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LETTER TO THE EDITOR

Placebo Run-in For Antidepressant Trials

I read with interest Dr. Trivedi and Rush's paper (1994) on placebo run-in for antidepressant trials. The authors make a convincing argument that a single blind placebo run-in is not necessary to study efficacy in trials of antidepressants. However, placebo run-ins, though time-consuming and clinically awkward, are mandatory to establish safety baselines that are less confounded by the patient's most recent exposure to other treatments. According to common definitions, adverse experiences (AEs) are unwanted events observed during treatment that are not present at baseline or, if present at baseline, occur during treatment at a greater intensity level than at baseline. However, without a placebo run-in period, AEs due to previous therapy are recorded as part of the pretherapy baseline. If the same effects are observed after baseline, they will not be counted as treatment emergent effects, and therefore not properly attributed to the test medication. For example, if orthostatic hypotension is associated with previous drug therapy, and orthostatic hypotension occurs in conjunction with the new treatment, then it will not be considered to be a treatment emergent effect. In addition, certain withdrawal AEs due to previous therapy will be incorrectly associated with test therapy when there is no washout period. On the other hand, when a nontreatment emergent system of AE experience reporting is used, and there is no washout period, carryover AEs due to previous therapy may be wrongly attributed to the new therapy. A placebo run-in period, moreover, provides a good way to detect disease-related symptoms that may have been otherwise identified as AEs. As the clinical utility of medications is based on the relationship of efficacy to safety, it is still important to establish clear baselines for safety evaluations.

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REFERENCE

Trivedi MH, Rush J (1994): Does a placebo run-in or a placebo-treatment cell affect the efficacy of antidepressant medications? Neuropsychopharmacology 11:33–43.

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