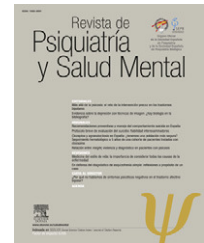




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EDITORIAL

The need to determine the best options for people with schizophrenia that is unresponsive to treatment[☆]

La necesidad de determinar la mejor alternativa para personas con esquizofrenia que no responden al tratamiento

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A recent commentary in *Nature* reported 10 patient-oriented research priorities for schizophrenia derived from a process that elicited the input of patients, clinicians, and other caregivers.¹ A James Lind Alliance Priority Setting Partnership (named after the 18th century Scottish physician who showed that citrus fruits cured scurvy) identified treatment uncertainties for schizophrenia that were then translated into priority research questions. Interestingly but not surprisingly, only four of the priorities are related to medication, reflecting a significant gap between current treatment research and the needs and desires of patients, their families, and other caregivers. This commentary concerns the number one priority: **What is the best way to treat people with schizophrenia that is unresponsive to treatment?**

Schizophrenia, as currently defined and understood, is characterized by symptoms in multiple domains—hallucinations, delusions, disorganization, negative symptoms, mood symptoms, and cognitive symptoms—that lead to social and functional impairments. The most basic treatment for schizophrenia includes an antipsychotic medication and pharmacologic management by the prescriber. Persistent symptoms in any of the domains may lead to additional medication maneuvers.

People with treatment-resistant schizophrenia face tremendous challenges including exacerbations that lead to hospitalization, disability that impairs ability to work,

poverty, impaired social functioning, dangerous behaviors, medical co-morbidities, and premature death. In addition to these personal sufferings and costs, treatment-resistant schizophrenia challenges families and other caregivers, psychiatrists and other health professionals, as well as health and social welfare systems. Identifying effective treatments for these individuals is indeed a public health priority.

A strict definition of treatment resistance requires no significant response to three or more antipsychotic medication trials of adequate dose and duration, and no period of good functioning in five years.² Clozapine is the only evidence-based medication for treatment-resistant schizophrenia, but clozapine is rarely prescribed. In practice adjunctive medications are used long before strict criteria for treatment resistance are met. Various classes of medications are commonly added to single antipsychotic treatments to target persistent symptoms. Clozapine is typically begun only after trials of serial antipsychotics, combinations of antipsychotics, and many adjunctive treatments.

Among adjunctive treatments, antidepressants are mostly used for depressive³ and negative symptoms,^{4–6} although evidence supporting these indications is weak.⁷ Lithium and several anti-epileptic drugs (including carbamazepine, lamotrigine, topiramate, and valproate) are used for persistent psychotic symptoms, aggression, manic symptoms, or “mood stabilization”, though none have strong support from randomized controlled trials to support these indications.^{7–18} Benzodiazepines are also widely used as adjunctive treatments in schizophrenia, again with little evidence demonstrating their effectiveness,¹⁹ although their most likely benefits are for acute agitation and catatonia.^{20–22} A recent retrospective study from Finland

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that reported that adjunctive benzodiazepine use is associated with increased mortality is concerning but needs replication.²³ In summary, current evidence suggests that adjunctive medications should be avoided when possible to promote better treatment compliance and to avoid potential side effects and drug-drug interactions.²⁴ If employed, adjunctive treatments should address specific target symptoms (e.g., antidepressants for depression, benzodiazepines for anxiety) and should be discontinued quickly if ineffective.

Finally, combining antipsychotics (antipsychotic polypharmacy) is an extremely common strategy for individuals who do not achieve recovery or adequate symptom relief from tolerable dosages of a single antipsychotic medication. Evidence supporting this practice from randomized trials is weak.²⁵ Results of the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study that found clozapine superior to switching to another (second-generation) antipsychotic among people with poor response to standard antipsychotics supports an expanded role for clozapine in people who do not meet strict criteria for treatment resistance.²⁶ But there remains a large area of clinical uncertainty. Many people with schizophrenia have only a partial response to antipsychotic medications—mood, psychotic, or anxiety symptoms may persist and interfere with recovery. Is clozapine the best choice for these “partial responders”? In this situation, how does clozapine compare to antipsychotic polypharmacy and to adjunctive antidepressants, lithium, anti-epileptics, or benzodiazepines in terms of risks and benefits?

In addition, there are substantial numbers of people who do not respond well to clozapine. For the people facing this situation, existing treatment recommendations are based primarily on expert opinion. For example, the expert-consensus based Texas Medication Algorithm Project (TMAP) recommends combining antipsychotics, adding mood stabilizers, or initiating electroconvulsive therapy if clozapine alone is not effective.²⁷

Research from randomized controlled trials, considered the gold standard for evidence and a minimum requirement for inclusion in reviews by the Cochrane Collaboration, is extremely sparse for adjunctive treatments for schizophrenia and for treatment-resistant schizophrenia. In spite of highly prevalent use of adjunctive treatments there is almost no research evidence to support their use. The most common refrain in adjunctive treatment reviews by the Cochrane Schizophrenia Group is that additional evidence is needed from pragmatic randomized trials to evaluate these treatments. Unfortunately, only some questions are likely to accumulate adequate evidence from such trials.

What is needed?

First, a rigorous comparison of the effectiveness of antipsychotic combinations (or antipsychotic polypharmacy) to clozapine for treatment-resistant schizophrenia is direly needed. Designing and conducting such a randomized controlled trial is extremely challenging because of the large number of possible antipsychotic combinations, which may be combined for many different reasons. Analyses of observational data are a promising way forward. For

example, retrospective studies using Finnish registry data have found clozapine to be associated with longer treatment duration, fewer hospitalizations, and lower mortality than antipsychotic combinations or other individual antipsychotics.^{28,29} The recent finding of decreased mortality with clozapine compared to other antipsychotics in Finland is surprising and controversial.^{28,30} Replication of these findings in other settings is needed.

Patients and clinicians also need to know what medication strategy works best when a single antipsychotic does not adequately reduce symptoms. How do antidepressants, lithium, anti-epileptics, and benzodiazepines compare as adjunctive treatments? Are any of these as good as switching to clozapine? Well-designed and conducted studies using large-scale databases are one hope for timely answers to these questions. Where results from such studies are ambiguous, pragmatic randomized trials will be needed to inform us about patient-oriented outcomes.

Although this commentary has focused on pharmacologic strategies, research on psychosocial treatments is also needed because it is highly probable for that for a large proportion of individuals with “unresponsive” schizophrenia these types of interventions will be critical in facilitating recovery.

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