Introduction

Early Onset of Antidepressant Action

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Early onset of antidepressant action is a relevant topic, as evident from the advantages an "early" onset of action might offer. Most notably, a shorter time to antidepressant action would reduce the personal and financial toll of the disorder by decreasing patients' time in distress, lost time from work, and the time the impairment affects family and friends. An efficacious and well-tolerated antidepressant with an earlier onset of action relative to similarly effective and well-tolerated medications would yield considerable benefits to the health care system.

Given the competitive and expensive marketplace, a faster-acting antidepressant presumably would offer a competitive advantage. However, for most clinicians, the key issue is the direct therapeutic implication. Advantages may include decreasing length of hospital stay for inpatients, decreasing the overall burden of suffering by more quickly improving patients' health, and diminishing the risk of suicide in the early days of treatment. Early, effective treatment could diminish the lethal impact of depression on patients with comorbid medical illnesses, such as heart disease and cancer. From the perspective of treatment strategy, a predictable, early emergence of therapeutic effect would advance the decision point of when to change or optimize treatment in the course of acute management of a depressed patient.

Questions needing consideration for this topic begin with defining onset of action. What actions are addressed? What changes are measured? For example, does an earlier onset mean the patient no longer meets diagnostic criteria at an earlier timepoint? Alternatively, is a quicker resolution of a symptom or symptoms required, or just reduction of the intensity of the symptoms? Are early signs of improvement sought, or is the criterion a full "clinical response" (i.e., 50% or greater improvement from baseline)? Should a more stringently defined outcome, such as an earlier remission, (e.g., a Hamilton Rating Scale for Depression score ≤ 7 for 3 weeks or more) be required? It is critical to confront the issue of what early changes are clinically meaningful as opposed to only statistically meaningful.

Once definitions are clarified, the key scientific questions are whether early onset of action actually occurs with some current therapies and whether it occurs with one therapy more than another. Is there, in fact, any evidence that one antidepressant can work more quickly than another? This supplement presents articles, discussions, and a debate examining the question of whether the data prove that one antidepressant does, or could, work faster than another.

Evaluating the data involves the key complicating methodological issue of distinguishing between early onset of efficacy and superior overall efficacy appearing early in a trial. If the data agree that early onset of action has been demonstrated, are there differences among these drugs that may account for these effects? Almost a decade ago, Robert Prien and colleagues[1] listed the methodological criteria they determined necessary in designing a study that examines earlier onset of action of one drug over another. First, to eliminate a chance finding when interpreting data after completion of a study, the terms defining early onset must be clearly established given the number of variables in a trial. Second, determining early onset requires that the standard clinical study be altered, permitting more frequent assessments and allowing patient improvement measurements at relevant timepoints. Third, aggressive dosing should be a criterion so all treatments are equally likely to show early onset of action. Without such a criterion, dosing of one treatment may be more aggressively administered at full or optimal therapeutic dose while others are not, resulting in the appearance that one treatment works faster than another. Fourth, the study population must be of adequate size and include a placebo control to measure antidepressant effect. Finally, an early onset response must be sustained to be considered significant.

With these questions and considerations in mind, the clinical researchers contributing to this supplement have scrutinized this issue, assessed available data and reports, and now offer insight into the state of the art of early time to onset of antidepressant efficacy.

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