US Regulatory Perspectives on Non-restorative sleep (NRS)

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Issues to be considered in thinking about a approving a treatment for NRS

- Who will a treatment be indicated in?
- How should they be identified?
- What are the outcomes we should be measuring?
- How should we be measuring them?
- What type of treatment should be considered for approval?
- Other issues, including safety

Who will a treatment be indicated in?

- NRS can occur in patients with documentable sleep latency and/or sleep maintenance problems, or in patients with no documentable sleep problem
- In patients with a documentable sleep problem, we are likely to consider NRS as a valid target only in those patients whose sleep abnormality has been normalized or minimized to the extent possible (because current drugs do not normalize sleep, we are likely to assume that the NRS is "simply" related to the sleep problem)

Who will a treatment be indicated in?

- In patients with no identifiable sleep problem, NRS (all other things being equal) seems like a reasonable target for drug development
- It is likely that a consensus of the expert community will be necessary before we could contemplate approving a treatment for NRS
- The question of concomitant illnesses seems particularly vexing

Who will a treatment be indicated in?

- Concomitant illnesses
- The symptoms of NRS can occur in the setting of many, many illnesses
- We have recently been advised to study hypnotics in the setting of other primary illnesses
- Should all the illnesses in which NRS-type symptoms occur be included? Ruled out?
- It seems that treating the underlying disease maximally would be prudent

How should patients be identified?

- Patients can mis-identify their disorder (in Roth, et al. *SLEEP*, 2010, 38% overall)
- In order to be sure we identify NRS-only patients, it seems reasonable to require PSG confirmation of the diagnosis (may be difficult-how many?)
- PROs acceptable, but an objective measure of dysfunction seems a good idea
- Ruling out (establishing other underlying, "responsible disorders) seems important and difficult

What are the outcomes we should be measuring?

- There are a wide range of complaints, but they seem to fall into two broad "categories":
  - Subjective feeling of inadequate sleep
  - Disordered functioning during the day (social, occupational, other)
- Assessing a treatment effect on a functional outcome (and/or sleepiness?) seems more compelling, but there is an argument for treating the subjective complaints alone

How should we measure the outcomes?

- We have traditionally required both objective and subjective measures
- In our view, together these have "guaranteed" a clinically meaningful effect
- PSG is unavailable in this case
- An objective measure of functioning seems important
- A validated measure of symptoms may also be needed (acceptable), though perceptions may be affected by the tx
- We should assess patients throughout the day, not just in the AM

What type of treatment should be considered for approval?

- There are no documentable changes in sleep measures
- We can ask if "traditional" sleep treatments are appropriate
- Why treat the night before (or in the middle of the night)?
- An AM treatment may be more appropriate

Other issues

- Duration
- Should be at least 12 weeks if not longer
- Depending upon the mechanism and kinetics of the treatment, we may need to assess the treatment's effects on sleep over time

Summary

- Even if NRS is not a primary sleep disorder, it may be an appropriate target for drug development
- Many conditions are defined by symptoms only
- However it does pose numerous challenges, including defining and identifying the patients, and deciding what to measure and how to measure it
- These problems seem tractable