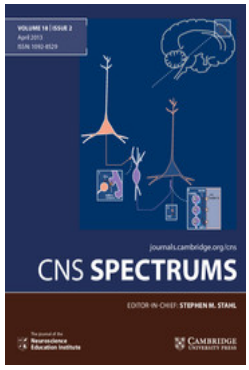

"Meta-guidelines" for the management of patients with schizophrenia

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CNS Spectrums / *FirstView* Article / May 2013, pp 1 - 13
DOI: 10.1017/S109285291300014X, Published online: 16 April 2013

CNS Spectrums, page 1 of 13. © Cambridge University Press 2013
doi:10.1017/S109285291300014X

REVIEW

"Meta-guidelines" for the management of patients with schizophrenia

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Guidelines for treating various conditions can be helpful in setting practice standards, but the presence of several sets of guidelines from different countries, experts, and settings, written at different times, can also create confusion. Here we provide a "guideline of guidelines" for the treatment of schizophrenia, or "meta-guidelines," which not only reconcile the various existing standards but also update them to include the use of several newer agents, most of which were marketed following the publication of existing standards.

Received 1 July 2012; Accepted 24 January 2013

Key words: Assessment, acute, maintenance, antipsychotics, depot.

Introduction

Managing patients with schizophrenia can be challenging, even for the most experienced of clinicians. Over the past decade, numerous experts in various countries have made recommendations in a number of published guidelines.[1–8] In addition, many institutions and hospitals have their own unpublished versions of guidelines for how to treat patients with schizophrenia. Often these recommendations contradict one another and are quickly out of date as the ever-increasing influx of new data accumulate and novel therapeutic agents are made available. In the "meta-guidelines" presented here, we have collected recommendations from various sources, both published and unpublished, and have updated and reconciled the differences from the Patient Outcomes Research Team (PORT), the Texas Medication Algorithm Project (TMAP), the American Psychiatric Association (APA), various state and federal hospitals, and current experts with decades of experience in treating this patient population in order to create an up-to-date "guideline of guidelines." These meta-guidelines have also been extensively reviewed by a number of anonymous peer reviewers. The goal was to create a comprehensive yet concise set of meta-guidelines that reflects all the current data in order to provide clinicians with an aid in the management of patients with schizophrenia at different stages of illness, including acute and maintenance phases. Although clinical judgment must be exercised in the care of individual patients, these meta-guidelines may serve to assist clinicians in choosing the most evidence-based and up-to-date strategies for addressing treatment selection, medication-induced side effects, treatment nonadherence, and other issues commonly encountered in treating patients with schizophrenia. These meta-guidelines are intended for rank-and-file patients with schizophrenia who are not violent, self-harming, or complicated by various comorbidities, as such patients are excluded from most evidence-based randomized controlled efficacy trials that are the basis of both previously published guidelines and also of the meta-guidelines provided here.[1–8] We will provide separate meta-guidelines for more complex, yet commonly encountered patients with schizophrenia, for use and guidance for what to do when the meta-guidelines provided here fail to provide adequate outcomes.[9–14] The meta-guidelines are presented here as Tables 1–15 and Figure 1.

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Table 1. *Overview and key points*

- Consider other psychiatric disorders in making a differential diagnosis
- Form and engage in a therapeutic alliance and encourage a supportive social network in order to improve long-term outcomes
- Reassess frequently, especially if a definitive diagnosis cannot be made or if diagnosis was made in the last 12 months
- Actively monitor for and treat comorbid conditions, including substance abuse
- Integrate treatments from multiple clinicians especially for comorbid conditions
- For first-episode schizophrenia, initiate treatment with atypical antipsychotics in lower doses
- Reserve conventional antipsychotics for use only after at least one unsuccessful trial with an atypical antipsychotic
- Strongly consider clozapine after two unsuccessful antipsychotic trials

Table 2. *Assessment*

- Evaluate causes for psychotic episode
- Interview individuals close to the patient if feasible
- Verify the diagnosis
- Complete psychiatric and general medical history and status
- Identify comorbid psychiatric and medical conditions
  - Substance use (eg, marijuana)
  - Infectious diseases (eg, syphilis, HIV)
- Evaluate general medical health
- Evaluate suicide risk
- Assess likelihood for dangerous, impulsive or aggressive behavior
- Identify patient strengths and limitations
- Assess baseline values that may be affected by antipsychotic treatment
  - Vital signs
  - Weight, height, body mass index (BMI), waist circumference
  - Extrapyramidal symptoms
  - Tardive dyskinesia (AIMS)
  - Cognition (MMSE)
  - Diabetes risk factors
  - Hyperprolactinemia
  - Lipid panel
  - ECG and serum potassium and magnesium
  - Ocular exam
  - Screen for changes in vision
  - Pregnancy and sexually transmitted disease (STD)
- Consider brain imaging for patients with a new onset of psychosis or atypical clinical presentation
- Engage in therapeutic alliance

Table 3. *Suggested physical and laboratory assessments to monitor physical status and detect concomitant physical conditions in patients with schizophrenia*

Assessment	Initial or baseline	Follow-up
Vital signs	Pulse, blood pressure, temperature	Pulse, blood pressure, temperature, every visit when possible and always as clinically indicated, particularly as medication doses are titrated
Body weight and height	Body weight, height, and calculate BMI; waist circumference when possible	BMI every visit for 6 months after changing antipsychotic medications and at least quarterly thereafter for outpatients; monthly for inpatients
Hematology	CBC	Weekly for clozapine-treated patients, and decrease intervals as appropriate; whenever indicated for other antipsychotics, when clinically indicated, and when considering possibility of neutropenia

Table 3. Continued

Assessment	Initial or baseline	Follow-up
Blood chemistries	Renal function tests (BUN/creatinine ratio) Liver function tests Thyroid function tests Electrolytes Lipid panel (see Table 4)	As clinically indicated
Infectious diseases	Test for syphilis Tests for hepatitis C and HIV	As clinically indicated
Pregnancy	Consider pregnancy test for women of childbearing potential	
Toxicology	Drug toxicology screen, heavy metal screen, if clinically indicated	Drug toxicology screen, if clinically indicated
Imaging/EEG	EEG, brain imaging (CT or MRI, with MRI being preferred), if clinically indicated	

Table 4. *Suggested physical and laboratory assessments to monitor possible treatment-induced side effects in patients with schizophrenia*

Assessment	Initial or baseline	Follow-up
Diabetes	Screening for diabetes risk factors; fasting blood glucose	Fasting blood glucose or hemoglobin a1c at no longer than 4 months after initiating a new treatment and annually thereafter for outpatients; more frequently (monthly to quarterly) for inpatients depending on the agent (with high-risk agents such as clozapine and olanzapine assessed more frequently)
Hyperlipidemia	Lipid panel	At least semi-annually, and more frequently for high risk agents such as clozapine and olanzapine
Triglycerides	Assessed monthly for the first 3 months	Assess annually once treatment is stabilized or more frequently for high-risk agents
Suspected congenital QTc prolongation (family history of fainting or early sudden death)	ECG and serum potassium and magnesium before treatment with thioridazine or pimozide; ECG before treatment with chlorpromazine, ziprasidone, or iloperidone in the presence of cardiac risk factors or concomitant QT-prolonging medications	ECG with significant change in dose of thioridazine, pimozide, and, in the presence of cardiac risk factors for ziprasidone, iloperidone, or addition of other medications (eg, chlorpromazine) that can affect QTc interval; annually for other patients
Hyperprolactinemia	Screening for clinical symptoms of hyperprolactinemia	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	Prolactin level, if indicated on the basis of clinical history
Extrapyramidal side effects, including akathisia	Clinical assessment of extrapyramidal side effects (dystonia and Parkinsonism)	Clinical assessment of extrapyramidal side effects weekly during acute treatment until antipsychotic dose is stable for at least 2 weeks, then at each clinical visit during stable phase

Table 4. Continued

Assessment	Initial or baseline	Follow-up
Tardive dyskinesia	Clinical assessment of abnormal involuntary movements [abnormal involuntary movement scale (AIMS), or similar scale]	Clinical assessment of abnormal involuntary movements every 6 months in patients taking conventional antipsychotics and every 12 months in those taking atypical antipsychotics In patients at increased risk, assessment should be done every 3 months with treatment using conventional antipsychotics and every 6 months with treatment using atypical antipsychotics
Cataracts	Clinical history to assess for changes in distance vision or blurred vision	Annual clinical history to assess for visual changes; ocular examination with visual acuity, cataract screening, and glaucoma screening recommended every 2 years for patients under age 40 and every year for patients over age 40
Therapeutic drug monitoring	Clinical assessment of drug serum levels to ensure they are within therapeutic range	Re-evaluation of serum drug levels, especially in cases where optimal drug efficacy is not obtained or medications known to alter levels are added

Table 5. *Treatment*

Setting and housing
● Hospitalize patients: ○ Who pose a threat to self or others ○ Who are unable to care for themselves ○ Who need constant supervision ○ For whom outpatient treatment is unsafe or ineffective ● Day or partial hospitalization, home care, family crisis therapy, crisis residential care, and assertive community treatment: ○ For patients who do not need formal hospitalization ○ Patients may be moved from one level of care to another as needed

Table 6. *Treatment plan*

- Formulate and implement a treatment plan
  - Identify treatment targets and use objective outcome measures to determine effectiveness of treatment
  - Set realistic expectations for what constitutes successful treatment
  - Use objective quantitative rating scales to monitor clinical status [eg, Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Negative Symptoms Assessment (NSA)]
- Develop a treatment alliance and promote treatment adherence
  - Relate patient's individual goals to treatment outcomes
  - Assess and address factors that affect adherence
    - Side effects
    - Lack of insight
    - Patient perception of medication risks and benefits
    - Cognitive/memory impairments
    - Therapeutic alliance
    - Financial, transportation, and other practical barriers
    - Cultural beliefs
    - Social support
  - Consider assertive outreach
- Provide patient and family education
  - Nature of the illness
  - Signs of relapse
  - Coping strategies

Table 6. Continued

- Treat comorbid conditions including nicotine dependence and other substance use disorders
  - Pharmacological treatments for alcohol abuse
  - Substance abuse rehabilitation programs
  - Nicotine replacement therapies
  - Bupropion (use with caution; may activate psychosis or be diverted for abuse)
  - Psychosocial interventions
- Ensure that services are coordinated
- Integrate treatments from multiple clinicians
- Document treatment over the course of illness

Table 7. *Acute-phase treatment*

- Reduce stressful environmental factors
- Educate patient
  - Nature and management of illness
- Establish relationship with patient's family
  - Refer family members to the National Alliance for the Mentally Ill (NAMI) (http://www.nami.org)
- Use of antipsychotics
  - Initiate treatment as soon as possible
  - Discuss medication risks and benefits with patient and obtain patient consent whenever possible
  - Minimize side effects
  - Select medication based on:
    - ➢ Severity of symptoms
    - ➢ Prior degree of symptom response
    - ➢ Prior experience of side effects
    - ➢ Dosing convenience (eg, once daily)
    - ➢ Side effect profile of medication
    - ➢ Patient's preference
    - ➢ Available formulation

    Note: Antipsychotics tend to have the same efficacy for positive symptoms in population-based studies.
  - Titrate as quickly as tolerated to the target therapeutic dose
  - If the patient is not improving, assess for:
    - ➢ Medication nonadherence
    - ➢ Rapid medication metabolism
    - ➢ Poor medication absorption
    - ➢ Consider measuring medication plasma concentration

    Note: If the patient has adequate medication plasma concentration but is not responding to treatment, raise dose or switch medications.
- Recommendations for acute-phase treatment
  - Rapid emergency treatments for acutely psychotic patients showing aggressive behaviors:
    - ➢ Short-acting parenteral antipsychotic with or without parenteral benzodiazepine and with or without a parenteral anticholinergic
    - ➢ Rapidly dissolving oral formulations or oral concentrates of atypical antipsychotics
  - Use atypical antipsychotics as first-line treatment
    - ➢ Atypical antipsychotics may have superior efficacy for treating cognitive, negative, and affective symptoms
    - ➢ Use lower doses in first-episode individuals because they are more sensitive to extrapyramidal side effects (EPS) and metabolic side effects
    - ➢ For some patients, conventional antipsychotics may be first choice

    Note: Conventional antipsychotics may be as effective as atypical antipsychotics for acute phase treatment.
  - Clozapine should be used in patients with persistent suicidality, violence, or substance abuse

  Note: Clozapine tends to be underutilized in some treatment settings, or utilized later than recommended (ie, following multiple antipsychotic treatment failures rather than just two or three)
  - Clozapine augmentation with an atypical or a conventional agent or electroconvulsive therapy (ECT) should be preceded by a treatment-refractory evaluation including:
    - ➢ Clozapine serum levels
    - ➢ Re-examining diagnosis
    - ➢ Substance abuse
    - ➢ Treatment adherence
    - ➢ Psychosocial stressors

    Note: Clozapine may also be superior for treatment-resistant symptoms.

Table 7. Continued

- Use long-acting injectable formulations of initial oral medication for patients with adherence issues, violent behavior, or even in early-onset schizophrenia
- Adjunctive medications in the acute phase
  - For comorbid conditions
    - Major depression

    Note: Some antidepressants may sustain or exacerbate psychotic symptoms
    - Other comorbidities
  - For certain symptom domains
    - Agitation
    - Aggression
    - Affective symptoms
    - Other symptoms

    Note: Benzodiazepines may be helpful for anxiety and agitation, particularly short-term, but monitor for dependence or abuse; also reported to increase mortality with long-term use
    - Mood stabilizers and beta-blockers may be useful for hostility and aggression
  - For sleep disturbances
  - For EPS, especially dystonia and Parkinsonism
    - For prophylactic treatment of EPS, consider:
      - Propensity of the antipsychotic to cause EPS
      - Patient preference
      - Patient's history of EPS
      - Other risk factors for EPS
      - Risk factors for and consequences of anticholinergic side effects
    - Consider lowering antipsychotic dose or switching to a different antipsychotic
  - For patients with persistent severe psychosis or suicidal ideation
    - Add electroconvulsive therapy (ECT) in the acute phase
- Special issues in the treatment of first-episode patients
  - Careful documentation of symptoms, which may evolve over time
  - Predictors of poor treatment response
    - Male gender
    - Prenatal or perinatal injury
    - Early onset
    - Severe hallucinations and delusions
    - Attentional impairments
    - Lack of affective component
    - Poor premorbid functioning
    - Longer duration of untreated psychosis
    - Development of EPS
    - Distressing emotional environment
  - Attempt to minimize risk of relapse in remitted patients
  - Alleviate exposure to cannabinoids and psychostimulants
  - Enhance stress management
  - Maintenance antipsychotic treatment
  - Patient education
    - Factors that increase relapse risk
    - Indefinite antipsychotic maintenance treatment
    - Medication discontinuation with close follow-up and a plan of antipsychotic reinstitution with symptom recurrence
  - Consider using a long-acting depot formulation
- Dosing
  - Many drugs dosed higher in practice than in clinical trials (eg, olanzapine, quetiapine, paliperidone ER, ziprasidone; see Tables 11 and 12)
  - Higher dosing for multi-episode patients
  - Maintenance doses lower than acute treatment doses
  - Lower doses in elderly and children
- Adequate treatment trial
  - Wait a minimum of 3 weeks and maximum of 6 weeks before making a major change to the treatment regimen
  - In patients showing a partial response, extend trial duration to 4–10 weeks

Table 8. *Stabilization phase treatment*

- Monitor medication response and dose for the next 6 months
- Assess adverse effects and adjust medication as needed to minimize them
- Continue psychotherapeutic interventions
- Patient and family education
  - Course and outcome of illness
  - Importance of treatment adherence
  - Realistic goal setting
- Arrange for continuity of care by assuring linkage of services between hospital and community treatment before the patient is discharged from the hospital

Table 9. *Stable phase treatment*

- Ongoing monitoring and assessment
  - EPS at each clinical visit
    - ➢ Abnormal involuntary movements
      - ✓ Every 6 months for patients taking conventional antipsychotics
      Note: Every 3 months for patients at increased risk
      - ✓ Every 12 months for patients taking atypical antipsychotics
      Note: Every 6 months for patients at increased risk
    - ➢ Weight and calculate BMI; waist circumference when possible
      - ✓ Every 3 months; quarterly thereafter for outpatients; monthly for inpatients
  - Triglycerides monthly in patients at high risk for metabolic complications or on high risk agents such as clozapine or olanzapine
  - Fasting glucose and glycosylated hemoglobin a1c at 3 months then annually for outpatients and low-risk antipsychotics; more frequently for inpatients and with high-risk agents
  - Electrolytes, renal, liver, and thyroid function annually
  - Vital signs, CBC, ECG; prolactin when clinically indicated (see Tables 3 and 4 for frequency)
  - Where feasible, maintain an alliance with individuals who are likely to notice resurgence of symptoms in the patient
- Psychosocial treatments in the stable phase
  - Select appropriate psychosocial treatments based on the patient's needs
    - ➢ Family interventions
    - ➢ Supported employment
    - ➢ Assertive community treatment (ACT)
    - ➢ Social skills training
    - ➢ Cognitive behavior therapy (CBT)
    - ➢ Weight management
    - ➢ Cognitive remediation
    - ➢ Peer support and peer-delivered services
    - ➢ Combined psychosocial interventions
- Antipsychotics in the stable phase
  - Administer conventional antipsychotics at a dose close to the EPS threshold
  - Atypical antipsychotics can usually be administered at doses that are therapeutic without inducing EPS
  - Weigh advantages of decreasing antipsychotic dose against risk of relapse
  - Differentiate between increasing agitation and akathisia
  - Evaluate negative symptoms
    - ➢ Secondary to Parkinsonian syndrome?
    - ➢ Untreated major depression?
    - ➢ Anticholinergics or other sedating agents?
- Adjunctive medications in the stable phase
  - Add psychotropic medications in order to:
    - ➢ Treat comorbid conditions
    - ➢ Treat aggression
    - ➢ Treat anxiety and other mood symptoms
    - ➢ Augment antipsychotic effects of the primary medication
    - ➢ Treat side effects
  - Weight management
    - ➢ Metformin
    - ➢ Topiramate

Table 9. Continued

- Use of ECT in the stable phase
  - Maintenance ECT may be useful
    - ➢ In patients who responded to acute ECT treatment
    - ➢ When pharmacologic prophylaxis is ineffective or intolerable
- Encourage patient to use self-help treatment organizations

Table 10. *Treatment in special circumstances*

- Treatment-resistant patients
  - Assess for adequate dose and treatment adherence
  - Consider clozapine
    - ➢ For patients with an inadequate response to 2 antipsychotics (at least one of which is an atypical antipsychotic)
    - ➢ For patients with persistent suicidality
  - Augmentation with another antipsychotic, anticonvulsant, or a benzodiazepine
  - Electroconvulsive therapy (ECT)
  - Cognitive remediation therapy (CRT)
  - Cognitive behavior therapy (CBT)
- Negative symptoms
  - Assess for factors that may contribute to negative symptoms
    - ➢ Treat with antipsychotics if secondary to positive symptoms
    - ➢ Treat with antidepressants if secondary to depression
    - ➢ Treat with anxiolytics if secondary to anxiety
    - ➢ Treat with antiparkinsonian agents or antipsychotic dose reduction if secondary to EPS
  - If negative symptoms are primary
    - ➢ Consider treatment with clozapine or other atypical antipsychotics
  - Adjunctive treatment for negative symptoms
    - ➢ SSRI, SNRI, or another antipsychotic
- Relapse
  - When taking oral antipsychotic
    - ➢ Switch to a different oral antipsychotic or increase dose of the current antipsychotic
  - If treatment nonadherence is suspected
    - ➢ Switch to a depot atypical antipsychotic
    - ➢ Switch to a depot conventional antipsychotic
- When taking a depot antipsychotic
  - ➢ Switch from depot conventional to depot atypical antipsychotic
  - ➢ Increase dose or frequency of injections
  - ➢ Supplement with oral formulation of the same antipsychotic until steady state is reached

Table 11. *Commonly used medications: conventional antipsychotics*

Medication *(brand)*	Recommended dose range (mg/day)*	Chlorpromazine equivalents (mg/day)**	Half-life (hours)
Phenothiazines			
Chlorpromazine *(Thorazine)*	300–1000	100	6
Fluphenazine *(Prolixin)*	6–20	2	33
Perphenazine *(Trilafon)*	12–64	10	10
Trifluoperazine *(Stelazine)*	15–50	5	34
Butyrophenone			
Haloperidol *(Haldol, Serenace)*	6–40*	2	21

**higher doses especially when failing to respond to doses up to 20 mg*

Table 11. Continued

Medication *(brand)*	Recommended dose range (mg/day)*	Chlorpromazine equivalents (mg/day)**	Half-life (hours)
Others			
Loxapine *(Loxitane)*	30–100	10	4
Thiothixene *(Navane)*	15–50	5	34

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

**Chlorpromazine equivalents represent the approximate dose equivalent to 100 mg of chlorpromazine (relative potency).

Table 12. *Commonly used medications: atypical antipsychotics*

Medication *(brand)*	Recommended dose range (mg/day)*	Half-life (hours)	Drug interactions*
Aripiprazole *(Abilify)*	10–30	75	Half dose with strong CYP3A4 or CYP2D6 inhibitors Double dose with CYP3A4 inducers
Asenapine *(Saphris)*	10–20	13–39	Cautiously approach coadministration with fluvoxamine and paroxetine; sublingual administration without food or drink for 10 minutes after administration
Clozapine *(Clozaril)*	150–600 (FDA max 900 mg)	12	Cautiously approach coadministration with drugs that involve CYP1A2, CYP2D6, and CYP3A4
Iloperidone *(Fanapt)*	12–24	18–33	Half dose with strong CYP2D6 and CYP3A4 inhibitors Half dose in poor metabolizers of CYP2D6
Lurasidone *(Latuda)*	40–160	18–31	Not recommended with strong CYP3A4 inhibitors or inducers Reduce dose with moderate CYP3A4 inhibitors; give after ≥350 calorie snack or meal
Olanzapine *(Zyprexa)*	10–30* *some settings allow 40 mg or more for difficult cases	33	Dose adjustment may be required with carbamazepine, fluvoxamine, fluoxetine, omeprazole, and rifampin
Paliperidone ER *(Invega)*	3–12	23	Dose adjustment may be required with carbamazepine and divalproex sodium
Quetiapine *(Seroquel, SeroquelXR)*	300–750* *some settings allow 1200 mg or more for difficult cases	6	A decrease in dose may be required with CYP3A and CYP2D6 inhibitors An increase in dose may be required with hepatic enzyme inducers such as carbamazepine, phenytoin, barbiturates, rifampicin, sulphonylureas, griseofulvin, and excess alcohol
Risperidone *(Risperdal)*	2–8	24	Dose adjustment may be required with cimetidine, ranitidine, clozapine, fluoxetine, paroxetine, carbamazepine, and other known enzyme inducers
Ziprasidone *(Geodon)*	80–160* *some settings allow up to 320 mg for difficult cases	7	Dose adjustment may be required with CYP3A4 inhibitors and inducers; give after ≥500 calorie snack or meal

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

Table 13. *Commonly used medications: other*

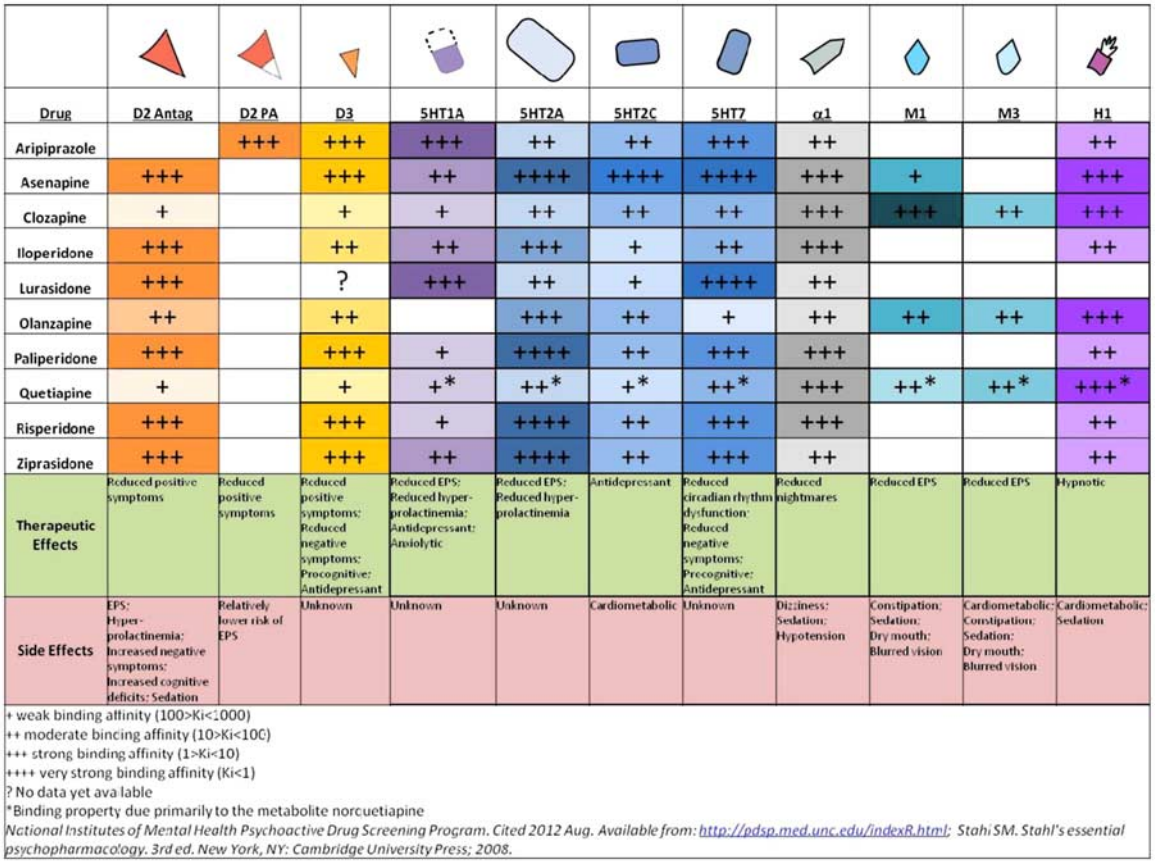
Medication *(brand)*	Recommended dose range*	Uses
Bupropion *(Wellbutrin)*	150–450 mg/day	Major depressive disorder, seasonal affective disorder, weight loss, smoking cessation. Issues include abuse potential, 2D6 inhibition
Benzodiazepines	Various	Agitation, insomnia, akathisia, anxiety
Benztropine *(Cogentin, generic)*	0.5–6 mg/day	Parkinsonism, EPS
Beta-blockers	Various	Akathisia, impulsivity, aggression
Carbamazepine *(Tegretol, generic)*	400–1200 mg/day	Seizures, mania, violence, treatment-resistant psychosis. Enzyme induction, 3A4, may significantly lower some antipsychotic levels
Diphenhydramine (*Benadryl*)	25–300 mg/day	Insomnia, EPS, EPS prophylaxis
Divalproex *(Depakote, DepakoteER, generic)*	Various	Seizures, mania, migraine prophylaxis, violence, treatment-resistant psychosis
Lamotrigine *(Lamictal, generic)*	Various	Seizures, bipolar depression, treatment resistant psychosis
Lithium *(Eskalith, generic)*	900–1800 mg/day	Mania
Metformin *(Fortamet, Glumetza, generic)*	1000–2000 mg/day	Diabetes mellitus, prophylaxis of weight gain
Oxcarbazepine *(Trileptal, generic)*	1200–2400 mg/day	Seizures, bipolar disorder
SNRIs	Various	Major depressive disorder, anxiety, chronic neuropathic pain
SSRIs	Various	Major depressive disorder, anxiety, obsessive compulsive disorder
Topiramate *(Topamax)*	200–400 mg/day	Partial onset or primary generalized tonic-clonic seizures Migraine prophylaxis, weight loss Not for treatment of mania
Trazodone *(Oleptro, Desyrel, generic)*	25–600 mg/day	Insomnia, depression at higher doses
Trihexyphenidyl *(Artane, generic)*	1–15 mg/day	Parkinsonism, EPS
Zolpidem *(Ambien)*	5–10 mg/day	Insomnia

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

Table 14. *Choice of medication in the acute phase of schizophrenia*

Patient profile	Atypical agents	Clozapine	Conventional agents	Long-acting injectables
First episode	Yes			Yes
Persistent suicidal ideation or behavior		Yes		Yes
Persistent hostility and aggressive behavior		Yes		Yes
Tardive dyskinesia	Yes, all atypical antipsychotics may not be equal in their lower or non-tardive dyskinesia liability	Yes		
History of sensitivity to extrapyramidal side effects	Yes, except risperidone			
History of sensitivity to prolactin-related side effects	Yes, except risperidone or paliperidone			
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia	Ziprasidone, lurasidone, asenapine, paliperidone ER, iloperidone, or aripiprazole			
Repeated nonadherence to pharmacological treatment				Yes

Table 15. *Receptor-binding profiles of atypical antipsychotics*



Drug	D2 Antag	D2 PA	D3	5HT1A	5HT2A	5HT2C	5HT7	α1	M1	M3	H1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	+		+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms: Reduced negative symptoms: Procognitive: Antidepressant	Reduced EPS: Reduced hyper-prolactinemia: Antidepressant: Anxiolytic	Reduced EPS: Reduced hyper-prolactinemia	Antidepressant	Reduced circadian rhythm dysfunction: Reduced negative symptoms: Procognitive: Antidepressant	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS: Hyper-prolactinemia: Increased negative symptoms: Increased cognitive deficits: Sedation	Relatively lower risk of EPS	Unknown	Unknown	Unknown	Cardiometabolic	Unknown	Dizziness: Sedation: Hypotension	Constipation: Sedation: Dry mouth: Blurred vision	Cardiometabolic: Constipation: Sedation: Dry mouth: Blurred vision	Cardiometabolic: Sedation

+ weak binding affinity (100>Ki<1000)
++ moderate bincing affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet ava lable
*Binding property due primarily to the metabolite norcuetiapine
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Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CBC, complete blood count; CBT, cognitive behavioral therapy; CRT, cognitive remediation therapy; CT, computerized tomography; ECG, electrocardiogram; ECT, electroconvulsive therapy; EEG, electroencephalogram; EPS, extrapyramidal symptoms; MRI, magnetic resonance imaging; NMS, neuroleptic malignant syndrome; SNRI, serotonin norepinephrine re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor.

Disclosures

Stephen Stahl has the following disclosures: Avanir, consultant, consulting fees; Biomarin, consultant, consulting fees; Forest, consultant, consulting fees; Genetech, consultant, consulting fees; Genomind, consultant, consulting fees; GSK, consultant, consulting fees; Jazz, consultant, consulting fees; Merck, consultant, consulting fees; Navigant, consultant, consulting fees; Novartis, consultant, consulting fees; Noveida Health, consultant, consulting fees; Otsuka, consultant, consulting fees; PamLambs, consultant, consulting fees; Reviva, consultant, consulting fees; Shire, consultant, consulting fees; Sunovion, consultant, consulting fees; Teva, consultant, consulting fees; Trius, consultant, consulting fees; Arbor Scientia, speakers bureau, speakers fee; Genomind, speakers bureau, speakers fee; Janssen, speakers bureau, speakers fee; Lilly, speakers bureau, speakers fee; Neuroscience Education Institute; PamLabs, speakers bureau, speakers fee; Pfizer, speakers bureau, speakers fee; Avanir, grant recipient, grant; Cenerex, grant recipient, grant; Dey Pharma, grant recipient, grant; Eli Lilly, grant recipient, grant; Forest, grant recipient, grant; Genomind, grant recipient, grant; Mylan, grant recipient, grant; Otsuka, grant recipient, grant; PamLabs, grant recipient, grant; Servier, grant recipient, grant; Shire, grant recipient, grant; Sunovion, grant recipient, grant; Takeda, grant recipient, grant. Dr. Stahl is also a board member of RCT Logic and GenoMind. Leslie Citrome has the following disclosures: Alexza, consultant, consultant fees; Alkermes, consultant, consultant fees; Avanir, consultant, consultant fees; Bristol-Myers Squibb, consultant, speaker, consultant and speaker fees, small amount of common stock; Eli Lilly, speaker, speaker fees, small amount of common stock; Envivo,

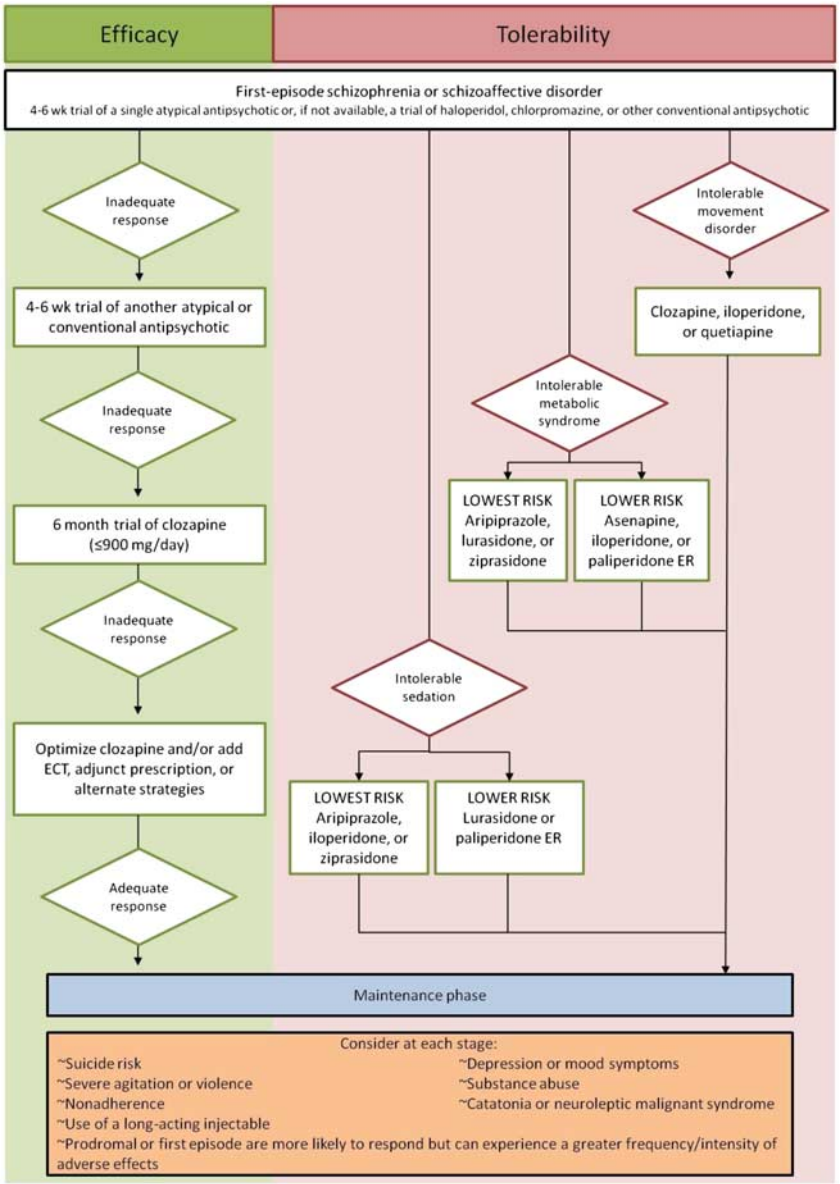

Figure 1. Antipsychotic algorithm for schizophrenia. For many acute inpatient settings with limited lengths of stay, trials of antipsychotics may be only 2–3 weeks prior to trying another. Many clinicians do not proceed to clozapine at all or until multiple failures with other antipsychotics; clozapine can be underutilized when this is the case. Response is generally defined as a clinically significant reduction in symptoms, eg, a modest 20% reduction in Positive and Negative Symptom Scale (PANSS) score observed at 2 weeks can predict a more robust 40% decrease in PANSS at 6 months. Lack of any response at 2 weeks is discouraging and requires reevaluation, including compliance and pharmacokinetics/therapeutic drug levels.

consultant, consultant fees; Forest, consultant, consultant fees; Genentech, consultant, consultant fees; Janssen, consultant, consultant fees; Lundbeck, consultant, consultant fees; Merck, speaker, speaker fees, small amount of common stock; Mylan, consultant, consultant fees; Novartis, consultant, speaker, consultant and speaker fees; Noven, consultant, consultant fees; Otsuka, consultant, speaker, consultant and speaker fees; Pfizer, speaker, speaker fees, small amount of common stock; Shire, consultant, consultant fees; Sunovion, consultant, speaker, consultant and speaker fees; J&J, small amount of common stock; AstraZeneca, speaker, speaker fees. Stephen Saklad has the following disclosures: Merck, speaker's bureau, honoraria; Novartis, speaker's bureau, honoraria; Sunovion, speaker's bureau, honoraria; Janssen, research (grant recipient), research support (grant). Jonathan Meyer has the following disclosures: Sunovion, speaker's

bureau, speaker's fees; BMS, speaker's bureau, speaker's fees; Genetech, advisor, consulting fees; Otsuka, advisor, consulting fees. The remaining authors do not have anything to disclose.

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