불면증 치료를 위한 오렉신 수용체 길항작용

수보렉산트의 무작위임상시험

Orexin receptor antagonism for treatment of insomnia

A randomized clinical trial of suvorexant

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목적: 불면증을 치료하는 새로운 방법으로써 오렉신 수용체 길항작용의 유용성을 평가하고자 함이다.
방법: 일차성 불면증 치료제로써 오렉신 수용체 길항체인 수보렉산트(suvorexant)를 무작위배정, 이중눈가림, 위약-대조군, 2-기간(한 번의 기간당 4주) 교차 수면다원검사 연구를 통해 평가하였다. 환자들은 수보렉산트(10 mg [n=62], 20 mg [n=61], 40 mg [n=59] 또는 80 mg [n=61])를 한 번의 기간 동안 복용하였고 다른 기간 동안 위약(n=249)을 복용하였다. 수면다원검사는 첫째 날 밤과 각 기간의 4주차의 마지막 날에 시행하였다. 공동일차 유효성 평가변수는 첫째 날과 4주차 마지막 날의 수면효율이다. 이차결과변수는 수면 후 깨어남(wake after sleep onset)과 지속적인 수면의 잠복기이다.
결과: 수보렉산트는 첫째 날 밤과 4주차의 마지막에 평가한 수면효율에 대한 공동일차 유효성 평가변수에서 위약과 비교 시 유의하게 용량과 비례하여 개선되는 것을 보여주었다(p values < 0.01). 용량 비례효과는 수면유도(지속적인 수면의 잠복기)와 유지(수면 후 깨어남)에서도 나타났다. 수보렉산트는 일반적으로 안전하였다.
결론: 이 자료는 오렉신 수용체 길항작용이 불면증을 치료하는 새로운 방법이 될 수 있다는 것을 제시한다.
근거의 분류: 이 연구는 수보렉산트가 젊은 성인 일차성 불면증환자에서 4주에 걸쳐 수면효율을 개선시킨다는 것에 대해 Class I의 근거를 제공한다.

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Table 4 Summary of clinical adverse events by placebo and suvorexant treatment[a]

	Placebo (n = 249)	10 mg (n = 62)	20 mg (n = 61)	40 mg (n = 59)	80 mg (n = 61)
≥1 adverse event	50 (20.1)	11 (17.7)	12 (19.7)	18 (30.5)	22 (36.1)
≥1 drug-related adverse event[b]	17 (6.8)	3 (4.8)	4 (6.6)	12 (20.3)	14 (23.0)
≥1 serious adverse event	0	0	0	0	0
Discontinued because of adverse event	3 (1.2)	0	0	0	1 (1.6)
Common adverse events (≥2% in any group)					
Somnolence	1 (0.4)	1 (1.6)	3 (4.9)	6 (10.2)	7 (11.5)
Headache	6 (2.4)	0	1 (1.6)	3 (5.1)	3 (4.9)
Dizziness	0	0	1 (1.6)	0	3 (4.9)
Abnormal dreams	2 (0.8)	1 (1.6)	0	0	3 (4.9)
Sedation	1 (0.4)	0	0	0	2 (3.3)
Urinary tract infection	2 (0.8)	0	0	3 (5.1)	2 (3.3)
Upper respiratory tract infection	1 (0.4)	1 (1.6)	2 (3.3)	0	2 (3.3)
Oropharyngeal pain	2 (0.8)	0	0	0	2 (3.3)
Muscular weakness	0	0	0	2 (3.4)	1 (1.6)
Alanine aminotransferase increased	1 (0.4)	1 (1.6)	0	2 (3.4)	1 (1.6)
Creatine phosphokinase increased	2 (0.8)	0	0	2 (3.4)	0

[a] Values are number (%) of patients included in the analysis.
[b] Determined by the investigator to be related to the drug.

Table 2 **Summary of efficacy on objective PSG sleep and sleep architecture measures and next-day residual effects[a]**

	Night 1				End of week 4			
Measure[b]	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
PSG sleep								
Primary								
SE, %	5.2 (1.9, 8.6)[c]	7.6 (4.2, 11.0)[d]	10.8 (7.4, 14.2)[d]	12.9 (9.5, 16.3)[d]	4.7 (1.6, 7.8)[c]	10.4 (7.2, 13.6)[d]	7.8 (4.6, 10.9)[d]	7.6 (4.4, 10.9)[d]
Secondary								
WASO, min	−21.2 (−33.5, −8.8)[d]	−24.7 (−37.0, −12.3)[d]	−33.9 (−46.4, −21.5)[d]	−36.8 (−49.4, −24.3)[d]	−21.4 (−34.2, −8.7)[d]	−28.1 (−41.0, −15.1)[d]	−33.2 (−46.3, −20.2)[d]	−28.9 (−42.1, −15.7)[d]
LPS, min	−3.4 (−15.6, 8.7)	−9.4 (−21.5, 2.9)	−23.1 (−35.3, −10.9)[e]	−25.4 (−37.7, −13.1)[e]	−2.3 (−12.2, 7.5)	−22.3 (−32.3, −12.3)[e]	−3.8 (−13.8, 6.3)	−9.5 (−19.7, 0.7)
Exploratory								
TST, min	25.1 (9.1, 41.2)[c]	36.2 (20.1, 52.4)[d]	52.4 (36.2, 68.7)[d]	61.9 (45.6, 78.3)[d]	22.3 (7.4, 37.2)[c]	49.9 (34.7, 65.0)[d]	36.8 (21.6, 52.0)[d]	36.6 (21.1, 52.0)[d]
NAW	0.3 (−1.4, 2.0)	0.6 (−1.1, 2.4)	0.1 (−1.6, 1.8)	−3.3 (−5.0, −1.6)[d]	−0.3 (−2.1, 1.5)	1.3 (−0.6, 3.1)	0.9 (−0.9, 2.8)	0.6 (−1.3, 2.4)
Sleep architecture								
Stage 1, min	4.1 (−0.3, 8.4)	2.6 (−1.7, 7.0)	6.0 (1.6, 10.4)[c]	1.2 (−3.2, 5.6)	3.0 (−1.7, 7.7)	5.1 (0.3, 9.9)[f]	4.3 (−0.5, 9.1)	3.0 (−1.8, 7.9)
Stage 2, min	6.8 (−5.3, 19.0)	16.4 (4.1, 28.7)[c]	20.6 (8.3, 32.9)[d]	22.9 (10.6, 35.3)[d]	7.1 (−4.8, 19.0)	23.0 (11.0, 35.1)[d]	16.0 (3.8, 28.1)[f]	25.0 (12.7, 37.3)[d]
SWS, min	2.9 (−4.8, 10.6)	−1.4 (−9.2, 6.4)	1.5 (−6.4, 9.3)	8.2 (0.6, 15.8)[f]	4.1 (−4.7, 13.0)	4.8 (−4.4, 14.1)	−2.9 (−12.1, 6.2)	−1.8 (−10.9, 7.4)
REM, min	12.1 (4.5, 19.8)[c]	13.8 (6.1, 21.5)[d]	22.3 (14.5, 30.1)[d]	28.6 (20.8, 36.4)[d]	11.4 (3.8, 19.1)[c]	18.7 (11.0, 26.4)[d]	15.4 (7.5, 23.2)[d]	11.4 (3.5, 19.3)[c]
Latency to REM, min	−22.3 (−39.6, −5.0)[f]	−32.4 (−49.8, −15.0)[d]	−37.8 (−55.5, −20.1)[d]	−33.2 (−50.7, −15.6)[d]	−37.1 (−56.5, −17.6)[d]	−35.2 (−54.8, −15.7)[c]	−10.7 (−30.6, 9.2)	−18.8 (−38.9, 1.3)
Residual effects								
DSST, correct	0.9 (−2.7, 4.5)	−6.1 (−9.7, −2.4)[d]	−2.6 (−6.3, 1.1)	0.3 (−3.4, 4.0)	−0.7 (−3.8, 2.3)	1.4 (−1.7, 4.5)	−0.6 (−3.8, 2.5)	−2.1 (−5.3, 1.1)
DSCT, correct	2.8 (−1.0, 6.5)	−0.3 (−4.1, 3.4)	−0.9 (−4.7, 2.9)	−0.8 (−4.6, 3.0)	1.2 (−2.5, 4.9)	−0.3 (−4.1, 3.4)	−5.1 (−8.9, −1.3)[c]	−3.5 (−7.3, 0.4)

Abbreviations: DSCT = Digit Symbol Copying Test; DSST = Digit Symbol Substitution Test; LPS = latency to persistent sleep; NAW = number of wakenings; PSG = polysomnography; SE = sleep efficiency; SWS = slow wave sleep; TST = total sleep time; WASO = wake after sleep onset.

[a] Values are difference (95% confidence interval) between suvorexant and placebo in least-squares mean changes from baseline. Results based on a mixed-effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2 × 2 crossover study (i.e., crossed with indicator variables for each 2 × 2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2 × 2 crossover studies.

[b] A testing strategy to adjust for multiplicity was applied to the primary and secondary end points.

[c] $p \leq 0.01$ vs placebo; nominal p values without adjustment for multiplicity.

[d] $p \leq 0.001$ vs placebo; nominal p values without adjustment for multiplicity.

[e] LPS comparisons were not significant according to the testing strategy to adjust for multiplicity; however, nominal p values were ≤0.001 vs placebo.

[f] $p \leq 0.05$ vs placebo; nominal p values without adjustment for multiplicity.