**
- **Drugs**
 - Naloxone, ampakines, O₂, acetazolamide, theophylline**
- **Phrenic N stimulation**

Opioids Cause Central and Complex Sleep Apnea in Humans:
 Reversal with Discontinuation
 Javaheri and Patel (J Clin Sleep Med; 2017)

Type of Study	On opioids				Off opioids		
	PSG	CPAP/Bilevel Titration	Bilevel Titration	ASV Titration	PSG	PSG	CPAP Titration
Date	5/9/06	5/23/06	2/3/07	3/6/07	3/5/08	9/28/10	10/12/10
AHI, n/hr	64	42	63	17	4.7	9.6	2.6
OAI, n/hr	0.2	0	1	1	0.2	0.1	0
CAI, n/hr – Total	30	35	52	1	1	0.1	0.2
CAI, n/hr – Non - REM	32	35	58	1	1		
CAI, n/hr – REM	11	0	13	0	4		

1. Treatments of OSA

CPAP is the treatment of choice

CPAP-emergent central sleep apnea
may occur

Opioids, OSA, CPAP-emergent CSA

Inclusion Criteria

- Opioid use \geq 12 months
- Diagnosis of OSA on diagnostic PSG (AHI $>$ 5)
- Age \geq 18 y; mean age = 46 y; 50% women
- Mean BMI= 25.5 kg/m²
- Naïve to positive airway pressure treatment or surgical treatment for OSA
- Absence of heart failure, CAD, renal failure, CVA, neurologic disease, history of head trauma

Polysomnographic and PAP data

Diagnostic PSG:

AHI= 44; 31 of 42 had AHI \geq 30/ h of sleep

CAI 0.6

CPAP titration: (mean pressure 14 ± 2 cm H₂O)

Mean OAHl = 0

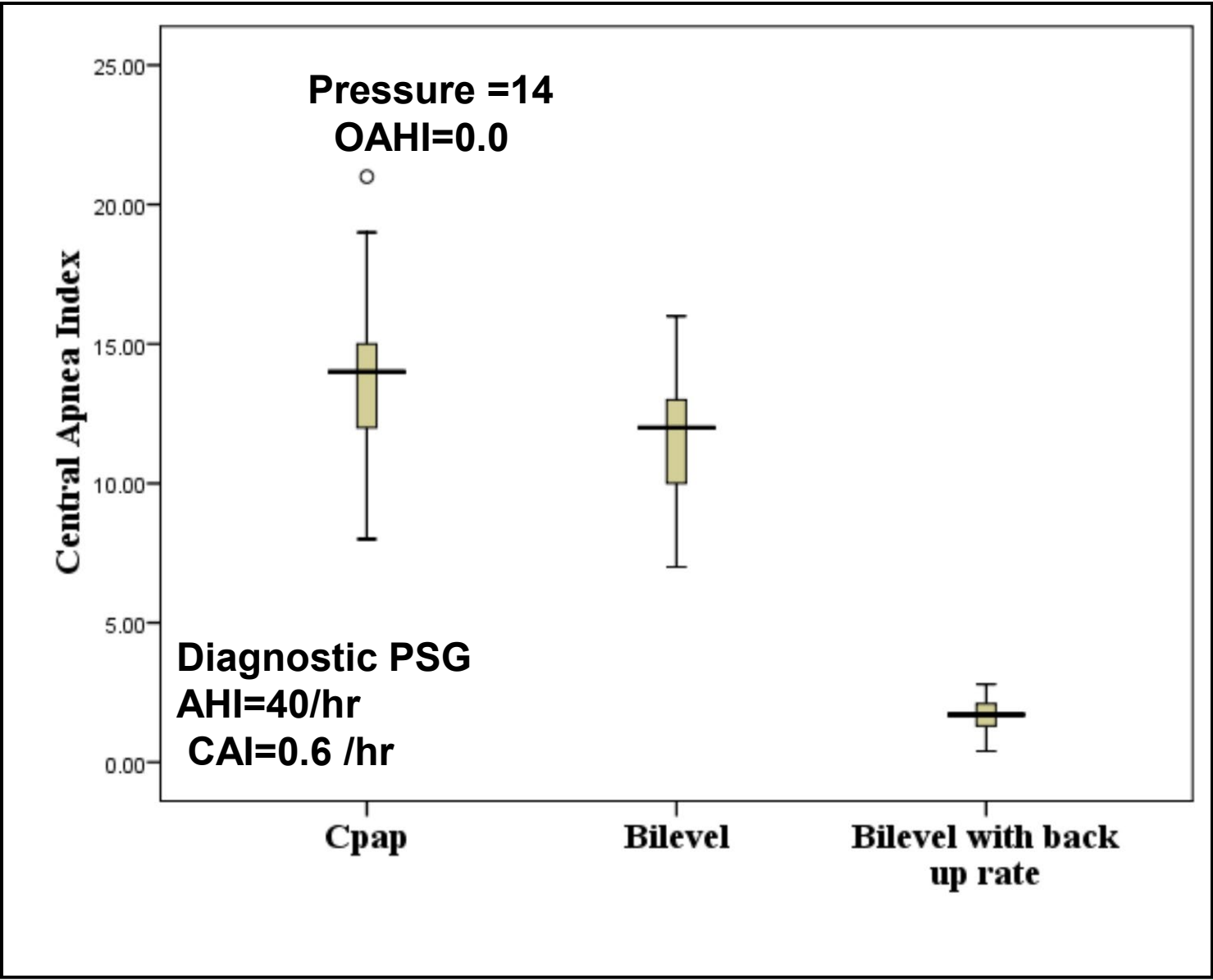
Mean CAI = 14

Bilevel titration: (mean IPAP 17, EPAP 12)

Mean CAI = 12

Bilevel with back up rate:

Mean CAI = 2



2. Treatment of opioid-induced central sleep apnea

CSA present on diagnostic PSG

Clinical presentation of CSA in patients on opioids could be identical to clinical presentation of OSA present in the

Historical findings in 20 patients on opioids referred for evaluation for OSA

	Variables	n
	-Male	13
	-Female	7
	Habitual snoring	16
	Witnessed apnea	14
	Nocturia	14
	Unrefreshing sleep	17
	Hypertension	12
	Depression	15
Javaheri et al JCSM,214		

Opioids and morphine equivalent dosage in 20 patients

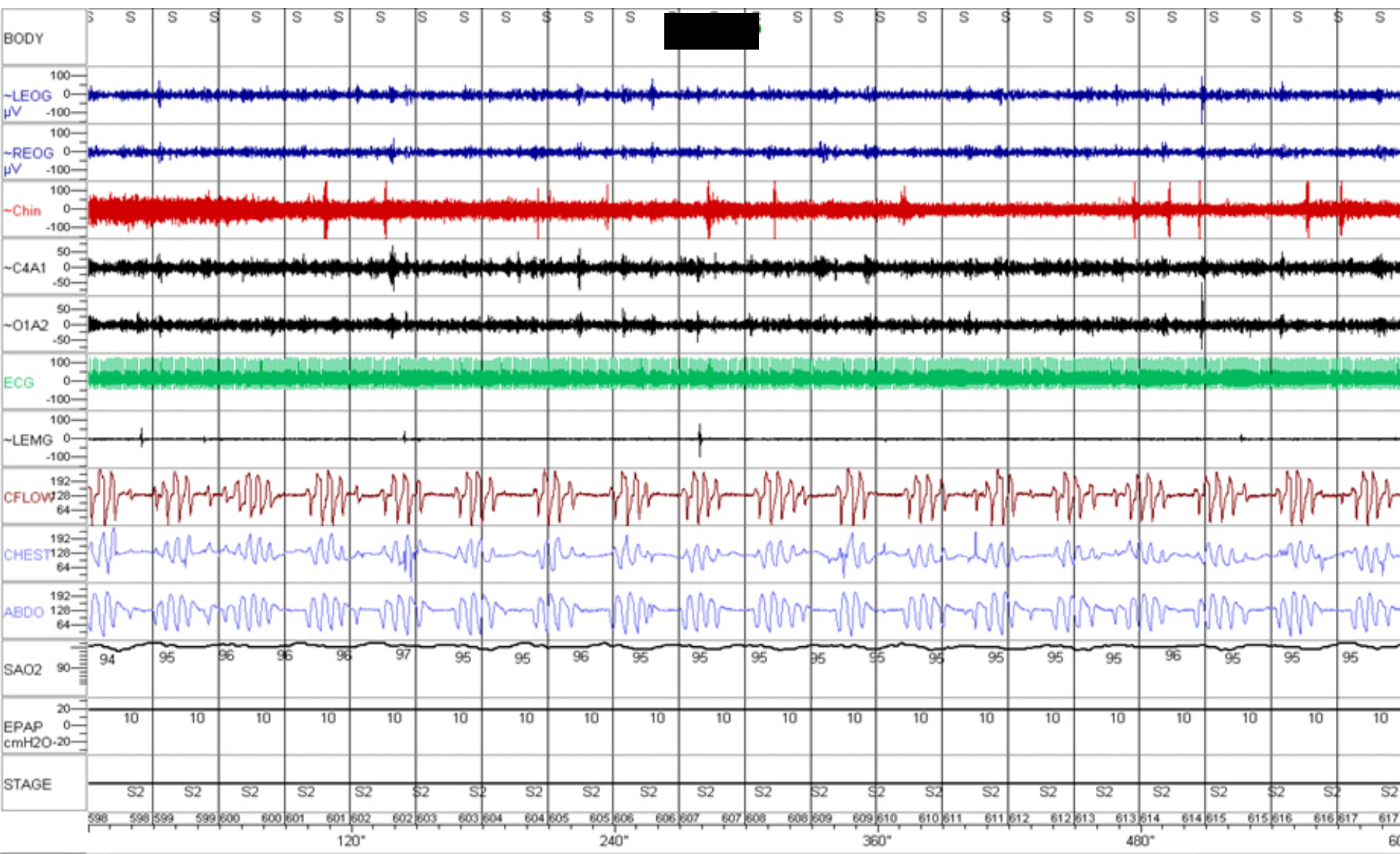
Opioid	n
Morphine	6
Oxycodone	13
Fentanyl transdermal	2
Methadone	3
Tramadol	1
Hydromorphone	3

**Morphine equivalent: range = 15 mg-915 mg
median=118mg**

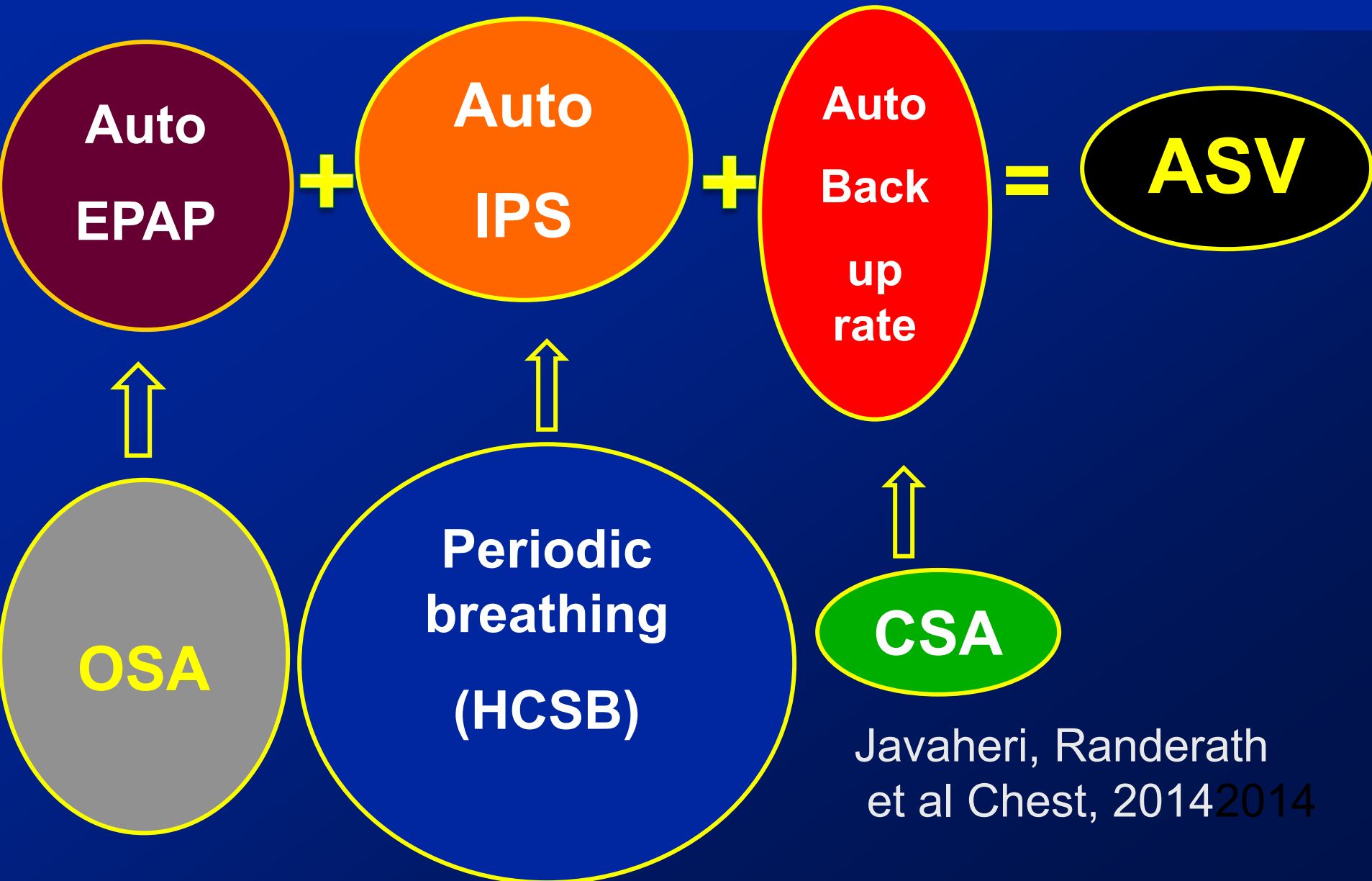
SA in 9 consecutive patients

Baseline	CPAP 1	CPAP 2
AHI: 45 ± 22	34 ± 19	33 ± 18
CAI : 20 ± 21	20 ± 14	19 ± 17
CPAP was not recommended for the remaining 11 patients.		

CPAP (10 cm H₂O)

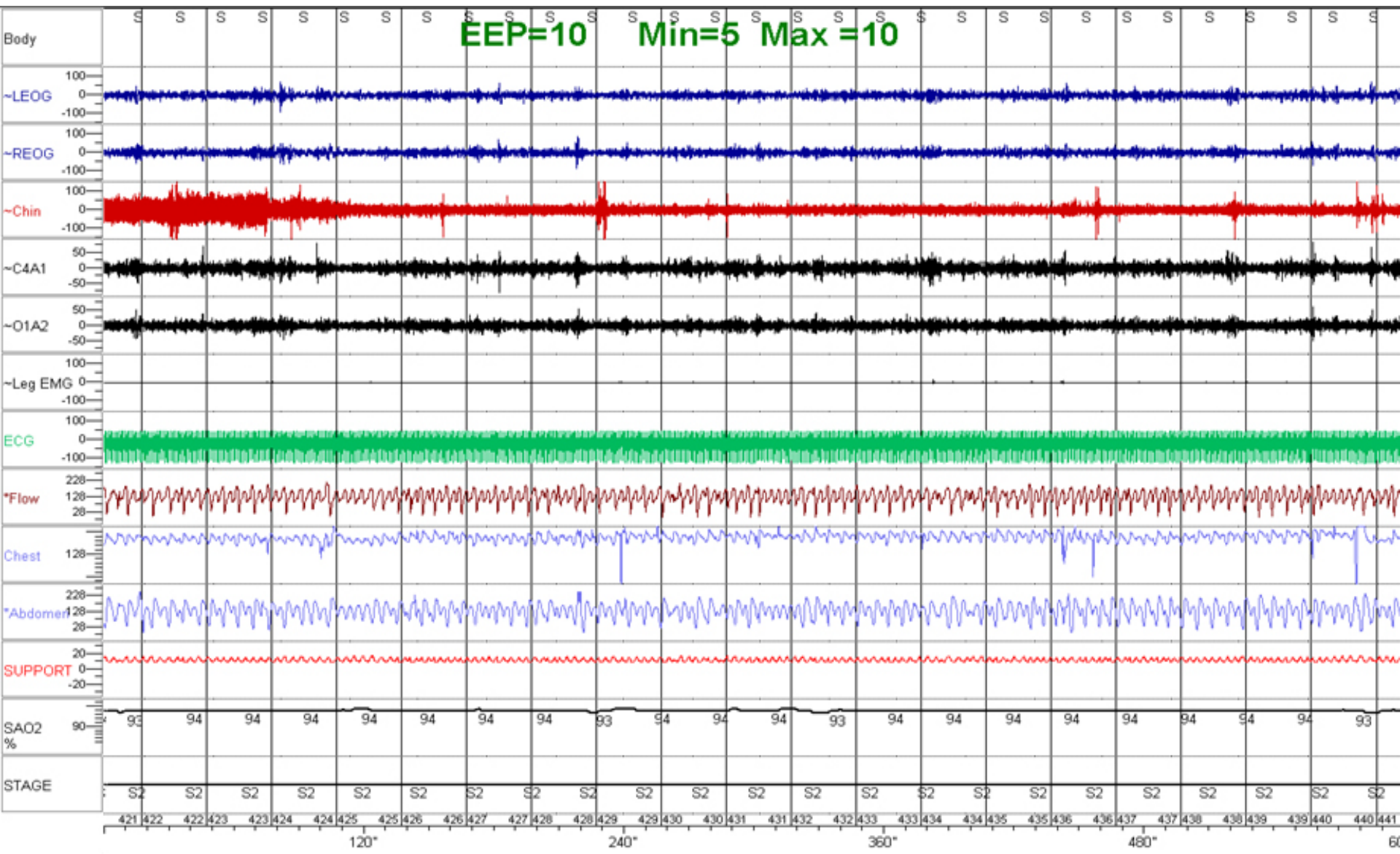


Components of new ASV devices

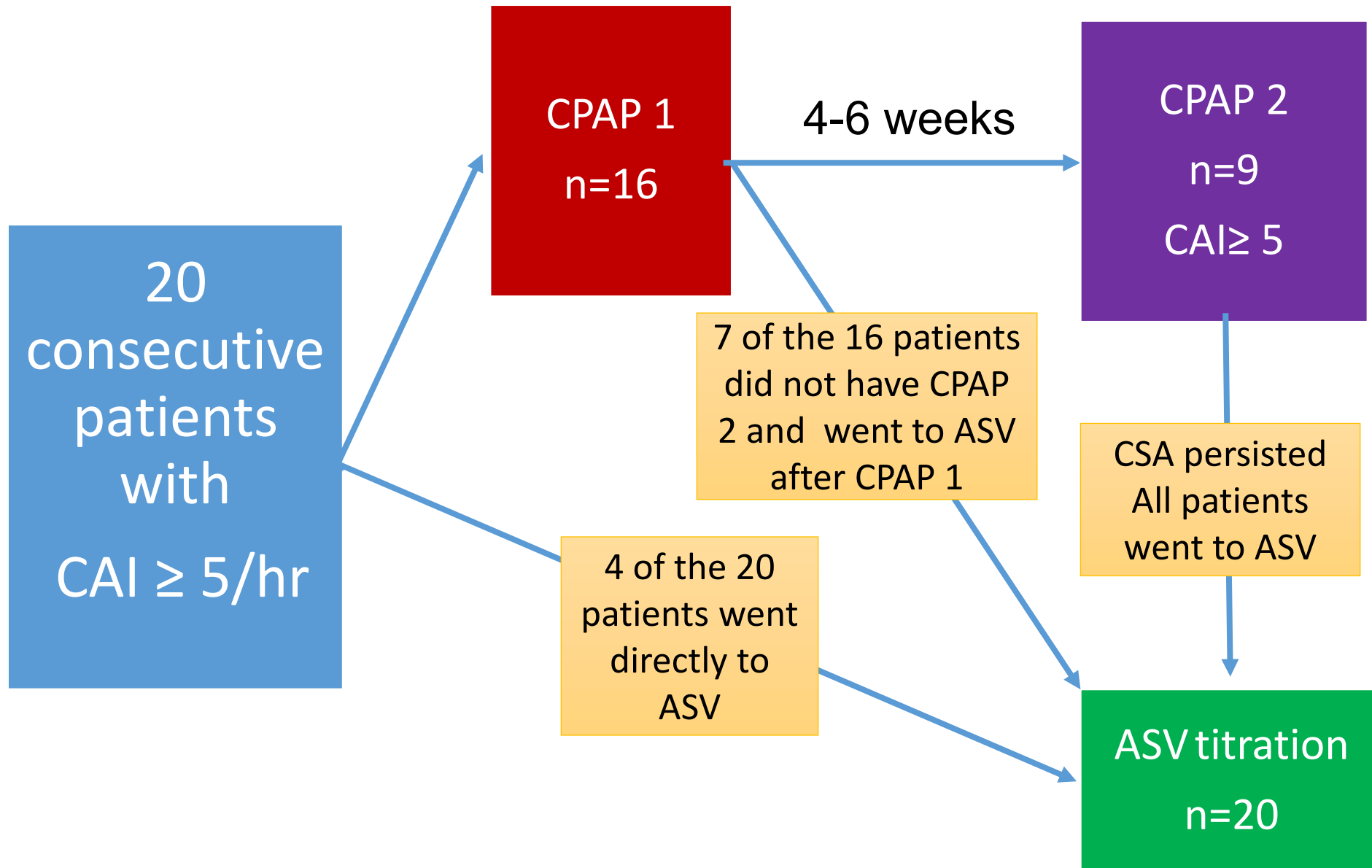


Javaheri, Randerath
et al Chest, 20142014

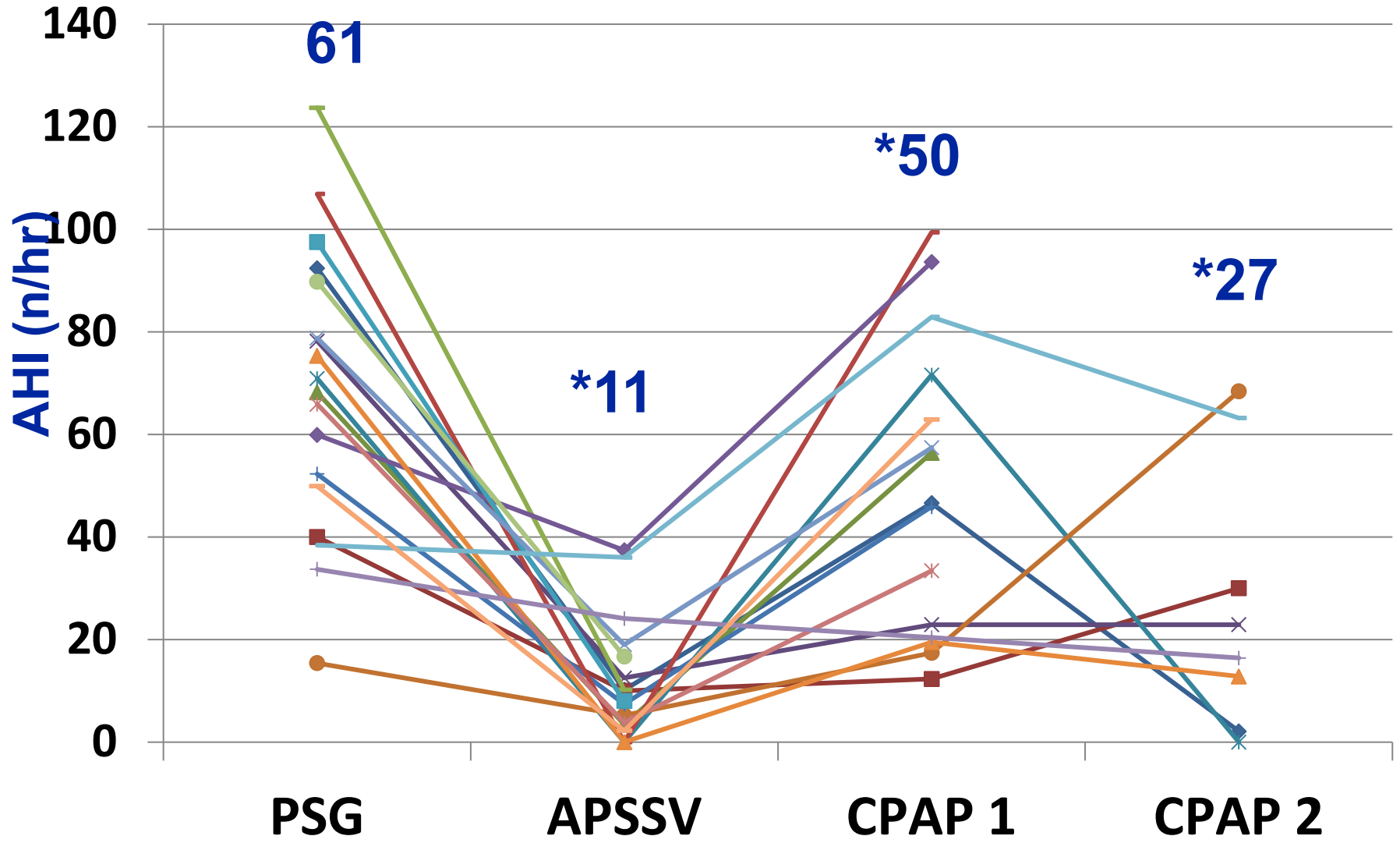
ASV



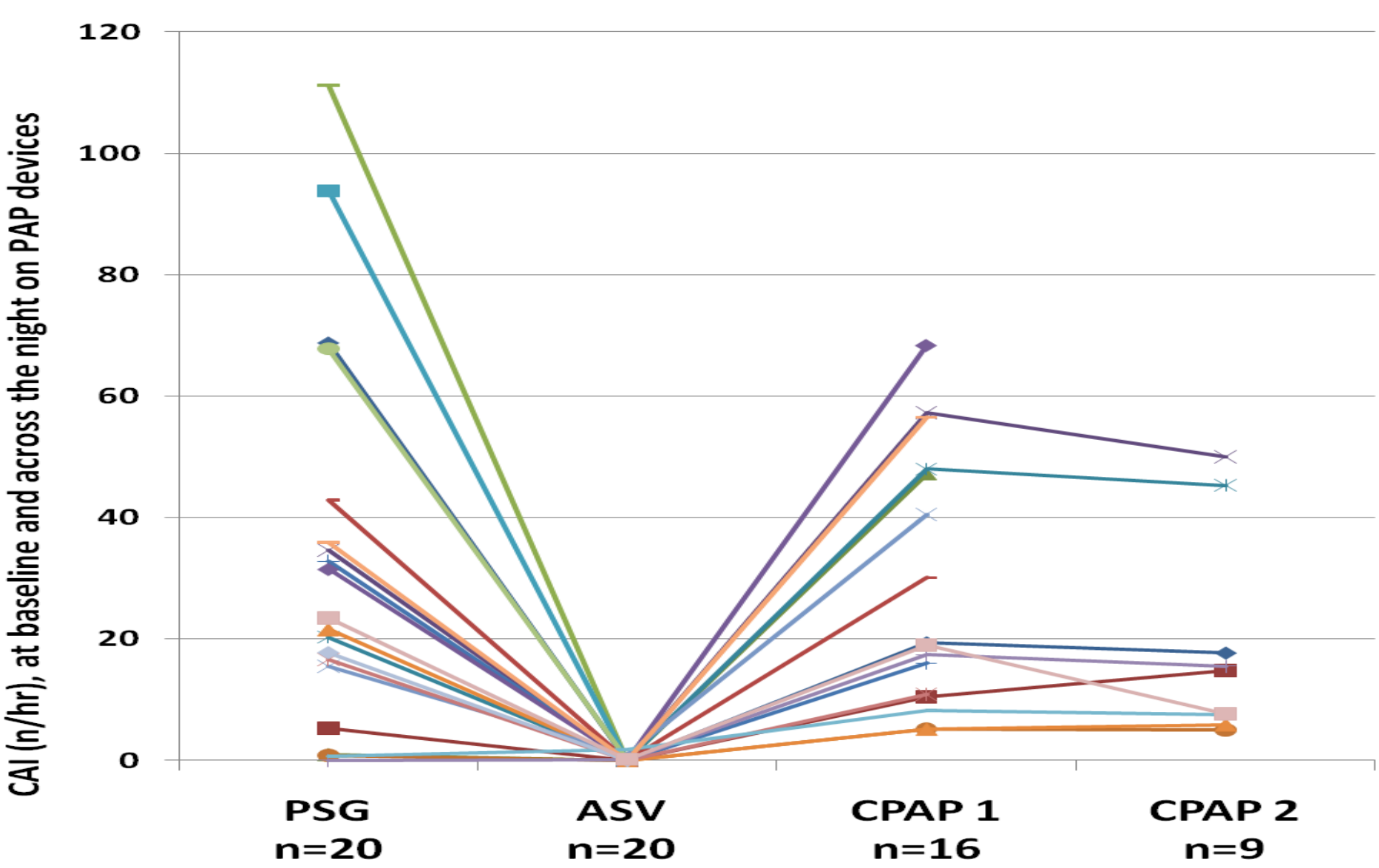
Flow chart of sequential management for 20 patients on opioid therapy (Javaheri et al, JCSM, 2014)



Apnea-hypopnea index (AHI) at baseline and on final PAP level. * indicates mean AHI (n/hr).



Central apnea index (CAI) across the night on PAP devices compared to baseline for the 20 patients



Pressure settings on ASV(n=20)

Javaheri , JCSM, 2014

Expiratory pressure, cm/H₂O	9 ± 3 (range 5-15)
Minimum IPS, cm/H₂O	5 ± 1 (range 3-6)
Maximum IPS cm/H₂O	10 ± 1 (range 8-13)

Long-term FU

1 patient refused using ASV and 2 lost to follow up in less than a month.

17 patients were followed for a minimum of 9 months and up to 6 years.

Mean \pm SD = 25 \pm 5.2 months

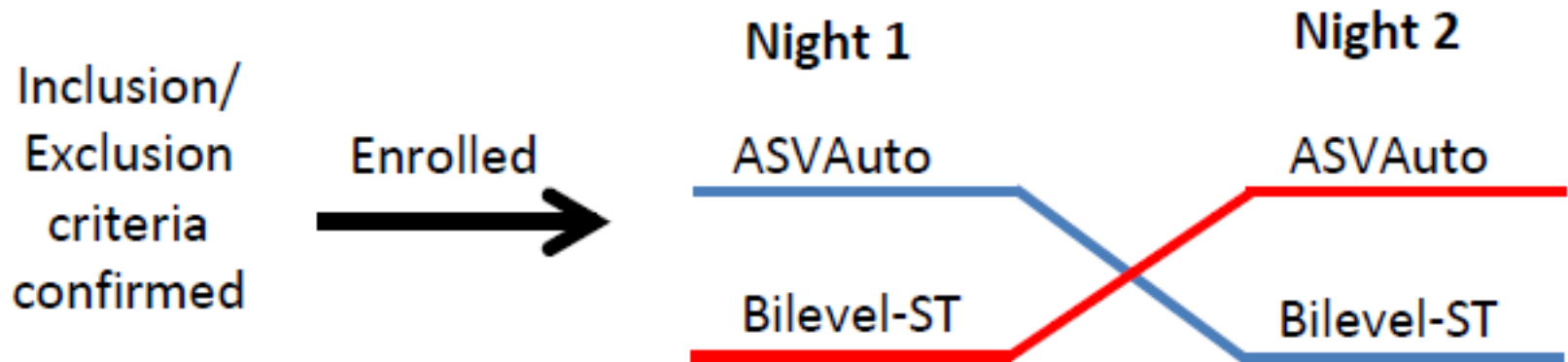
The mean long-term adherence was 5.1 \pm 2.5 hours

The mean ESS 12.4 \pm 4.6 at baseline

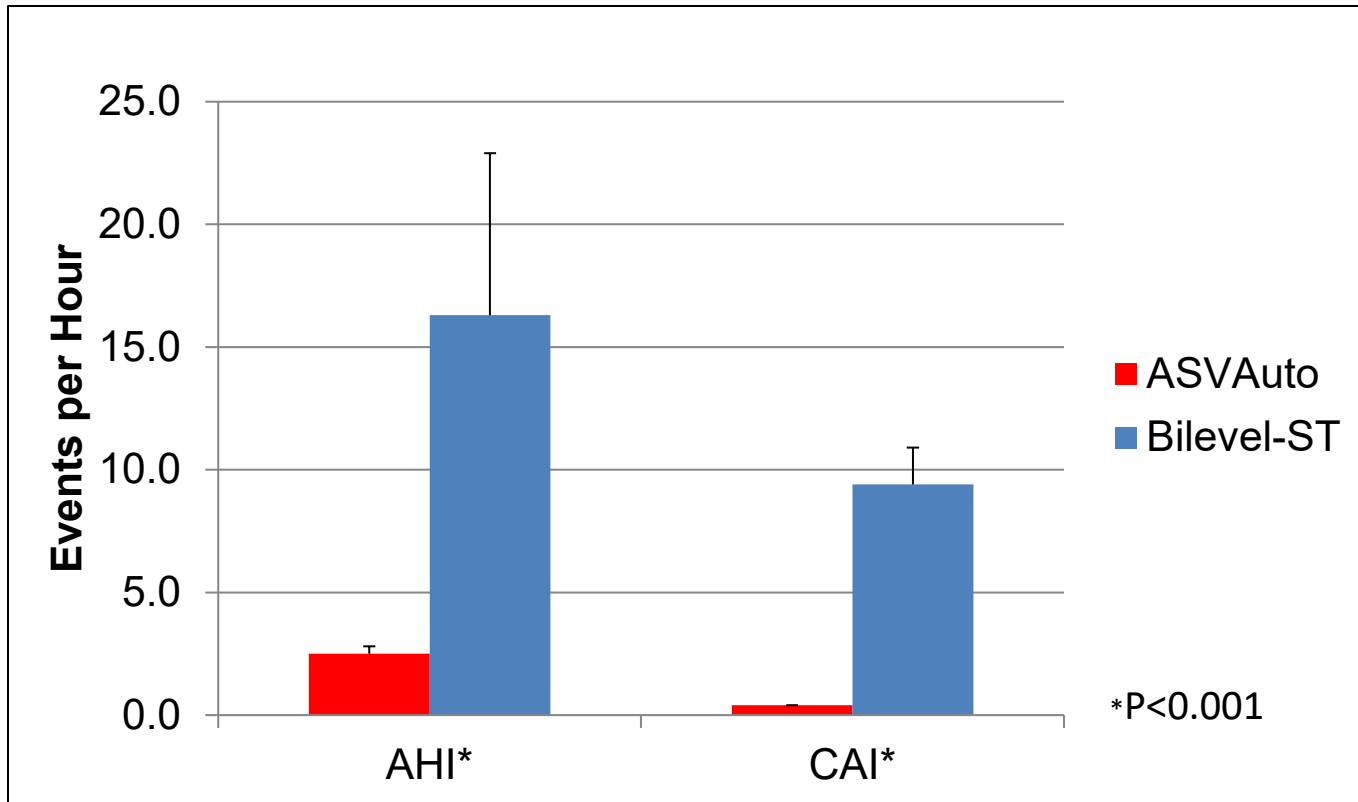
10.4 \pm 4.6 on ASV at final FU

Study Design

The pre-entry baseline PSG showed an overall AHI and CAI of 50 ± 22 (45) and 13 ± 19 (5), respectively [mean \pm SD (median)]



AHI and CAI with ASV Auto and Bilevel-ST



Conclusions

1. CNCPC are common and opioids have become part of contemporary management of chronic pain
2. Opioids could cause severe sleep apnea independent of age, weight and gender
3. Opioids-associated sleep apnea can be effectively treated with PAP devices
4. Best treatment is detoxification