

Letters to the Editor

ABPM PART OF FDA REVIEWS

To the Editor,

Dr O'Brien asks, in part, "why the bodies that regulate the approval of antihypertensive drugs have not made BP measurement over 24 hours mandatory for studies of drug efficacy" (1). He goes on to build a strong case in favor of using ABPM in antihypertensive drug development.

In fact, we at FDA and developers of antihypertensive agents have pretty well adopted ABPM, for at least some of the reasons Dr O'Brien cites—we have not carefully considered the case for assessment of blood pressure in one part of the day or effects on diurnal rhythm. In some cases, the ABPM data have made it into labeling (2,3), but sometimes it may only be clear by reading the clinical reviews (4,5) or perhaps published results. In few cases has ABPM been the primary endpoint, but not because FDA would object. We have objected to 24-hour mean ABPM as a primary endpoint, but averaging ABPM over the last few hours of the interdosing interval is fine.

In my view, a better question regarding ABPM is whether *all* systemically available drugs intended for chronic use merit a careful assessment of their effects on vital signs by ABPM.

Respectfully,

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References

1. O'Brien E. Why ABPM should be mandatory in all trials of blood pressure-lowering drugs. *Drug Inf J*. 2011;45:233–239.
2. Tribenzor. Highlights of prescribing information. 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/200175s001lbl.pdf.
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REPLY TO DR STOCKBRIDGE

To the Editor,

Thank you for the opportunity to comment on Dr Stockbridge's response (above) to my article "Why ABPM Should Be Mandatory in All Trials of Blood Pressure-lowering Drugs" (1). If I take each of his comments in order it will be apparent that we are in remarkable agreement on this important issue. Dr Stockbridge acknowledges that the FDA has "pretty well adopted ABPM" in antihypertensive drug development, but, without objecting to the concept, concurs that the FDA has not, as yet, "carefully considered the case for assessment of blood pressure in one part of the day or effects on diurnal rhythm." He goes on to point out that the analysis of ambulatory data in studies submitted to the FDA may not always be to the fore, but that it can be found either in the labeling data, the clinical reviews, or the published results. Additionally, although ABPM is rarely utilized as a primary endpoint, this is an investigator choice rather than an FDA stipulation. Again, we would be in agreement that 24-hour mean ABPM should not be used as a primary endpoint, and that averaging ABPM over the last few hours of the interdosing interval makes good pharmacokinetic sense.

Finally, Dr Stockbridge's closing statement that "a better question regarding ABPM is

whether *all* systemically available drugs intended for chronic use merit a careful assessment of their effects on vital signs by ABPM” is in agreement with my view that the technique has a broader application in the study of “the unwanted effects of drugs for general noncardiovascular use” which “can elevate, or more commonly, reduce blood pressure, especially in the elderly and often in specific periods of the 24-hour profile, such as the postprandial (or siesta) window or the nocturnal period” (1).

All in all, the central issue is making sure that a system of ABPM analysis is used in pharmacological trials that permits real-time analysis of ABPM data so as to prompt a repeat recording in the event of failure to comply with the protocol requirements, and one that is capable of handling the wealth of data from this technique (2).

Yours sincerely,

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References

1. O'Brien E. Why ABPM should be mandatory in all trials of blood pressure-lowering drugs. *Drug Inf J*. 2011;45:233–239.
2. O'Brien E. Ambulatory blood pressure measurement: a trove of hidden gems. *Hypertension*. 2006;48:364–365.

ABPM IN CLINICAL RESEARCH TRIALS

To the Editor:

In his article “Why ABPM Should Be Mandatory in All Trials of Blood Pressure-Lowering Drugs” (1), Dr O'Brien presents a compelling

argument for abandoning the archaic auscultatory technique for a modern-day automated blood pressure methodology that eliminates operator variability, improves accuracy, and captures the circadian BP variations over 24 hours. It appears that the EMA clearly advocates the use of ABPM for antihypertensive agents, and although the FDA grants recognition to the use of ABPM in similar studies, it remains focused on trough-to-peak values and equivocal as to the methodology deployed. Neither regulatory body currently requires the use of ABPM to evaluate the effect on blood pressure on all new chemical entities that undergo clinical assessment.

I prefer to expand upon Dr O'Brien's conclusion and ask why ABPM should not be made mandatory for all clinical research trials that are designed to assess cardiovascular risk of new compounds as well as those that seek efficacy in targeted populations. This does not imply a need for a “Thorough BP” trial. Vital signs are already taken at several time points that follow the PK curve in Thorough QT trials. In our experience ABPM does not interfere with ambulatory ECG recordings. Why not obtain vital signs with greater accuracy, independent of operator variability, and a 24-hour BP profile that may potentially shed light on long-term risk?

Respectfully,

Lawrence Satin

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References

1. O'Brien E. Why ABPM should be mandatory in all trials of blood pressure-lowering drugs. *Drug Inf J*. 2011;45:233–239.