FDA Psychopharmacologic Drugs Advisory Committee Meeting March 27, 2018 on Lofexidine

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We have no financial conflicts of interest

FDA's Discussion Question about meaningfulness of just treating withdrawal symptoms

- ..discuss the relationship between the two concepts, mitigation of symptoms of opioid withdrawal, and facilitation of completion of detoxification, and whether the data support both claims.

- Is it possible to make a claim of symptomatic relief without [longer-term] evidence that the effect translates to improvement in completion of detoxification?

Primary outcomes

- **The proper primary efficacy endpoint for this drug should be completion of medically managed withdrawal. The sponsor used completion proportion as the primary endpoint in study 3002 but did not use this clinically meaningful endpoint in study 3003. Instead, in 3003, they resorted to a subjective symptom score as their primary endpoint.**

  - **Symptom relief is an intermediate outcome**
  - **Symptom relief is a means to a more important end**
  - **Symptom relief is, ultimately, meaningless without addiction treatment follow-up**
  - **The purpose of symptom relief is to allow patients to focus on treating their addiction**

Differences Between Britannia's Approved UK lofexidine dosing and World Medical's Proposed dosing

"Initial dosage should be 0.8mg per day in divided doses...may be increased by increments of 0.4–0.8mg per day up to a maximum of 2.4mg per day, according to the patient's response. Maximum single dose should not exceed 0.8mg..In cases where no opiate use occurs during detoxification a duration of treatment of 7-10 days is recommended. In some cases a longer treatment period may be warranted. At the end of treatment, dosage should be reduced gradually over a period of at least 2-4 days."

Thus, the approved UK starting dose (0.8 mg/day) is 1/4 of the US-proposed 3.2mg/day.

Maximum UK dose of 2.4 mg/day is 2/3 of the US proposed 3.2mg/day

UK duration of treatment is from 9 to 14 days, with gradual dosage reduction.

Discuss the adequacy of the available safety data to support use between 7 and 14 days

- **Treatment during the submitted trials lasted 5-7 days**
- **Only 37 subjects were exposed to 2.4 mg/d for more than 7 days**
- **Only 14 subjects were exposed to any lofexidine dose for more than 14 days**
- **This lack of data limits the inferences one can make about safety over a two-week course which might be preferred for all patients, especially for people with extended-release opioid use disorders**

Comparative Dose-related Benefit vs Harm Data

Dose:

- 3.2 mg/d afforded no added benefit over 2.4 mg/d

- 3.2 mg/d generated more adverse events vs 2.4 mg/d

  High-dose lofexidine had more treatment-emergent SAE

  - **treatment-emergent AE that led to discontinuation**
  - **treatment-emergent AE that led to a dose-hold**
  - **treatment-emergent LFT elevation**

Treatment Day 5 Completers	3003
Completers on 3.2 mg/d	**47%**
Completers on 2.4 mg/d	**46%**
Completers on placebo	**32%**

Dose comparisons: serious cardiovascular adverse events	3001, 3002, 3003
Treatment-emergent serious adverse events (syncope, hypotension, and bradycardia) on 3.2 mg/d	**2.3%**
Treatment-emergent serious adverse events on 2.4 mg/d	**0.0%**

Do you recommend approval of lofexidine?

No, for the following multiple reasons

Given that there is only one RCT for the 2.4 mg dose, how can the advisory committee recommend or FDA approve the 3.2 mg daily dose that is no more effective in trial completion but is significantly more dangerous than the 2.4 mg dose?

Unless the advisory committee and the FDA believe that for the past 25+ years the UK has erred in approving lofexidine, why is the proposed U.S. starting dose four times higher than that in the UK, the daily dose 50% higher and the recommended duration 9 to 14 days instead of 5 days?

Why, especially given the previous opiate use history of those in these trials and of so many others, are companies not required to have a much more adequate patient follow-up before raising their currently misleading victory flag?