Polypharmacy for Schizophrenia
Jacob Ballon, T. Scott Stroup

Abstract and Introduction

Abstract

Purpose of review Combining psychotropic medications is common for people diagnosed with schizophrenia facing a variety of clinical circumstances. This review provides an update on evidence regarding the effectiveness of polypharmacy approaches.

Recent findings Epidemiology studies have demonstrated that polypharmacy is extremely common, but evidence regarding all polypharmacy approaches for schizophrenia from randomized controlled trials remains scarce. Combinations of antipsychotic medicines are unsupported by evidence. Antidepressants are commonly used to treat depressive symptoms; this logical role for antidepressants has little support from randomized controlled trials (RCTs) but may be associated with lower suicide and all-cause mortality. Insufficient evidence supports the use of benzodiazepines for schizophrenia; possible risks of benzodiazepines, including increased mortality rates revealed in observational studies, warrant caution and further study.

Summary The lack of evidence regarding common treatment strategies exacerbates the tremendous challenge of providing optimal pharmacotherapy for individuals with schizophrenia. Comparative effectiveness research, using observational methods when appropriate and RCTs when possible, is needed to inform clinical practice, use resources wisely and improve outcomes.

Introduction

Identifying optimal treatments for individuals diagnosed with schizophrenia remains challenging. Despite the availability of a large number of antipsychotic agents, achieving the therapeutic goals that are important to patients is all too rare. A reduction of positive symptoms is the standard measure of therapeutic efficacy for schizophrenia treatments, not coincidentally because antipsychotics are most effective for these symptoms. But this marker of treatment success leaves much to be desired because other symptoms of schizophrenia and comorbidities are often present and contribute to distress and disability. In fact, negative symptoms and cognitive symptoms have the greatest impact on overall functioning among individuals with schizophrenia, yet there are no proven pharmacological strategies that improve these symptoms. Unfortunately, there is little evidence to guide decision-making for situations beyond the core psychotic symptoms.

Schizophrenia That is Unresponsive to Treatment

Stakeholders including patients, clinicians and researchers who recently collaborated to identify the 10 most important questions about schizophrenia treatment concluded that schizophrenia that is 'unresponsive to treatment' is the most pressing issue facing schizophrenia researchers. Although numbers depend on what is meant by 'responsive', a substantial proportion of people with schizophrenia are unsatisfied with treatment outcomes. Up to 70% of patients do not achieve full remission, even when taking antipsychotic medications as recommended.

Combinations of antipsychotics are commonly used in schizophrenia when a single agent does not relieve symptoms adequately. In a recent meta-analysis, Correll et al. presented findings arguing that antipsychotic polypharmacy may have a clinical advantage over standard (nonclozapine) monotherapy in nonresponsive patients. Although the overall results may offer some support for antipsychotic combinations, the finding diminishes significantly if studies from China are removed, and thus, the generalizability of those findings is questionable.
Benefits of antipsychotic combinations were also not seen in short-term studies, which points to the need for more long-term trials of this strategy.\(^4\) However, clozapine remains the only proven treatment for patients who do not respond fully to other antipsychotics. Despite this knowledge, clozapine uptake is low in most communities. No randomized clinical trial has directly compared clozapine with combinations of antipsychotics.

Essock \textit{et al.}\(^5\) took advantage of the fact that combinations of antipsychotics are common in clinical practice by conducting a trial that randomized people who were stable on a combination of two antipsychotics either to discontinue one of the antipsychotics or to continue on both. They found that dropping one antipsychotic was associated with fewer side effects, but that more patients assigned to stay on two antipsychotics stayed in the assigned condition than stayed in the switch to monotherapy condition. People who did not stay in the monotherapy condition typically resumed the previous combination of antipsychotics. Overall, people assigned to the switch to monotherapy condition did not experience more symptoms or hospitalizations.\(^5\) The authors acknowledged that this study did not address the issue of whether initiating combinations was effective, but concluded that a switch to monotherapy for people taking two antipsychotics may well have benefits that exceed risks.

Despite clozapine’s superiority for refractory symptoms, it is not effective for every patient with treatment-resistant schizophrenia. A major issue is that the drug’s side effects can be limiting, and for at least one-third of patients clozapine is discontinued within the first year of treatment.\(^6,7\) Because clozapine is the last step on evidence-based treatment algorithms, this presents a problem when further strategies are needed. Evidence to guide treatment decisions when clozapine fails is notably limited. Many consider trying previous antipsychotic medications at higher doses, others use long-acting agents and many consider augmenting clozapine with an additional psychotropic.

A Cochrane review of combining antipsychotics with clozapine for treatment-resistant schizophrenia found only small trials that were inconclusive.\(^8\) More recently, clozapine augmentation with aripiprazole\(^9\) showed benefit on Positive and Negative Syndrome Scale (PANSS) scores but did not demonstrate benefits in cognitive measures.

Targeting Nonpsychotic Symptoms

The core positive and negative symptoms of schizophrenia are rarely the only targets for treatment. Mood, anxiety and obsessive-compulsive symptoms frequently require attention, but evidence for how best to approach these comorbidities is scant (see ).\(^12–19\)

| Table 1. Summary statements of systematic reviews of antipsychotic augmentation |
| --- | --- | --- |
| **Type** | **Cochrane reviews\(^a\)** | **Schizophrenia PORT\(^b\)** |
| Antidepressant | Inconclusive evidence on use of antidepressants for depression or negative symptoms in people with schizophrenia.\(^12,13\) | Possibly effective for postpsychotic depression; not enough evidence to support a recommendation for negative symptoms.\(^14\) |
| Anxiolytic | Inadequate evidence to recommend benzodiazepines as either a sole or an adjunctive agent in schizophrenia.\(^15\) | Insufficient evidence to make a recommendation.\(^14\) |
| Antimanic | Reviews found inadequate evidence to recommend augmentation of antipsychotics with valproate,\(^16\) lamotrigine,\(^17\) carbamazepine,\(^18\) or lithium.\(^19\) | None with sufficient evidence to warrant a recommendation.\(^14\) |

\(^a\)Cochrane reviews
\(^b\)Schizophrenia PORT
Cochrane Collaboration Systematic Reviews are meta-analyses based on evidence from randomized controlled trials.

The Schizophrenia Patient Outcomes Research Team (PORT) systematically reviews evidence on treatments for schizophrenia and synthesizes this information; when evidence is sufficient, the PORT makes a treatment recommendation.

A parsimonious approach is to begin by optimizing antipsychotic monotherapy and psychosocial supports. An obvious but unproven approach is to treat these problems symptomatically by using treatments proven effective for mood and anxiety disorders. However, the need for internal validity when seeking regulatory approval for new medications leads to excluding people with comorbidities from clinical trials. For example, because people with schizophrenia are systematically excluded from trials of putative antidepressants and anxiolytics, the results of these trials only clearly apply to people without schizophrenia.

Whether the conventional treatments for common clinical symptoms such as depressed mood or anxiety are similarly effective for people with schizophrenia is not clear. Treating mood symptoms, for example, is particularly difficult in schizophrenia. Differentiating between negative symptoms and depression is clinically challenging, and, although there may be phenotypic overlaps, it is not known precisely what the pathophysiological differences are, and how those differences may affect the benefits of certain medications.

Although antipsychotic medications reduce ratings of negative symptoms, this benefit is thought primarily to result from improvement of secondary negative symptoms and a resulting decrease in social withdrawal. In the absence of proven treatments for primary negative symptoms, or those that do not improve with antipsychotic treatment alone, antidepressants are often considered for use. Evidence is varied on the effectiveness of antidepressants for negative symptoms. In a meta-analysis, a modest effect size of 0.48 was shown overall in favour of using antidepressants, though with the removal of three outlier results the effect size dropped to 0.33. Notably, in this meta-analysis, more studies showed inconclusive benefit than those that showed statistically significant benefits for antidepressants. Moreover, the only commonly used antidepressant to show a benefit was fluoxetine (trazodone and ritanserin were also statistically significant in one study each) and did so in only one of four reported trials. Other antidepressants failed to show a distinct and significant benefit when data were combined. A study of escitalopram conducted after the above systematic review also failed to demonstrate substantial benefits. A single small study using mirtazapine demonstrated small benefit for mirtazapine on negative symptoms, but individuals on mirtazapine gained 5 kg more than those on placebo.

Antidepressants may yield benefits beyond direct symptomatic improvements in people diagnosed with schizophrenia. A recent pharmacoepidemiology study from Finland found antidepressants to be associated with decreased mortality. The finding appears to extend beyond just decreased suicide rates. In the same study, benzodiazepines were associated with increased mortality, which was also not related to increased suicide rates. The findings of this observational study require replication and need to be understood in the context of possible confounds, but highlight the significant impact, positive and negative, that additional medications may have in addition to measurable symptom differences.

Benzodiazepines are frequently used to target symptoms, including anxiety and insomnia. Although rates of benzodiazepine augmentation likely vary around the world, a recent report from Taiwan indicated that nearly 80% of schizophrenia patients were receiving benzodiazepines over the course of 1 year. Large differences in rates of benzodiazepine use between close geographic areas have been described, though this small area variation remains to be fully described for people with schizophrenia. The significant variations in use highlight the lack of evidence-based recommendations regarding benzodiazepines. The most recent systematic review data from the Cochrane group do not find evidence that benzodiazepines are useful beyond short-term sedation in schizophrenia. However, the lack of evidence in support of benzodiazepines does not rule out their use, as there are
circumstances in which they can be helpful. The recent adverse mortality data, however, should be considered when using benzodiazepines, particularly if for more than short-term treatment.

The use of anticonvulsants, either to potentiate the effect of antipsychotic medications or to help prevent mania, has a long and complicated history. Valproic acid is sometimes used to accelerate the response to antipsychotics. Although helpful in the acute situation, there is no demonstrated benefit to this strategy after 6 months. This leads to the common polypharmacy scenario in which the regimen is no longer supported by research evidence, but, unless the patient is demonstrating side effects or other reasons to discontinue the treatment, a regimen that was apparently beneficial acutely is continued indefinitely. Although this seems innocuous, maintaining unnecessary medications exposes the patients to the potential for side effects on a treatment regimen with unclear benefit.

Lamotrigine is seen as an adjunctive medication for schizophrenia due to its mood-elevating properties. There have been few controlled studies of lamotrigine in schizophrenia other than for patients who did not respond fully to clozapine. In a recent meta-analysis, it was concluded that lamotrigine did not do better than placebo as a clozapine-augmentation strategy. Smaller studies have focused on topiramate. Initial reports show little benefit on topiramate on positive or negative symptoms. Cognitive side effects are common with topiramate and thus further limit its clinical utility.

Targeting Side Effects

Among the greatest difficulties in treating schizophrenia is that two of the most effective antipsychotic medications, olanzapine and clozapine, are also associated with the greatest risk for metabolic side effects. A treatment that maximized the antipsychotic effects of these medications but did not expose patients to metabolic risk would be ideal. Polypharmacy approaches overall have been shown to contribute towards the risk of metabolic syndrome. Often tolerability issues drive the need to combine antipsychotics. To minimize side effects, lower doses of individual antipsychotic medications are often utilized. Although there is a basis for dose-dependence in the development of extrapyramidal symptoms, this has not been conclusively established with metabolic side effects of second-generation antipsychotics.

A specific approach to limiting the adverse metabolic consequences of clozapine is to use a low but effective dose of clozapine in combination with a second antipsychotic with fewer metabolic effects. The most studied version of this strategy uses aripiprazole as the adjunctive agent. Aripiprazole is an attractive agent for this purpose because it causes relatively little sedation and weight gain. In a double-blind, placebo-controlled trial, those assigned to aripiprazole augmentation lost an average of 3 kg (vs. 0.5 kg in the placebo group) over 8 weeks. After an open-label extension, the weight loss was maintained at 28 weeks. However, a randomized study comparing clozapine augmentation with aripiprazole to haloperidol found no advantage for aripiprazole on duration of treatment or symptoms, although patients perceived aripiprazole as more tolerable.

There are few weight loss agents available on the market, and thus far none of them have been shown effective in use in schizophrenia, because of either lack of efficacy or unacceptable side effects. Although not a weight loss agent per se, topiramate’s weight loss properties are often sought to help mitigate side effects of high metabolic risk antipsychotics. In a recent study from India (n = 67), drug-naïve, first-episode individuals randomized to topiramate along with olanzapine lost 1 kg over 12 weeks compared with those only on olanzapine, who gained an average of 6 kg. Zonisamide was also used in a study to try to prevent olanzapine-induced weight gain. Although individuals gained slightly less weight with zonisamide, similarly to topiramate, the benefit is limited by cognitive side effects. In this study, 25% had cognitive side effects while on zonisamide, compared with 0% on placebo. A study conducted by the National Institute of Mental Health (NIMH)-sponsored Schizophrenia Trials Network found that metformin was well tolerated and modestly effective in reducing weight in overweight or obese patients with chronic schizophrenia taking any one or two antipsychotics. A meta-analysis of four previous studies also found improvements in weight gain, glucose and waist circumference in people who took metformin concurrently with olanzapine.
Future Directions and Conclusion

Treatment of individuals with schizophrenia who have complicated courses of illness, particularly those who do not benefit adequately from antipsychotic monotherapy, remains beyond the current state of evidence-based practice. Algorithms that are based on research evidence are often unable to provide specific recommendations. When clozapine is not an option, or has not worked, evidence for various treatment options is scarce. Many wish to try regimens that combine antipsychotics with different purported receptor mechanisms. Although this technique makes sense in an in-vitro model, it presupposes that schizophrenia can be fixed by fine-tuning the activity at these receptors. Unfortunately, this 'jigsaw puzzle' approach has not been shown to be of benefit, though limitations in clinical trial methods and capabilities have hampered developing a strong evidence base for different treatment combinations. One practical approach to combining antipsychotics, if this approach is attempted, is to avoid drugs with similar side effect profiles to avoid additive adverse effects.

The need to make treatment decisions in the absence of guiding evidence is common for all clinicians. When treating individual patients in situations of uncertainty, the patient's history and preferences are primary considerations. Combinations of psychotropic medications may be necessary and beneficial, but should be used carefully with the understanding that evidence supporting even common polypharmacy practices is weak at best.

Research will never be able to address every clinical scenario, but future of clinical research in schizophrenia must allow broader conclusions to be drawn. Current clinical trial models emphasize internal validity, often at the cost of external validity. Rigid designs that limit the types of augmentation agents or baseline antipsychotics limit generalizability of overall findings. Pragmatic clinical trials, which emphasize external validity through more real-world entry criteria, are expensive and require substantial sample sizes to overcome the need for greater power to achieve significant results. Despite these limitations, further development in clinical trial design is critical for developing rational treatments for these commonly vexing clinical situations. Observational comparative effectiveness methods using large databases can begin to answer many of these questions, but, in some cases, confounding means that only randomized trials will yield reliable results.

In conclusion, many schizophrenia treatment decisions are not adequately informed by research. Polypharmacy approaches are often reasonable strategies, but should be undertaken with the knowledge that these are not evidence-based practices. As with any new medication strategy, target symptoms and treatment goals for any added psychotropic should be identified and adverse effects monitored. If the desired benefits of an additional medication are not realized, or if adverse effects exceed benefits, the new drug should be discontinued.

Sidebar

Key Points

- Optimal treatment of schizophrenia must address more than just positive symptoms.
- There is limited evidence to support using multiple antipsychotic medications concurrently.
- There is limited evidence to support using SSRI s, benzodiazepines or anticonvulsants as long-term adjunctive agents in schizophrenia.
- Pragmatic clinical trials and other forms of comparative effectiveness research should incorporate multiple outcomes to guide future care decision.

References


* A randomized clinical trial evaluating the time to discontinuation and other risks and benefits of switching from polypharmacy to monotherapy.


*A large registry study to look at mortality risks from antipsychotic augmentation strategies.


*A systematic review and meta-analysis of both pharmacologic and nonpharmacologic augmentation strategies for people who do not fully respond to clozapine.


**A systematic review looking at rates of adverse events in antipsychotic polypharmacy.


Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

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