Optimizing Outcome with Antipsychotic Treatment in First-Episode Schizophrenia: Balancing Efficacy and Side Effects

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Abstract

The initial tailoring of antipsychotic medication for an individual experiencing a first episode of psychosis (FEP) is a critical empirical process with potentially far-reaching consequences. This article reviews the results of randomized treatment trials of clinically available first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in individuals experiencing FEP, addressing these medications' relative therapeutic potentials and their proclivities to produce a range of unwanted side effects. The authors will argue that the best clinical long-term outcomes will be achieved with: 1) a "succeed-first" strategy of identifying those treatment-responsive individuals who will have a good response to neuroleptic threshold doses of well-tolerated FGAs (thereby avoiding weight gain, insulin resistance, and prolactin-induced changes in gender-specific physiology); and, 2) an early trial of clozapine in treatment-nonresponsive FEP patients.

Key Words: First Episode, Outcome, Schizophrenia, Antipsychotic

Introduction

The immediate therapeutic purpose of antipsychotic treatment for individuals experiencing a first episode of psychosis (FEP) is to reduce the intensity and pervasiveness of psychopathological phenomena in order to alleviate suffering and prevent bad outcomes associated with active psychosis such as suicide, violence, loss of job, etc. Once symptomatic remission has been achieved, prevention of another episode becomes paramount so the recovering individual can focus upon, and act productively to achieve, her/his short- and long-term goals. Individuals experiencing an FEP have differing susceptibilities to the therapeutic effects and to the unwanted side effects of antipsychotic medications. All antipsychotic medications have unwanted actions that limit short- and long-term tolerability; these differ in nature and intensity across the agents and between patients. The task for prescribing clinicians is to work with each patient experiencing an FEP to identify that individual's goals, and to tailor pharmacological and non-pharmacological (with the involvement of members of the treatment team and other stakeholders) interventions that best hand the individual along the trajectories (school, work, relationships) that s/he has chosen.

All participants in this process, including the individual experiencing the FEP, should understand that the process is exploratory and iterative and often requires a trial-and-error approach. After identifying with the patient the psycho-

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Clinical Implications

The initial tailoring of antipsychotic medication for an individual experiencing a first episode of psychosis (FEP) is a critical empirical process with potentially far-reaching consequences. This article reviews the results of randomized treatment trials of clinically available first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in individuals experiencing FEP, addressing these medications' relative therapeutic potentials and their proclivities to produce a range of unwanted side effects. The authors will argue that the best clinical long-term outcomes will be achieved with: 1) a "succeed-first" strategy of identifying those treatment-responsive individuals who will have a good response to neuroleptic threshold doses of well-tolerated FGAs (thereby avoiding weight gain, insulin resistance, and prolactin-induced changes in gender-specific physiology); and, 2) an early trial of clozapine in treatment-nonresponsive FEP patients.

pathological phenomena that are the initial targets of treatment (e.g., distressing auditory hallucinations and inability to sleep) and the potential side effects that s/he would most like to avoid (e.g., weight gain), an antipsychotic medication is started and its effects observed over the ensuing days and weeks of treatment. Then, the individual experiencing the FEP, the prescribing clinician, and other members of the treatment team must again share information and decide together whether the therapeutic and tolerability portfolios of that antipsychotic medication are acceptable in this particular case. Changes in dose, a switch to another antipsychotic agent, the addition of adjunctive medications to address other persistent psychopathology (e.g., lithium to address irritability) or a concomitant medication to manage iatrogenic morbidity (e.g., metformin to address evolving weight gain and insulin resistance) may be decided upon. Often, sequential, time-limited antipsychotic treatment trials are required to identify the best individualized medication(s).

The available literature does not tell clinicians what to recommend for any one individual experiencing a first episode of psychosis. Most studies report what happens across a group of individuals when a particular antipsychotic medication is administered to them. We can only say that if 100 individuals are given drug A and another 100 individuals are given drug B, on average X% of individuals taking drug A and Y% of individuals taking drug B will achieve a criterion level of reduction in psychopathology or a criterion level of weight gain over the ensuing treatment period.

We will review the results of randomized treatment trials of clinically available first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in individuals experiencing FEP, addressing these medications' relative therapeutic potentials and their proclivities to produce a range of unwanted side effects. We searched PubMed using the key words, "first-episode schizophrenia, randomized, first-generation antipsychotics, second-generation antipsychotics" to identify relevant trials for inclusion. For this paper, we focused on large, randomized trials reported over the past decade. We then synthesized our interpretation of the clinical treatment trials to suggest giving first-generation antipsychotics serious consideration as a very reasonable "succeed-first" strategy. "Succeed first" is a re-conceptualization of the "fail-first" requirements in medication algorithms, usually intended to contain costs. The "succeed-first" label avoids associating first-generation antipsychotics with "failure" and the implicit assumption that newer is better.

Clinical Trials Comparing FGAs with SGAs

Olanzapine/Haloperidol Comparisons

Sanger et al. (1) reported on 83 individuals experiencing FEP treated from a large 6-week registration trial comparing haloperidol (mean 11 mg daily) with olanzapine (mean 12 mg daily). Olanzapine-treated individuals showed greater improvement on the Positive and Negative Syndrome Scale (PANSS). However, interpretation of this trial is difficult given the high haloperidol doses used and the high dropout rate in the haloperidol arm (only 38% of haloperidol-treated patients completed six weeks of treatment compared to 73% of olanzapine-treated patients). In first-episode patients, a low-dose strategy with haloperidol doses between 2 to 4 mg/day is considered sufficient and clinically appropriate (2, 3). At the haloperidol doses used in the Sanger study, haloperidol-treated individuals quit the study early because of distressing extrapyramidal side effects (EPSE), had less time for therapeutic response to unfold, and had their last psychopathology assessments contaminated by subjective distress associated with EPSE.

Lieberman et al. (4) reported on 263 individuals with FEP randomly assigned to up to twelve weeks of double-blind treatment with haloperidol (mean modal 4 mg daily) or olanzapine (mean modal 9 mg daily). Both haloperidol and olanzapine reduced symptom severity with no significant differences demonstrated on last-observation-carried-forward analyses. However, in a post hoc mixed-model analysis, olanzapine-treated individuals had significantly

greater decreases on the PANSS Total score and Negative and General Psychopathology subscale scores but not on PANSS Positive subscale scores. Olanzapine-treated individuals experienced a lower rate of EPSE, but had significantly more weight gain compared with haloperidol-treated individuals (16 pounds versus 6 pounds on average, respectively). Overall, significantly more olanzapine-treated individuals than haloperidol-treated individuals completed the 12-week acute phase of the study (67% versus 54%).

During the ensuing two years of follow-up (5), the mean haloperidol dose was 5 mg daily, and the mean olanzapine dose was 10 mg daily. 67% of olanzapine-treated individuals and 60% of haloperidol-treated individuals met pre-determined response criteria. 23% of olanzapine-treated individuals, but only 12% of haloperidol-treated individuals, were still on their initially assigned antipsychotic medication at the end of two years, and time to discontinuation of olanzapine was significantly longer (322 versus 230 days) than time to discontinuation of haloperidol.

Risperidone/Haloperidol Comparisons

Emsley et al. (6) randomized 183 acutely ill, first-episode patients to up to six weeks of blinded, flexible-dose treatment with risperidone (mean 6 mg daily, range up to 16 mg daily) or haloperidol (mean 6 mg daily, range up to 16 mg daily). 63% of risperidone-treated patients had a reduction in PANSS scores of at least 50% compared to 56% of haloperidol-treated patients (nonsignificant). The authors noted that lower doses of either antipsychotic (not more than 6 mg) were better tolerated as judged by EPSE severity, and did not lead to a loss of efficacy.

Schooler et al. (7) reported on 555 individuals experiencing FEP who were randomly assigned to blinded treatment with either low-dose haloperidol (mean modal dose 3 mg daily) or low-dose risperidone (mean modal dose 3 mg daily). There were no significant differences between the treatment groups in the rates of discontinuation of the assigned treatments or in reasons for discontinuation. Clinical improvement (>20% decline in PANSS Total score) occurred in 76% of haloperidol-treated patients and in 74% of risperidone-treated patients. Treatment-emergent EPSE were more frequent and severe with haloperidol. Weight gain was greater at three months with risperidone (means 10 versus 8 pounds) but similar at endpoint (means 17 versus 14 pounds). Prolactin levels were higher and prolactin-related side effects more frequent with risperidone. Among the patients who met criteria for clinical improvement, relapse was delayed longer in risperidone-treated patients than in haloperidol-treated patients.

Moller et al. (8) reported an eight-week, randomized, double-blind comparison of haloperidol (mean 4 mg daily) and risperidone (mean 4 mg daily) in 146 acutely ill, hospitalized patients with FEP. The treatments were equally effective in improving the primary outcome variable (i.e., change in PANSS negative symptom score) and secondary outcome variables (e.g., positive symptoms scores). Those patients assigned to haloperidol showed a higher rate of EPSE (52% versus 37%); significantly more patients in the haloperidol group than in the risperidone group dropped out (54% versus 39%). During a one-year follow-up phase, double-blind maintenance treatment was continued in remitted patients (74 haloperidol-treated and 77 risperidone-treated patients; 24 patients who did not participate in the eight-week trial were allowed "lateral" study entry following open-label treatment to remission with haloperidol followed by randomization to blinded treatment with haloperidol or risperidone to increase the number of subjects in this trial phase) (9). There were no differences between the two antipsychotic medications with regards to relapse or drop-out rate (68% overall) (9).

Clozapine/Chlorpromazine Comparison

Lieberman et al. (10) randomly assigned 160 patients with FEP in China to up to 52 weeks of treatment with chlorpromazine (mean 600 mg at 12 weeks and 400 mg at 52 weeks) or clozapine (mean 400 mg at 12 weeks and 300 mg at 52 weeks). 79% of chlorpromazine-treated patients and 81% of clozapine-treated patients achieved >50% reduction in BPRS total score (pre-defined as remission), but remission occurred earlier with clozapine and was more persistent. Chlorpromazine produced more EPSE. Weight gain, assessed after >2 years of treatment, was approximately 20 pounds in both groups.

Other First-Generation/Second-Generation Antipsychotic Medication Comparisons

Sikich et al. (11) randomly assigned 50 pediatric patients 8–19 years of age with prominent positive psychotic features to up to 8 weeks of double-blind treatment with haloperidol (1–5 mg daily), olanzapine (2.5–12.5 mg daily) or risperidone (0.5–3 mg daily). Given the small sample size, only exploratory descriptive analyses were done. All three antipsychotic medications reduced psychotic features significantly. Significant weight gain was observed in all treatment groups (risperidone: 11 pounds; olanzapine: 16 pounds; haloperidol: 8 pounds). EPSE occurred in all treatment groups but were most prominent in the haloperidol group.

Robinson et al. (12) reported on 112 individuals with FEP who were randomly assigned to up to four months of

blinded treatment with olanzapine (mean 12 mg daily) or risperidone (mean 4 mg daily). Stringently defined response rates requiring sustained and significant improvement with only mild symptoms (44% with olanzapine and 54% with risperidone), and EPSE ratings did not differ significantly between the treatments. Both olanzapine and risperidone caused rapid and substantial weight gain, but this was greater with olanzapine (mean 27 pounds) than with risperidone (17 pounds).

None of the clinical trials support a clear and convincing therapeutic advantage for any class (FGA versus SGA) or individual antipsychotic medication as initial treatment for individuals experiencing FEP.

Sikich et al. (13) randomly assigned 116 individuals 8–19 years of age with early onset schizophrenia or schizoaffective disorder to up to 8 weeks of blinded treatment with molindone (10–140, mean 60 mg daily), olanzapine (2.5–20, mean 11 mg daily) or risperidone (0.5–6, mean 3 mg daily). The primary outcome measure was response to treatment, defined by a ≥20% reduction in PANSS Total score and a CGI Improvement score of 1 or 2. No significant differences unfolded in response rates (50% for molindone, 34% for olanzapine, and 46% for risperidone), or in the magnitude of improvement in this difficult-to-treat group of patients with an early onset of psychosis. Treatment with olanzapine (13 pounds) or risperidone (8 pounds) was associated with significantly greater weight gain than treatment with molindone (1 pound). Molindone was associated with more akathisia. Olanzapine produced greater increases in both total and LDL-cholesterol and in fasting insulin levels, while risperidone produced greater elevations in prolactin.

Findling et al. (14) followed those participants who had improved during the aforementioned 8-week, randomized, double-blind acute trial of olanzapine, risperidone, or molindone (14) for up to 44 additional weeks under double-blind conditions. Of the 116 individuals initially randomized in the acute trial, only 54 entered maintenance treatment (20 on molindone, 13 on olanzapine, and 21 on risperidone). Only fourteen (26%) completed the subsequent 44 weeks of treatment; adverse effects (n=15), inadequate efficacy (n=14), or study non-adherence (n=8) were the most common reasons for discontinuation. The three treatment arms did not significantly differ in symptom reduction or time to treatment discontinuation. Akathisia was more common with molindone and elevated prolactin was more common with risperidone. Although weight gain and metabolic adverse events had occurred more often with olanzapine and risperidone during the acute trial, no significant between-drug differences emerged in these parameters during maintenance treatment.

The European First Episode Schizophrenia Trial (EUFEST) was a 12-month, randomized but open-label, flexible dose study in 498 patients with FEP comparing haloperidol (mean dose 3 mg/day), amisulpride (mean dose 450 mg/day), olanzapine (mean dose 13 mg/day), quetiapine (mean dose 499 mg/day) and ziprasidone (mean dose 107 mg/day) (15). The EUFEST treatment discontinuation rates were lower with all of the SGAs than with haloperidol; discontinuation rates did not differ among the SGAs. However, inference making is confounded because the clinicians deciding on treatment continuation or discontinuation were not blinded to treatment assignment. The treatment groups, including the haloperidol-treatment group, did not differ on PANSS ratings. Average weight gain was substantial with all treatments (haloperidol 15 pounds, amisulpride 21 pounds, olanzapine 31 pounds, quetiapine 23 pounds, and ziprasidone 11 pounds).

First-Generation Antipsychotics as "Succeed-First" Choice

Which Medication to Start With

None of the clinical trials support a clear and convincing therapeutic advantage for any class (FGA versus SGA) or individual antipsychotic medication as initial treatment for individuals experiencing FEP (16). The most recent updated NICE Guideline from the British National Health Service (available at http://guidance.nice.org.uk/CG82) no longer prefers second-generation antipsychotics over first-generation antipsychotics for the treatment of FEP, but instead suggests taking into account relative adverse event profiles in selecting an antipsychotic medication.

When considering FGA medications, none appear to offer superior therapeutic benefit while the variability in adverse event profiles is substantial. Dosing also matters greatly. For example, the EPSE-dose response curve is very close to the therapeutic benefit-dose response curve for fluphenazine or haloperidol; only a very narrow dose range (the neuroleptic threshold) is available for each individual patient within which therapeutic benefit can be achieved without coarse EPSE (2, 17). The distribution of those individual dose ranges is well below the dose range that clinicians commonly use, and for some individuals who are susceptible to EPSE a tolerable dose of fluphenazine or haloperidol cannot be found. An argument can be made that haloperidol or flu-

phenazine be used primarily when the plan is to transition to the long-acting injected preparations of these antipsychotic medications.

Other FGAs (e.g., loxapine at doses of 5–20 mg daily or perphenazine 4–16 mg daily) offer a wider range within which therapeutic benefit can be achieved without coarse EPSE (molindone, which performed well in the Treatment of Early-Onset Schizophrenia Spectrum Disorders [TEOSS] trial, is unfortunately no longer manufactured); in this dose range, weight gain and prolactin elevations are minimal. The clinical variable most strongly associated with the development of tardive dyskinesia (TD) is the induction of coarse EPSE. Tailoring FGA doses to just below where coarse EPSE appear removes the adverse event burden of FGAs for many patients; in the subgroup of patients in whom this is not possible, a switch to an SGA is reasonable.

Yet other FGAs (e.g., thioridazine) are associated with substantial weight gain, disproportionate prolactin elevations and autonomic side effects, and it is difficult to imagine a situation in which they would be indicated.

In considering SGAs, olanzapine may offer additional therapeutic advantage for individuals who do not benefit from other non-clozapine antipsychotic medications, but it is associated with substantial weight gain and metabolic abnormalities, and the PORT Guidelines specifically recommend against using olanzapine (or clozapine) as a first-line treatment for FEP unless there are overriding factors (16). Risperidone and quetiapine are associated with weight gain and quetiapine produces substantial metabolic abnormalities; neither has been shown to provide greater efficacy than appropriately dosed FGAs. Risperidone is associated with disproportionate prolactin abnormalities. Aripiprazole (or the newest SGAs: asenapine, iloperidone, or lurasidone) has not been formally studied in well-designed, first-episode trials.

Trying neuroleptic threshold doses of well-tolerated FGAs such as loxapine or perphenazine as initial treatment is not a "fail-first" strategy; it is a "succeed-first" strategy. It allows identification of those individuals who are fortunate enough to respond favorably to a treatment comparatively free of self-image-changing and physical-capacity-limiting weight gain, life-shortening metabolic alterations, and prolactin elevations that interfere with multiple gender-specific functions of importance to young individuals. The main risk with FGAs, tardive dyskinesia, is likely to be low with well-tolerated FGAs like loxapine or perphenazine at doses below those that produce coarse EPSE. However, this uncertainty should not steer clinicians and patients away from a potentially well-tolerated "succeed-first" FGA medication trial. A switch to an SGA can be immediately undertaken in EPSE-sensitive individuals for whom a therapeutic sub-EPSE dose cannot be found, or who demonstrate any early evidence of TD.

In those individuals for whom an FGA does not provide adequate relief of psychopathology or where a movement disorder is a clinical concern, olanzapine and ultimately clozapine may offer additional therapeutic benefit. In those individuals sensitive to EPSE who cannot tolerate even low-dose loxapine or perphenazine, any of the SGAs may be more comfortable. However, any individual treated with an SGA requires primary care follow-up including monitoring of weight, lipid profile, and fasting blood sugar, and appropriate interventions as needed. If risperidone or paliperidone is considered, the individuals should be counseled beforehand regarding potential effects on sexual and endocrine function.

Unfortunately, many individuals recovering from FEP discontinue prescribed antipsychotic medication within a few months of treatment (18). Partial adherence or treatment discontinuation is often not recognized by families and clinicians until too late. Long-acting injectable (LAI) antipsychotic medications provide a critical piece of information: whether or not an individual is receiving treatment with an antipsychotic medication as prescribed, making adherence transparent. Despite the obvious clinical relevance, there are no large and well-conducted randomized trials regarding the efficacy of LAI in first-episode patients. However, clinical situations that include individuals with co-morbid substance use disorders, lack of acknowledgment of illness, or chaotic social situations seem to be reasonable indications where LAI preparations should be considered early. Those individuals who tolerate and respond to neuroleptic threshold doses of fluphenazine or haloperidol can be readily transitioned to the LAI preparations at very low doses (fluphenazine decanoate 6.25–12.5 mg q2weeks; haloperidol decanoate 12.5–50 mg q4weeks) without the weight gain, prolactin elevations, and metabolic abnormalities associated with LAI risperidone, paliperidone, or olanzapine. We recommend starting with very low doses (e.g., 6.25 mg q2weeks) of fluphenazine decanoate with oral supplementation as needed for the first several weeks; if an excessive initial FGA long-acting injected dose is given, the individual may suffer coarse EPSE for weeks.

When Clozapine Should be Considered

When clozapine is compared to non-clozapine antipsychotic medications in populations containing many treatment-responsive individuals (like first-episode patients) its advantages are small (10). Clozapine becomes salient when individuals who will not respond adequately to non-clozapine antipsychotic medications have been distilled from the larger population of people with schizophrenia. Agid and

colleagues (19) reported on 123 individuals with FEP who received algorithm- and measurement-based treatment with SGAs (olanzapine, quetiapine, or risperidone); the algorithm provoked clinicians to offer a clozapine trial as early as treatment month 7 to individuals with inadequate therapeutic response after trials of two of the SGAs. 93/123 individuals responded to the first SGA, leaving 30 initial nonresponders. Only 7 out of the 30 nonresponders benefitted from a switch to a second SGA, leaving 23 nonresponders to two SGAs. 13 of those nonresponders agreed to be switched to clozapine. 10/13 (77%) who received clozapine responded, while no clinical change was seen in those individuals who decided to stay on an SGA.

An important question remains to be answered. Recent work suggests that antipsychotic responders declare themselves early (20, 21). It might, therefore, be unnecessary to wait six months for a response (that will not occur) before moving to clozapine. Studies comparing intervention with very early and early use of clozapine after 1, 3, or 6 months of inadequate therapeutic response are needed.

Individuals with intense suicidal ideation, self-injurious behavior, or extreme violence should be considered for clozapine earlier.

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First-episode individuals treated with clozapine need an experienced physician to monitor and preemptively manage risk for agranulocytosis, myocarditis, pulmonary embolism, dyslipidemia, insulin resistance and weight gain. The best prevention strategies for cardiovascular disease need to go beyond metabolic screening and simply monitoring weight gain. Instead, preemption may need to include the addition of metformin to improve insulin resistance (22), or other cardioprotective strategies (e.g., aspirin, fish oil, a statin, and an ACE inhibitor).

Summary

What patients experiencing FEP want is something to do and good people to do it with. Medications are only aids that first-episode patients can utilize to advance themselves forward toward their goals. Clinicians' duties include providing their patients with accurate and salient information about taking versus not taking medications, and about the likely benefits and risks of each medication. Recommendations and preferences are expressed, negotiations undertaken, and shared decisions achieved; then the empirical trial of this particular medication in this particular individual begins (trial of n=1). Honest and accurate reports of symptoms, side effects and adherence will facilitate sensible and timely course corrections as needed: as Churchill noted, "However beautiful the strategy, one should occasionally look at the results."

We believe that the "succeed-first" strategy of identifying those treatment-responsive individuals who will have a good therapeutic effect at neuroleptic threshold doses of well-tolerated FGAs (thereby avoiding weight gain, insulin resistance, and prolactin-induced changes in gender-specific physiology), the early use of long-acting injected preparations of antipsychotic medications in individuals at risk for non-compliance, and an early trial of clozapine in treatment-nonresponsive individuals will lead to the best outcomes.

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