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APA PRACTICE GUIDELINE ON THE TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

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INTRODUCTION

BACKGROUND

SCHIZOPHRENIA…

- Significant health, social, occupational, and economic burdens as a result of its early onset and its severe and often persistent symptoms
- One of the top 20 causes of disability worldwide
- Lifetime prevalence estimated to be approximately 0.7%, although findings vary with the study design
- An estimated cost of more than $150 billion annually in the United States, related to direct health care costs and lost productivity based on 2013 data

BACKGROUND

- Increased mortality, with a shortened life span and standardized mortality ratios reported to be twofold to fourfold those in the general population
  - Related to obesity, diabetes, hyperlipidemia, greater use of cigarettes, reduced engagement in health maintenance (e.g., diet, exercise), and disparities in access to preventive health care and treatment for physical conditions
  - Common co-occurrence of other psychiatric disorders, including substance use disorders (SUDs), is another contributor
  - Suicide in about 4%–10% of persons with schizophrenia, with rates that are highest among males in the early course of the disorder
  - Lack of access to adequate psychiatric treatment

GOAL OF GUIDELINE

- To enhance the treatment of schizophrenia for affected individuals, thereby reducing the mortality, morbidity, and significant psychosocial and health consequences of this important psychiatric condition.

- Guidelines are:
  - Assessments of current scientific and clinical information
  - Not inclusive of all proper treatments
  - Not a comprehensive standard of care
  - Not able to account for all types of individual variation
  - Not intended to replace independent clinical judgment

SCOPE OF GUIDELINE

- Shaped by *Treatments for Schizophrenia in Adults* (McDonagh et al. 2017), a systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) that serves as a principal source of information for this guideline

- Evidence is limited, but guideline statements should generally be applicable to patients with co-occurring conditions, including those in integrated collaborative care or inpatient or outpatient medical settings.

- Topics that were not specifically included in the review and are outside of the guideline scope include:
  - Identification or treatment of attenuated psychosis syndrome or related syndromes of high psychosis risk
  - Treatment of individuals with schizoaffective disorder
  - Cost-effectiveness considerations

STEPS IN GUIDELINE DEVELOPMENT

- Systematic review conducted of available evidence (mostly by AHRQ for this guideline with a few additional specialized searches)
- Risk of bias (for individual studies) rated and strength of research evidence (overall for specific benefits/harms) determined
- Guideline statements (recommendations or suggestions) developed based on the relative balance of benefits and harms of the assessment or intervention
- Modified Delphi approach used to achieve group consensus
- External review completed by stakeholders
- APA Assembly and Board of Trustees approved guideline

RATING THE STRENGTH OF STATEMENT AND RESEARCH EVIDENCE

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Strength of statement describes the level of confidence that potential benefits of an intervention outweigh potential harms. This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences.

- A "*recommendation*" (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of an intervention clearly outweigh the harms.
- A "*suggestion*" (denoted by the numeral 2 after the guideline statement) indicates greater uncertainty. Although the benefits of the statement are still viewed as outweighing the harms, the balance of benefits and harms is more difficult to judge, or the benefits or the harms may be less clear. Patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made.

RATING THE STRENGTH OF STATEMENT AND RESEARCH EVIDENCE

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Strength of research evidence describes the level of confidence that findings from scientific observation and testing of an intervention reflect a true effect.

- **A** = High confidence. Further research is very unlikely to change the estimate of effect.
- **B** = Moderate confidence. Further research may change the estimate of effect and our confidence in it.
- **C**= Low confidence. Further research is likely to change the estimate of effect and our confidence in it.

Strength of research evidence is not the same as the magnitude of the effect as a result of the intervention.

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ASSESSMENT & TREATMENT PLANNING

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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1. **APA *recommends* (1C) that the initial assessment of a patient with a possible psychotic disorder include the reason the individual is presenting for evaluation; the patient's goals and preferences for treatment; a review of psychiatric symptoms and trauma history; an assessment of tobacco use and other substance use; a psychiatric treatment history; an assessment of physical health; an assessment of psychosocial and cultural factors; a mental status examination, including cognitive assessment; and an assessment of risk of suicide and aggressive behaviors, as outlined in APA's *Practice Guidelines for the Psychiatric Evaluation of Adults* (3rd edition).**

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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SUPPORTING EVIDENCE

- Expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves diagnostic accuracy, appropriateness of treatment selection, and treatment safety.

IMPLEMENTATION

- Understanding the patient's goals, their view of the illness, and treatment preferences gives a framework for recovery and serves as a starting point for person-centered care and shared decision-making.
- A detailed assessment is important in establishing a diagnosis, recognizing co-occurring conditions, identifying psychosocial issues, and developing a treatment plan to reduce associated symptoms, morbidity, and mortality.
- Tests such as imaging, genetic testing, or an EEG may help identify conditions with an increased risk of developing schizophrenia (e.g., 22q11.2 deletion syndrome) or that may mimic schizophrenia (e.g., neurosyphilis, Huntington's disease, Wilson's disease, anti-NMDA receptor encephalitis).
- See Tables 1 and 2 in the full text guideline for other recommended aspects of the initial psychiatric evaluation and detailed footnotes related to laboratory and physical health assessments.

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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Assessments to monitor physical status and detect concomitant physical conditions

Assessment	Initial or Baseline	Follow-up
Vital signs	Pulse, blood pressure	Pulse, blood pressure, temperature as clinically indicated
Body weight and height	Body weight, height, BMI	BMI every visit for 6 months and at least quarterly thereafter
Hematology	CBC, including ANC	CBC, including ANC if clinically indicated (e.g., with clozapine)
Blood chemistries	Electrolytes, renal function tests, liver function tests, TSH	As clinically indicated
Pregnancy	Pregnancy test for women of childbearing potential	
Toxicology	Drug toxicology screen, if clinically indicated	Drug toxicology screen, if clinically indicated

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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Assessments to monitor physical status and detect concomitant physical conditions (continued)

Assessment	Initial or Baseline	Follow-up
Electrophysiological studies	EEG, if indicated on the basis of neurological exam or history	
Imaging	Brain imaging (CT or MRI, with MRI being preferred), if indicated on the basis of on neurological exam or history	
Genetic testing	Chromosomal testing, if indicated on the basis of physical exam or history, including developmental history	

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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Assessments related to other specific side effects of treatment

Assessment	Initial or Baseline	Follow-up
Diabetes	Screening for diabetes risk factors, fasting blood glucose	Fasting blood glucose or hemoglobin A1C at 4 months after initiating new treatment and at least annually thereafter
Hyperlipidemia	Lipid panel	Lipid panel at 4 months after initiating a new antipsychotic medication and at least annually thereafter
Metabolic syndrome	Determine whether metabolic syndrome criteria are met	Determine whether metabolic syndrome criteria are met at 4 months after initiating a new antipsychotic medication and at least annually thereafter
QTc prolongation	ECG before treatment with chlorpromazine, droperidol, iloperidone, pimozide, thioridazine, or ziprasidone or in the presence of cardiac risk factors	ECG with significant change in dose of chlorpromazine, droperidol, iloperidone, pimozide, thioridazine, or ziprasidone or with the addition of other medications that can affect QTc intervals in patients with cardiac risk factors or elevated baseline QTc intervals.

ASSESSMENT OF POSSIBLE SCHIZOPHRENIA

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Assessments related to other specific side effects of treatment (continued)

Assessment	Initial or Baseline	Follow-up
Hyperprolactinemia	Screening for symptoms of hyperprolactinemia Prolactin level, if indicated on the basis of clinical history	Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactin Prolactin level, if indicated on the basis of clinical history
Antipsychotic-induced movement disorders	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia Assessment with a structured instrument (e.g., AIMS, DISCUS) if such movements are present	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia, at each visit Assessment with a structured instrument (e.g., AIMS, DISCUS) at a minimum of every 6 months in patients at high risk of tardive dyskinesia and at least every 12 months in other patients as well as if a new onset or exacerbation of pre-existing movements is detected at any visit

USE OF QUANTITATIVE MEASURES

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2. **APA *recommends* (1C) that the initial psychiatric evaluation of a patient with a possible psychotic disorder include a quantitative measure to identify and determine the severity of symptoms and impairments of functioning that may be a focus of treatment.**

USE OF QUANTITATIVE MEASURES

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SUPPORTING EVIDENCE

- Based on general principles of assessment and clinical care in psychiatric practice.

IMPLEMENTATION

- Patient self-report ratings and clinician-based ratings:
  - Provide a structured replicable way to document baseline symptoms
  - Determine which symptoms should be the target of intervention
  - Track treatment effects or the need for a shift in the treatment plan

- Example measures: 6-item and 30-item versions of Positive and Negative Syndrome Scale (PANSS-6, PANSS-30), Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS), World Health Organization Disability Schedule 2.0 (WHODAS 2.0)

EVIDENCE-BASED TREATMENT PLANNING

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3. **APA *recommends* (1C) that patients with schizophrenia have a documented, comprehensive, and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.**

SUPPORTING EVIDENCE

- Based on general principles of assessment and clinical care in psychiatric practice.

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IMPLEMENTATION

- A comprehensive and person-centered treatment plan will typically delineate treatments aimed at improving functioning, reducing positive and negative symptoms, and addressing co-occurring psychiatric symptoms or disorders.

- It is essential to consider both nonpharmacological and pharmacological treatment approaches and recognize that a combination of nonpharmacological and pharmacological treatments will likely be needed to optimize outcomes.

- **Subsequent guideline statements on pharmacotherapy and psychosocial interventions should not be viewed as standing alone.**

- Strategies to promote adherence are always important to consider in developing a patient-centered treatment plan.

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Other elements of a comprehensive and person-centered treatment plan

- **Addressing other goals of treatment** (e.g., social support networks; interpersonal, family, or intimate relationships; parenting status; living situation; past trauma or victimization; school or employment; financial considerations, including disability income support; insurance status; legal system involvement)
- **Intervening to reduce the risk of suicide and aggressive behaviors**
- **Determining the optimal setting of treatment**
- **Encouraging smoking cessation (if relevant) and treating other co-occurring substance use disorders**

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Other elements of a comprehensive and person-centered treatment plan (continued)

- **Adjusting treatment if clinically indicated for:**
  - **Other co-occurring psychiatric symptoms or diagnoses**
  - **Other specific circumstances such as correctional settings**
  - **Women who plan to become pregnant or are pregnant or breastfeeding**
- **Identifying additional needs** for history or mental status examination; physical examination; laboratory testing, imaging, electrocardiography, or other clinical studies (if indicated based on the history, examination, and planned treatments)
- **Collaborating with other treating clinicians** (including provision of integrated care) to avoid fragmentation of treatment efforts and assure care for co-occurring substance use disorders and physical health conditions

EVIDENCE-BASED TREATMENT PLANNING

- **Engaging patients, family members and others involved in the patient's life and providing them with information** (e.g. about treatment options, early symptoms of relapse, need for ongoing monitoring, coping strategies, case management services, and community resources, including peer-support programs)

- Even when a patient does not wish for a specific person to be involved in his or her care, the clinician may listen to information provided by that individual, as long as confidential information is not provided to the informant (American Psychiatric Association 2016).

- General information that is not specific to the patient can be provided (e.g., common approaches to treatment, general information about medications and their side effects, available support and emergency assistance).

EVIDENCE-BASED TREATMENT PLANNING

- To prevent or lessen a serious and imminent threat to the health or safety of the patient or others, the "Principles of Medical Ethics" (American Psychiatric Association 2013a) and HIPAA (Office for Civil Rights 2017a, 2017b) permit clinicians to disclose necessary information about a patient to family members, caregivers, law enforcement, or other persons involved with the patient.

- HIPAA also permits health care providers to disclose necessary information to the patient's family, friends, or other persons involved in the patient's care or payment for care when such disclosure is judged to be in the best interests of the patient and the patient is not present or is unable to agree or object to a disclosure because of incapacity or emergency circumstances (Office for Civil Rights 2017b).

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PHARMACOTHERAPY

ANTIPSYCHOTIC MEDICATIONS

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4. **APA *recommends* (1A) that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.**

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SUPPORTING EVIDENCE

- Based on the AHRQ review as well as other high-quality meta-analyses that examined findings from randomized controlled trials (RCTs) of antipsychotic medications in schizophrenia.
  - Consistent in showing benefits of antipsychotic medications for reducing positive symptoms.
  - Limited information from head-to-head clinical trials that suggests consistent superiority of a specific antipsychotic agent, with the possible exception of clozapine.
  - Not possible to note a preference for either SGAs or FGAs.
  - However, there may be clinically meaningful distinctions in response and tolerability of different antipsychotic medications in an individual patient.

SGA vs. SGA

- AHRQ meta-analysis (McDonagh et al. 2017): 1 good-quality systematic review that included 138 head-to-head RCTs (N=47,189), 31 observational studies (N=602,547), and 24 newer RCTs (N=6,672) (mostly fair quality studies).
  - SGAs did not differ in effects on social, occupational, or global functioning.
  - Older SGAs (clozapine, risperidone oral and LAI, olanzapine, quetiapine, and ziprasidone) were not found different from one another on a variety of quality of life measures, although small but significant improvements were seen from baseline.
  - Response was significantly more likely with olanzapine (odds ratio [OR] 1.71. 95% CI 1.11-2.68) and risperidone (OR 1.41, 95% CI 1.01-2.00) than quetiapine, based on a network meta-analysis of 46 head-to-head RCTs (low SOE)

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SGA vs. SGA (continued)

- All-cause mortality was not different between the SGAs in incidental reports in RCTs or retrospective cohort studies, but evidence was not available for the newest SGAs.
- There were no significant differences between the SGAs in the proportions of patients reporting overall adverse events, based on 72 RCTs and 31 drug comparisons.
- There are fewer data available for the newer drugs; results for these drugs should be interpreted with caution.

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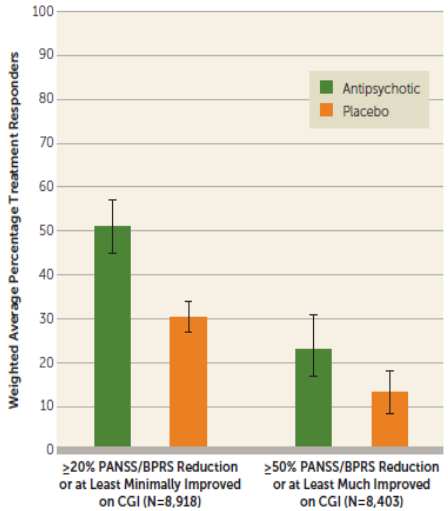
FGA vs. SGA

- AHRQ meta-analysis (McDonagh et al. 2017): 1 good-quality systematic review (111 RCTs and two cohort studies; N=118,503) and five RCTs (N=1,055) not included in the systematic review.
  - There was little evidence of a differential effect between FGAs and SGAs in quality of life outcomes.
  - There was no difference in response rates between haloperidol and risperidone (16 RCTs, N=3,452; relative risk [RR] 0.94, 95% CI 0.87-1.02; moderate SOE), aripiprazole (5 RCTs, N=2,185; RR 1.01, 95% CI 0.76-1.34; low SOE), quetiapine (6 RCTs, N=1,421; RR 0.99, 95% CI 0.76-1.30; low SOE), and ziprasidone (6 RCTs, N=1,283; RR 0.98, 95% CI 0.74-1.30; low SOE).
  - Response with olanzapine was significantly better than with haloperidol (14 RCTs, N=4,099; RR 0.86, 95% CI 0.78–0.96; low SOE).

ANTIPSYCHOTIC MEDICATIONS

- Leucht et al. 2017: A systematic review of 167 studies (total N=28,102)
  - Moderate benefit of antipsychotics, with positive symptoms improving the most but also improvements in negative symptoms, depression, quality of life, and social functioning

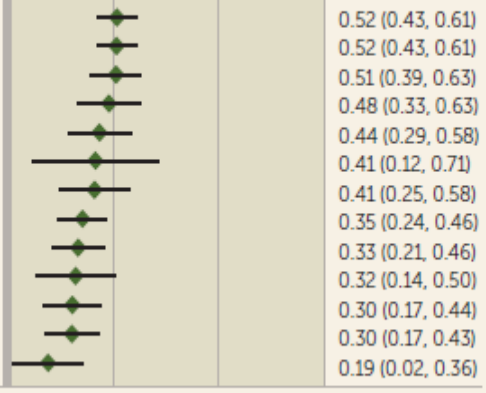
FIGURE 1. Proportions of Patients Taking Antipsychotics and Placebo Who Were at Least Minimally Improved and at Least Much Improved After Treatment[a]



[a] PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions Scale improvement rating. Error bars represent 95% credible intervals.

A: Positive Symptoms

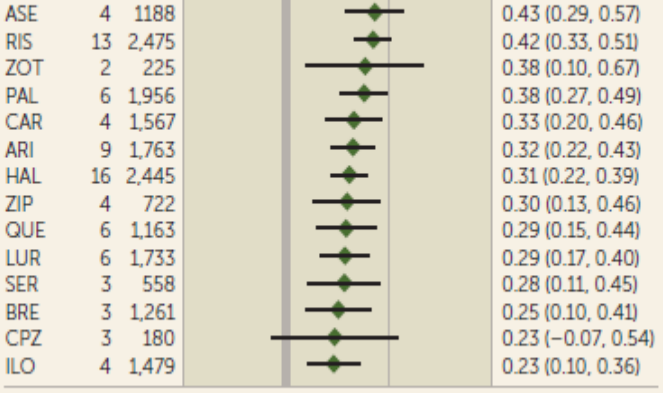
Drug[b]	Studies	N	SMD (95% CrI)
CPZ	1	54	1.00 (0.44, 1.56)
RIS	12	2,368	0.63 (0.54, 0.73)
HAL	14	2,286	0.52 (0.43, 0.61)
OLA	16	2,624	0.52 (0.43, 0.61)
PAL	6	1,956	0.51 (0.39, 0.63)
ASE	4	1,189	0.48 (0.33, 0.63)
QUE	6	1,237	0.44 (0.29, 0.58)
BLO	1	240	0.41 (0.12, 0.71)
ZIP	4	722	0.41 (0.25, 0.58)
ARI	8	1,694	0.35 (0.24, 0.46)
LUR	6	1,733	0.33 (0.21, 0.46)
SER	3	573	0.32 (0.14, 0.50)
CAR	4	1,567	0.30 (0.17, 0.44)
ILO	4	1,479	0.30 (0.17, 0.43)
BRE	3	1,259	0.19 (0.02, 0.36)



Heterogeneity SD=0.10 (95% CrI 0.05, 0.15)

B: Negative Symptoms

Drug[b]	Studies	N	SMD (95% CrI)
BLO	1	240	0.47 (0.19, 0.76)
OLA	16	2,625	0.46 (0.37, 0.54)
ASE	4	1188	0.43 (0.29, 0.57)
RIS	13	2,475	0.42 (0.33, 0.51)
ZOT	2	225	0.38 (0.10, 0.67)
PAL	6	1,956	0.38 (0.27, 0.49)
CAR	4	1,567	0.33 (0.20, 0.46)
ARI	9	1,763	0.32 (0.22, 0.43)
HAL	16	2,445	0.31 (0.22, 0.39)
ZIP	4	722	0.30 (0.13, 0.46)
QUE	6	1,163	0.29 (0.15, 0.44)
LUR	6	1,733	0.29 (0.17, 0.40)
SER	3	558	0.28 (0.11, 0.45)
BRE	3	1,261	0.25 (0.10, 0.41)
CPZ	3	180	0.23 (−0.07, 0.54)
ILO	4	1,479	0.23 (0.10, 0.36)



Heterogeneity SD=0.09 (95% CrI 0.02, 0.14)

ANTIPSYCHOTIC MEDICATIONS

- Huhn et al. 2019: An additional network meta-analysis of 402 placebo-controlled and head-to-head RCTs (total N=53,463)
  - Of 32 oral antipsychotics, the majority of treatment was associated with a statistically significant reduction in overall symptoms as compared with placebo, and there were few significant differences between individual drugs.
  - In terms of positive symptoms, negative symptoms, and depressive symptoms, the majority of the medications showed a statistically significant difference from placebo
  - Discontinuation rates for inefficacy paralleled the findings for treatment efficacy.
  - As in the Leucht et al. 2017 meta-analysis, side effect profiles differed considerably among the antipsychotic medications.

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IMPLEMENTATION

- Choice of an antipsychotic agent will typically occur in discussion with the patient about likely benefits and possible side effects of medication options.

- When choosing an antipsychotic medication, consider:
  - Patient preferences
  - Past responses to treatment (including symptom response and tolerability)
  - Medication's typical side effect profile
  - Presence of physical health conditions that may be affected by medication side effects
  - Other medication related factors such as available formulations, potential for drug-drug interactions, receptor binding profiles, and pharmacokinetic considerations.*

*Tables 3 to 9 in the full text of the guideline provide details on pharmacological properties of the antipsychotic medications and can assist in choice of an antipsychotic agent.

ANTIPSYCHOTIC MEDICATIONS

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First generation antipsychotic formulations	Trade name	Tablet or Capsule	Oral concentrate, Solution or Elixir	Short-acting injection	Other formulation
Chlorpromazine	Thorazine	✓		✓	
Fluphenazine	Prolixin	✓	✓	✓	
Haloperidol	Haldol	✓	✓	✓	
Loxapine	Loxitane	✓			Aerosol powder
Molindone	Moban	✓			
Perphenazine	Trilafon	✓			
Pimozide	Orap	✓			
Thioridazine	Mellaril	✓			
Thiothixene	Navane	✓			
Trifluoperazine	Stelazine	✓			

ANTIPSYCHOTIC MEDICATIONS

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Second generation antipsychotic formulations	Trade name	Tablet or Capsule	Rapidly dissolving tablet	Oral concentrate, Solution or Elixir	Short-acting injection	Other formulation
Aripiprazole	Abilify	✓	✓	✓		Tablet with ingestible event marker
Asenapine	Saphris; Secuado					Sublingual tablet; Transdermal system
Brexpiprazole	Rexulti	✓				
Cariprazine	Vraylar	✓				
Clozapine	Clozaril; FazaClo; Versacloz	✓	✓	✓		
Iloperidone	Fanapt	✓				
Lurasidone	Latuda	✓				
Olanzapine	Zyprexa	✓	✓		✓	
Paliperidone	Invega	✓				
Quetiapine	Seroquel	✓				
Risperidone	Risperdal	✓	✓	✓		
Ziprasidone	Geodon	✓			✓	

ANTIPSYCHOTIC MEDICATIONS

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First generation antipsychotics	Initial oral dose (mg/day)	Typical oral dose range (mg/day)	Maximum daily oral dose (mg/day)
Chlorpromazine	25 - 100	200 - 800	1,000 – 2,000
Fluphenazine	2.5 - 10	6 - 20	40
Haloperidol	1 - 15	5 - 20	100
Loxapine	20	60 - 100	250
Molindone	50 - 75	30 - 100	225
Perphenazine	8 - 16	8 - 32	64
Pimozide	0.5 - 2	2 - 4	10
Thioridazine	150 - 300	300 - 800	800
Thiothixene	6 - 10	15 - 30	60
Trifluoperazine	4 - 10	15 - 20	50

Much lower doses are typically needed for IM formulations of antipsychotic medications; check labelling for specific information.

ANTIPSYCHOTIC MEDICATIONS

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Second generation antipsychotics	Initial oral dose (mg/day)	Typical oral dose range (mg/day)	Maximum daily oral dose (mg/day)
Aripiprazole	10 - 15	10 - 15	30
Asenapine	10	20	20
Asenapine	3.8	3.8 - 7.6	7.6
Brexpiprazole	1	2 - 4	4
Cariprazine	1.5	1.5 - 6	6
Clozapine	12.5 - 25	300 - 450	900
Iloperidone	2	12 - 24	24
Lurasidone	40	40 - 120	160
Olanzapine	5 - 10	10 - 20	20
Paliperidone	6	3 - 12	12
Quetiapine	IR: 50; XR: 300	400 - 800	800
Risperidone	2	2 - 8	8
Ziprasidone	40	80 - 160	320

ANTIPSYCHOTIC MEDICATIONS
- RELATIVE SIDE EFFECTS

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	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyper-prolactinemia
Chlorpromazine	++	++	++	+++	+
Fluphenazine	+++	+++	+++	+++	+++
Haloperidol	+++	+++	+++	+++	+++
Loxapine	++	++	++	++	++
Molindone	++	++	++	++	++
Perphenazine	++	++	++	++	++
Pimozide	+++	+++	++	+++	+++
Thioridazine	+	+	+	+	++
Thiothixene	+++	+++	+++	+++	+++
Trifluoperazine	++	++	++	++	++
Aripiprazole	++	+	+	+	+
Asenapine	++	+	++	++	++
Brexpiprazole	++	+	+	+	+
Cariprazine	++	+	+	+	+
Clozapine	+	+	+	+	+
Iloperidone	+	+	+	+	++
Lurasidone	++	++	++	++	+
Olanzapine	++	++	+	+	++
Paliperidone	++	++	++	++	+++
Quetiapine	+	+	+	+	+
Risperidone	++	++	++	++	+++
Ziprasidone	++	+	+	+	++

+ = SELDOM; ++ = SOMETIMES; +++ = OFTEN

ANTIPSYCHOTIC MEDICATIONS
- RELATIVE SIDE EFFECTS

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	Anticholinergic	Sedation	Seizures	Orthostasis
Chlorpromazine	+++	+++	++	+++
Fluphenazine	+	+	+	+
Haloperidol	+	+	+	+
Loxapine	++	++	+	++
Molindone	+	++	+	+
Perphenazine	++	++	+	++
Pimozide	+	+	+++	+
Thioridazine	+++	+++	++	+++
Thiothixene	+	+	+++	+
Trifluoperazine	++	+	+	+
Aripiprazole	+	+	+	+
Asenapine	+	++	+	++
Brexpiprazole	+	++	+	+
Cariprazine	++	++	+	+
Clozapine	+++	+++	+++	+++
Iloperidone	+	++	+	+++
Lurasidone	+	++	+	+
Olanzapine	++	+++	++	++
Paliperidone	+	+	+	++
Quetiapine	++	+++	++	++
Risperidone	+	++	+	++
Ziprasidone	+	++	+	++

+ = SELDOM; ++ = SOMETIMES; +++ = OFTEN

ANTIPSYCHOTIC MEDICATIONS
- RELATIVE SIDE EFFECTS

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	QT prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities
Chlorpromazine	+++	++	+	++
Fluphenazine	++	++	+	+
Haloperidol	++	++	+	+
Loxapine	++	+	+	+
Molindone	++	+	+	+
Perphenazine	++	++	+	+
Pimozide	+++	+	+	+
Thioridazine	+++	++	+	+
Thiothixene	++	+	+	+
Trifluoperazine	++	++	+	+
Aripiprazole	+	+	+	+
Asenapine	++	++	++	++
Brexpiprazole	++	+	++	+
Cariprazine	++	++	+	+
Clozapine	++	+++	+++	+++
Iloperidone	+++	++	+	++
Lurasidone	+	+	++	++
Olanzapine	++	+++	+++	+++
Paliperidone	++	++	++	+
Quetiapine	++	++	+++	++
Risperidone	++	++	+	++
Ziprasidone	+++	+	+	+

+ = SELDOM; ++ = SOMETIMES; +++ = OFTEN

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

First generation antipsychotics	Metabolism	Additional considerations
Chlorpromazine	Major substrate of CYP2D6.	
Fluphenazine	Major substrate of CYP2D6.	
Haloperidol	Major substrate of CYP2D6 and CYP3A4.	
Loxapine		See REMS requirements for oral inhalation formulation (Adasuve) due to potential for bronchospasm.
Molindone	Major substrate of CYP2D6.	
Perphenazine	Major substrate of CYP2D6.	

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

First generation antipsychotics	Metabolism	Additional considerations
Pimozide	Major substrate of CYP2D6, CYP1A2, and CYP3A4. Avoid concomitant inducers or inhibitors. Conduct CYP2D6 testing before doses of more than 4 mg/day; adjust dose in CYP2D6 poor metabolizers.	Long drug half-life.
Thioridazine	Major substrate of CYP2D6. Avoid use with CYP2D6 inhibiting drugs.	Not for 1st line use due to risk of QTc prolongation. Avoid use if QTc interval is > 450 msec or with QTc prolonging drugs. Baseline ECG and serum potassium recommended. High doses can cause pigmentary retinopathy.
Thiothixene	Major substrate of CYP1A2.	
Trifluoperazine	Major substrate of CYP1A2.	

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Second generation antipsychotics	Metabolism	Additional considerations
Aripiprazole	Major substrate of CYP2D6 and CYP3A4. Adjust dose if poor metabolizer or with concomitant use of a CYP inhibitor or inducer.	Do not split/crush MyCite tablet. FDA safety alert for impulse control disorders (e.g., gambling, binge eating). Long drug half-life.
Asenapine	Major substrate of CYP1A2. Consider dose adjustment in smokers and with concomitant CYP1A2 inhibitor use.	Do not split, crush, or swallow dissolving tablet or eat/drink for 10 minutes after taking. Can cause oral hypoesthesia. Contraindicated with severe hepatic impairment.
Brexpiprazole	Major substrate of CYP2D6 and CYP3A4. Adjust dose if poor metabolizer or with concomitant use of a CYP inhibitor or inducer.	Adjust dose if significant hepatic or renal impairment. Long drug half-life.

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Second generation antipsychotics	Metabolism	Additional considerations
Cariprazine	Major substrate of CYP3A4. Adjust dose with concomitant use of a strong CYP3A4 inhibitor or inducer.	Long drug half-life. Not recommended for use with severe hepatic impairment.
Clozapine	Major substrate of CYP1A2. Adjust dose with concomitant use of strong CYP1A2 inhibitors and with strong CYP3A4 inducers. Smoking reduces clozapine levels via CYP1A2 induction. Clozapine levels can help in making dose adjustments.	Clozapine REMS program is required (https://www.clozapinerems.com/) with ANC monitoring. Increased salivation, orthostasis, and sexual dysfunction are common; constipation, paralytic ileus, and bowel infarction possible; seizures can occur with rapid dose increase or high dose; early in treatment, fever can occur, myocarditis is infrequent, and severe neutropenia and cardiomyopathy are rare. Adjust dose with significant hepatic or

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Second generation antipsychotics	Metabolism	Additional considerations
Iloperidone	Major substrate of CYP2D6; weak CYP3A4 inhibitor. Adjust dose with use of strong inhibitors and poor CYP2D6 metabolizers.	Titrate slowly with treatment initiation or resumption. Not recommended for use with severe hepatic impairment.
Lurasidone	Major substrate of CYP3A4; weak CYP3A4 inhibitor. Adjust dose with use of strong inhibitors or inducers.	Administer with food (≥350 calories). Adjust dose with significant hepatic or renal impairment. Some patients have dose-related creatinine increase.
Olanzapine	Major substrate of CYP1A2. Smokers may require a 30% greater daily dose due to CYP1A2 induction. Women may need lower doses.	Concomitant use of IM olanzapine with parenteral benzodiazepines is not recommended due to potential for excessive sedation and cardiorespiratory depression.

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Second generation antipsychotics	Metabolism	Additional considerations
Paliperidone		Uses OROS osmotic delivery system for tablet; do not split or crush. Not recommended with significant renal impairment.
Quetiapine	Major substrate of CYP3A4. Adjust dose for concomitant use of strong CYP3A4 inhibitors or inducers.	Do not split or crush extended release tablets. Give extended release tablets without food or <300 calories. Re-titrate dose for treatment gap of more than 1 week.

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Second generation antipsychotics	Metabolism	Additional considerations
Risperidone	Major substrate of CYP2D6. Adjust dose with concomitant use of inducers or inhibitors of CYP2D6.	Adjust dose with significant hepatic or renal impairment. Oral disintegrating tablets should not be split/crushed and contain phenylalanine.
Ziprasidone		Give capsules with >500 calories of food. Use with caution with significant hepatic impairment. Use IM with caution with significant renal impairment.

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Long-acting injectable antipsychotics

	Trade name	Available strengths in the U.S. (mg, unless otherwise noted)	Comments
Fluphenazine	Prolixin Decanoate	25/mL (5 mL)	Monitor for hypotension. In sesame oil; be alert for allergy.
Haloperidol	Haldol Decanoate	50/mL (1 mL, 5 mL), 100/mL (1 mL, 5 mL)	No more than 3 mL per injection site. In sesame oil; be alert for allergy.
Aripiprazole monohydrate	Abilify Maintena	300, 400	Rotate injection sites.
Aripiprazole lauroxil	Aristada Initio	675/2.4 mL	Use only as single dose to initiate Aristada treatment. Not for repeat dosing. Not interchangeable with Aristada. Avoid concomitant injection of Aristada Initio and Aristada into the same muscle.
Aripiprazole lauroxil	Aristada	441/1.6 mL 662/2.4 mL 882 /3.2 mL 1064/3.9 mL	Not interchangeable with Aristada Initio. Avoid concomitant injection of Aristada Initio and Aristada into the same muscle.

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Long-acting injectable antipsychotics

	Trade name	Available strengths in the U.S. (mg, unless otherwise noted)	Comments
Olanzapine	Zyprexa Relprevv	210, 300, 405	Requires use of FDA REMS program due to risk of post-injection delirium/sedation syndrome. Must give in registered healthcare facility with ready emergency response access. Patient must be observed for at least 3 hours post injection and accompanied upon discharge. (www.zyprexarelprevvprogram.com/public/Default.aspx)
Paliperidone palmitate	Invega Sustenna	39/0.25 mL, 78/0.5 mL, 117/0.75 mL, 156/mL, 234/1.5 mL	The two initial deltoid IM injections help attain therapeutic concentrations rapidly. Alternate injections (right and left deltoid muscle).
Paliperidone palmitate	Invega Trinza	273/0.875 mL, 410/1.315 mL, 546/1.75 mL, 819/2.625 mL	
Risperidone	Risperdal Consta	12.5, 25, 37.5, 50	Alternate injection sites.
Risperidone	Perseris	90/0.6 mL, 120/0.8 mL	Abdominal subcutaneous injection only Alternate injection sites. Inject only in area without skin conditions, irritation, reddening, bruising, infection, or scarring.

AMERICAN PSYCHIATRIC ASSOCIATION

Initiation

- The initial dose depends on such factors as the medication formulation, the characteristics of the patient, and whether a prior trial of antipsychotic medication has occurred.
- Once an initial dose is tolerated, the dose of most antipsychotic medications can be increased relatively quickly to a typical therapeutic dose.
  - A slower rate of dose titration is needed for patients with an initial episode of schizophrenia; in those who are older, severely debilitated, or sensitive to side effects; and for those with a preexisting central nervous system condition, including individuals with 22q11.2 deletion syndrome
- Clozapine requires a slow dose titration to minimize the risks of seizure, orthostatic hypotension, and excessive sedation.
  - See labelling for specific recommendations
  - Re-titration is needed after a gap in treatment

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

Partial or no response to antipsychotic treatment

- If showing response within several weeks of treatment initiation
  - Continue with the same medication and monitor for continued improvement.

- If no significant improvement after several weeks of treatment (e.g., <20% improvement in symptoms) or if improvement plateaus before achieving substantial improvement (e.g., >50% improvement in symptoms, minimal impairment in functioning)
  - Consider obtaining serum drug levels, if available and clinically useful
  - Determine whether factors are present that are influencing treatment response (e.g., concomitant substance use, rapid medication metabolism, difficulties with adherence)
    - If so, address them.
    - If not, consider short-term increase in dose or trial of another antipsychotic medication.

AMERICAN PSYCHIATRIC ASSOCIATION

Partial or no response to antipsychotic treatment (continued)

- If minimal or no response to two trials of antipsychotic treatment of 2–4 weeks' duration at an adequate dose
  - Recommend a trial of clozapine (see Statement 7).

- Augmentation treatment can also be considered
  - Note that a trial of clozapine should not be delayed by multiple attempts at augmentation therapy.
  - For patients with negative symptoms or depression, consider augmentation with an antidepressant medication

ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

- Monitoring for the presence of side effects is important throughout the course of antipsychotic treatment because treatment-emergent side effects may be…
  - Prominent with treatment initiation but dissipate, at least to some extent, with continued treatment (e.g., sedation, nausea)
  - Present initially and increase in severity with titration of the medication dose effects (e.g., hypotension, akathisia, QTc prolongation)
  - Emerging only after longer periods of treatment (e.g., tardive dyskinesia) or become more noticeable to patients as their acute symptoms are better controlled (e.g., sexual dysfunction).

- Clozapine has additional harms associated with its use, including sialorrhea, seizures, neutropenia (which can be severe and life-threatening), myocarditis, and cardiomyopathy.

AMERICAN PSYCHIATRIC ASSOCIATION

5. **APA *recommends* (1A) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.**

SUPPORTING EVIDENCE

- Primarily from clinical trials for antipsychotic efficacy in improving symptoms and quality of life as well as promoting functioning (see Statement 4)

CONTINUING MEDICATIONS

- Additional evidence from registry database studies
  - Kiviniemi et al. 2013: Nationwide prospective registry study (N=6,987) of first-onset schizophrenia. SGAs had significant decrease in all-cause mortality vs. no antipsychotic medication (OR 0.69; p=0.005) at 5 years.
  - Tiihonen et al. 2018: Nationwide prospective registry study (N=8,719) showed lowest rates of rehospitalization or death with continued antipsychotic treatment for up to 16.4 years. Discontinuation vs. continuous use associated with 174% higher risk of death (hazard ratio [HR] 2.74, 95% CI 1.09-6.89) and increased treatment failure (38% vs. 29.3%).

CONTINUING MEDICATIONS

- Evidence from meta-analyses of mortality data with antipsychotic treatment
  - Vermeulen et al. 2017: With follow-up longer than 1 year, mortality was increased with no antipsychotic medication vs. with antipsychotic treatment (pooled risk ratio 0.57; 0.46-0.76; $p<0.001$).
  - Vermeulen et al. 2019: With continuous clozapine, mortality was lower in long term follow-up (median 5.4 years) as compared to other antipsychotic treatment (mortality rate ratio 0.56, 95% CI 0.36-0.85; $p=0.007$).

CONTINUING MEDICATIONS

- Evidence from meta-analysis of discontinuation studies
  - Kishi et al. 2019: Relapse rates were lower with continued antipsychotic treatment vs. discontinuation of treatment (RR 0.47, 95% CI 0.35-0.62; $p<0.00001$; $I^2=31\%$; NNT=3).
  - Thompson et al. 2018: Relapse rates were lower in individuals who received maintenance treatment (19%; 95% CI 0.05%-37%; N=230) as compared to those who stopped antipsychotic medication (53%; 95% CI: 39%-68%; N=290).

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Benefits and risks of continuing treatment with an antipsychotic medication should be reviewed with the patient in the context of shared decision-making.
  - Benefits of continuing treatment include lower rates of relapse, rehospitalization, and death.
  - Risks of continuing treatment are heterogenous but can include greater rates of weight gain, sedation, and movement disorders.
    - It may be possible to mitigate some of these risks by preventive interventions (e.g., early intervention for weight gain, screening for lipid and glucose abnormalities) and careful monitoring for side effects of medication.

CONTINUING THE SAME MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

6. **APA *suggests* (2B) that patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.**

SUPPORTING EVIDENCE

- Based on studies for antipsychotic efficacy (see Statement 4) for continuing with antipsychotic treatment (see Statement 5)

CONTINUING THE SAME MEDICATIONS

- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Essock et al. 2006; Rosenheck et al. 2009)
  - At randomization, some individuals were assigned to medication they were already taking whereas others were assigned to a different antipsychotic medication.
  - Individuals who were assigned to a different antipsychotic medication (N=269) had an earlier time to all-cause treatment discontinuation than those assigned to continue the same antipsychotic medication (N=129; Cox proportional HR 0.69; p=0.007).
  - A change from olanzapine to a different antipsychotic medication was beneficial in terms of a reduction in weight but no other differences in outcome measures.

CONTINUING THE SAME MEDICATIONS

- Study of medication change to reduce metabolic risk (Stroup et al. 2011)
  - Individuals were followed for 24 weeks after being assigned to continue on their current olanzapine, quetiapine, or risperidone (N=106) or to switch to aripiprazole (N=109).
  - Individuals who switched medication were more likely to stop medication (43.9% vs 24.5%; p=0.0019) and treatment discontinuation occurred earlier in those who switched medication (HR 0.456, 95% CI 0.285-0.728; p=0.0010) although efficacy did not differ.
  - Modest but statistically significant improvements did occur in weight, serum non-HDL-C, and serum triglycerides in individuals who switched to aripiprazole

CONTINUING THE SAME MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- The typical approach is a gradual cross-taper in which the second antipsychotic medication is begun and gradually increased in dose as the initial antipsychotic medication is gradually tapered.

- Possible benefits and risks of a medication change should be reviewed with the patient in the context of shared decision-making.

- Careful monitoring is essential to avoid the risks of reduced adherence and clinical destabilization.

- Different side effects of medications may also emerge (e.g., insomnia with a shift to a less sedating medication).

AMERICAN PSYCHIATRIC ASSOCIATION

7. APA *recommends* (1B) that patients with treatment-resistant schizophrenia be treated with clozapine.

SUPPORTING EVIDENCE

- Based on multiple RCTs, observational studies (including clinical trials and studies using administrative databases), and meta-analyses

CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

AMERICAN PSYCHIATRIC ASSOCIATION

- AHRQ meta-analysis (McDonagh et al. 2017)
  - Independent of prior treatment history, clozapine improved core illness symptoms more than other SGAs (except for olanzapine) and was associated with a lower risk of suicide or suicide attempts than olanzapine, quetiapine, and ziprasidone.
  - In treatment-resistant patients, clozapine was associated with a lower rate of treatment discontinuation due to lack of efficacy than the other SGAs that were studied.
  - In terms of side effects, clozapine had a higher risk of study withdrawal due to adverse events than some other SGAs but did not show differences in overall rates of adverse events as compared to risperidone.

CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

AMERICAN PSYCHIATRIC ASSOCIATION

- Network meta-analysis of placebo-controlled and head-to-head RCTs (Huhn et al. 2019)
  - Of 32 antipsychotic medications, clozapine, amisulpride, zotepine, olanzapine, and risperidone had greater efficacy than many other antipsychotics for overall symptoms with the greatest benefit noted with clozapine (standardized mean difference [SMD] -0.89, 95% CrI -1.08 to -0.71)
  - Clozapine did better than placebo and the majority of the other antipsychotic medications in all cause discontinuation (SMD 0.76, 95% CrI 0.59-0.92) and effects on positive symptoms (SMD -0.64, 95% CrI -1.09 to -0.19), negative symptoms (SMD 0.62, 95% CrI -0.84 to -0.39), and depressive symptoms (SMD -0.52, 95% CrI -0.82 to -0.23).
- Administrative database and cohort studies also show benefits for clozapine but other meta-analyses show greater side effects with clozapine.

IMPLEMENTATION

- Treatment-resistant schizophrenia is commonly said to be present if a patient's symptoms have shown no response or partial and suboptimal response to two antipsychotic medication trials of at least 6 weeks each at an adequate dose of medication.
  - Some definitions specify using medications from different classes (e.g., SGA vs. FGA).
  - Suboptimal response can include significant symptoms or impairments in functioning.
- Slow titration of clozapine is essential to minimize the risks of seizure, orthostatic hypotension, and excessive sedation.
  - Starting dosage of 12.5 mg once or twice daily; increased by, at most, 25–50 mg/day; subsequent dose increases, if needed, of 100 mg or less, once or twice weekly.
  - Re-titration after any gap in treatment.

CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

AMERICAN PSYCHIATRIC ASSOCIATION

- Monitor for therapeutic benefits and side effects of clozapine throughout the dose titration phase
  - Although efficacy is often seen at a dosage of 300–450 mg/day, some individuals may need higher dosages of clozapine, to a maximum daily dose of 900 mg, for full response.
  - Useful to obtain blood levels of clozapine and its major active metabolite, norclozapine (N-desmethylclozapine).
  - Generally clozapine levels are greater:
    - in nonsmokers than in smokers
    - in heavy caffeine users than in nonusers
    - in women than in men
    - in older individuals than in younger individuals

CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

AMERICAN PSYCHIATRIC ASSOCIATION

- Clozapine REMS Program (www.clozapinerems.com) is required in the United States to minimize the risk of adverse events
  - ANC monitoring is mandatory for clozapine to be dispensed by a pharmacy
  - ANC monitoring is more frequent early in treatment because the highest risk of severe neutropenia (ANC <500/µL) occurs within the initial 6 months of clozapine treatment

- Although some patients may express concerns about burdens of required blood work and heightened initial monitoring, one large survey found that the vast majority of those taking clozapine for schizophrenia or schizoaffective disorder were adherent to treatment and found it helpful.

CLOZAPINE IN SUICIDE RISK

AMERICAN PSYCHIATRIC ASSOCIATION

8. APA *recommends* (1B) that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.

SUPPORTING EVIDENCE

- Based on retrospective cohort studies and a large pragmatic, open-label RCT.

CLOZAPINE IN SUICIDE RISK

- InterSePT trial (Meltzer et al. 2003; N=980)
  - In high risk patients, clozapine was superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide (HR 0.76, 95% CI 0.58-0.97) as well as preventing a worsening in suicidality severity (CGI-S; HR 0.78, 95% CI 0.61-0.99)
  - Fewer clozapine-treated patients attempted suicide (p=0.03); required hospitalizations (p=0.05) or rescue interventions (p=0.01) to prevent suicide; or required concomitant treatment with antidepressants (p=0.01) or with anxiolytics or soporifics (p=0.03).

- Wimberley et al. 2017: Population-based cohort study with 2,370 patients with treatment-resistant schizophrenia also found less self-harm with clozapine than other antipsychotic medications (HR 1.36, 95% CI 1.04-1.78).

CLOZAPINE IN AGGRESSIVE BEHAVIOR

AMERICAN PSYCHIATRIC ASSOCIATION

9. **APA *suggests* (2C) that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.**

CLOZAPINE IN AGGRESSIVE BEHAVIOR

SUPPORTING EVIDENCE

- Less robust than for use of clozapine for treatment-resistant schizophrenia or persistent risk of suicide.

- 2 studies (1 RCT, N=157; 1 open-label, N=44) in inpatients with schizophrenia spectrum disorders:
  - Clozapine was superior to haloperidol in reducing Overt Aggression Scale scores (Conley et al. 2003; Ratey et al. 1993).

- 4 RCTs (3 in inpatients, 1 in outpatients) reported superiority of clozapine:
  - vs. chlorpromazine (N=151, Claghorn et al. 1987; N=48, Niskanen et al. 1974)
  - vs. haloperidol (N=167, Citrome et al. 2001; N=71, Kane et al. 2001).

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- As in other circumstances in which patients do not appear to be responding fully to treatment, attention to adherence is crucial.

- A number of potentially modifiable risk factors (e.g., poor adherence, core symptoms of schizophrenia, co-occurring symptoms) can serve as targets of intervention in constructing a plan of treatment.

AMERICAN PSYCHIATRIC ASSOCIATION

10. APA *suggests* (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.

SUPPORTING EVIDENCE

- As with oral antipsychotic agents, LAIs are associated with improvements in symptoms in individuals with schizophrenia.
- However, meta-analyses of head-to-head RCTs comparing LAIs and oral antipsychotic agents show no significant differences in outcomes.
- In contrast, registry database studies, cohort studies, and mirror image studies show consistent benefits of LAIs as compared to oral antipsychotic medications.

LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

- Tiihonen et al. 2017: Prospective national database study in Sweden using individuals as their own controls found LAIs were associated with a 20%-30% lower risk of rehospitalization than oral formulations (HR 0.78, 95% CI 0.72-0.84 for total cohort; HR 0.68, 95% CI 0.53-0.86 for incident cohort).

- Tiihonen et al. 2011: Nationwide cohort of 2,588 consecutive patients in Finland with an initial admission for schizophrenia found LAI antipsychotic had a lower adjusted hazard ratio (aHR) than the equivalent oral formulation (aHR 0.36, 95% CI 0.17-0.75; p=0.007 and aHR 0.41, 95% CI 0.27-0.61; p=<0.0001, respectively) for rehospitalization and for all-cause discontinuation.

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Additional benefits of LAIs for patients:
  - A subjective sense of better symptom control.
  - Needing to take fewer medications daily offers greater convenience and fewer opportunities to miss a medication dose.
  - Reduced conflict with family members or other persons of support related to medication-related reminders.

- Patients, clinicians, and family members have greater assurance with LAIs that a patient will receive medication continuously as a missed visit or injection can be identified and rapidly addressed.

LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATIONS

AMERICAN PSYCHIATRIC ASSOCIATION

- Approaches to minimize discomfort with injections include:
  - Use of second-generation antipsychotics rather than first-generation antipsychotics, which have sesame oil-based vehicles.
  - Selection of an LAI with a small injection volume or lower administration frequency.

- Tables 7, 8, and 9 in the full text of the guideline and product labeling for each medication give additional information on:
  - Converting from an oral dose of medication to a corresponding dose of an LAI.
  - Information on administration technique, drug storage requirements and reconstitution.

ANTICHOLINERGIC MEDICATIONS FOR ACUTE DYSTONIA

AMERICAN PSYCHIATRIC ASSOCIATION

11. APA *recommends* (1C) that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.

ANTICHOLINERGIC MEDICATIONS FOR ACUTE DYSTONIA

AMERICAN PSYCHIATRIC ASSOCIATION

SUPPORTING EVIDENCE

- Based on expert opinion and supported by studies of the prophylactic use of anticholinergic medications to reduce the risk of acute dystonia in the initial phases of antipsychotic therapy.

- Arana et al. 1988: A review of 4 randomized, blinded trials (total N=232); 2 open trials (total N=856); 3 retrospective studies (total N=278)
  - Prophylactic use of an anticholinergic medication was associated with 1.9-fold reduction in risk of acute dystonia (14.8% without prophylaxis vs. 7.7% with prophylaxis).
  - The benefits of prophylactic anticholinergic medication were even more pronounced with a high-potency antipsychotic agent (e.g., haloperidol) yielding a 5.4-fold reduction in risk (46.8% without prophylaxis vs. 8.7% with prophylaxis).

ANTICHOLINERGIC MEDICATIONS FOR ACUTE DYSTONIA

AMERICAN PSYCHIATRIC ASSOCIATION

MEDICATION-INDUCED ACUTE DYSTONIA…

- "[a]bnormal and prolonged contraction of the muscles of the eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk developing within a few days of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms." (American Psychiatric Association 2013b, p. 711)

- Can be life-threatening when involving tongue or pharyngeal muscles.

- May be incorrectly attributed to catatonic signs or unusual behavior on the part of patients, and oculogyric crises can sometimes be misinterpreted as indicative of seizure activity.

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Diphenhydramine, a histamine receptor antagonist with anticholinergic properties
  - Typically, administered intramuscularly (25 to 50 mg IM).
  - Intravenously (25 to 50 mg IV) in emergent situations, as with acute dystonia associated with laryngospasm.
- Alternatively, benztropine (intramuscularly, 1 to 2 mg IM)

- Once the acute dystonia has resolved, it may be necessary to continue an oral anticholinergic medication such as benztropine or trihexyphenidyl to prevent recurrence, at least until other changes in medications can take place such as reducing the dose of medication or changing to an antipsychotic medication that is less likely to be associated with acute dystonia.

ANTICHOLINERGIC MEDICATIONS FOR ACUTE DYSTONIA

AMERICAN PSYCHIATRIC ASSOCIATION

- Be mindful of the potential for medication side effects and interactions with other medications that a patient is taking.
  - Dry mouth, blurred vision, precipitation of acute angle-closure glaucoma, constipation (and in some cases fecal impaction), tachycardia, urinary retention, effects on thermoregulation (e.g., hyperthermia in hot weather), impaired learning and memory, slowed cognition, and anticholinergic toxicity (with delirium, somnolence, and hallucinations).

AMERICAN PSYCHIATRIC ASSOCIATION

12. APA *suggests* (2C) the following options for patients who have parkinsonism associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.

SUPPORTING EVIDENCE

- Based on knowledge of pharmacology and pharmacokinetics and clinical experience.

AMERICAN PSYCHIATRIC ASSOCIATION

MEDICATION-INDUCED PARKINSONISM…

- "[p]arkinsonian tremor, muscular rigidity, akinesia (i.e., loss of movement or difficulty initiating movement), or bradykinesia (i.e., slowing movement) developing within a few weeks of starting or raising the dosage of a medication (e.g., a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms. (American Psychiatric Association 2013b, p. 709)"

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Lowering dosage of the antipsychotic medication
  - Symptoms of medication-induced parkinsonism are dose-dependent and generally resolve with discontinuation of antipsychotic medication.
- Switching to another antipsychotic medication
  - For individuals who are highly sensitive to medication-induced parkinsonism, clozapine may be considered.

- However, before making these changes, the benefits of reduced parkinsonism should be weighed against the potential for an increase in psychotic symptoms.

TREATMENTS FOR PARKINSONISM

AMERICAN PSYCHIATRIC ASSOCIATION

- The use of an anticholinergic medication such as benztropine or trihexyphenidyl is another option.
  - On a short-term basis, until a change in dose or a change in medication can occur, or
  - On a longer-term basis, if a change in dose or change in medication is not feasible
- Oral or intramuscular diphenhydramine can also be used acutely.

- Different symptoms of parkinsonism (e.g., rigidity, tremors, akinesia) may have a differential response to anticholinergic medications, and different treatment approaches may be needed to address each of these symptoms.
- See Table 10 “Medications for Treatment of Medication-Induced Parkinsonism” in the full text guideline for additional details.

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13. APA *suggests* (2C) the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.

SUPPORTING EVIDENCE

- Based on knowledge of pharmacology and pharmacokinetics
- A good-quality systematic review (Lima et al. 2002) identified some benefits of benzodiazepines for akathisia associated with antipsychotic therapy, but only 2 studies (total N=27) met the inclusion criteria.

TREATMENTS FOR AKATHISIA

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MEDICATION-INDUCED ACUTE AKATHISIA…

- "[s]ubjective complaints of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms." (American Psychiatric Association 2013b, p. 711)

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IMPLEMENTATION

- Lowering dosage of the antipsychotic medication or switching to another antipsychotic medication
  - Akathisia is sometimes difficult to distinguish from psychomotor agitation associated with psychosis, leading to a cycle of increasing doses of antipsychotic medication that lead to further increases in akathisia.
  - Before reducing the dose of medication or changing to another antipsychotic medication, the benefits of reduced akathisia should be weighed against the potential for an increase in psychotic symptoms.

TREATMENTS FOR AKATHISIA

- Benzodiazepine medications, including lorazepam and clonazepam
  - Somnolence, cognitive difficulties, and problems with coordination can be associated with benzodiazepine use.
  - Respiratory depression can be seen with high doses of a benzodiazepine, particularly in combination with alcohol, other sedating medications, or opioids.

- β-adrenergic blocking agent propranolol is another option
  - Important to monitor blood pressure with increases in dose and recognize that taking propranolol with protein-rich foods can increase bioavailability by 50%.

14. APA *recommends* (1B) that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).

SUPPORTING EVIDENCE

- Based on information from a good-quality systematic review (Solmi et al. 2018) on deutetrabenazine and valbenazine treatment and less robust clinical trials on tetrabenazine

- **Deutetrabenazine**
  - Two 12 week double-blind, placebo-controlled RCTs of moderate to severe TD with doses of 12-48 mg/day (Anderson et al. 2017; Fernandez et al. 2017).
  - Associated with a significant decrease in total AIMS scores (N=413; weighted mean difference [WMD] -1.44, 95% CI -0.67 to -2.19, $p<0.001$) and significantly greater rates of response (defined as an AIMS score reduction of at least 50%; RR 2.13, 95% CI 1.10-4.12, $p=0.024$; NNT=7, 95% CI 3-333, $p=0.046$) (Solmi et al. 2018).
  - Treatment response rate increased with treatment duration during the open-label extension phase (Hauser et al. 2019).
  - Trial completion rates and rates of adverse effects were similar to placebo

VMAT2 MEDICATIONS FOR TARDIVE DYSKINESIA

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- **Valbenazine**
  - 4 double-blind, placebo-controlled trials (Correll et al. 2017; Hauser et al. 2017; Kane et al. 2017; O'Brien et al. 2015; total N=488) of 4-6 weeks each using doses of 12.5-100 mg/day in moderate to severe TD.
  - Meta-analysis (Citrome 2017) showed valbenazine was associated with a significant decrease in total AIMS scores (N=421; WMD -2.07, 95% CI -1.08 to -3.05, $p<0.001$) and significantly greater rates of response (RR 3.05, 95% CI 1.81-5.11, $p<0.001$; NNT 4, 95% CI 3-6, $p<0.001$).
  - The rate of treatment response increased with treatment duration during the open label extension phase of the study (Factor et al. 2017).
  - In the KINECT3 study, a dose-response relationship was observed with greater benefit at doses of 80 mg/day as compared to 40 mg/day (Hauser et al. 2017).
  - Trial completion rates and adverse effect rates were similar to placebo.

- **Tetrabenazine**
  - A single-blind trial of 20 subjects (Ondo et al. 1999), a double-blind crossover trial of 6 subjects (Godwin-Austen and Clark 1971), and another double-blind crossover trial of 24 subjects (Kazamatsuri et al. 1972)
  - Benefits seen at dosages of up to 150 mg/day
  - More frequent adverse effects with tetrabenazine than placebo: drowsiness, sedation or somnolence, parkinsonism, insomnia, anxiety, depression, and akathisia.

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TARDIVE DYSKINESIA…

- "[i]nvoluntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles)" (American Psychiatric Association 2013b, p. 712), whereas tardive dystonia and tardive akathisia resemble their acute counterparts in phenomenology.

IMPLEMENTATION

- Identification of tardive dyskinesia and other tardive syndromes requires regular assessment through clinical examination or use of a structured evaluative tool (e.g., AIMS, DISCUS).
- Choice of a VMAT2 medication:
  - In general, deutetrabenazine or valbenazine is preferred over tetrabenazine because there are more side effects with tetrabenazine and the evidence base is more robust.
  - Tetrabenazine and deutetrabenazine are contraindicated in individuals with hepatic impairment.
  - Valbenazine is not recommended for use in individuals with severe renal impairment.
  - See Table 11 “Reversible inhibitors of human vesicular monoamine transporter type 2” in full text guideline for additional details.

VMAT2 MEDICATIONS FOR TARDIVE DYSKINESIA

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- In addition to use in moderate to severe or disabling tardive syndromes, may consider a VMAT2 inhibitor for patients with mild TD on the basis of such factors as patient preference, associated impairment, or effect on psychosocial functioning.

- Anticholinergic medications do not improve and may even worsen tardive dyskinesia in addition to producing significant side effects.

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Medical leadership for mind, brain and body.

PSYCHOSOCIAL INTERVENTIONS

COORDINATED SPECIALTY CARE PROGRAMS

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15. APA *recommends* (1B) that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.

SUPPORTING EVIDENCE

- Based on recent clinical trials as presented in the AHRQ review as well as an additional study (Anderson et al. 2018) that showed reduced mortality at 2 years for those who had participated in an early intervention program.

COORDINATED SPECIALTY CARE PROGRAMS

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- 4 Recent studies (total N=2,363) with up to 2-year treatment (typically 15-16 weeks) and up to 10-year follow-up (McDonagh et al. 2017)
  - Higher global functioning (pooled results of 3 RCTs; WMD 3.88, 95% CI 0.91-6.85; I^2=64%; moderate SOE).
  - More people (22%) working or in school (3 RCTs; RR 1.22, 95% CI 1.01-1.47; moderate SOE).
  - Significant benefit on quality of life scores (2 studies; pooled effect size 0.84, 95% CI 0.14-1.55; moderate SOE).
  - Lower likelihood of relapse (2 RCTs; RR 0.64, 95% CI 0.52-0.79; moderate SOE).
  - There was no significant difference in housing function, reduction in self-harm, or core illness symptoms (low SOE).

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IMPLEMENTATION

- Coordinated specialty care (CSC) programs, which are sometimes referred to as team-based, multicomponent interventions, integrate a number of evidence-based interventions into a comprehensive treatment package.

- Example: NAVIGATE program developed for the Recovery After an Initial Schizophrenia Episode (RAISE) Early Treatment research initiative
  - A collaborative, shared decision-making approach that incorporates family involvement and education, individual resiliency training, supported employment and education, and individualized medication treatment.

COORDINATED SPECIALTY CARE PROGRAMS

AMERICAN PSYCHIATRIC ASSOCIATION

- Consultation and implementation materials available to help guide the establishment of new programs with evidence-based approaches
  - https://www.nimh.nih.gov/health/topics/schizophrenia/raise/state-health-administrators-and-clinics.shtml
  - http://navigateconsultants.org/
  - https://ontrackny.org/Resources

- Additional studies of individuals with new onset psychosis or attenuated or high-risk psychosis syndromes are also available (see Addington et al. 2017; Cotton et al. 2016; Malla and McGorry 2019).

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16. APA *recommends* (1B) that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis (CBTp).

SUPPORTING EVIDENCE

- Multiple RCTs and meta-analyses as described in the AHRQ review.

COGNITIVE-BEHAVIORAL THERAPY FOR PSYCHOSIS

AMERICAN PSYCHIATRIC ASSOCIATION

- 3 Good quality systematic review with 89 studies (total N=7,154) and 5 recent studies (total N=823) with up to 3-year treatment and 3-year follow-up (McDonagh et al. 2017)
  - Better global and social/occupational function in the short term (GAF scale, 6 trials, mean difference [MD] 5.49, 95% CI 1.85-9.14; SOFAS scores, 2 trials, MD 9.11, 95% CI 6.31-11.91) (moderate SOE).
  - Better quality of life in the short term (2 trials; 12 to 24 weeks follow-up) but this not found with longer follow-up (2 trials; 18 to 24 months) (low SOE).
  - Fewer core illness symptoms (8 weeks to 5 years) (SMD -0.33, 95% CI -0.47 to -0.19; moderate SOE).
  - No difference in global and social/occupational function in long term (low SOE).
  - No meaningful difference in negative symptoms (low SOE).

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Cognitive-behavioral therapy for psychosis (CBTp) differs from CBT for other indications.
  - Focuses on guiding patients to develop their own alternative explanations for maladaptive cognitive assumptions that are healthier and realistic and do not perpetuate the patient's convictions regarding the veracity of delusional beliefs or hallucinatory experiences.

- Videos that demonstrate some of the approaches to CBTp available at:
  - I Can Feel Better, www.icanfeelbetter.org/cbtpskills

COGNITIVE-BEHAVIORAL THERAPY FOR PSYCHOSIS

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- CBTp can be:
  - Started in any treatment setting, including inpatient settings, and during any phase of illness.
  - Conducted in group as well as in individual formats, either in person or via Web-based delivery platforms.
  - Available to family members or other persons of support.

- The duration of treatment with CBTp has varied in research and clinical practice, with a range from 8 weeks to 5 years of treatment reported in the literature (McDonagh et al. 2017); many recommend a minimum treatment duration of 16 sessions.

PSYCHOEDUCATION

17. APA *recommends* (1B) that patients with schizophrenia receive psychoeducation.

SUPPORTING EVIDENCE

- Based on a good-quality systematic review (Pekkala and Merinder 2002) as described in the AHRQ review.

PSYCHOEDUCATION

- 1 Good quality systematic review with 10 studies (total N=1,125).
  - Better global functional outcomes at 1 year of follow-up (3 studies; MD -5.23, 95% CI -8.76 to -1.71; I^2=79%; low SOE).
  - Greater effect on relapse rates (with or without readmission) at 9 to 18 months of follow-up (6 studies; RR 0.80, 95% CI 0.70-0.92; I^2=54%; moderate SOE).
  - No difference in rates of harms (low SOE).

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IMPLEMENTATION

- **Formal, systematically delivered programs of psychoeducation**
  - Either in an individual or group format, often in conjunction with family members or other individuals who are involved in the patient's life.
  - Typically 12 sessions in clinical trials.
  - Typically done on an outpatient basis, but elements of formal psychoeducation programs can also be incorporated into inpatient care.
  - Includes key information about diagnosis, symptoms, psychosocial interventions, medications, and side effects as well as information about stress and coping, crisis plans, early warning signs, and suicide and relapse prevention.
- Useful information to patients and families as a part of psychoeducation available through SMI Adviser: https://smiadviser.org

18. APA *recommends* (1B) that patients with schizophrenia receive supported employment services.

SUPPORTING EVIDENCE

- Based on 1 study (Mueser et al. 2004) comparing supported employment with usual care as well as an RCT and meta-analysis (Cook et al. 2005; Kinoshita et al. 2013) comparing supported employment with other vocational interventions as described in the AHRQ review.

SUPPORTED EMPLOYMENT SERVICES

- 1 Good quality systematic review with 14 studies (total N=2,265) and 2 recent studies (total N=1,477) with up to 2-year treatment and up to 2-year follow-up (McDonagh et al. 2017)
  - Significantly better employment outcomes over 2 years using the individual placement and support (IPS) model
    - more likely to obtain competitive work (75% vs. 27.5%, p=0.001; moderate SOE)
    - less time to achieve competitive work (22 days less, p<0.001; low SOE)
    - more patients working >20 hrs per week (34% vs 13%, p=0.00)
    - more weeks of employment (24 more competitive and 11 more overall, p< 0.001)
    - longer tenure per individual job (4 weeks, p= 0.048)
    - more earnings ($2,078/month vs $617.59/month, p< 0.001)

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IMPLEMENTATION

- Supported employment differs from other vocational rehabilitation services
  - Provides assistance in searching for and maintaining competitive employment concurrently with job training, embedded job support, and mental health treatment.

- Individual placement and support (IPS)
  - Focus on rapid attainment of competitive employment.
  - Emphasis on patient preferences in the types of jobs sought, the nature of the services that are delivered, and the outreach that occurs with potential employers.
  - Individualized long-term job support and integration of employment specialists with the clinical team. Employment specialists also develop relationships with community employers and provide personalized benefits counseling to participants.

SUPPORTED EMPLOYMENT SERVICES

AMERICAN PSYCHIATRIC ASSOCIATION

- Information for clinicians and organizations wishing to learn more about supported employment or develop supported employment programs
  - SMI Adviser: https://smiadviser.org
  - NAVIGATE: https://navigateconsultants.org/manuals
  - Boston University Center for Psychiatric Rehabilitation: https://cpr.bu.edu
  - Substance Abuse and Mental Health Services Administration: Supported Employment Evidence-Based Practices (EBP) KIT: https://store.samhsa.gov/product/Supported-Employment-Evidence-Based-Practices-EBP-Kit/SMA08-4364

19. APA *recommends* (1B) that patients with schizophrenia receive assertive community treatment if there is a history of poor engagement with services leading to frequent relapse or social disruption (e.g., homelessness; legal difficulties, including imprisonment).

SUPPORTING EVIDENCE

- Based on information from the AHRQ review, which used a good-quality systematic review as a primary source (Marshall and Lockwood 2000) and also considered 1 additional RCT (Sytema et al. 2007).

ASSERTIVE COMMUNITY TREATMENT

AMERICAN PSYCHIATRIC ASSOCIATION

- 1 Good quality systematic review with 14 studies (total N=2,281) and 1 recent study (total N=118) with up to 2-year treatment and up to 2-year follow-up (McDonagh et al. 2017)
  - Less likely to be homeless (4 trials, OR 0.24, 95% CI 0.12-0.48) and not living independently (4 trials; OR 0.52, 95% CI 0.35-0.79) (moderate SOE).
  - Less likely to be unemployed (3 trials; OR 0.46, 95% CI 0.21-0.99; moderate SOE).
  - Core illness symptoms improved with both ACT and TAU, with no differences between groups (1 trial; also systematic review showed MD -0.14, 95% CI -0.36 to 0.08) (moderate SOE).
  - Less likely to be admitted to hospital (6 RCTs; OR 0.59, 95% CI 0.41-0.85, I^2=73%); duration of hospital stay also likely to be less
  - No improvement in social function vs TAU and no significant differences in arrests, imprisonment, and police contacts (low SOE)

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IMPLEMENTATION

- Assertive community treatment (ACT) is a multidisciplinary, team-based approach in which patients receive individualized care outside a formal clinical setting (e.g., patients' homes, workplaces, other community locations).
  - Personalized and flexible care that addresses the patient's needs and preferences without time limits or other constraints on services.
  - ACT teams working with a smaller number of individuals than traditional outpatient clinicians or case managers do.

ASSERTIVE COMMUNITY TREATMENT

AMERICAN PSYCHIATRIC ASSOCIATION

- Resources for organizations or state mental health systems that are implementing ACT programs
  - Center for Evidence-Based Practices 2019: www.centerforebp.case.edu/practices/act
  - Substance Abuse and Mental Health Services Administration 2008: https://store.samhsa.gov/product/Assertive-Community-Treatment-ACT-Evidence-Based-Practices-EBP-KIT/SMA08-4344
  - Thorning H, Marino L, Jean-Noel P, et al: Adoption of a blended training curriculum for ACT in New York State. Psychiatr Serv 67(9):940–942, 2016 27181739

20. APA *suggests* (2B) that patients with schizophrenia who have ongoing contact with family receive family interventions.

SUPPORTING EVIDENCE

- Based on 1 fair-quality systematic review (Pharoah et al. 2010) and 6 additional studies (Barrowclough et al. 1999; Dyck et al. 2000; Garety et al. 2008; Kopelowicz et al. 2012; Mayoral et al. 2015; Sellwood et al. 2001, 2007; Valencia et al. 2007) as described in the AHRQ review.

FAMILY INTERVENTIONS

- 1 Fair quality systematic review with 27 studies (total N=2,297) and 6 recent studies (total N=562) with up to 3-year treatment and 8-year follow-up (McDonagh et al. 2017)
  - Reduction in core illness symptoms in both groups (4 trials; SMD -0.46, 95% CI -0.73 to -0.20; low SOE).
  - Lower relapse rates at:
    - 0 to 6 months (23% vs. 37%, RR 0.62, 95% CI 0.41-0.92; low SOE)
    - 7 to 12 months (significantly lower) (31% vs. 45%, RR 0.67. 95% CI 0.54-0.83; moderate SOE).
    - 13-24 months (49% vs. 61%, RR 0.75, 95% CI 0.58-0.99; low SOE)
    - 5 years follow-up (78% vs. 94%, RR 0.82, 95% CI 0.72-0.94; low SOE).
  - No differences in social function/not being able to live independently and unemployment rates at 1 year.

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IMPLEMENTATION

- Family interventions are systematically delivered, extend beyond conveying of information, and focus on the future rather than on past events.
  - May include structured approaches to problem-solving, training in how to cope with illness symptoms, assistance with improving family communication, provision of emotional support, and strategies for reducing stress and enhancing social support networks.
  - May or may not include the patient and can be conducted with a single family or a multifamily group.

FAMILY INTERVENTIONS

AMERICAN PSYCHIATRIC ASSOCIATION

- Guidance on developing family intervention programs focused on psychoeducation
  - NAVIGATE Family Education Program: http://www.navigateconsultants.org/wp-content/uploads/2017/05/FE-Manual.pdf
  - Substance Abuse and Mental Health Services Administration: https://store.samhsa.gov/product/Family-Psychoeducation-Evidence-Based-Practices-EBP-KIT/sma09-4422
  - National Alliance on Mental Illness' Family-to-Family program, which has led to a significant expansion in the availability of family interventions: www.nami.org/Find-Support/NAMI-Programs/NAMI-Family-to-Family

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21. APA *suggests* (2C) that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.

SUPPORTING EVIDENCE

- Based on a fair-quality systematic review (Zou et al. 2013) and 1 additional fair-quality study (Hasson-Ohayon et al. 2007) as described in the AHRQ review as well as a meta-analysis of person-oriented recovery approaches (Thomas et al. 2018).

SELF-MANAGEMENT SKILLS AND RECOVERY-FOCUSED INTERVENTIONS

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- 1 Fair quality systematic review with 13 studies (total N=1,404) and 1 recent study (total N=210) with up to 1-year treatment and 2-year follow-up (McDonagh et al. 2017)
  - Greater likelihood of a reduction in core illness symptom severity based on the BPRS (5 RCTs; pooled WMD=-4.19, 95% CI -5.84 to -2.54; moderate SOE).
  - Greater reduction in the likelihood of experiencing relapse with completion of 10 or more sessions (OR 0.41, 95% CI 0.21-0.79; low SOE).
  - With 10 or fewer sessions, smaller and nonsignificant reduction in the risk of relapse (OR 0.67, 95% CI 0.39 to 1.15; low SOE).
  - No change in negative symptoms based PANSS – negative subscale. (low SOE).

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Recovery-focused interventions

- Thomas et al. 2018: A meta-analysis of person-oriented recovery approaches (7 RCTs, N=1,739) showed a modest improvement in person-oriented recovery, empowerment, and hope immediately after the intervention (effect size 0.24, 95% CI 0.04-0.44) and at follow-up (effect size 0.21, 95% CI 0.06-0.35).

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IMPLEMENTATION

- **Illness self-management training programs**
  - Goals include reducing the risk of relapse, recognizing signs of relapse, developing a relapse prevention plan, and enhancing coping skills to address persistent symptoms, with the aim of improving quality of life and social and occupational functioning.
  - Generally delivered in a group setting with sessions of 45-90 minutes each.
  - Better outcomes in patients who participated in at least 10 self-management intervention sessions.

SELF-MANAGEMENT SKILLS AND RECOVERY-FOCUSED INTERVENTIONS

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- **Recovery-focused interventions**
  - Can include similar approaches to illness self-management but are focused primarily on supporting a recovery-oriented vision that strives for community integration in the context of individual goals, needs, and strengths.
  - Include components and activities that allow participants to share experiences and receive support, learn and practice strategies for success, and identify and take steps toward reaching personal goals.
  - In a mix of group and individual formats as well as a mix of peer- and professional-led activities.

SELF-MANAGEMENT SKILLS AND RECOVERY-FOCUSED INTERVENTIONS

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- Resources
  - Toolkit for developing illness management and recovery-based programs in mental health: https://store.samhsa.gov/product/Illness-Management-and-Recovery-Evidence-Based-Practices-EBP-KIT/sma09-4463
  - Boston University Center for Psychiatric Rehabilitation: https://cpr.bu.edu
  - Center on Integrated Health Care and Self-Directed Recover: www.center4healthandsdc.org
  - Digital Opportunities for Outcomes in Recovery Service: https://skills.digitalpsych.org
  - Mental Health America: www.mhanational.org/self-help-tools
  - National Alliance on Mental Illness: www.nami.org
  - NAVIGATE: https://navigateconsultants.org/manuals
  - SMI Adviser: https://smiadviser.org/individuals-families
  - Temple University Collaborative on Community Inclusion: www.tucollaborative.org

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22. APA *suggests* (2C) that patients with schizophrenia receive cognitive remediation.

SUPPORTING EVIDENCE

- Based on 2 good-quality systematic reviews (Cella et al. 2017; Wykes et al. 2011); 1 good-quality trial (Deste et al. 2015; Vita et al. 2011), and 3 fair-quality trials (Farreny et al. 2012; Mueller et al. 2015; Twamley et al. 2012) as described in the AHRQ review.

COGNITIVE REMEDIATION

- 2 Good quality systematic review with 57 studies (total N=2,885) and 4 recent studies (total N=341) with up to 2-year treatment and 2-year follow-up (McDonagh et al. 2017)
  - Small positive effect on social, occupational, living situation and global function (6 RCTs; effect sizes ranged from 0.16 to 0.40; low SOE).
  - Small improvements in core illness symptoms (2 trials; N=153; SMD -0.62, 95% CI-1.01 to -0.24; low SOE).
  - Significant negative symptom improvement (1 systematic review of 18 RCTs; effect size -0.36, 95% CI -0.52 to -0.20; moderate SOE).

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IMPLEMENTATION

- Cognitive remediation approaches are intended to address cognitive difficulties that can accompany schizophrenia, with the aim of enhancing function and quality of life.
  - Typically in group or computer-based formats in an effort to enhance cognitive processes such as attention, memory, executive function, social cognition, or meta-cognition.
  - Some programs add aspects of social and communication skills to neurocognitive elements of remediation.
  - Web-based programs may provide options for patients without access to in-person programs.

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23. APA *suggests* (2C) that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.

SUPPORTING EVIDENCE

- Based on 3 fair-quality RCTs (Bartels et al. 2014; Mueser et al. 2010; Valencia et al. 2007, 2013) as described in the AHRQ review.

SOCIAL SKILLS TRAINING

- 3 Recent studies (total N=433) with up to 2-year treatment and 3-year follow-up (low SOE) (McDonagh et al. 2017)
  - Significantly better social function in patients receiving treatment for:
    - 6 months (SMD on GAF 1.60; 95% CI 1.19-2.02).
    - 1 year (SMD on GAF 2.02; 95% CI 1.53-2.52).
    - 2 years (SMD on Multnomah Community Ability Scale 0.65; 95% CI 0.36-0.95).
  - Greater improvement in core illness symptoms at:
    - 6 months (SMD on PANSS -1.50; 95% CI -1.92 to -1.09).
    - 2 years (SMD on PANSS -0.81; 95% CI -1.22 to -0.40).
  - Better negative symptoms (SMD range -0.45 to -1.30)

IMPLEMENTATION

- An overarching goal of improving interpersonal and social skills
  - can be delivered using cognitive-behavioral, social-cognitive, interpersonal, and functional adaptive skills training.
- Delivered in a group format.
- Group sessions can be augmented with video or technologically based interventions, in vivo community trips to practice social skills, and involvement of support people who are accessible, pleasant, and knowledgeable about the local environments' resources and limitations.
- Information about social skills training available for organizations that wish to develop such programs
  - https://www.mirecc.va.gov/visn5/training/sst/sst_clinicians_handbook.pdf

SUPPORTIVE PSYCHOTHERAPY

24. APA *suggests* (2C) that patients with schizophrenia be treated with supportive psychotherapy.

SUPPORTING EVIDENCE

- Based on studies that compared supportive psychotherapy with usual care in 1 good-quality systematic review (Buckley et al. 2015) as described in the AHRQ review.

SUPPORTIVE PSYCHOTHERAPY

- 1 Good quality systematic review with 5 studies (total N=822) (McDonagh et al. 2017)
  - No difference in global or social function (low SOE)

- Because the evidence related to its benefits is limited, supportive psychotherapy should not take precedence over other evidence-based psychosocial treatments (e.g., CSC, CBTp, psychoeducation)

AMERICAN PSYCHIATRIC ASSOCIATION

IMPLEMENTATION

- Supportive psychotherapy commonly aims to help patients cope with symptoms, improve adaptive skills, and enhance self-esteem.

- Examples of techniques include reassurance; praise; encouragement; explanation; clarification; reframing; guidance; suggestion; and use of a conversational, nonconfrontational style of communication.

- Typically, supportive psychotherapy is conducted in conjunction with medication management at a frequency that can vary from weekly to every few months depending on the needs of the individual patient.

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