Box 8. Assessment Scales for Adult Schizophrenia

- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression (CGI) Scale
- Clinician-Rated Dimensions of Psychosis Symptoms Severity (CRDPSS)
- Positive and Negative Syndrome Scale (PANSS)

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see pages 2-3.

Conduct comprehensive assessment and use measurement-based care. Preferred tools recommended. Refer to Principles of Practice on pages 4-9.

Most importantly, assess social support system (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Proper antipsychotic trial sequence:

- Begin with systematic 6 to 10-week trial of one antipsychotic with optimal dosing.
- If inadequate response, follow with systematic trial of monotherapy with one or more antipsychotics at adequate dose and duration.
- If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic.
- Follow with a trial of clozapine, if not tried before.

Note: Recent evidence suggests that long-acting injectable antipsychotic medications should be offered early as a treatment option for all individuals diagnosed with schizophrenia to reduce the risk of non-adherence, prevent future relapse/deterioration, and improve treatment outcomes.

- If insufficient response with the previously listed therapies, consider other strategies (e.g. antipsychotic polypharmacy).

Level 1 Initial Treatment:

- Monotherapy with an antipsychotic (SGA) other than clozapine*—either oral, or oral antipsychotic followed by the same SGA-LAI (if tolerable and sufficiently efficacious).
- If initial trial of antipsychotic monotherapy unsuccessful, try monotherapy with another SGA antipsychotic (either oral or LAI) with low metabolic adverse effects.

**Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select a medication with lower metabolic risk, lower risk of extrapyramidal symptoms (EPS), sedation, and sexual side-effects. For more detail on LAIs, refer to page 42.*

Level 2A If non-adherent or refractory to Level 1:

- Long-acting injectable antipsychotic medication (LAI)

Level 2B If Level 1 is ineffective in at least two antipsychotic trials:

- Clozapine

Note: Clozapine requires monitoring through the United States Food and Drug Administration Risk Evaluation and Mitigation Strategies (REMS) program. The clozapine REMS program can be found at: https://www.newclozapinerems.com/home.

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Diagnostic review to include substance use, other psychiatric comorbidities, social determinants (e.g., housing) and/or consultation
- Clozapine if not tried earlier
- Antipsychotic, including clozapine + electroconvulsive therapy (ECT)
- Augmentation of clozapine with aripiprazole, lamotrigine, topiramate or if partial or incomplete response to clozapine

Level 4 If Levels 1, 2, and 3 are ineffective and/or not well tolerated:

- Two antipsychotics, ideally with different pharmacological mechanisms* and side-effect profiles (evidence is weak). Avoid additive side effects.
- First generation antipsychotic use

**Full antagonist with partial agonist; loose binding with tight binding*

Table 5. Recommended Medications for the Treatment of Schizophrenia: Oral Antipsychotics

Medication	Chlorpromazine Equivalents[1]	Acute Therapy	Maintenance Therapy[2]
First Generation Antipsychotics (FGAs)			
Chlorpromazine	100	300–1,000 mg/day	300–800 mg/day
Fluphenazine HCl	2	5–20 mg/day	5–15 mg/day
Haloperidol	2	5–20 mg/day	6–12 mg/day
Loxapine	10	30–200 mg/day	30–100 mg/day
Molindone	10	30–200 mg/day	30–100 mg/day
Perphenazine	8	16–80 mg/day	16–64 mg/day
Thiothixene	5	15–50 mg/day	15–30 mg/day
Trifluoperazine	5	15–50 mg/day	15–30 mg/day
Second Generation Antipsychotics (SGAs)			
Aripiprazole	N/A	10-30 mg/day	10–30 mg/day
Asenapine	N/A	10–20 mg/day	10–20 mg/day
Brexpiprazole	N/A	2–4 mg/day	2–4 mg/day
Cariprazine	N/A	1.5–6 mg/day	3–6 mg/day
Clozapine	N/A	150–800 mg/day	150–800 mg/day
Iloperidone	N/A	12–24 mg/day	12–24 mg/day
Lumateperone	N/A	42 mg/day	42 mg/day
Lurasidone	N/A	40–160 mg/day	40–160 mg/day
Olanzapine	N/A	10–30 mg/day	10–20 mg/day
Olanzapine/Samidorphan*	N/A	5mg/10mg or 10mg/10mg once per day	10mg/10mg, 15mg/10mg, or 20mg/10mg once per day
Paliperidone	N/A	3–12 mg/day	3–12 mg/day
Quetiapine	N/A	300–800 mg/day	300–800 mg/day
Risperidone	N/A	2–8 mg/day	2–8 mg/day
Ziprasidone	N/A	80–240 mg/day	80–160 mg/day

Notes:

Recommendations may be below FDA maximum approved doses but are based on current evidence and expert consensus.

Samidorphan is an opioid receptor antagonist approved for use in combination with olanzapine to mitigate olanzapine-associated metabolic side effects.

Consider lower doses for first episode due to better response and higher side effects to medications in pharmaceutically naïve patients. Use atypical antipsychotics and avoid haloperidol completely due to well-documented neuronal cell death caused by haloperidol (and also fluphenazine and perphenazine). Thioridazine is not recommended due to concerns about ventricular arrhythmias (Torsades de Pointes).

1 Approximate dose equivalent to 100 mg of chlorpromazine (relative potency); it may not be the same at lower versus higher doses. Chlorpromazine equivalent doses are not relevant to the second-generation antipsychotics and therefore are not provided for these agents.

2 Drug-drug interactions (DDIs) can impact dosing. Maintenance dose should generally be no less than half of the initial clinically effective dose, as that can result in reduced effectiveness of relapse prevention.

Treatment of Schizophrenia with Long-Acting Injectable Antipsychotic Medications (LAIs)

Note: Treatment recommendations are based on levels of evidence and expert opinion. For a description of the criteria for each level, see pages 2-3.

Conduct a comprehensive assessment and use measurement-based care as found in the Principles of Practice on pages 4-9.

Assess social determinants (housing, family, other caregivers) and evaluate threats to continuity of care (access to medication, adherence, etc.).

Strongly recommend psychiatric consultation prior to initiation of therapy + psychotherapeutic medication using a multi-disciplinary approach if treated by a non-psychiatrist.

Level 1 Initial Treatment:

- After stabilization or obtaining sufficient evidence for efficacy and tolerability, offer any of the following long-acting injectable antipsychotics (LAI). Base the selection on past efficacy and tolerability patterns to specific oral or LAI, expected tolerability advantages*, desired injection intervals, and procedural (oral overlap needed – yes versus no)/logistic/access/cost considerations:
  - Aripiprazole monohydrate
  - Aripiprazole lauroxil
  - Paliperidone palmitate
  - Risperidone microspheres
  - Risperidone extended release subcutaneous injectable.
- If initial, adequate trial (minimum 3 to 4 months) of LAI is unsuccessful, try monotherapy with another LAI from the above group or address potential reasons for efficacy difficulty on the LAI. Refer to Figure 1: Management of Breakthrough Psychosis with LAI for options to consider if psychotic symptoms persist despite adequate medication trial.

**Note: Balance efficacy, side-effects, individual vulnerabilities and preferences. Select medication with lower propensity for metabolic and extrapyramidal side-effects.*

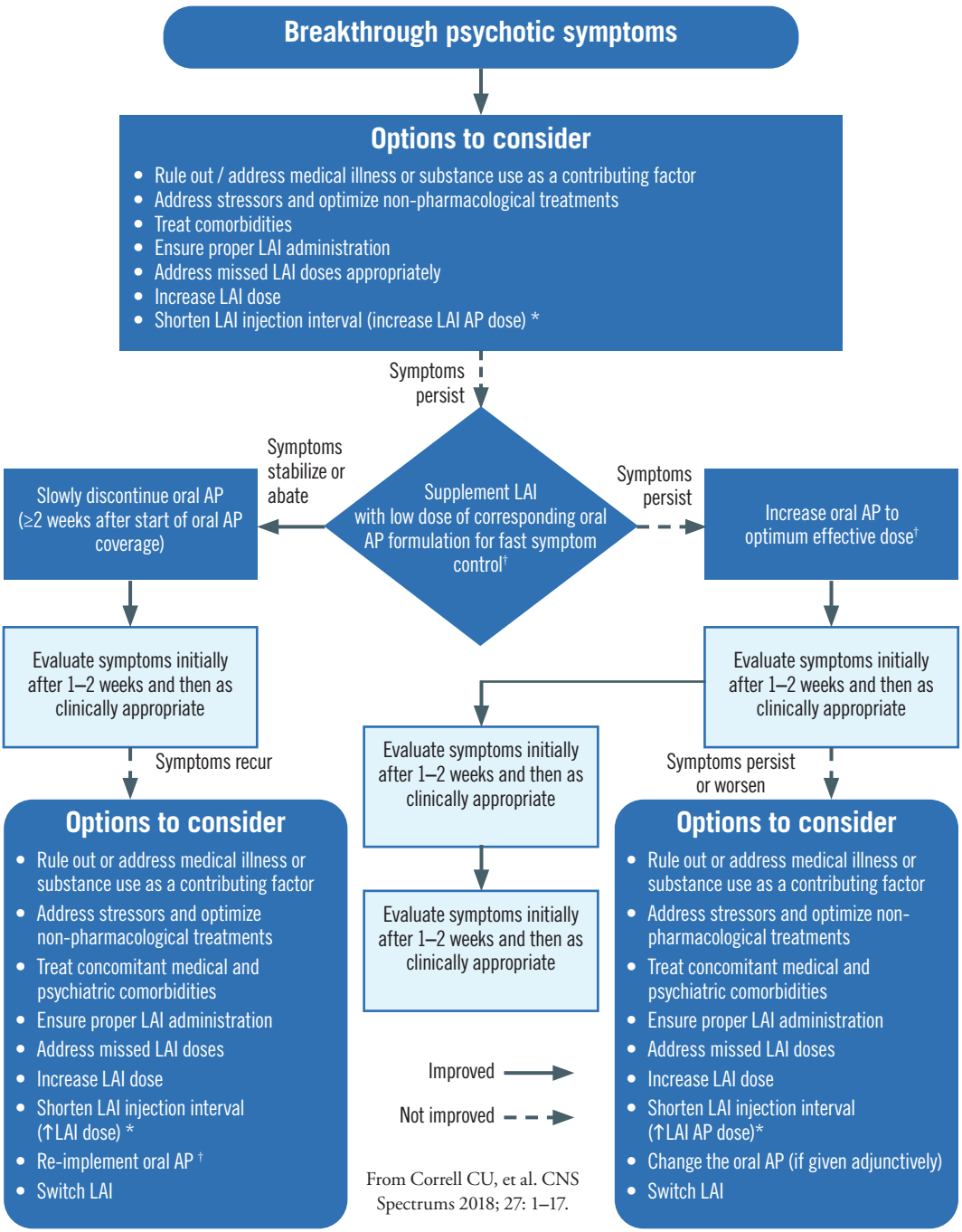
Level 2 If multiple Level 1 trials are ineffective and/or not well tolerated:

- Consider LAI with greater adverse effect risk [olanzapine: post-injection delirium/sedation syndrome (PDSS); FGA-LAIs: EPS, TD]
  - Olanzapine pamoate
  - Fluphenazine decanoate
  - Haloperidol decanoate

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Diagnostic review and/or consultation
- Consider switch to an oral antipsychotic not available as an LAI (if adherence can be assured)
- Clozapine if not tried earlier
- LAI + electroconvulsive therapy (ECT) or oral antipsychotic
- Clozapine + ECT

Figure 1. Management of Breakthrough Psychosis with Long-Acting Injectable Antipsychotics (LAIs)



From Correll CU, et al. CNS Spectrums 2018; 27: 1–17.

**Off-label strategy; based on expert opinion.*

†Caution should be exercised with this strategy, because data on the safety of concomitant use of LAI and oral APs are limited, especially over extended periods of time.

Table 6. Recommended Medications for the Treatment of Schizophrenia: Long-Acting Injectable Antipsychotics

Medication	Dose Interval	Dosage Strengths/ Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State
First-Generation Long-Acting Injectable Antipsychotics*							
Fluphenazine decanoate	Varies	25 and 100 mg/mL ampoules/vials/ syringes	Varies, 12.5 mg	Varies, 12.5 to 100 mg	No	2 to 4 days	2 to 3 months
Haloperidol decanoate	4 weeks	50 and 100 mg/mL ampoules	Varies, 50 mg	Varies, 300 mg	No	6 to 7 days	2 to 3 months
Second-Generation Long-Acting Injectable Antipsychotics*							
Aripiprazole monohydrate (Abilify Maintena®)	Monthly	300, 400 mg vial kits and dual-chamber syringe	400 mg	400 mg (300 to 400 mg)	2 weeks	5 to 7 days	400 mg: 4 to 8 months 300 mg: 3 to 4 months
(Aripiprazole lauroxil (Aristada®)	Monthly for 441 mg dose; monthly to every 6 weeks for 882 mg dose; bimonthly for 1,064 mg dose	441; 662; 882; 1,064 mg prefilled syringes	Varies 441 mg to 1,064 mg**	Varies, 441 to 882 mg	3 weeks if Aristada Initio® is not administered at the beginning of treatment. If initiating treatment with Aristada Initio®, 1 day oral supplementation with aripiprazole 30 mg tablet is required.	4 days	4 to 6 months
Aripiprazole lauroxil (Aristada Initio®)	Once at the beginning to initiate aripiprazole lauroxil (Aristada®) treatment	675 mg	675 mg	Not applicable (N/A)	1 day (aripiprazole 30 mg tablet) —therapeutic levels in 4 days	27 days	With single IM injection of Aristada initio® and 30 mg oral aripiprazole at time of first Aristada® dose, aripiprazole concentration reaches therapeutic levels within 4 days

Table 6 (continued). Recommended Medications for the Treatment of Schizophrenia: Long-Acting Injectable Antipsychotics

Medication	Dose Interval	Dosage Strengths/ Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State
Olanzapine pamoate‡ (Zyprexa Relprevv®)	2 to 4 weeks	210, 300, 405 mg vial kits	Varies, up to 300 mg every 2 weeks	Varies, up to 300 mg every 2 weeks	No	4 days	3 months
Paliperidone palmitate (Invega Sustenna®)	Monthly	38, 117, 156, 234 mg prefilled syringes	234 mg (day 1) + 156 mg (day 8)	117 mg (38 to 234 mg)	No	13 days	7 to 11 months
Paliperidone palmitate (Invega Trinza®)	Once every 3 months	273, 410, 546, 819 mg prefilled syringes	Depends on once-monthly paliperidone palmitate (Invega Sustenna®) dose	Varies, 273 to 819 mg	No	30 to 33 days	Continues steady state at equivalent dose
Paliperidone palmitate (Invega Hafyera™)	Once every 6 months	1,092 mg and 1,560 mg prefilled syringes	Depends on last dose of one-month (Invega Sustenna®) or three-month (Invega Trinza®) formulation of paliperidone palmitate	Varies; 1,092 mg or 1,560 mg	No	29-32 days	Continues steady state at equivalent dose of one-month or 3-month formulation of paliperidone palmitate
Risperidone microspheres (Risperdal Consta®)	Once every 2 weeks	25, 37.5, 50 mg vial kits	Varies, 12.5 mg to 25 mg	Varies, 12.5 mg to 50 mg	3 weeks	4-6 weeks	Steady state reached after 4 injections and maintained for 4-6 weeks after last injection
Risperidone extended release subcutaneous injectable (Perseris®)	Monthly	90 mg, 120 mg powder and liquid filled syringes	90 mg, 120 mg	90 mg, 120 mg	No	4-48 hours	4-6 weeks

Adapted and updated from: Correll CU, Kane JM, Citrome LL. Epidemiology, Prevention, and Assessment of Tardive Dyskinesia and Advances in Treatment. J Clin Psychiatry. 2017 Sep/Oct;78(8):1136-1147.

Notes: For the most updated Florida Medicaid Preferred Drug List, visit https://ahca.myflorida.com/medicaid/Prescribed_Drug/pharm_thera/fmpdl.shtml.

**First-generation long-acting injectable antipsychotic medications (fluphenazine decanoate and haloperidol decanoate) have an oil base. Second-generation long-acting injectable antipsychotic medications (aripiprazole monohydrate, aripiprazole lauroxil, olanzapine pamoate, 1-month and 3-month paliperidone palmitate, and risperidone microspheres) have a water base.*

*** Initial Aristada® dose is based on current oral aripiprazole dose as follows: If oral aripiprazole dose is 10 mg/day, initial Aristada® dose is 441 mg once monthly. If oral aripiprazole dose is 15 mg/day, initial Aristada® dose is either 882 mg once monthly, 882 mg Aristada every 6 weeks, or 1,064 mg Aristada® every 2 months. If oral aripiprazole dose is ≥20 mg/day, initial Aristada® dose is 882 mg once monthly.*

‡Olanzapine pamoate (Zyprexa Relprevv) requires prescriber certification and patient enrollment with the Risk Evaluation and Mitigation Strategy (REMS) program. Administration of olanzapine pamoate requires at least 3-hours of post-injection monitoring for post-injection delirium/sedation syndrome (PDSS). Olanzapine has been found to cause more weight gain and related metabolic side effects than other SGAs

Summary: Treatment of Schizophrenia

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Introduction

The primary objectives in the treatment of schizophrenia are to reduce frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, prevent relapses, and improve functional capacity and quality of life. Treatment includes medication and a range of psychosocial interventions. Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia. The twenty-three antipsychotics available in our country have traditionally been classified into two major groups: 10 first-generation (conventional) agents (FGAs) and 13 second-generation (atypical) agents (SGAs), although this dichotomization can be misleading. Since the last iteration of the Florida Center for Behavioral Health Improvements and Solutions (FCBHIS) guidelines in 2019, one new antipsychotic agent (lumateperone [®Caplyta]) and a new combination (olanzapine-samidorphan [®Lybalvi]) have been introduced into clinical practice along with some new long-acting injectable formulations of existing antipsychotic agents. Basic principles of the Florida FCBHIS guidelines for the treatment of schizophrenia are summarized.

Pharmacological Treatment of Schizophrenia: What Do Antipsychotics Do?

Schizophrenia is characterized by positive (reality distortion and disorganization), negative, cognitive, and mood symptoms, with the types and severity of symptoms differing among patients and over the course of the illness. With its typical onset in early adulthood, schizophrenia tends to be a chronic illness with a relapsing and remitting course. Antipsychotic medications are the mainstay in the pharmacological treatment of schizophrenia. In addition to reducing symptoms in the acute psychotic phase of the illness, antipsychotic medications are very effective in reducing the likelihood of psychotic relapses in stable patients. Antipsychotics are most effective in ameliorating positive and disorganization symptoms, but ineffective in treating negative and cognitive symptoms. They can help but can also worsen mood symptoms (eg., neuroleptic dysphoria) and motor symptoms (eg., neuroleptic malignant syndrome). In DSM-5TR, the distinction between the different psychopathological dimensions of schizophrenia is explicitly catalogued and a simple scale for measurement of each dimension over the course of treatment (SCoRS) is provided.

Comparative Efficacy

Although it was formerly believed that FGAs are less effective than SGAs, recent trials have not confirmed this belief. Clozapine is the only antipsychotic agent that is found to be more effective than other antipsychotic agents in treating positive symptoms in otherwise refractory patients and in reducing suicidality. All other agents are found to be about equally effective, although different degrees of ease-of-use lead to minor differences in efficacy being observed in routine clinical practice. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia, without any consistent differences among agents. Since medication non-adherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates.

Safety and Tolerability

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genitourinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotics differ markedly in adverse-effect profiles. Compared with the FGAs, SGAs generally have a lower risk of EPS. However, due to differences in pharmacological profiles within the FGA and SGA classes, there is substantial variation within both classes in their propensity to cause EPS and metabolic adverse effects. Thus, no categorical distinction can be made between so-called FGAs and SGAs with regard to these risks. Antipsychotic medications also differ in their propensity to cause other side effects, such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, and anticholinergic effects, with substantial variation within both the FGAs and the SGAs for each of these effects, without any definitive categorical separation between the two classes. Patients with schizophrenia also vary in their vulnerability to develop various adverse effects with different agents. The likelihood that a patient will develop a particular side effect thus depends on the agent selected, how that agent is used (e.g., dose, titration method, in combination with what other agents), and the patient's vulnerability.

Optimizing Individual Outcomes

Given the significant variability in drug pharmacokinetics and treatment responsivity in individual patients, it should be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in individual patients. It is not currently possible to predict which antipsychotic may be optimal for a given patient. There is no best agent or best dose for all patients, although dose ranges for optimal effectiveness do appear to exist. Decisions about antipsychotic therapy therefore often entail a trial-and-error process involving careful monitoring of response and adverse effects, an ongoing risk-benefit assessment, and judicious switching if necessary. To achieve optimal therapy for schizophrenia, clinicians must balance efficacy benefits and side-effect costs of treatments in a way that is customized for the needs and vulnerabilities of the individual patient. The meticulous application of this approach can reduce the significant gap between what we know about best practices and the therapy that is actually provided for patients with schizophrenia.

The Florida Center for Behavioral Health Improvements and Solutions (FCBHIS) guidelines for the pharmacological treatment of schizophrenia were developed on the basis of our current understanding of what they do and how they compare and a clinician-friendly elaboration of key principles.

Clinical Guidance

Schizophrenia is characterized by positive, negative, cognitive, disorganization, and mood symptoms. Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia. Findings concerning efficacy for positive symptoms and disorganization suggest no consistent differences among available antipsychotics, with the exception of clozapine's superior efficacy for treatment-resistant schizophrenia. Efficacy for negative, depressive, and cognitive symptoms appears to be determined by: (i) the extent to which reduction in positive symptoms brings about improvement in these other domains and (ii) the extent to which extrapyramidal side effects (EPS) and anticholinergic effects (of the antipsychotic and of agents used to treat EPS) exacerbate them. Thus, the ability of antipsychotics to produce a potent antipsychotic effect without EPS and need for concomitant anticholinergic therapy yields multiple therapeutic benefits. In contrast to their broadly similar efficacy, antipsychotics differ markedly in their propensity to cause various adverse effects. Choice of antipsychotic medication should be

based on individual preference, prior treatment response and side-effect experience, medical history and risk factors, and adherence history, with side-effect profile a major determinant of antipsychotic choice [Box 9].

Summary

Whereas the efficacy of these antipsychotic agents in the treatment of schizophrenia is broadly similar (with the exception of clozapine's greater efficacy in otherwise treatment-refractory patients), there are significant differences in their side-effect profiles. Optimal individualized pharmacological treatment of schizophrenia requires an understanding of the nature of schizophrenia (multiple pathological dimensions, remitting and relapsing course), knowledge about the similarities and differences between available antipsychotic treatments, and awareness of how to use these treatments most effectively (targeted, measurement-based, individualized). Targeted use of a range of non-antipsychotic medications can be useful in reducing comorbid symptoms. Antipsychotic polypharmacy may be reasonable after dose optimization and consideration of clozapine and long-acting injectable antipsychotic agents.

Box 9. Steps to achieve optimum outcomes with currently available antipsychotics

1. Considerations in selecting the best antipsychotic for a particular patient

- Equivalent efficacy across agents
- Individual variability in response
- No good predictor of individual response to different agents
- Different agents have different side effects
- Different patients have different vulnerabilities and preferences

2. Proper antipsychotic trial sequence

- Begin with systematic 6-10 week trial of one antipsychotic with optimal dosing
- If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration
- If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic
- Follow with a trial of clozapine, if not tried before
- Only then consider other strategies (e.g., antipsychotic polypharmacy)

3. Good practice guidelines for ongoing antipsychotic treatment

- Measurement-based individualized care
- Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales)
- Careful assessment of adverse effects
- Care consistent with health monitoring protocols
- Standard protocols customized to individual vulnerabilities/needs and specific agent
- Ongoing collaboration with patient in decision-making

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