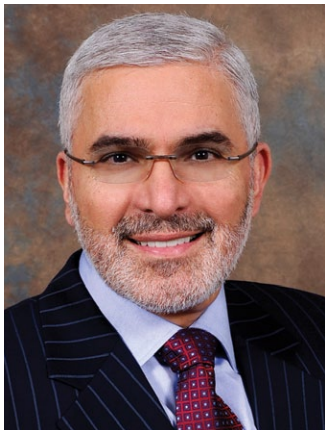
Current PSYCHIATRY



Henry A. Nasrallah, MD
Editor-in-Chief

Combination therapy is here to stay

Although psychiatrists commonly combine psychotropic medications, researchers malign the practice as "not evidence-based." Research is finally catching up with clinical practice, however, and evidence is rapidly accumulating that for many patients with severe psychiatric disorders, 2 drugs are better than 1.

The negative connotation of polypharmacy will fade as combination therapies become the new standard of care

This should not be surprising because "real world" patients with schizophrenia, bipolar disorder, major depression, anxiety disorders, or obsessive-compulsive disorder (OCD) often do not achieve remission and are hobbled—even disabled—by their illness without combination therapy. The same principle holds true for general medical illnesses such as hypertension, cancer, or diabetes, where combination therapy is the norm rather than the exception.

Recent studies have confirmed better efficacy with combination therapy compared with monotherapy for several psychiatric illnesses:

Unipolar depression. Blier et al[1] demonstrated a remarkable superiority of 3 different combinations of 2 antidepressants compared with fluoxetine monotherapy. The remission rate with combination therapy (46% to 58%) was double that of fluoxetine alone (25%). When 1 of the 2 antidepressants was blindly discontinued in high responders, 40% relapsed. Tolerability to the combination was the same as to monotherapy. Recent FDA approval of 2 atypical antipsychotics—aripiprazole[2] and quetiapine[3]—as adjuncts to antidepressants to increase the remission rates further supports the case for combination therapy.

Bipolar disorder. Psychiatrists know that combining a mood stabilizer with an antipsychotic exerts more efficacy that either drug alone.[4] But what about combining 2 mood stabilizers? A recent study[5] confirmed the superiority of combining lithium plus valproate compared with either 1 alone. Score another victory for polypharmacy in bipolar disorder, where FDA studies of combination therapy are more common than in any other psychiatric disorder.

Schizophrenia. It is highly unrealistic to expect 1 drug (such as a dopamine antagonist) to show efficacy for schizophrenia's disparate symptoms, including positive symptoms, negative symptoms, cognitive impairment, mood dysregulation, and substance use. Yet antipsychotic monotherapy remains the standard of care in schizophrenia, and there are no FDA combination trials of antipsychotics. However, in the United States, more than one-third of persons with chronic schizophrenia receive ≥2 antipsychotics because their psychiatrist

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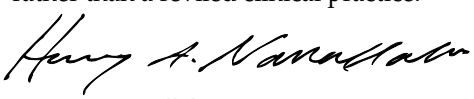
found that combinations exerted more efficacy compared with just 1 antipsychotic agent. A combination of 2 atypical antipsychotics may be superior to monotherapy, but controlled studies have not been conducted.

In addition, patients receiving clozapine for refractory schizophrenia experienced significant improvement with the addition of lamotrigine.[6] Another anticonvulsant, valproate, also was shown to accelerate response to an antipsychotic.[7] Clinical trials are being conducted for new agents that enhance memory[8] and negative symptoms.[9] If the results are positive, the future of schizophrenia pharmacotherapy will shift decisively to polytherapy of 3 or even 4 drugs targeting positive, negative, cognitive, and mood symptoms.[10]

Anxiety. Recent studies confirm the benefits of combining small doses of atypical antipsychotics to an antidepressant/anxiolytic regimen.[11] Most patients with anxiety receive benzodiazepines as well.

OCD. Most patients with OCD do not achieve a remission with a selective serotonin reuptake inhibitor. Many studies have indicated additional improvement from adding an atypical antipsychotic.[12] Other studies have added the glutamate modulating agent memantine with reported benefit.

The writing is now on the psychopharmacology wall: Although many psychiatric patients achieve some response to a single agent, combination therapy often leads to higher remission rates, which is the foremost goal of pharmacotherapy. The negative connotation of polypharmacy will fade as combination therapies become the new standard of care rather than a reviled clinical practice.



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