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Innovative polypharmacy When dopamine blockade is not enough

Polypharmacy has been a 4-letter word for a long time in schizophrenia management. Prescribing more than 1 antipsychotic to a patient with refractory symptoms has evoked images of a potentially harmful, nonevidence-based cocktail with no proven advantage over monotherapy.

‘Futuristic’ adjuncts to antipsychotics could better address persistent positive and negative symptoms and impaired cognition

Compare schizophrenia with bipolar disorder, for which combination therapy—an antipsychotic plus a mood stabilizer plus an antidepressant/antianxiety agent—is the standard of care. Similarly, augmentation therapy is viewed as necessary for difficult cases of unipolar depression.

In the United States, approximately 40% of schizophrenia patients receive 2 or more concomitant antipsychotics (atypical and conventional agents).¹ Clearly, many clinicians resort to antipsychotic polypharmacy in a desperate attempt to manage chronic, treatment-resistant illness, even though no published data support this practice.

This situation may be changing, however, because of evolving understandings of schizophrenia’s neurobiology. Before long, clinicians may employ concomitant agents with different mechanisms in novel approaches to improve outcomes in patients with schizophrenia.

Novel polypharmacy. The dopamine pathways approach is inadequate for achieving true remission across all of chronic schizophrenia’s symptom domains. Positive and negative symptoms and cognitive impairment that persist despite antipsychotic therapy call for new treatment approaches. Here are some of my speculations—suggested by emerging data about schizophrenia’s pathophysiology—about “futuristic” adjuncts to antipsychotics:

Add a glutamate modulator (such as lamotrigine). This combination has shown benefit in patients who have not responded to clozapine.² Many lines of evidence show that the glutamate system is impaired in schizophrenia, and this approach is promising.

continued

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Add a GABA agonist (such as valproate or benzodiazepines). Recent findings of a GABA deficit in frontal lobe chandelier cells in schizophrenia gives this combination legitimacy.³

Add an anti-inflammatory agent (such as a COX-2 inhibitor). Several studies report increased inflammatory cytokines in patients with schizophrenia. Others have found an antipsychotic/anti-inflammatory combination more efficacious than an antipsychotic alone.⁴

Add a cognitive enhancing agent. Antipsychotics as monotherapy fail to reverse schizophrenia's severe cognitive deficits (~2 standard deviations below healthy individuals' cognition). The National Institute of Mental Health-sponsored MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia)⁵ is testing potential neuroprotective and myelin-repair agents to improve deficits in memory, attention, and executive function in schizophrenia. Potential mechanisms include alpha 7 nicotinic receptor agonists, D1 receptor agonists, or AMPA glutamatergic receptor agonists. These agents might become available in a few years.

Add a neuroprotective agent. As a neurodegenerative disorder, schizophrenia could benefit from induction of neurotrophic factors (such as nerve growth factor [NGF], brain-derived neurotrophic factor [BDNF], or vascular endothelial growth factor [VEGF]) and neurogenesis stimulation. Atypical antipsychotics—but not typical agents—have shown neurotrophic activity,⁶ but combining them with other neurotrophic agents such as lithium or selective serotonin reuptake inhibitors⁷ might expedite brain tissue regeneration and improve patients' function.

Add a myelin repair agent. Many schizophrenia studies suggest impaired myelin (white-matter) structure, which may explain the "disconnection" among brain regions that results in thought disorder. A recent report indicates that citalopram restored white-matter integrity in patients with obsessive-compulsive disorder

after a few weeks of use.⁸ If these results are replicated in schizophrenia, antipsychotic-myelin repair agent combinations may become a rational polypharmacy.

What lies ahead. Future schizophrenia treatment almost certainly will include drug combinations that:

- address clinical domains not managed with current antipsychotic monotherapy
- help override treatment resistance or refractoriness (hallucinations or delusions).

Combinations of 3 or more drugs often are used to treat serious medical disorders such as cancer, HIV, or malignant hypertension. Management of a severe, disabling psychiatric disorder such as schizophrenia should be no less aggressive.



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