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## Background

- Narcolepsy is a chronic neurologic disorder characterized by disturbed nocturnal sleep, excessive daytime sleepiness, and symptoms characteristic of disrupted rapid eye movement (REM) sleep such as cataplexy, sleep paralysis, sleep-related hallucinations, and frequent vivid dreams<sup>1</sup>
- It is associated with short sleep latency, and sleep-onset REM periods on the multiple sleep latency test<sup>2</sup>
- Due to disturbed sleep regulation, individuals tend to skip the initial phases of sleep and directly enter into REM sleep, resulting in less amount of sleep in the N3 deep-sleep stage<sup>2,3</sup>
- Sodium oxybate (SXB), the sodium salt of GHB ( $\gamma$ -hydroxybutyrate), is the only drug that has demonstrated efficacy across multiple narcolepsy symptoms,<sup>3</sup> and many randomized controlled trials (RCTs) have proven its safety and clinical efficacy in narcolepsy<sup>3,4</sup>
- We were interested to examine if the beneficial effects of SXB in patients with narcolepsy are also reported from studies conducted in real-world settings

## Objective

- To examine the clinical (safety, effectiveness) and humanistic (QoL and other PROs) outcomes associated with SXB when used in the management of narcolepsy in real-world settings

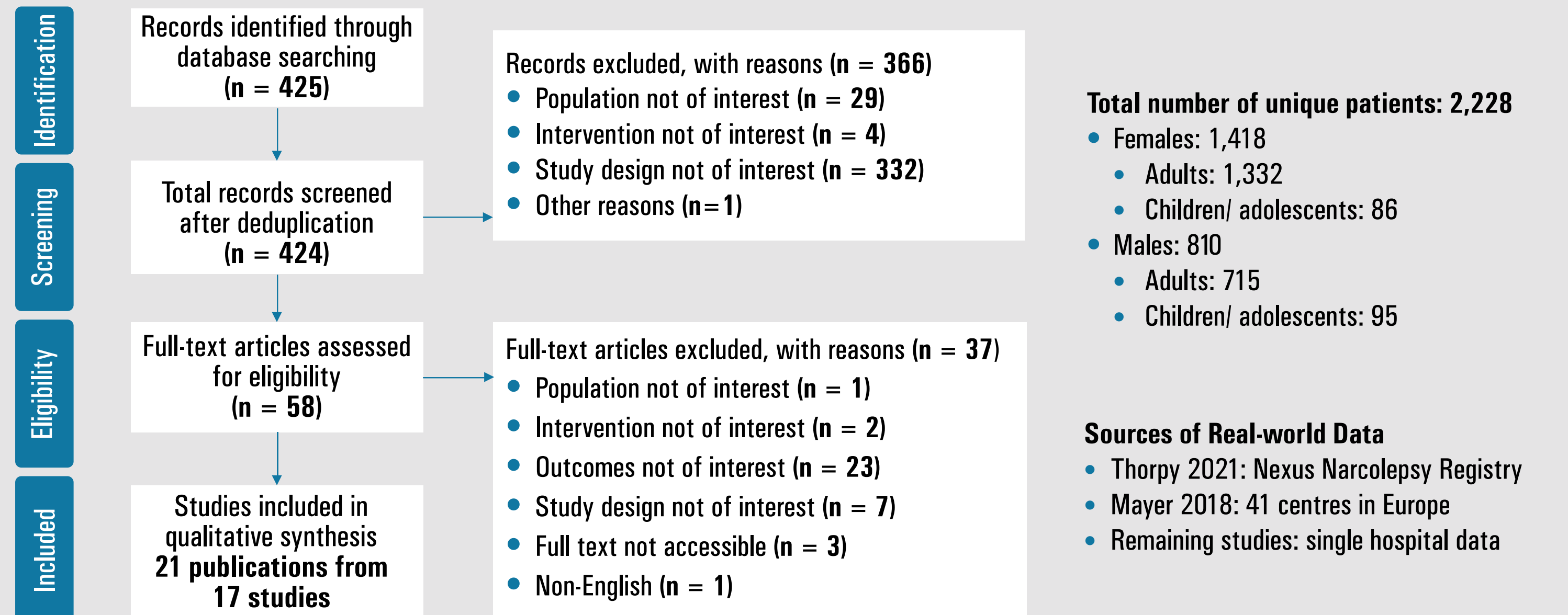
## Methodology

### Eligibility Criteria

Facet	Inclusion Criteria
Population	Patients of either gender and any age with any type of narcolepsy
Intervention vs all comparators	Sodium oxybate vs all comparators
Outcomes	<b>Clinical: Efficacy Outcomes</b> <ul style="list-style-type: none"> <li>Change in average weekly number of cataplexy attacks from baseline</li> <li>Change in average sleep latency as measured by the MWT</li> <li>Change in average sleep latency as measured by the MSLT</li> <li>Change in ESS score</li> <li>Change in polysomnography readings (e.g., sleep duration, sleep efficiency, time in rapid eye movement sleep, etc.)</li> </ul>
	<b>Clinical: Safety Outcomes</b> <ul style="list-style-type: none"> <li>Any AE</li> <li>Treatment-related AE</li> <li>Discontinuation due to AE</li> <li>Serious AE</li> </ul>
	<b>Humanistic Outcomes</b> <ul style="list-style-type: none"> <li>EQ-5D, EQ-5D-VAS</li> <li>SF-36, SF-10, SF-12</li> <li>MCS, PCS</li> <li>PGIC, CGIC</li> <li>WHOOQL-BREF</li> <li>PHQ-9</li> <li>FOSQ</li> </ul>
Study design	Observational, RWE studies; we excluded RCTs and non-primary studies (such as reviews, editorials, case reports, etc)

MWT: maintenance of wakefulness test; MSLT: multiple sleep latency test; ESS: Epworth sleepiness scale; AE: adverse event; EQ-5D: EuroQol-5 dimension; VAS: visual analog scale; SF-36: 36-item short-form; SF-10: 10-item short-form; SF-12: 12-item short-form; MCS: mental component summary; PCS: physical component summary scores; PGIC: patient global impression of change; CGIC: clinical global impression of change; WHOOQL-BREF: WHO quality of life-BREF; PHQ-9: patient health questionnaire-9; FOSQ: functional outcomes of sleep questionnaire; RWE: real-world evidence; RCT: randomized controlled trials

## Results



### Key features of included studies

Study Name	Study design	Study Duration	Population description	Sample size	Mean $\pm$ SD age in years	Types of outcomes
<b>Studies involving children and adolescents</b>						
Filardi 2022	Prospective observational	1 yr	Children and adolescents with NT1	18	14.4 $\pm$ 2.0 (range 10-17)	E
Antelmi 2021	Prospective observational	NR	Children with a final diagnosis of NT1	19	12.5 $\pm$ 2.7	E
Filardi 2018	Prospective observational	1 yr	Drug naïve children & adolescents with NT1	24	12.2 $\pm$ 2.9	E, Q
Huang 2009	Prospective observational	3 mths	Adolescents with recently diagnosed NC	SXB for NC: 13 Baclofen for NC: 13	SXB for NC: 15.3 $\pm$ 1.7 Baclofen for NC: 15.2 $\pm$ 1.9	E
Aran 2010	Retrospective observational	NR	Children with NC	51	11.8 $\pm$ 0.5 (SEM)	E, S
Murali 2006	Retrospective observational	NR	Children with severe NC	8	12.4 $\pm$ 2.5 (range 8-15)	E, S
Antelmi 2018	Case-control study	NR	Drug naïve children with NT1	Cases: 12 Controls: 23	Cases: 11.3 $\pm$ 3.2 Controls: 11.3 $\pm$ 3.5	E
<b>Studies involving adult patients</b>						
Thorpy 2021	Prospective observational	2.5 yrs	Adult patients with Narcolepsy	SXB: 267 No SXB: 716	SXB: 37.8 (95% CI 36.7-38.9) No SXB: 38.1 (95% CI 37.3-38.8)	Q
Mayer 2018	Prospective observational	10.5 yrs	Adult patients who received SXB treatment	SXB for narcolepsy: 670 SXB for other reason: 60	Narcolepsy: 39.4 $\pm$ 16.5 No narcolepsy: 35.4 $\pm$ 13.6	S
Poryazova 2011	Prospective observational	26 $\pm$ 13 mths	Adult patients with NC and HLA-DQB1*0602-positive	Overall: 18 Treated with SXB: 13	Overall: 43.0 $\pm$ 16.0 Treated with SXB: NR	E
Drakatos 2017	Retrospective observational	NR	Adult patients with severe NC	90	42.5 $\pm$ 14.9	E, S
Leu-Semenescu 2016	Retrospective observational	NR	Adult patients who received SXB treatment	SXB for NT1: 47 SXB for IH: 46	NT1: 44.1 $\pm$ 18 (range 18-86) IH: 35.7 $\pm$ 12.6 (range 18-67)	E, S
Van der Heide 2016	Case-control study	NR	SXB naïve adults with NT1	Cases: 25 Controls: 15	Cases: 34.8 $\pm$ 3.4 Controls: 33.9 $\pm$ 14.0	E
Van der Heide 2015	Case-control study	5 d	Adult male patients with NT1	Cases: 8 Controls: 8	Cases: 38.0 $\pm$ 4.7 Controls: 37.1 $\pm$ 4.1	E
Plazzi 2014	Case-control study	1 d	Adult patients with NC	Cases: 16 Controls: 16	Cases: 40.2 $\pm$ 18.2 Controls: 42.0 $\pm$ 18.6	E
Donjacour 2013	Case-control study	5 d	Adult male patients with NC	Cases: 8 Controls: 8	Cases: 38.0 $\pm$ 13.4 Controls: 37.9 $\pm$ 11.6	E
Donjacour 2012	Case-control study	5 d	Adult male patients with NC	Cases: 7 Controls: 7	Cases: 34.3 $\pm$ 3.4 (SEM) Controls: 34.7 $\pm$ 3.0 (SEM)	E
Donjacour 2011(a)	Case-control study	5 d	Adult male patients with NC	Cases: 8 Controls: 8	Cases: 38.0 $\pm$ 4.7 (SEM) Controls: 37.9 $\pm$ 4.1 (SEM)	E
Donjacour 2011(b)	Case-control study	5 d	Adult male patients with NC	Cases: 8 Controls: 8	Cases: 38.0 $\pm$ 4.7 (SEM) Controls: 37.9 $\pm$ 4.1 (SEM)	E
Broughton 1980	Prospective observational	7-10 d	Adult patients with NC	14	41.8 $\pm$ 13.6	E, S
Broughton 1979	Prospective observational	12 mths	Adult patients with NC	16	41.8 $\pm$ 13.6	S

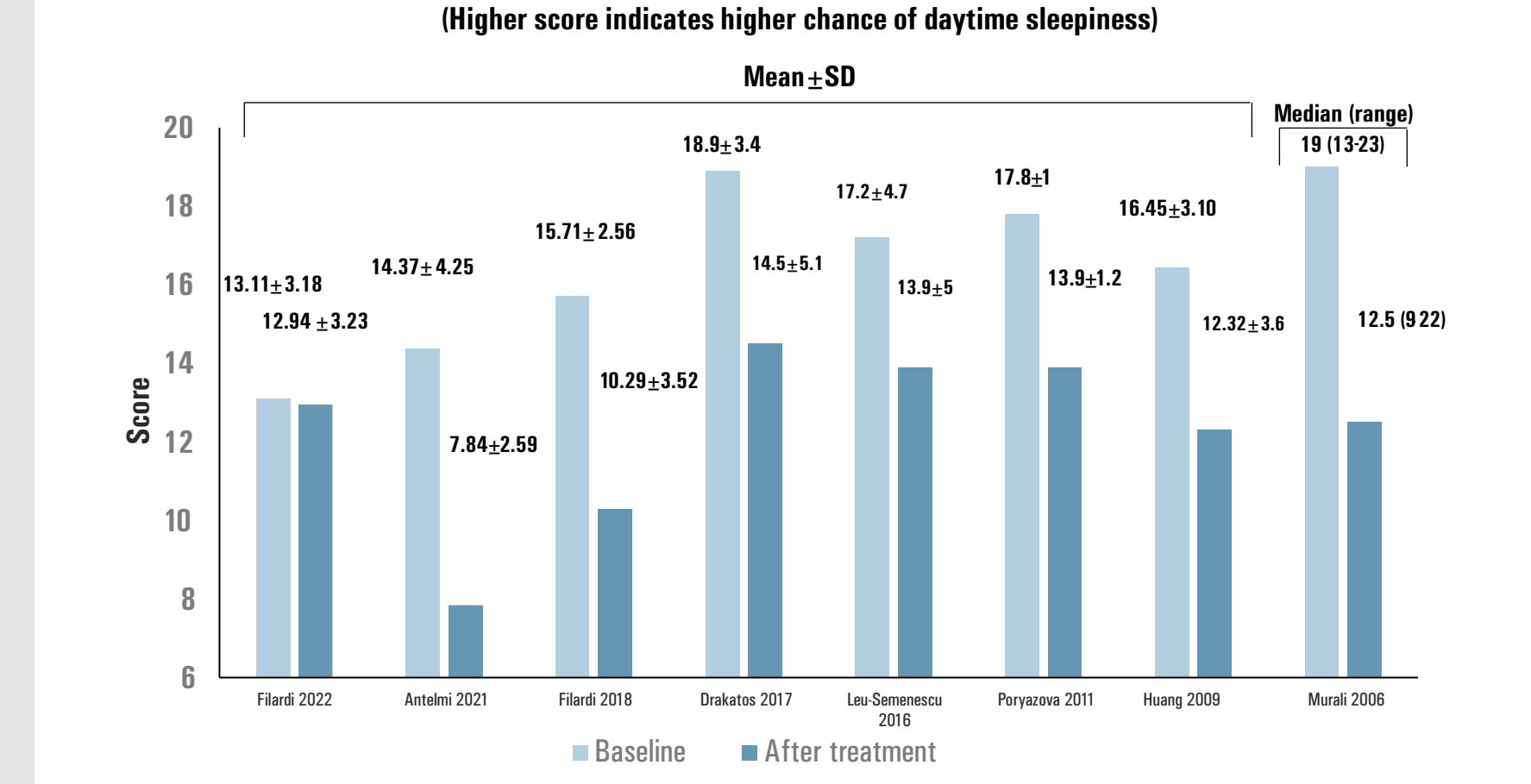
Note: NT1: Narcolepsy Type 1; NC: Narcolepsy with Cataplexy; SXB: Sodium Oxybate; E: Efficacy; S: Safety; Q: Quality of life; two publications by Broughton R represent the same study; four publications by Donjacour CE represent the same study

## Intervention Dosing

- In studies reporting adult patients (N = 10), the dosage of SXB was:
  - As per recommended dose in 6 studies (4.5 g/night in 2 divided doses)
  - Less than recommended dose in 5 studies 2 studies did not report dosage
- In studies reporting pediatric patients (N = 7), the dosage of SXB was:
  - Highly variable across 5 studies
  - At 60-90 mg/kg per day in 1 study
  - 1 study did not report dosage

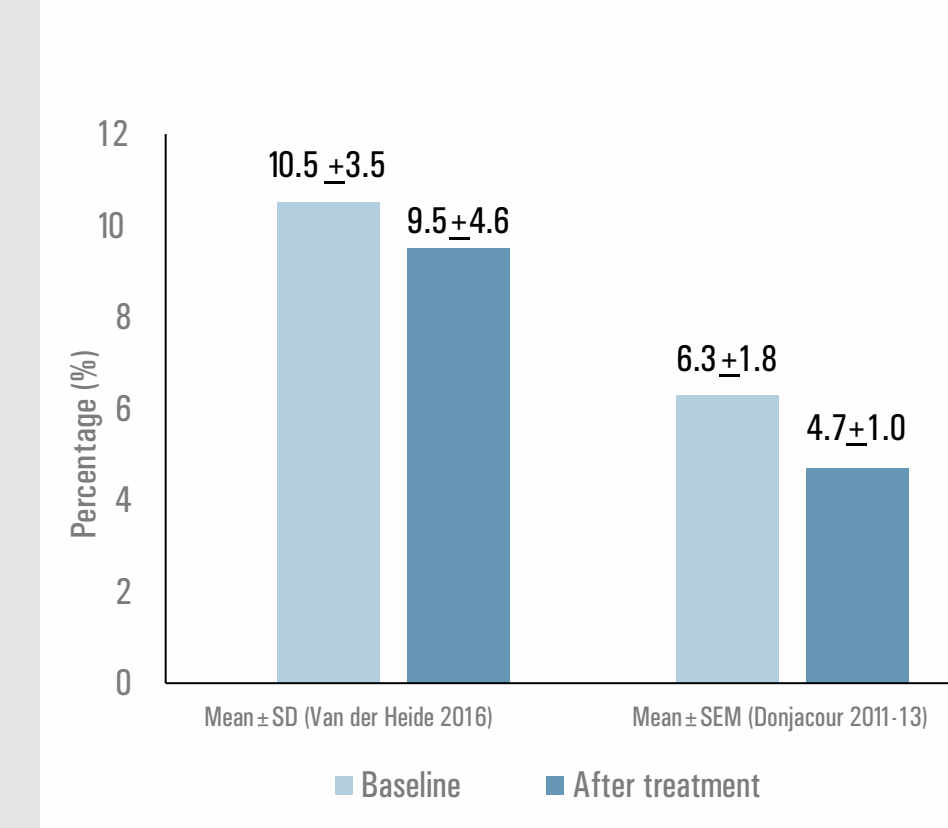
## Effectiveness Outcomes

### SXB treatment reduced the mean/median Epworth sleepiness score (8 studies)

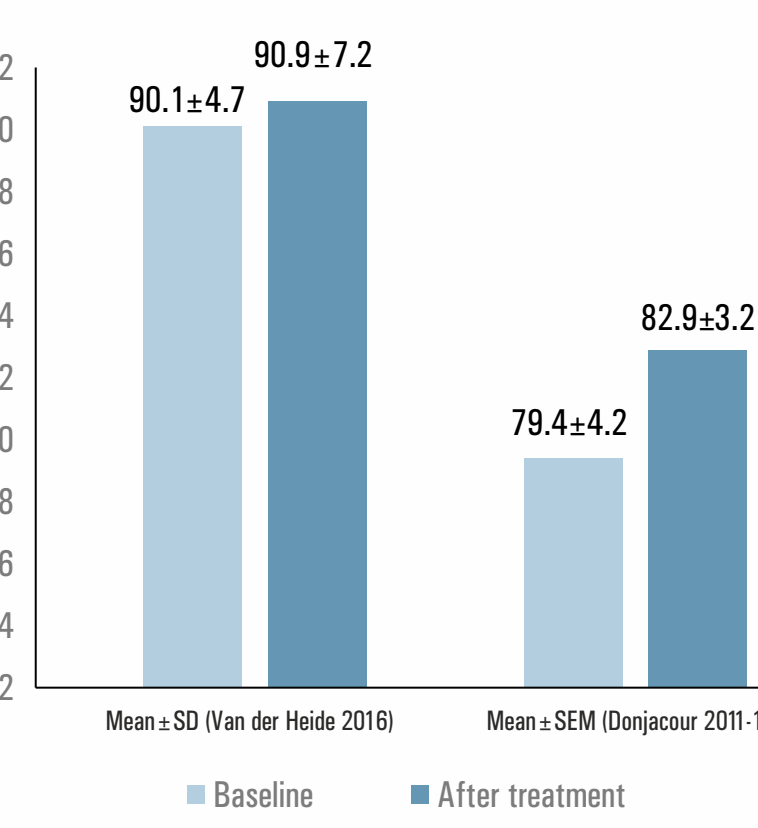


- Treatment with SXB was also associated with inconsistent and conflicting changes in other sleep parameters, including sleep efficiency, total sleep time, REM sleep latency, overall sleep latency, and wakefulness after sleep onset

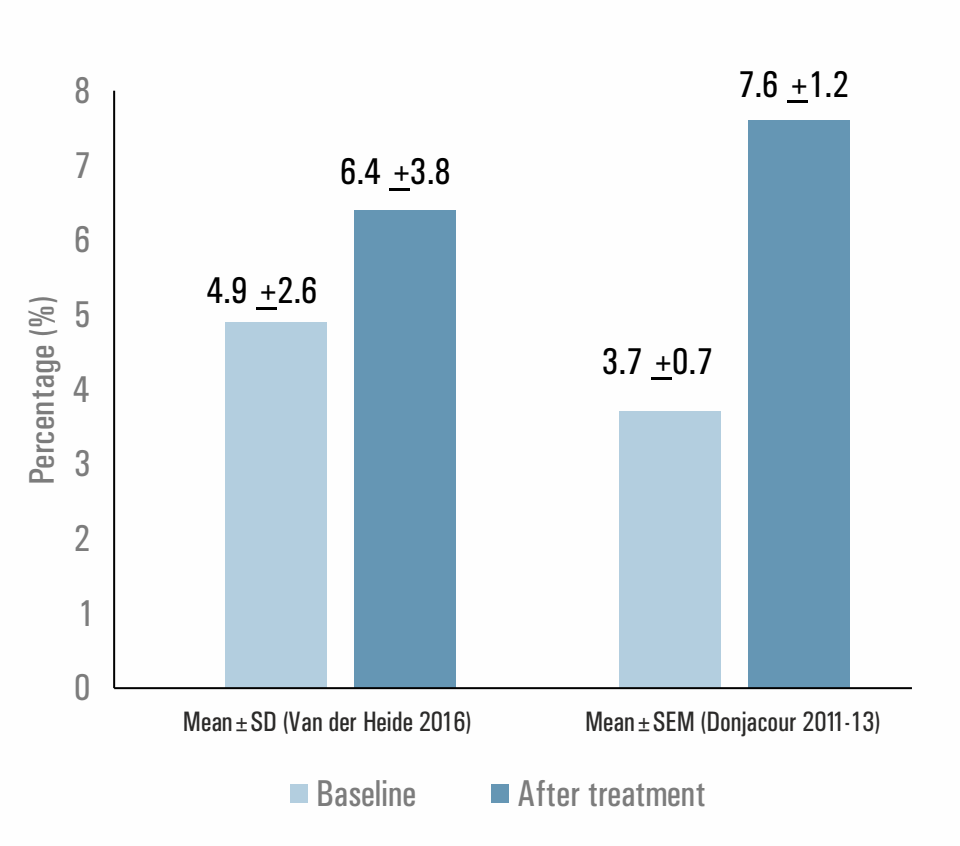
### SXB treatment reduced the proportion of REM sleep (2 studies)



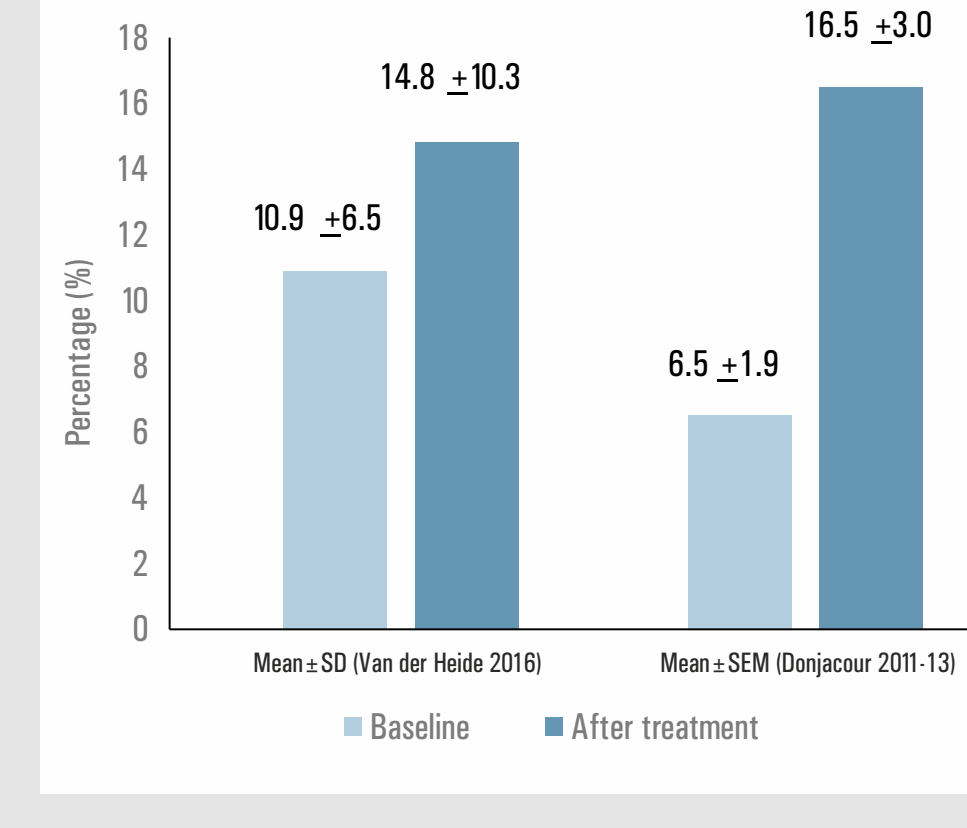
### SXB treatment increased the % of daytime wakefulness (2 studies)



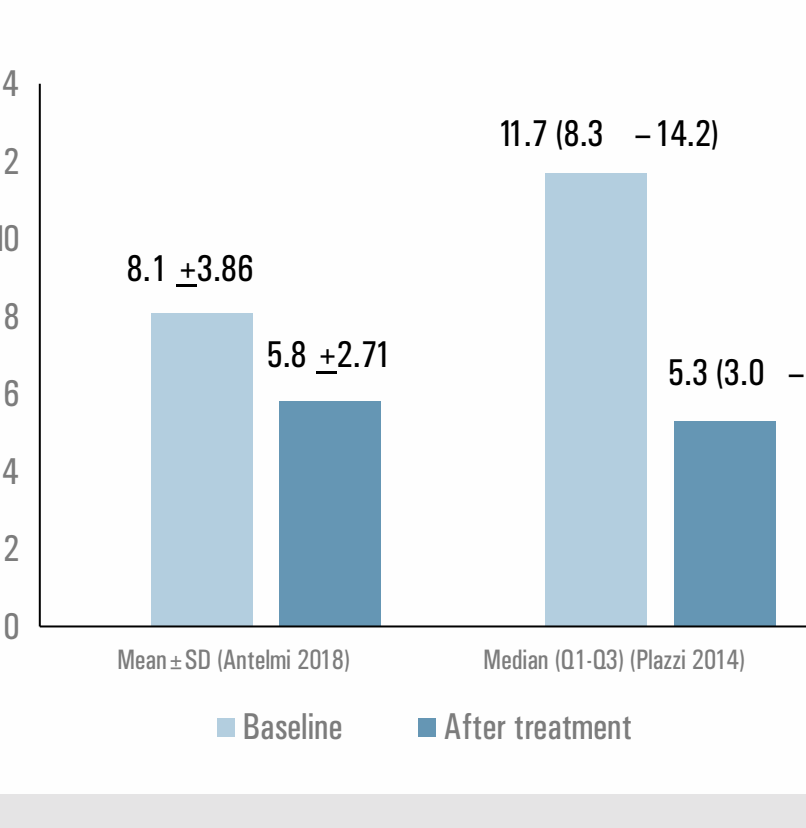
### SXB treatment increased the proportion of overall slow wave sleep (2 studies)



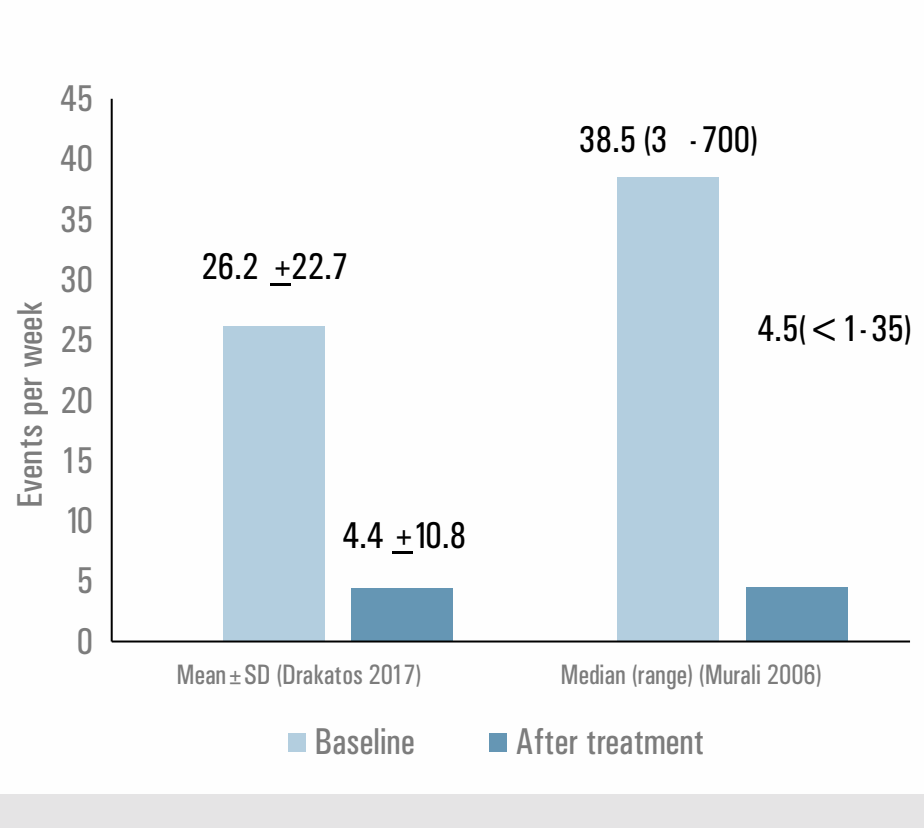
### SXB treatment increased the proportion of night-time slow wave sleep (2 studies)



### SXB treatment reduced total number of awakenings per hour (2 studies)



### SXB treatment reduced the number of cataplexy events per week (2 studies)



## Safety Outcomes (5 studies)

- No new safety signals of concern were reported

## Humanistic Outcomes (2 studies)

- Thorpy et al 2021 reported that SXB was associated with statistically significant improvements in sleep quality, daytime functioning, SF-36 HRQoL scores, presenteeism, overall work and activity impairment, and risk of motor vehicle accidents
- Filardi et al 2018 did not find any statistically significant changes in the rMEQ-CA (reduced Morningness-Eveningness questionnaire for children and adolescents) after 1 year of SXB treatment

## Discussion

- In this SLR of effectiveness, safety, and humanistic outcomes of SXB in narcolepsy patients in real-world setting, all 17 included studies evaluated effectiveness outcomes, 5 studies evaluated safety outcomes and only 2 studies evaluated humanistic outcomes
- Only few studies evaluated the same outcomes, resulting in inadequate data to strongly determine improvements in effectiveness, safety, and humanistic outcomes
- SXB was found to be safe and effective in the treatment of narcolepsy in both adults and children in the real-world setting, and was associated with:
  - Reduction in:** Epworth sleepiness score, total sleep time, proportion of REM sleep, wakefulness after sleep onset, awakenings, and cataplexy
  - Increase in:** Sleep efficiency, proportion of slow wave sleep (night and total), proportion of daytime wakefulness, sleep latency
  - Improvement in:** Humanistic outcomes such as sleep quality, daytime functioning scores, HROQL, PROs
- No new safety signals were noted with the real-world usage of SXB
- Contrary to our expectation, REM sleep latency was reduced in 4 out of 5 studies; this would require further exploratory analysis
- We observed a lack of uniformity in the outcomes assessed in the 17 RWE studies included in our review

### Limitations

- Search was limited to PubMed; databases like Embase was not included
- Only English language publications were searched

## Conclusion

- In line with findings of previous RCTs, SXB was found to be safe and effective in narcolepsy patients treated in real-world settings
- Future real-world studies need to evaluate standard outcomes consistently to enable pooling and collective analysis of data that can lead to more conclusive evidence on the effectiveness and safety of SXB in narcolepsy

## References

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- Patel AK et al. Physiology, Sleep Stages. <https://www.ncbi.nlm.nih.gov/books/NBK526132/>
- Kushida CA et al. Sleep 2022;45:zsab200
- Plazzi G et al. Lancet Child Adolesc Health 2018;2:483-494.