

End of 'Trial and Error' Approach to Depression, Schizophrenia?

Kenneth Bender | August 14, 2015

Two recently launched studies will help define optimal medication strategies for depression and acute schizophrenia when initial treatment fails, potentially ending the current "trial and error" approach to therapy.

For depression, the VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study, from the Veterans Affairs Cooperative Study Program, will compare outcomes from either adding another antidepressant or an atypical antipsychotic when there is inadequate response to an initial medication regimen.

For schizophrenia, a European study, SWITCH, centered at the Technischen Universität München, Munich, Germany, will determine whether there is benefit to switching antipsychotic medication if response is inadequate at 2 weeks, rather than 4 to 8 weeks, which has traditionally been considered necessary for delayed medication onset.

The rationale and design of the VAST-D study were [posted online](#) August 5 in *Psychiatry Research*. The SWITCH study was [published](#) July 31 in *European Archives of Psychiatry and Clinical Neuroscience*.

After STAR*D

Somaia Mohamed, MD, PhD, VA Connecticut Health Care System, and coauthors of the article describing the VAST-D study credit the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study for highlighting the frequent inadequate response to initial treatments, but point out that the study did not ultimately identify optimal interventions after initial treatment failure.

They also note that the STAR*D study did not include an atypical antipsychotic augmentation treatment arm, because the study was conducted prior to FDA approval of that indication for an agent in this class.

The VAST-D study will incorporate atypical antipsychotic augmentation in the protocol, and the authors indicate that it will answer two principle questions unanswered by STAR*D: "For which patients, under what circumstances, is switching to vs augmenting with other antidepressants the most effective 'next-step' strategy, and how does augmentation with atypical antipsychotics compare to either switching or augmenting with antidepressants?"

The VA study will randomly assign more than 1500 participants who fail to respond to an antidepressant regimen of appropriate dosage consisting of an SSRI, an SNRI, or mirtazapine (*Remeron*, Organon Pharmaceuticals USA Inc) to either a switch to bupropion (multiple brands) or to augmentation with bupropion or aripiprazole (*Abilify*, Otsuka Pharmaceutical Co, Ltd). Dr Mohamed and coauthors anticipate "rigorous comparison of the benefits, risk and costs of switching vs augmentation with antidepressants and of augmentation with an atypical antipsychotic...."

After CATIE

Stephan Heres, MD, and coauthors, in describing the SWITCH study, refer to a recent meta-analysis in rejecting the premise that antipsychotic medication effect follows several weeks of delayed onset. In addition, they point to studies in which patients with acute schizophrenia who failed to respond after 4 to 8 weeks of medication treatment were able to be identified as early as 2 weeks after treatment initiation.

"The early onset of antipsychotic action makes response detection possible at a very early stage in the course of a treatment attempt," they write, "and may also enable us to predict later non-response when early response is not achieved."

In the SWITCH study, olanzapine (multiple brands) or amisulpride (multiple brands) will be used to treat the index acute episode of schizophrenia or schizoaffective disorder. Participants who fail to meet criteria for response in 14 days will be randomly assigned either to a switch to the other agent or to remaining on the initial agent as the continuation control.

The investigators chose these agents with distinct receptor binding profiles after the possible benefit of changing between agents with different profiles was described in phase 2 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) trial.

Dr Heres and coauthors hope that the SWITCH study will clarify the duration of antipsychotic treatment necessary for defining a failure to respond and will help determine when it is appropriate to proceed to "next step" measures.

"Identifying a time span as short as possible that represents a meaningful cutoff for accurately predicting later poor response is of high clinical relevance," they conclude.

The authors' relevant financial relationships are available in the original articles.

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