Clinical Evidence With the Combination of Ibuprofen and Diphenhydramine for the Management of Pain and Sleeplessness

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Purpose

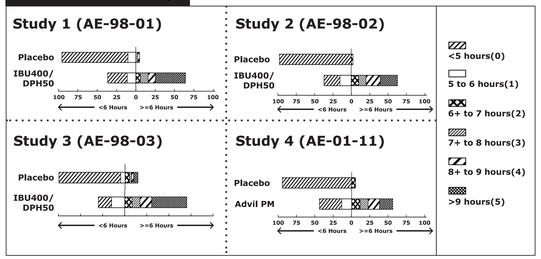
- Based on Center for Disease Control (CDC) data approximately 35% of the population does not get enough sleep.[1]
- The CDC recommends that adults from 18 to 60 years of age should get 7 hours of sleep per day, and children and older adults are recommended to get even more sleep.[2]
- Inadequate sleep can have a significant impact on health, including effects on immunity, metabolism, stress, heart health, risk for chronic conditions, and cognitive function.[3]
- Pain is a major contributor to sleeplessness, and sleeplessness can accentuates pain sensation.
- Both acute and chronic pain can lead to to sleeplessness, and if not managed, the combination of pain and sleeplessness can play a role in onset of disability.[4-7]
- There are a broad range of options to independently treat pain and sleeplessness, which include over-the-counter (OTC) and prescription (Rx) products.
- There are also a number of combination products that include an analgesic and a sleep aid, including readily accessible OTC products.
- One of the most commonly used combinations that has a long history of use includes ibuprofen/diphenhydramine (IBU/DPH).
- In this analysis, we evaluate the IBU/DPH data compared to placebo (PBO) from four clinical studies of subjects with pain and sleeplessness.
- We also looked at data from a study using an actigraphy device as an objective evaluation tool.

Methods

- Four randomized, placebo (PBO)-controlled, single dose clinical studies were conducted that included treatment with the following:
  - » Two Advil PM Liqui-Gels® (ibuprofen 400 mg / diphenhydramine hydrochloride 50 mg)
  - » Two placebo liquigels
- Study subjects were males and females 16-45 years of age who had undergone surgical removal of one or two impacted third molars, one of which was at least a partial bony mandibular impaction (if two molars were extracted, the other was the corresponding maxillary molar).
- An additional study evaluated two Advil PM Liqui-Gels®, and it was similar in design and study population to the above studies. This study used an actigraphy device to evaluate key study endpoints, along with subjective and observational measures. The actigraphy device measures movement as an objective tool to assess outcomes.
- The post-third molar extraction subjects all had moderate to severe pain. They were housed and observed at a clinic site overnight. When subjects experienced at least moderate pain and it was between approximately 6:30 PM and 8:00 PM (at least 3 hours earlier than their usual bedtime), they received a dose of study medication and were required to go to bed for the evening. Sleep was evaluated by an observer for a range of pain and global endpoints.
- **In this analysis, we summarise common endpoints in the studies including 'duration of sleep', 'global rating of sleep', 'onset of sleep', and 'rescue medication use'.**

Results

Duration of Sleep



Study 1 (AE-98-01)

Treatment	Number (%) of subjects in each category							
	0	1	2	3	4	5	Mean	S.D.
Placebo (n=40)	34 (85.0%)	4 (10%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0.28	0.82
IBU400/DPH50 (n=119)	30 (25.2%)	13 (10.9%)	7 (5.9%)	12 (10.1%)	11 (9.2%)	46 (38.7%)	2.83	2.10

Study 2 (AE-98-02)

Treatment	Number (%) of subjects in each category							
	0	1	2	3	4	5	Mean	S.D.
Placebo (n=40)	39 (97.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.05	0.32
IBU400/DPH50 (n=119)	26 (21.8%)	18 (15.1%)	12 (10.1%)	12 (10.1%)	23 (19.3%)	28 (23.5%)	2.61	1.92

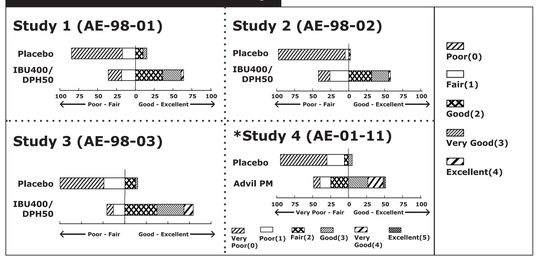
Study 3 (AE-98-03)

Treatment	Number (%) of subjects in each category							
	0	1	2	3	4	5	Mean	S.D.
Placebo (n=41)	33 (80.5%)	2 (4.9%)	2 (4.9%)	1 (2.4%)	1 (2.4%)	2 (4.9%)	0.56	1.34
IBU400/DPH50 (n=121)	18 (14.9%)	18 (14.9%)	10 (8.3%)	11 (9.1%)	16 (13.2%)	48 (39.7%)	3.10	1.94

Study 4 (AE-01-11)

Treatment	Number (%) of subjects in each category							
	0	1	2	3	4	5	Mean	S.D.
Placebo (n=37)	35 (94.6%)	0 (0.0%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.11	0.46
Advil PM (n=155)	47 (30.3%)	21 (13.5%)	18 (11.6%)	17 (11.0%)	24 (15.5%)	28 (18.1%)	2.22	1.92

Global Assessment of Sleep



Study 1 (AE-98-01)

Treatment	Number (%) of subjects in each category						
	0	1	2	3	4	Mean	S.D.
Placebo (n=40)	27 (67.5%)	7 (17.5%)	4 (10.0%)	2 (5.0%)	0 (0.0%)	0.53	0.88
IBU400/DPH50 (n=119)	21 (17.6%)	22 (18.5%)	43 (36.1%)	29 (24.4%)	4 (3.4%)	1.77	1.11

Study 2 (AE-98-02)

Treatment	Number (%) of subjects in each category						
	0	1	2	3	4	Mean	S.D.
Placebo (n=40)	37 (92.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.10	0.38
IBU400/DPH50 (n=119)	19 (16.0%)	31 (26.1%)	38 (31.9%)	28 (23.5%)	3 (2.5%)	1.71	1.08

Study 3 (AE-98-03)

Treatment	Number (%) of subjects in each category						
	0	1	2	3	4	Mean	S.D.
Placebo (n=41)	25 (61.0%)	10 (24.4%)	5 (12.2%)	1 (2.4%)	0 (0.0%)	0.56	0.81
IBU400/DPH50 (n=121)	9 (7.4%)	16 (13.2%)	45 (37.2%)	38 (31.4%)	13 (10.7%)	2.25	1.06

Study 4 (AE-01-11)

Treatment	Number (%) of subjects in each category							
	0	1	2	3	4	5	Mean	S.D.
Placebo (n=37)	24 (64.9%)	9 (24.3%)	2 (5.4%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	0.51	0.84
Advil PM (n=155)	14 (9.0%)	23 (14.8%)	38 (24.5%)	42 (27.1%)	33 (21.3%)	5 (3.2%)	2.46	1.31

***Note:** The graph (study 4) includes an additional parameter, "**Very Poor (0),**" which is not present in the other three graphs.

Onset of Sleep

Study 1 and 2 (AE-98-01 and AE-98-02)

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=40)	>180.0	N/A
IBU400/DPH50 (n=122)	42.9	40.0, 60.0

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=40)	>180.0	N/A
IBU400/DPH50 (n=119)	45.0	40.0, 60.0

Study 3 and 4 (AE-98-03 and AE-01-11)

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=41)	63.8	40.0, > 180.0
IBU400/DPH50 (n=123)	30.8	30.0, 40.0

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=37)	70.5	50.0, > 180.0
IBU400/DPH50 (n=155)	43.2	40.0, 50.0

Rescue Medication Use

Study 1 and 2 (AE-98-01 and AE-98-02)

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=40)	1.7	1.5, 2.2
IBU400/DPH50 (n=122)	>12.0	N/A

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=40)	1.6	1.4, 1.7
IBU400/DPH50 (n=119)	>12.0	N/A

Study 3 and 4 (AE-98-03 and AE-01-11)

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=41)	1.8	1.6, 2.9
IBU400/DPH50 (n=120)	>12.0	N/A

Treatment	Medium time (Minutes)	95% CI (Minutes)
Placebo (n=37)	2.1	2.1, 2.2
IBU400/DPH50 (n=155)	>12.0	N/A

Actigraphy Study

Study 5 (AE-04-14A)

Parameter	Summary Statistic	IBU 400/DPH 50 n=165
Sleep Duration- Actigraph	Mean (hr)	9.3
Sleep Duration - Subject	Mean (hr)	7.9
Sleep Efficiency - Actigraph	%	75.9
Wake After Sleep Onset - Actigraph	Mean (hr)	2.3
Sleep Latency - Actigraph	Median (min)	23.3
Sleep Latency - Observer based	Median (min)	17.6
Time to rescue	Median (hr)	>12.0
% taking rescue	%	28.5

Results

1. **Sleep duration:** The range of subjects with duration of sleep >6 hours with IBU/DPH was 57%-70% versus PBO 3%-15%
2. **Global assessment of sleep:** Rated as good, very good, excellent for 51.6-79.3% with IBU/DPH versus 2.5-14.6% with PBO
3. **Average minutes to sleep:** 30.8-45 minutes with IBU/DPH versus 63.8->180 minutes with PBO
4. **Average time to use of rescue medication:** >12 hours with IBU/DPH versus ≤2.1 hours with PBO, and rescue medication use was 33.6%-45.8% with IBU/DPH versus 81%-95% with PBO
5. **Actigraphy:** It provided a validated tool to objectively measure sleep related endpoints, with potential for higher sensitivity than the subjective and observational approaches also used in the study.

Discussion

1. Ibuprofen/diphenhydramine was significantly better than placebo for the sleep and analgesic efficacy assessments.
2. Duration of sleep has well defined targets that correlate to a broad range of health benefits. In the four studies evaluated, the majority of subjects were able to achieve 6+ to 9+ hours of sleep, which lines up with the CDC's targets for sleep duration.
3. Improvement of other key endpoints of onset of sleep and quality were also clinically and significantly improved with the use of IBU/DPH. This added to the benefits offered with the product in improving the overall quality of sleep while managing the underlying pain for the dental procedure, which was associated with moderate to severe pain.
4. Lastly, the use of the IBU/DPH reduced the need for rescue medication. This is important as the next in line option for a sleep aid and a pain reliever could both be controlled substances (a benzodiazepine and opioid, respectively).

Conclusion

Pain and sleeplessness are commonly experienced and can have long term impact on health including progression to disability. Solubilized IBU/DIPH is well-established for treatment of pain with sleeplessness. In the four clinical studies evaluated, the product consistently provided longer duration of sleep, a better global sleep experience, faster onset of sleep, and less rescue medication use. The improved total sleep and pain experience allows the user to optimize the benefits of sleep on overall health.

Abbreviations:
CDC: Center for Disease Control; **OTC:** over-the-counter; **PBO:** Placebo; **Rx:** Prescription; **IBU/DPH:** Ibuprofen/Diphenhydramine

References:

1. Data Source: CDC Behavioral Risk Factor Surveillance System (BRFSS), 2013–2022. FastStats: Sleep in Adults | Sleep | CDC.; **2.** CDC, Sleep, Getting Enough Sleep. About Sleep | Sleep | CDC.; **3.** CDC, Sleep, Benefits of Sleep. About Sleep | Sleep | CDC.; **4.** McBeth J, Wilkie R, Bedson J, et al. Sleep disturbance and chronic widespread pain. Curr Rheumatol Rep. 2015 Jan;17(1):469.; **5.** Cho SJ, Song TJ, Chu MK. Sleep and Tension-Type Headache. Curr Neurol Neurosci Rep. 2019 May 30;19(7):44.; **6.** Okifuji K, Hare BD. Do sleep disorders contribute to pain sensitivity? Curr Rheumatol Rep. 2011 Dec;13(6):528-34.; **7.** Sivertsen B, Lallukka T, Petrie KJ, et al. Sleep and pain sensitivity in adults. Pain. 2015 Aug;156(8):1433-1439.