Current PSYCHIATRY

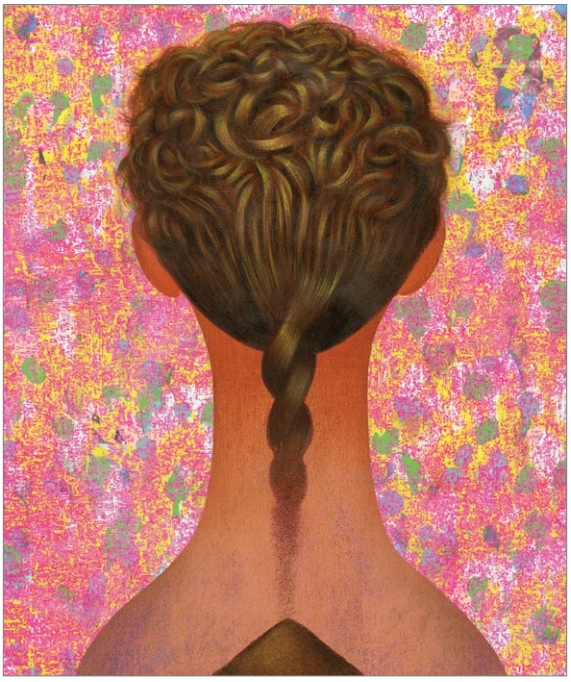
MANAGING FIRST-EPISODE PSYCHOSIS

Rationale and evidence for nonstandard first-line treatments for schizophrenia

Consider long-acting injectable antipsychotics; use clozapine as second- or third-line therapy only

First-episode psychosis (FEP) in schizophrenia is characterized by high response rates to antipsychotic therapy, followed by frequent antipsychotic discontinuation and elevated relapse rates soon after maintenance treatment begins.[1,2] With subsequent episodes, time to response progressively increases and likelihood of response decreases.[3,4]

To address these issues, this article—the second[a] of 2 parts[5]—describes the rationale and evidence for using nonstandard first-line antipsychotic therapies to manage FEP. Specifically, we discuss when clinicians might consider monotherapy exceeding FDA-approved maximum dosages, combination therapy, long-acting injectable antipsychotics (LAIA), or clozapine.



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Monotherapy beyond FDA-approved dosages

Treatment guidelines for FEP recommend oral antipsychotic dosages in the lower half of the treatment range and lower than those that are required for multi-episode schizophrenia.[6-16] Ultimately, clinicians prescribe individualized dosages for their patients based on symptom improvement and tolerability. The optimal dosage at which to achieve a favorable D2 receptor occupancy likely will vary from patient to patient.[17]

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[a]Part 1 appeared in the May 2015 issue and is available at CurrentPsychiatry.com.

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First-episode psychosis

Clinical Point

Evidence is lacking that lower dosages of individual antipsychotics used in combination may avoid high-dosage prescriptions

To control symptoms, higher dosages may be needed than those used in FEP clinical trials, recommended by guidelines for FEP or multi-episode patients, or approved by the FDA. Patients seen in everyday practice may be more complicated (eg, have a comorbid condition or history of nonresponse) than study populations. Higher dosages also may be reasonable to overcome drug–drug interactions (eg, cigarette smoking-mediated cytochrome P450 1A2 induction, resulting in increased olanzapine metabolism),[18] or to establish antipsychotic failure if adequate trials at lower dosages have resulted in a suboptimal response and the patient is not experiencing tolerability or safety concerns.

In a study of low-, full-, and high-dosage antipsychotic therapy in FEP, an additional 15% of patients responded to higher dosages of olanzapine and risperidone after failing to respond to a standard dosage.[19] A study of data from the Recovery After an Initial Schizophrenia Episode Project's Early Treatment Program (RAISE-ETP) found that, of participants identified who may benefit from therapy modification, 8.8% were prescribed an antipsychotic (often, olanzapine, risperidone, and haloperidol) at a higher-than-recommended dosage.[20] Of note, only olanzapine was prescribed at higher than FDA-approved dosages.

Antipsychotic combination therapy

Prescribing combinations of antipsychotics—antipsychotic polypharmacy (APP)—has a negative connotation because of limited efficacy and safety data,[21] and limited endorsement in schizophrenia treatment guidelines.[9,13] Caution with APP is warranted; a complex medication regimen may increase the potential for adverse effects, poorer adherence, and adverse drug-drug interactions.[9] APP has been shown to independently predict both shorter treatment duration and discontinuation before 1 year.[22]

Nonetheless, the clinician and patient may share the decision to implement APP and observe whether benefits outweigh risks in situations such as:

- to optimize neuroreceptor occupancy and targets (eg, attempting to achieve adequate D2 receptor blockade while minimizing side effects secondary to binding other receptors)
- to manage co-existing symptom domains (eg, mood changes, aggression, negative symptoms, disorganization, and cognitive deficits)
- to mitigate antipsychotic-induced side effects (eg, initiating aripiprazole to treat hyperprolactinemia induced by another antipsychotic to which the patient has achieved a favorable response).[23]

Clinicians report using APP to treat as many as 50% of patients with a history of multiple psychotic episodes.[23] For FEP patients, 23% of participants in the RAISE-ETP trial who were identified as possibly benefiting from therapy modification were prescribed APP.[20] Regrettably, researchers have not found evidence to support a reported rationale for using APP—that lower dosages of individual antipsychotics when used in combination may avoid high-dosage prescriptions.[24]

Before implementing APP, thoroughly explore and manage reasons for a patient's suboptimal response to monotherapy.[25] An adequate trial with any antipsychotic should be at the highest tolerated dosage for 12 to 16 weeks. Be mindful that response to an APP trial may be the result of additional time on the original antipsychotic.

Long-acting injectable antipsychotics in FEP

Guideline recommendations. Most older guidelines for schizophrenia treatment suggest LAIA after multiple relapses related to medication nonadherence or when a patient prefers injected medication (***Table 1***).[6-13] Expert consensus guidelines also recommend considering LAIA in patients who lack insight into their illness. The Texas Medication Algorithm Project (TMAP) guidelines[7] state LAIA can be considered for inadequate adherence *at any stage*, whereas the 2010 British Association for Psychopharmacology (BAP) guidelines[9] express uncertainty about their use in FEP, because of limited evidence. Both the BAP and National Institute for Health and Care Excellence guidelines[13] urge cli-

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Table 1

Comparing guidelines: When to consider LAIA or clozapine in adults with schizophrenia[a]

Guideline	LAIA recommendations	Clozapine recommendations
American Psychiatric Association, 2004[6]	Inadequate adherence; patient preference	No response or partial and suboptimal response to 2 antipsychotic trials (including an SGA); persistent suicidal ideation or behavior that has not responded to other treatments
Texas Medication Algorithm Project, 2008[7]	Inadequate adherence	Two failed antipsychotic trials; persistent suicidality, substance abuse, violence regardless of number of antipsychotic trials; persistent positive symptoms during 2 years of consistent medication treatment regardless of number of antipsychotic trials; 5 years of inadequate response regardless of number of antipsychotic trials
Schizophrenia Patient Outcomes Research Team, 2009[8]	Patient preference	Persistent, clinically significant positive symptoms after 2 adequate trials of other antipsychotics; persistent hostility or violent behavior; marked, persistent suicidal thoughts or behaviors
British Association for Psychopharmacology, 2011[9]	Inadequate adherence; patient preference; when adherence is a clinical priority; uncertainty about use in first-episode psychosis	Poor response to or intolerance of neurologic side effects in trials of 2 antipsychotics at adequate dosage and duration; schizophrenia characterized by persistent aggression and hostility
World Federation of Societies of Biological Psychiatry, 2012[10]	Treatment resistance (defined as the failure of 2 antipsychotic trials)	Lack of significant improvement after 2 different antipsychotic trials from 2 different chemical classes, including an SGA
Scottish Intercollegiate Guidelines Network, 2013[11]	Patient preference; inadequate adherence	Treatment-resistant schizophrenia, with or without hostility/aggression; nonresponse to 2 antipsychotics, including an SGA
French Association for Biological Psychiatry and Neuropsychopharmacology, 2013[12]	SGA as first-line maintenance treatment for schizophrenia and schizoaffective disorder and for individuals experiencing a first recurrent episode	N/A
National Institute for Health and Care Excellence, 2014[13]	Patient preference; when avoiding covert nonadherence is a clinical priority	Nonresponse or inadequate response despite sequential use of adequate doses of at least 2 antipsychotics, including an SGA

[a]For more schizophrenia treatment guidelines, see References 13-15

LAIA: long-acting injectable antipsychotic; SGA: second-generation antipsychotic

Clinical Point

Expert consensus guidelines recommend considering LAIA in patients who lack insight into their illness

nicians to consider LAIA when avoiding nonadherence is a treatment priority.

Recently, the French Association for Biological Psychiatry and Neuropsychopharmacology (AFPBN) created expert consensus guidelines[12] on using LAIA in practice. They recommend long-acting injectable second-generation antipsychotics (SGAs) as first-line maintenance treatment for schizophrenia and schizoaffective disorder and for individuals experiencing a first recurrent episode. The World Federation of Societies of Biological Psychiatry guidelines contain LAIA dosage recommendations for FEP (***Table 2, page 40***).[10]

Advances have been made in understanding the serious neurobiological adverse effects of psychotic relapses, including neuroinflammation and oxidative stress, that may explain the atrophic changes observed with

First-episode psychosis

Clinical Point

Compared with oral antipsychotics, LAIA offers the clinical advantage of a better pharmacokinetic profile (lower 'peaks' and higher 'valleys')

Table 2

WFSBP treatment guidelines: Recommended LAIA dosages in first-episode psychosis

Depot antipsychotic	Dosage interval (weeks)	Recommended dosage (mg/d)
Second-generation antipsychotic		
Aripiprazole long-acting injectable[a]	4	—
Olanzapine pamoate	2 to 4	150 to 210/over 2 weeks 300 to 405/over 4 weeks
Paliperidone palmitate	4[b]	25 to 75[c]
Risperidone microspheres	2	25
First-generation antipsychotic		
Fluphenazine decanoate	2 to 4	6.25 to 37.5
Haloperidol decanoate	4	50 to 100

[a]FDA approved depot aripiprazole in February 2013, after the WFSBP guidelines were completed. Aripiprazole was added to this table to show all SGAs available to date. Approval of another LAIA formulation of aripiprazole is pending
[b]A novel 3-month formulation of paliperidone was approved in May 2015
[c]Dosing in base equivalents where paliperidone palmitate, 39 mg = paliperidone, 25 mg

LAIA: long-acting injectable antipsychotic; SGA: second-generation antipsychotics; WFSBP: World Federation of Societies of Biological Psychiatry

Source: Reference 10

psychotic episodes starting with the FEP. Protecting the patient from a second episode has become a vital therapeutic management goal[26] (***Figure 1***[27]).

Concerns. Compared with oral antipsychotics, LAIA offers clinical advantages:

- improved pharmacokinetic profile (lower "peaks" and higher "valleys")
- more consistent plasma concentrations (no variability related to administration timing or food effects)
- no first-pass metabolism, which can ease the process of finding the lowest effective and safe dosage
- reduced administration burden and objective tracking of adherence with typical dosing every 2 to 4 weeks
- less stigmatizing than oral medication for FEP patients, such as college students living in a dormitory.[28,29]

Barriers to LAIA use include:

- slow dosage titration and increased time to reach steady state drug level
- oral supplementation for some (eg, risperidone microspheres and aripiprazole long-acting injectable)
- logistical challenges for some (eg, 3-hour post-injection monitoring for delirium sedation syndrome with olanzapine pamoate)
- additional planning to coordinate care for scheduled injections
- higher expenses up front
- local injection site reactions
- dosage adjustment difficulties if adverse effects occur.[28,29]

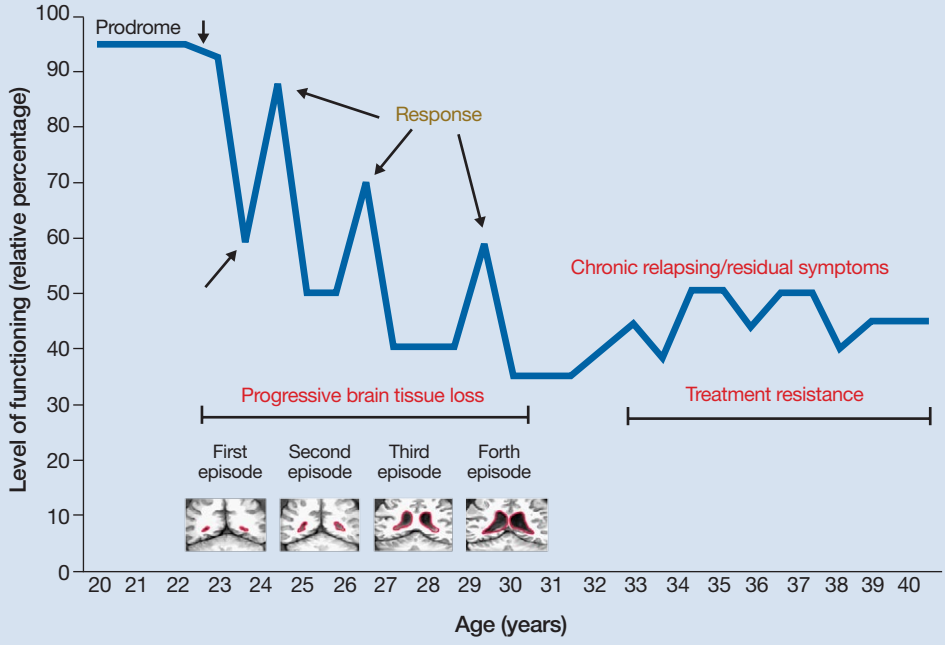
Adoption rates of LAIA are low, especially for FEP.[30] Most surveys indicate that (1) physicians believe LAIA treatment is ineffective for FEP[31] and (2) patients do not prefer injectable to oral antipsychotics,[32] despite evidence to the contrary.[33,34] A survey of 198 psychiatrists identified 3 factors that influenced their decisions against using LAIA patients with FEP:

- limited availability of SGA depot formulations (4, to date, in the United States)
- frequent rejection by the patient when LAIA is offered without adequate explanation or encouragement
- skepticism of FEP patients (and their family) who lack experience with relapse.[35]

In reality, when SGA depots were introduced in the United Kingdom, prescribing rates of LAIA did not increase. As for patient rejection being a major reason for not prescribing LAIA, few patients (5% to 36%) are offered depot injections, particularly in FEP.[29] Most patients using LAIA are chronic, multiepisode, violent people who are receiving medications involuntarily.[29] Interestingly, this

Figure 1

Deteriorating course, brain tissue loss, and treatment resistance with repetitive relapses after the first episode in schizophrenia



Source: Reference 27

survey did *not* find 2 factors to be influential in psychiatrists' decision not to use LAIA in FEP:

- guidelines do not explicitly recommend depot treatment in FEP
- treatment in FEP may be limited to 1 year, therefore depot administration is not worthwhile.[35]

Preliminary evidence. At least a dozen studies have explored LAIA treatment for FEP, with the use of fluphenazine decanoate,[36] perphenazine enanthate[37] (discontinued), and risperidone microspheres.[37-48] The research demonstrates the efficacy and safety of LAIA in FEP as measured by these endpoints:

- improved symptom control[38,40-43,46,48]
- adherence[43,44,48]
- reduced relapse rates[37,43] and rehospitalizations[37,47]
- lesser reductions in white matter brain volume[45]
- no differences in extrapyramidal side effects or prolactin-associated adverse effects.[48]

A few small studies demonstrate significant differences in outcomes between risperidone LAIA and oral comparator groups (***Table 3, page 42***).[43-45] Ongoing studies of LAIA use in FEP are comparing paliperidone palmitate with risperidone microspheres and other oral antipsychotics.[49-51] No studies are examining olanzapine pamoate in FEP, likely because several guidelines do not recommended its use. No studies have been published regarding aripiprazole long-acting injectable in FEP. This LAIA formulation was approved in February 2013, and robust studies of the oral formulation in FEP are limited.[52]

Discussion and recommendations. Psychiatrists relying on subjective measures of antipsychotic adherence may inaccurately assess whether patients meet this criterion for LAIA use.[53] LAIA could combat the high relapse rate in FEP, yet depot antipsychotics are prescribed infrequently for FEP patients (eg, for only 9.5% of participants in the RAISE-ETP study).[20] Most schizophrenia treatment guidelines do not discuss LAIA use specifically in FEP, although the AFPBN expert consensus guidelines published in 2013 do recommend SGA depot formulations in FEP.[12]

continued

Clinical Point

The efficacy and safety of LAIA in FEP can be measured by improved symptom control and adherence and by reduced relapse and rehospitalization rates

First-episode psychosis

Clinical Point

LAIA is advisable in any patient with schizophrenia for whom long-term antipsychotic therapy is indicated

Table 3

Studies showing significant differences in outcomes between risperidone LAI and oral antipsychotics for first-episode psychosis

Study and design	Endpoints/ dosage (mg)	Results	Comments
Kim et al, 2008[43] 2-year, flexible-dose, open-label comparison of risperidone LAI, ≤50 mg every 2 weeks (n = 22), with oral risperidone (RisO), ≤6 mg/d (n = 28)	Primary: adherence, relapse rate, PANSS, GAF, CGI Secondary: adverse events and ESRS Mean dose (mg): RLAI: 28.98 ± 6.00 every 2 weeks RisO: 2.79 ± 0.89 daily	RLAI vs RisO: Higher adherence at 1 and 2 years; lower relapse rates at 1 year (18% vs 50%) and 2 years (23% vs 75%); significant reduction in PANSS, GAF, and CGI; no difference in ESRS scores or prolactin-related adverse events	Time to nonadherence predicted relapse; small sample size
Weiden et al, 2009[44] 12-week, flexible-dose, prospective RCT comparing patient choice to switch to risperidone LAI, 25 to 50 mg every 2 weeks (n = 19) vs continue oral AP[a] (n = 18; 11 randomly assigned, 7 did not accept recommended switch)	LAI acceptance; initial adherence outcomes; adherence attitudes Mean dose (mg): RLAI 25 = 68% (13/19) RLAI 37.5 = 32% (6/19) RisO = 4.0 ± 1.89 daily	RLAI vs RisO: 73% (19/26) accepted RLAI therapy; increased adherence (89% vs 59% in as-actually-treated group; no difference in medication attitudes	Majority of patients accepted RLAI; rationale for maintenance medication was provided in 1 or 2 psychoeducation sessions; data for only 12 weeks
Bartzokis et al, 2011[45] 6-month, prospective RCT comparing brain MRI images in patients receiving risperidone LAI (n = 11) vs RisO (n = 13) vs healthy controls (n = 14)	Changes in frontal lobe white matter volume Mean dose (mg): RLAI: 26.4 ± 4.2 every 2 weeks (range 12.5 to 37.5) RisO: 2.9 ± 1.8 (range 1 to 7.5 daily)	RisO vs RLAI: reduction in white matter volume	Consistent drug levels from LAI antipsychotics might maintain higher white matter volume; groups did not differ in medication exposure before randomization; only 2 time points examined with duration <1 year

[a]Oral antipsychotics (AP) included risperidone (81%, n = 30), haloperidol (11%, n = 4), olanzapine (5%, n = 2), and quetiapine (3%, n = 1)

AP: antipsychotic; CGI: Clinical Global Impression scale; ESRS: Extrapyramidal Symptom Rating Scale; GAF: Global Assessment of Functioning scale; LAI: long-acting injectable; PANSS: Positive and Negative Symptom Scale; RCT: randomized controlled trial; RisO: oral risperidone; RLAI: long-acting injectable risperidone

SGA LAIA may be preferable, given its neuroprotective effects, in contrast to the neurotoxicity concerns of FGA LAIA.[54,55]

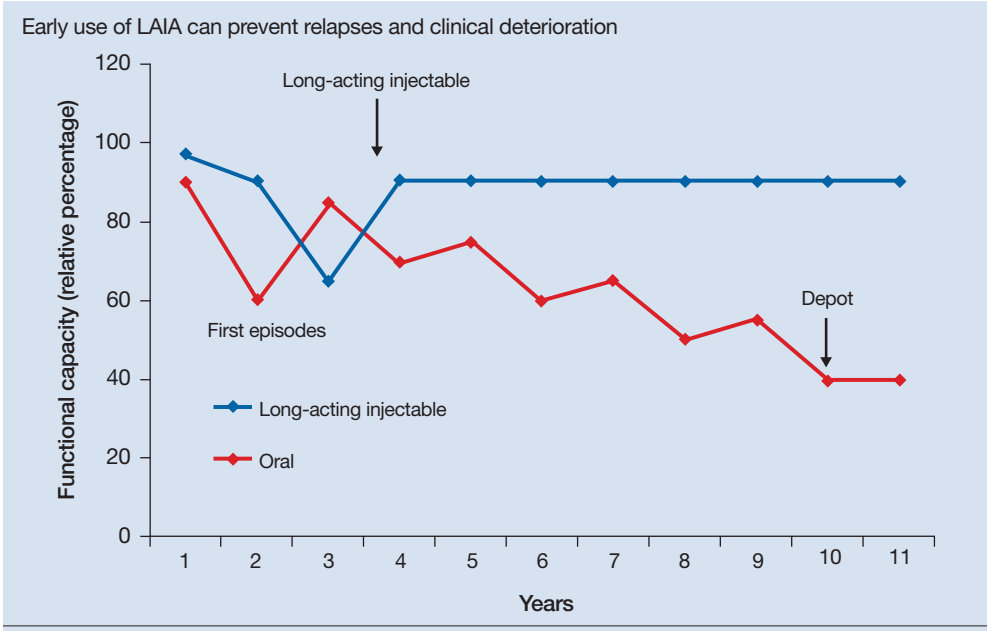
Relapses begin within a few months of illness stabilization after FEP, and >50% of patients relapse within 1 or 2 years[2]—the recommended minimum treatment duration for FEP.[8,9,13] The use of LAIA is advisable in any patient with schizophrenia for whom long-term antipsychotic therapy is indicated.[56] LAIA administration requirements objectively track medication adherence, which allows clinicians to be proactive in relapse prevention. Not using an intervention in FEP that improves adherence and decreases relapse rates contradicts our goal of instituting early, effective treatment to improve long-term functional outcomes (***Figure 2***).[29]

Considering clozapine in FEP

Guideline recommendations. Schizophrenia treatment guidelines and FDA labeling[57] reserve clozapine for third-line treatment of refractory schizophrenia after 2 adequate antipsychotic trials have failed despite optimal dosing (***Table 1, page 39***).[6-13] Some guidelines specify 1 of the 2 failed antipsychotic trials must include an SGA.[6,7,10,11,13-16] Most say clozapine may be considered in patients with chronic aggression or hostil-

Figure 2

2 treatment paradigms for schizophrenia: LAIA and depot



LAIA: long-acting injectable antipsychotic
Source: Reference 29

ity,[7-9,14,16] or suicidal thoughts and behaviors.[6-8,14,16] TMAP guidelines recommend a clozapine trial with concomitant substance abuse, persistent positive symptoms during 2 years of consistent medication treatment, and after 5 years of inadequate response ("treatment resistance"), regardless of the number of antipsychotic trials.[7]

Rationale and concerns. Clozapine is a superior choice for treatment-refractory delusions or hallucinations of schizophrenia, because it markedly enhances the response rate to antipsychotic therapy.[58] Researchers therefore have investigated whether clozapine, compared with other antipsychotics, would yield more favorable initial and long-term outcomes when used first-line in FEP.

Preliminary evidence. Five studies have explored the use of clozapine as first-line therapy in FEP (***Table 4,*** in this article at CurrentPsychiatry.com).[59-63] Interpreting the results is difficult because clozapine trials may be brief (mostly, 12 to 52 weeks); lack a comparator arm; suffer from a high attrition rate; enroll few patients; and lack potentially important outcome measures such as negative symptoms, suicidality, and functional assessment.

Overall, these studies demonstrate clozapine is as efficacious in this patient population as chlorpromazine (no difference in remission at 1-year, although clozapine-treated patients remitted faster and stayed in remission longer)[60,61] or risperidone (no difference in Positive and Negative Syndrome Scale scores).[62]

At present, clozapine has not been shown superior to other antipsychotics as a first-line treatment for FEP. Research does underscore the importance of a clozapine trial as third-line treatment for FEP patients who have not responded well to 2 SGA trials.[63] Many of these nonresponders (77%) have demonstrated a favorable response when promptly switched to clozapine.[64]

Discussion and recommendations. The limited evidence argues against using clozapine earlier than as third-line treatment in FEP. Perhaps the high treatment response that characterizes FEP creates a ceiling effect that obscures differences in antipsychotic efficacy at this stage.[65] Clozapine use as first-line treatment should be re-evaluated with

Clinical Point

Clozapine has *not* been shown to be superior to other antipsychotics as a first-line treatment for FEP

See this article at CurrentPsychiatry.com for a table of studies exploring clozapine as first-line therapy in FEP

First-episode psychosis

Related Resource

- Recovery After an Initial Schizophrenia Episode (RAISE) Project Early Treatment Program. National Institute of Mental Health. http://raiseetp.org.

Drug Brand Names

Aripiprazole • Abilify, Abilify Maintena
Chlorpromazine • Thorazine
Clozapine • Clozaril
Fluphenazine decanoate • Prolixin-D
Haloperidol • Haldol
Haloperidol decanoate • Haldol-D
Olanzapine • Zyprexa
Olanzapine pamoate • Zyprexa Relprevv
Paliperidone palmitate • Invega Sustenna
Quetiapine • Seroquel
Risperidone • Risperdal
Risperidone microspheres • Risperdal Consta

Clinical Point

For now, continue to reserve clozapine as a second- or third-line treatment in patients with FEP

more robust methodology. One approach could be to assess its benefit in FEP by the duration of untreated psychosis.

The odds of achieving remission have been shown to decrease by 15% for each year that psychosis has not been treated.[59] Studies exploring the use of clozapine as a second-line agent for FEP also are warranted, as antipsychotic response during subsequent trials is substantially reduced. In fact, the Scottish Intercollegiate Guidelines Network guidelines recommend this as an area for future research.[11]

For now, clozapine should continue to be reserved as second- or third-line treatment in a patient with FEP. The risks of clozapine's potentially serious adverse effects (eg, agranulocytosis, seizures, obesity, diabetes, dyslipidemia, myocarditis, pancreatitis, hypotension, sialorrhea, severe sedation, ileus) can be justified only in the treatment of severe and persistent psychotic symptoms.[57]

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Bottom Line

Nonstandard use of antipsychotic monotherapy dosages beyond the approved FDA limit and combination antipsychotic therapy may be reasonable for select first-episode psychosis (FEP) patients. Strongly consider long-acting injectable antipsychotics in FEP to proactively combat the high relapse rate and more easily identify antipsychotic failure. Continue to use clozapine as second- or third-line therapy in FEP: Studies have *not* found that it is more efficacious than other antipsychotics for first-line use.

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Table 4

4 studies that examined the use of clozapine in first-episode psychosis[a]

Study and design	Endpoints/dosage (mg)	Results	Comments
Woerner et al, 2003[59] Open-label, 221-week (mean 114 week) observation of 34 patients given CLZ as first antipsychotic treatment	Treatment response[b] Dosage: At time of response = 206 ± 133 Responders = 234 ± 126 Nonresponders = 297 ± 153	56% met response criteria; only 32% remained on CLZ; 42% discontinued CLZ within 6 months; mean time in treatment 50 ± 47 weeks	No comparison group; given high dropout rate, long-term benefits could not be assessed
Lieberman et al, 2003[60] 52-week flexible-dose, randomized, double-blind trial comparing CPZ (plus benztropine) vs CLZ (plus placebo)	Time to first remission; proportion of time remaining in remission; clinical symptoms and side effects Median doses at 12 weeks: CPZ = 600; CLZ = 400; Median doses at 52 weeks: CPZ = 400; CLZ = 300	CLZ vs CPZ: Faster time to first remission (8 vs 12 weeks); odds of remission nearly doubled (OR = 1.73); no differences in remission at 52 wk (81% vs 79%); improved BPRS anergia factor, SANS total, SANS affective and avolition subscales at 12 weeks but not 52 weeks; lower rate of EPS	Groups comparable in duration of untreated psychosis (18.4 months ± 17.8; median = 10.7 months); CPZ dropouts had higher BPRS scores vs CLZ dropouts (may be a factor in nonsignificance at 52 weeks)
Girgis et al, 2011[61] 2-year RCT and 7-year naturalistic treatment comparing CPZ (n = 61) vs CLZ (n = 63); 9-year follow-up of Lieberman et al[60]	Remission status Dosage: NA	CLZ vs CPZ: Similar remission (78%) and relapse (14%) rates; longer time until first discontinuation of medication (39 vs 23 months); at 9 years, more patients remained on original medication (26% vs 10%)	Initial exposure to either treatment did not alter long-term course; limitations include high attrition rate, crossover (30% of CPZ group took CLZ at some time), and other medications
Sanz-Fuentenebro et al, 2013[62] 52-week, randomized, open-label trial comparing efficacy of CLZ (n = 15) vs risperidone (n = 15)	Number of drop-outs and treatment switched; PANSS, UKU Side Effect Rating Scale Mean dosage: CLZ: 220 ± 112; RIS: 5 ± 1.5	CLZ vs RIS: Total discontinuation rate 53.3%; no difference in number of patients who never switched from original treatment (40% vs 67%); no difference in PANSS or UKU scores	Only study to actively compare CLZ with an SGA; higher adherence in CLZ group is consistent with Lieberman et al[60]

[a]A fifth study (Yang et al[61]) explored the use of clozapine as first-line therapy for FEP, but details are limited
[b]Treatment response defined as no psychotic symptoms rated greater than mild on the Schedule for Affective Disorders and Schizophrenia - Change Version and being rated much improved or very much improved on the Clinical Global Impression scale for at least 2 months

BPRS: Brief Psychiatric Rating Scale; CLZ: clozapine; CPZ: chlorpromazine; EPS: extrapyramidal symptoms; PANSS: Positive and Negative Symptom Scale; RIS: risperidone; SGA: second-generation antipsychotic; SANS: Scale for Assessment of Negative Symptoms; UKU: Udvalg for KliniskeUndersøgelser scale