# MIN-101 IMPROVES SLEEP IN PATIENTS SUFFERING FROM SCHIZOPHRENIA: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE BLIND STUDY

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## Background

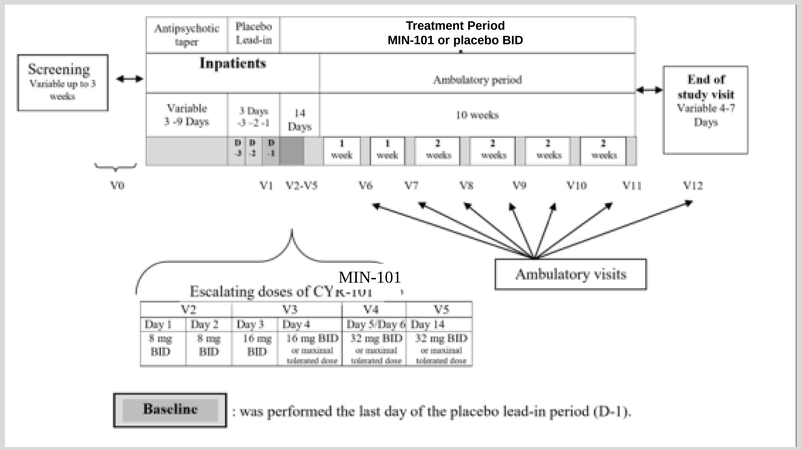
Schizophrenia is associated with abnormalities in circadian rhythms and sleep disturbances. Several recent studies point to strong links between circadian rhythms, dopamine dysregulation and psychosis, suggesting that improvement of circadian disturbance may be a useful therapeutic target in ameliorating symptoms of patients suffering from schizophrenia.

MIN-101 is a novel cyclic amido derivative, which is being developed to treat negative symptoms in patients suffering from schizophrenia. In vivo functional studies have established that MIN-101 is an antagonist at both 5-HT2A and sigma2 receptors.

The results reported here are based on sleep assessment using polysomnographic recordings carried out after 2 weeks of treatment with MIN-101 in schizophrenic patients suffering from an acute psychotic relapse.

## Methods

- Multi-center, Phase 2A, double-blind, randomized, placebo-controlled study.
- 96 patients with DSM-IV schizophrenia and PANSS total score >60.
- Random assignment to monotherapy MIN-101 32 mg BID or placebo in a 1:1 ratio
- Treatment duration 3 months.
- Polysomnographic recordings at baseline and after two weeks of treatment in a sub-set of patients.

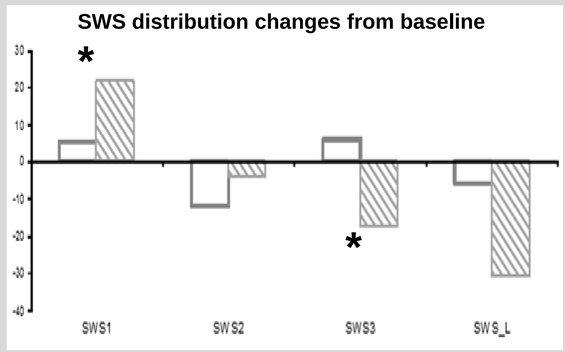



## Results

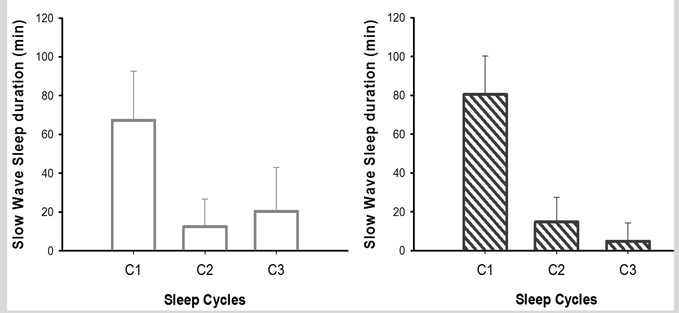
- Compared to placebo, MIN-101 shortened the duration of sleep latency and normalized the SWS ultradian distribution.
- The mixed model performed on the sleep profile parameters indicates two significant treatment effects ($p<0.05$) on the distribution of slow wave sleep across the first and the last third of the sleep period time (SPT).
- Significant contrasts ($p<0.05$) revealed that, compared to placebo, MIN-101 increased SWS in the first third of SPT (SWS1) by 23.6% and decreased it during the last third (SWS3) by 22.1%.

| PPC for PSG (n=19) | PBO | | | M IN-101 | | | Difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | LS-Mean | p-value | 95%CI | LS-Mean | p-value | 95% CI | Estimate | p-value | 95%CI |
| **Sleep Initiation Parameters** | | | | | | | | | |
| Sleep onset latency (min (SD)) | 72.2 | 0.0074 | (22.4, 122.0) | 48.5 | ns | (-10.7, 107.8) | -23.7 | ns | (-84.2, 36.8) |
| Latency to persistent sleep (min) | 76.3 | 0.0044 | (27.6, 125.0) | 50.6 | ns | (-5.4, 106.6) | -25.7 | ns | (-82.1, 30.7) |
| **Sleep Maintenance Parameters** | | | | | | | | | |
| Total slee p time (min(SD)) | 356. 2 | 0.001 | (292.5, 419.9) | 342.5 | 0.001 | (273.1, 411.9) | -13.7 | ns | (-84.5, 572) |
| Sleep efficiency index(%) | 73.1 | <0.001 | (59.9, 86.3) | 70.6 | <0.001 | (56.3, 85.0) | -2.4 | ns | (-10.1, 63.3) |
| Duration of wake after sleep onset (min) | 56.9 | 0.0015 | (25.5, 88.3) | 83.5 | <0.001 | (46.0, 121.1) | 26.6 | ns | (-10.1, 63.3) |
| Index of intrasleep arousal (n/h) | 4.7 | <0.001 | (2.3, 7.1) | 3.9 | 0.0053 | (1.4, 6.5) | -0.7 | ns | (-3.4, 1.9) |
| Total intrasleep wake time (min) | 48.2 | 0.0029 | (19.2, 77.2) | 78.5 | <0.001 | (45.8. 111.3) | 30.3 | ns | (-3.1, 63.6) |
| Index of intrasleep wake episode(n/h) | 3 | <0.001 | (1.5, 4.4) | 2.8 | 0.0016 | (1.3, 4.4) | -0.2 | ns | (-1.7, 1.4) |
| Total intrasleep a wakening time ( min) | 33 | 0.0193 | (62, 59.9) | 61.3 | <0.001 | (30.9. 91.7) | 28.3 | ns | (-3.1, 59.7) |
| Index of intrasleep awakening (n/h) | 0.03 | ns | (-0.0, 0.7) | 0.5 | 0.0185 | (0.1, 0.9) | 0.2 | ns | (-.03, 0.6) |
| Sleep fragmentation index(n/h) | 3.4 | <0.001 | (2.3, 4.5) | 3.6 | <0.001 | (2.4, 4.7) | 0.2 | ns | (-1.1, 1.4) |
| **Sleep Distribution Parameters** | | | | | | | | | |
| Total time awake (min) | 124.4 | 0.0013 | (56.9, 191.9) | 139.8 | 0.001 | (66.4. 213.1) | 15.3 | ns | (-60.0, 90.7) |
| Time spent in stage 1 (min) | 28.7 | <0.001 | (16.3, 41.0) | 27.4 | <0.001 | (13.8, 40.9) | -1.3 | ns | (-15.4, 12.8) |
| %Time spent in stage 1 | 8.4 | <0.001 | (5.1, 11.7) | 8.1 | <0.001 | (4.5, 11.7) | -0.4 | ns | (-4.1, 3.4) |
| Time spent in stage 2 (min) | 179 | <0.001 | (130.5. 227.6) | 174.9 | <0.001 | (122.9, 226.9) | -4.1 | ns | (57.1, 48.9) |
| % Time spent in stage 2 | 47.4 | <0.001 | (38.1, 56.7) | 48.3 | <0.001 | (38.4, 58.1) | 0.8 | ns | (-9.4, 11.1) |
| Time spent in SWS (min) | 63.8 | <0.001 | (36.8, 90.9) | 79.2 | <0.001 | (49.9, 108.5) | -4.1 | ns | (-15 0, 45_8) |
| % Time spent in SWS | 19 | <0.001 | (12.1, 26.0) | 24.4 | <0.001 | (16.9, 31.8) | 5.3 | ns | (-2.4, 130) |
| Time spent in REM (min) | 93.2 | <0.001 | (66.1, 120.3) | 68.3 | <0.001 | (38.8. 97.8) | -24.9 | ns | (-55.3, 5.5) |
| % Time spent in REM | 26.2 | <0.001 | (19.9, 32.6) | 20.2 | <0.001 | (13.3, 27.1) | -6 | ns | (-13.1, 1.1) |
| Time spent in NREM (min) | 244.2 | <0.001 | (193.5, 295.0) | 255.5 | <0.001 | (200.4. 310.6) | 11.3 | ns | (-44.5, 67.1) |
| % Time spent in NREM | 67.5 | <0.001 | (59.2, 75.7) | 72.9 | <0.001 | (64.0, 81.7) | 5.4 | ns | (-3.8, 14.6) |

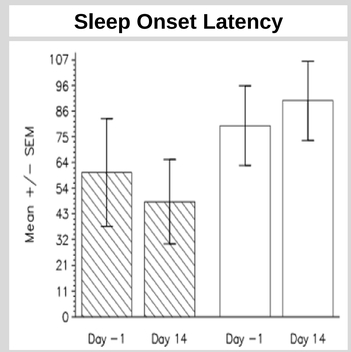
**SWS distribution changes from baseline**




**SWS distribution: Day 14**




**Sleep Onset Latency**




Placebo MIN-101

## Conclusion

**MIN-101 improves sleep induction and normalizes SWS ultradian distribution during the night, which are two key sleep parameters that are disturbed in schizophrenic patients (Davies G et al. 2016). The disturbances of sleep architecture and continuity might be associated with memory consolidation, which is impaired in schizophrenia. These effects on sleep parameters may contribute to clinical improvements in the overall symptomatology observed in patients suffering from schizophrenia treated with MIN-101.**

Davies G et al. *Sleep Med Rev. 2016*. A systematic review of the nature and correlates of sleep disturbance in early psychosis.

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