1.01 Approaches to Positive Psychotic Symptoms

QUICK CHECK

Introduction In community settings, the most common barriers to independent living, employment, and stable interpersonal relationships for patients suffering from schizophrenia spectrum disorders or other psychotic disorders are negative symptoms and cognitive deficits [1]. In contrast, severely mentally ill individuals, often incarcerated or chronically institutionalized, more frequently experience substantial barriers related to positive psychotic symptoms leading to problematic behaviors such as aggression or violence [2]. This is not to say that among the chronically institutionalized severely mentally ill population that positive psychotic symptoms are the only, or even majority, source of problematic behaviors. A survey conducted within the California Department of State Hospitals, a circa 7000-bed system dedicated to the treatment of conserved and forensically committed patients, reviewed 839 episodes of aggression or violence by 88 persistently aggressive inpatients and found that 54% of such episodes were impulsive, 39% were predatory or instrumental, and 17% were psychotically driven [3]. Nevertheless, amelioration or control of positive psychotic symptoms commonly forms the initial treatment focus among the severely mentally ill [4].

Ⓐ Dopamine and Positive Symptoms Elevated dopamine signal transduction in the meso-limbic dopamine pathway (ventral tegmentum to temporal lobe) and/or inadequate top-down glutamate modulation of dopamine signaling in the meso-limbic dopamine circuit by frontal lobe structures is thought to underlie the expression of such positive psychotic signs and symptoms as illusions, hallucinations, delusions and psychomotor agitation. Respectively, these views of the roles of dopamine and glutamate have been termed the dopamine and glutamate hypotheses of psychosis [5, 6].

Ⓑ Evaluation of Problem Behaviors As in all of medicine, the initial step in treatment is evaluation. Table 1.1 below outlines the initial evaluation of patients in whom preliminary data point to positive psychotic signs and symptoms as a principle source of problematic behaviors and impairment of psychosocial functioning.

Published online by Cambridge University Press

Table 1.1 Initial Review and Treatment of Severely Ill Psychotic Patients [13–17]

Decisions	Assessments	Brief Comments
Problem behaviors arise from psychosis • Yes, continue • No, alternate treatment approaches	Review prior history and assessments • Frequency of problem behaviors • Severity of problem behaviors • Patient factors associated with problem behaviors • Environmental factors associated with problem behaviors • Cause of latest decompensation • Comorbid violence factor - Substance abuse - Impulse dyscontrol - Predatory violence	
Patient poses an immediate risk • Yes, then decide level of control • No, then repeat risk assessment as clinically indicated	Evaluate need for segregation or restraint • Clinical observation • Clinical interview • Use of rating scale, e.g. DASA	Be familiar with relevant regulations/procedures governing seclusion or use of physical restraints
Physical conditions contribute to behavior risk • No, continue • Yes, treat physical condition	Physical evaluations • Psychomotor agitation • Evaluate for akathisia • Evaluate for pain or physical discomfort • Evaluate for delirium • Evaluate for intoxication or withdrawal • Evaluate for complex partial seizures • Evaluate sleep	
Abnormal labs contribute to problem behaviors • Yes, correct underlying abnormality • No, continue	Evaluation of laboratory data • Plasma glucose • Plasma calcium • WBC to rule out sepsis • Infectious disease screens as clinically indicated • Plasma sodium to rule out hyponatremia or hypernatremia • Oxygen saturation if suspect • Serum ammonia if suspect • Thyroid status • Sedimentation rate and C-reactive protein if history of inflammatory disease	Serum ammonia useful only if elements of delirium clinically present

A second important element in approaching the treatment of positive psychotic symptoms is evaluation of past treatment responses and of elements that may affect medication responses such as nonadherence to oral medications, altered medication kinetics or past pharmacodynamic issues. A systematic approach is described below in Table 1.2.

Table 1.2 Evaluation of Psychopharmacology for Severe Psychosis [4, 18, 19]

Decisions	Assessments	Brief Comments
Inadequate treatment contributes • Yes, adjust treatment • No, observe treatment response	Evaluate adequacy of current treatment • Duration (four to six weeks) • Dose (at least standard) • Dosing (e.g. with food if needed) • Adherence • Plasma concentrations • Hepatic inducers, e.g. carbamazepine or phenytoin	See Chapter 2 regarding use of plasma concentrations
Adverse medication effects present • Yes, adjust treatment or treat adverse effect • No, continue	Presence of adverse antipsychotic effects • Neurological ⇒ Akathisia ⇒ Dystonia ⇒ Parkinsonism • Sedation • Orthostasis Presence of adverse anticonvulsant effects • Ataxia • Tremor • Cognitive impairment Presence of adverse lithium effects • Polyuria • Nausea, vomiting, diarrhea • Tremor • Cognitive impairment Presence of adverse beta blocker effects • Hypotension • Bronchospasm • Bradycardia	• Many adverse effects respond to time or gradual dose reduction
Patient is responding to treatment • Yes, optimize and continue • No, alter treatment approach	Evaluate response to current treatment • Partial response • No response	• A partial response (< 20% to 30% improvement on the PANSS or BPRS) with minimal or no adverse effects argues for a higher-dose trial of the present antipsychotic • Failure of ≥ 2 adequate trials with at least one being a second-generation antipsychotic, argues for a clozapine trial • A partial response (small decline in BIS-11) with adequate anticonvulsant plasma concentrations argues for the addition of an anticonvulsant or other medication with distinct mechanism of action

Treatment of Psychosis After evaluation of the patient and of the patient's pharmacotherapy, the next step is to design the primary pharmacological approach to the patient's illness. In this context, it should be remembered that all medication trials have one of three endpoints: (1) the patient's illness improves; (2) intolerable adverse effects occur which cannot be adequately addressed to permit continuation of the medication trial; or (3) a point of futility is reached. An example of reaching a point of futility would be a patient whose olanzapine plasma concentration has reached circa 150 ng/ml without improvement over four to six weeks. By a plasma concentration of circa 200 ng/ml, olanzapine's receptor occupancy curve for dopamine D_2 receptors has become very flat, such that doubling the drug's plasma concentration would increase receptor occupancy by only an additional 2–3%. An approach to a choice of a principle medication trial is outlined below in Table 1.3.

Table 1.3 Principal Medication Choice (Excluding Elderly Demented) [4, 20, 21]

Decisions	Assessments	Brief Comments
Patient responding to optimal treatment • Yes, continue • No, adjust treatment	Patient's frequency and severity of problem behaviors are improving with adequate dose and plasma concentration, then continue present treatment	Note that although no response by weeks four to six of adequate to high-dose treatment portends a poor outcome, many patients show ongoing improvement for many weeks to months following a favorable, albeit partial, response to early treatment
Patient response absent • Yes, check adherence • No, consider alternate treatment	Patient has demonstrated an inadequate response in problem behavior's frequency or severity to present antipsychotic treatment • Adherent to oral medications • Not adherent to oral medications	• Preferred oral agents: olanzapine; fluphenazine; haloperidol • Preferred long-acting injectable agents: fluphenazine; haloperidol; paliperidone
Plasma concentrations are adequate • Yes, continue • No, adjust dosing or switch to depot	Dosing and plasma concentrations (oral medications)	• Olanzapine: 40–60 mg/d with plasma concentration 120–150 ng/ml • Fluphenazine: 20–60 mg/d with plasma concentration of 0.8–2.0 ng/ml • Haloperidol: 20–80 mg/d with plasma concentration of 5–18 ng/ml
Plasma concentrations are adequate • Yes, continue • No, adjust dosing	Dosing and plasma concentrations (depot medications)	• Fluphenazine: 25–100 mg/14d with plasma concentration of 0.8–2.0 ng/ml • Haloperidol: 200–300 mg/28d after loading with 200–300 mg weekly times three with steady state plasma concentrations 5–18 ng/ml • Paliperidone: 234 mg followed one week by 156 mg then continuing at 117–234 mg every 28d

Note that some patients may require higher than cited antipsychotic plasma concentrations to achieve stabilization, e.g. haloperidol up to 18 ng/ml or fluphenazine up to 4.0 ng/ml.

Ⓓ Geriatric Patients Due to risks of increased mortality among elderly patients suffering from neurocognitive disorders on antipsychotic exposure, starting with less dangerous alternatives and progressing toward antipsychotic treatment only as forced by failure of safer treatments is prudent [7]. An approach to the elderly demented patient who develops problematic behaviors related to positive psychotic symptoms is shown below in Table 1.4.

Table 1.4 Principal Medication Choice in Major Neurocognitive Disorder with Severe Psychosis [4]

Decisions	Assessments	Brief Comments
Antipsychotic precautions • Yes, consider alternatives • No, treatment with antipsychotic	Patient has increased risk with antipsychotics • Elderly • Vascular disease • Dementia with Lewy bodies • Parkinson's disease • Huntington's disease	
Increased risk with antipsychotics • Yes, select alternative • No, continue	Pharmacological alternatives to antipsychotics in patients with major cognitive disorders • Lithium • Valproic acid • Clonidine • Guanfacine • Memantine • Prazosin • SSRI antidepressant • Trazodone	
Alternative effective • Yes, continue • No, choose recommended antipsychotic	Evidence-based antipsychotics • Aripiprazole • Clozapine • Olanzapine • Quetiapine • Risperidone	• Antipsychotics increase mortality risk by 1.5- to 2.0-fold among elderly demented patients but may be worthwhile if alternative choices to control problem behaviors or violence are ineffective • For major cognitive disorder with Lewy bodies or Parkinson's disease, aripiprazole, clozapine and quetiapine appeared to be the best tolerated antipsychotics if pimavanserin is ineffective

SSRI: selective serotonin reuptake inhibitors.

Some authors have suggested tapering and discontinuing antipsychotic medications after major neurocognitive disorders have stabilized or progressed and/or to periodically test whether the prior antipsychotic dose is required to maintain stability. Given mortality risks in elderly demented patients, begin with the least dangerous options and progress to more dangerous options only as forced by treatment failure.

Ⓔ Adjunctive Medications In many cases of severe psychotic illness even optimal antipsychotic treatment may not adequately address all the patient's target symptoms. In this context, while the effect sizes of adjunctive treatments are modest, they may exert important effects on specific illness domains [8]. An outline of the approach to the use of adjunctive medications is given below in Table 1.5.

Table 1.5 Adjunctive Medications [20, 22]

Decisions	Assessments	Brief Comments
Mood stabilizers	• Irritability • Mood lability • Suicidality (lithium)	• VPA can be loaded at 20–30 mg/kg, reaching steady state at circa three days. • Lithium can be initiated at 600 mg once per day and titrated by 300 mg every other day to 900–1200 mg once per day. Lithium also can be loaded at 30 mg/kg up to 3000 mg by giving three ER doses at 1600, 1800 and 2000 hours on day one and then measuring a plasma concentration the following morning. If the plasma concentration is < 1.0 meq/l, then give 1200 mg IR q bedtime. If the plasma concentration is > 1.0 meq/l, then give 900 mg IR q bedtime. Once per day dosing spares renal function. Plasma concentrations should be 0.6–1.0 meq/l. • Lamotrigine may be helpful for dysphoric or negative symptoms but may promote hypomania or mania.
Clonazepam	• Agitation or anxiety incompletely responsive to primary treatment	Dose at 0.5–2.0 mg TID and then taper as the patient stabilizes. Avoid use in major neurocognitive disorders.
Selective serotonin reuptake inhibitor antidepressants	• Residual negative symptoms • Impulsive behavior or suicidality	Avoid use in patients in whom bipolarity may be present. May increase irritability in brain injured or autism patients. Avoid use of fluvoxamine with clozapine or olanzapine, as fluvoxamine may increase clozapine or olanzapine plasma concentrations five- to ten-fold.
Sedatives	• Insomnia worsens irritability, dysphoria, agitation and mood lability in many patients • Consider trials of zolpidem 5–10 mg at bedtime, eszopiclone 1–8 mg at bedtime, hydroxyzine 100 mg at bedtime, diphenhydramine 25–50 mg at bedtime or trazodone 25–100 mg at bedtime until the patient stabilizes	Note that antihistamines may cause idiosyncratic excitation and agitation and that diphenhydramine, but not hydroxyzine, will add to anticholinergic burden
Beta blockers	• Propranolol has excellent CNS penetration and the most evidence for response • ECT	Propranolol contraindicated in those with asthma. Monitor blood pressure to avoid hypotension. If adjunctive medications fail, then ECT should be considered. This is especially true if the patient is taking clozapine and continues to have inadequate response

CNS: central nervous system; ECT: electroconvulsive therapy.

Pro Re Nata Medications While a patient's routine treatment regimen is expected to be the mainstay of pharmacological treatment, fluctuations in symptom severity or behavior may require as needed or PRN medications. This is especially true early in treatment prior to achieving an optimal response from the patient's routine psychopharmacological treatment. Principles and practice in using PRN or STAT medications are described below in Table 1.6.

Table 1.6 PRN and STAT Medications [23]

Decisions	Assessments	Brief Comments
Patient unstable • No, continue • Yes, provide frequent PRN or STAT treatment	Estimate severity of agitation • Mild • Moderate • Severe	• For mild agitation, give lorazepam 1–2 mg or hydroxyzine 25–50 mg PO or IM every two hours not to exceed four doses per 24 hours. Titrate against agitation based on observation, not patient complaint. • For moderate to severe agitation, give antipsychotic ± lorazepam 2 mg ± diphenhydramine 25–50 mg or hydroxyzine 25–50 mg PO or IM not to exceed four doses per 24 hours. (See caveats following table.)
Stability improved • No, continue frequent PRN or STAT medications and adjust primary treatment • Yes, simplify PRN and STAT treatment and eventually discontinue	Estimate frequency of breakthrough agitation • Seldom • Moderately frequent • Very frequent	As determined by frequency and severity of breakthrough psychomotor agitation, gradually increase PRN dose interval and reduce the number of medications or doses prescribed. Once agitation is controlled, discontinue PRN orders for agitation.

Caveats: Whenever possible choose an antipsychotic that also is being used as part of the primary treatment. Available dose forms may limit this option.

The most commonly prescribed PRN and STAT antipsychotics are haloperidol, fluphenazine, chlorpromazine, olanzapine and risperidone. Of these, haloperidol, fluphenazine, chlorpromazine, olanzapine and ziprasidone are available in oral and injectable formulations.

Haloperidol and fluphenazine carry the highest risks of acute neurological adverse effects, especially given parenterally. Chlorpromazine carries a risk of orthostasis. Olanzapine is not effective orally due to an absorption time to peak plasma concentration of six to nine hours. Olanzapine, especially at higher parenteral doses, is prone to cause severe orthostasis if combined with a benzodiazepine, usually lorazepam. Intramuscular ziprasidone should be limited to two doses of 20 mg per 24 hours, especially if given in addition to oral ziprasidone.

Diphenhydramine, but not hydroxyzine, adds to anticholinergic burden.

Limit doses of potent dopamine antagonists in Parkinson's disease and major cognitive disorder with Lewy bodies. Limit benzodiazepine and anticholinergic use in all major neurocognitive disorders.

Treatment Resistance An important issue among individuals suffering from psychotic severe mental illness is that a substantial portion of such patients are treatment resistant [9]. John Kane et al. defined treatment-resistant schizophrenia according to very stringent criteria. These included failures of three antipsychotic trials of at least six weeks duration at doses of at least 1000 mg chlorpromazine equivalents, absence of any period of good functioning during the prior five years, and failure of a prospective high-dose (haloperidol 60 mg per day or greater) trial to produce a significant reduction in psychotic signs and symptoms [10]. Because the criteria created by Kane et al. are difficult to complete outside a research setting, treatment resistance has more recently been redefined as failure of two six-week trials of antipsychotic medications from two different classes at least 600 mg chlorpromazine equivalents. If one of the antipsychotics was a long-acting injectable formulation, then the trial duration should have been four months. One check of plasma concentration, as well as two other measures of medication adherence were defined as a minimal requirement. Optimal assurance of medication adherence was held to include two measurements of plasma concentration separated by at least two weeks without informing the patient prior to laboratory sampling [6].

The development of treatment resistance is of critical importance because the vast majority of antipsychotic medications become largely ineffective in this context. That is, response rates to almost all antipsychotic medications are 0–5% in treatment-resistant psychosis. High plasma concentration olanzapine does slightly better at 7%. Fortunately, in treatment-resistant psychotic patients clozapine at plasma concentrations of 350 ng/ml to circa 1000 ng/ml produces a decrease in psychotic signs and symptoms of at least 20–30% in up to 60% of such patients [10, 11]. Even clozapine, however, begins to show a decline in efficacy after resistant psychosis has been ongoing for > 2.8 years, arguing strongly for not delaying clozapine treatment among patients determined to be treatment resistant [12].

Summary Points

- Positive psychotic symptoms are frequently the cause of institutionalization or incarceration for complex severely mentally ill psychotic patients.
- Positive psychotic symptoms are driven by dopaminergic overactivity in the meso-limbic circuit, making dopamine antagonist antipsychotics the first step in treatment.
- Failure to respond to two adequate dopamine antagonist antipsychotic trials should strongly prompt consideration of treatment with clozapine.
- Even clozapine's superior antipsychotic efficacy begins to fade after about 2.8 years of treatment-resistant status, indicating that use of clozapine should not be delayed in such cases.

References

1. Kaneko, K. (2018). Negative symptoms and cognitive impairments in schizophrenia: two key symptoms negatively influencing social functioning. *Yonago Acta Med*, 61, 91–102.
2. Dack, C., Ross, J., Papadopoulos, C., et al. (2013). A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. *Acta Psychiatr Scand*, 127, 255–268.
3. Quanbeck, C. D., McDermott, B. E., Lam, J., et al. (2007). Categorization of aggressive acts committed by chronically assaultive state hospital patients. *Psychiatr Serv*, 58, 521–528.
4. Stahl, S. M., Morrissette, D. A., Cummings, M., et al. (2014). California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. *CNS Spectr*, 19, 449–465.
5. Merritt, K., McGuire, P., Egerton, A. (2013). Relationship between glutamate dysfunction and symptoms and cognitive function in psychosis. *Front Psychiatry*, 4, 151.
6. Howes, O. D., McCutcheon, R., Agid, O., et al. (2017). Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry*, 174, 216–229.
7. Maust, D. T., Kim, H. M., Seyfried, L. S., et al. (2015). Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*, 72, 438–445.
8. Galling, B., Roldan, A., Hagi, K., et al. (2017). Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World Psychiatry*, 16, 77–89.
9. Nucifora, F. C., Jr., Woznica, E., Lee, B. J., et al. (2018). Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. *Neurobiol Dis*, 131, 104–257.
10. Kane, J., Honigfeld, G., Singer, J., et al. (1988). Clozapine for the treatment-resistant schizophrenic. a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*, 45, 789–796.
11. Stroup, T. S., Gerhard, T., Crystal, S., et al. (2016). Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. *Am J Psychiatry*, 173, 166–173.
12. Yoshimura, B., Yada, Y., So, R., et al. (2017). The critical treatment window of clozapine in treatment-resistant schizophrenia: secondary analysis of an observational study. *Psychiatry Res*, 250, 65–70.
13. Ogloff, J. R., Daffern, M. (2006). The dynamic appraisal of situational aggression: an instrument to assess risk for imminent aggression in psychiatric inpatients. *Behav Sci Law*, 24, 799–813.
14. Hankin, C. S., Bronstone, A., Koran, L. M. (2011). Agitation in the inpatient psychiatric setting: a review of clinical presentation, burden, and treatment. *J Psychiatr Pract*, 17, 170–185.
15. Vaaler, A. E., Iversen, V. C., Morken, G., et al. (2011). Short-term prediction of threatening and violent behaviour in an Acute Psychiatric Intensive Care Unit based on patient and environment characteristics. *BMC Psychiatry*, 11, 44.
16. Volavka, J., Citrome, L. (2011). Pathways to aggression in schizophrenia affect results of treatment. *Schizophr Bull*, 37, 921–929.
17. Joshi, A., Krishnamurthy, V. B., Purichia, H., et al. (2012). "What's in a name?" Delirium by any other name would be as deadly. A review of the nature of delirium consultations. *J Psychiatr Pract*, 18, 413–418.
18. Ruberg, S. J., Chen, L., Stauffer, V., et al. (2011). Identification of early changes in specific symptoms that predict longer-term response to atypical antipsychotics in the treatment of patients with schizophrenia. *BMC Psychiatry*, 11, 23.
19. Lopez, L. V., Kane, J. M. (2013). Plasma levels of second-generation antipsychotics and clinical response in acute psychosis: a review of the literature. *Schizophr Res*, 147, 368–374.
20. Meyer, J. M., Cummings, M. A., Proctor, G., et al. (2016). Psychopharmacology of persistent violence and aggression. *Psychiatr Clin North Am*, 39, 541–556.
21. Siskind, D., Siskind, V., Kisely, S. (2017). Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can J Psychiatry*, 62, 772–777.
22. Lally, J., Tully, J., Robertson, D., et al. (2016). Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. *Schizophr Res*, 171, 215–224.
23. Stein-Parbury, J., Reid, K., Smith, N., et al. (2008). Use of pro re nata medications in acute inpatient care. *Aust N Z J Psychiatry*, 42, 283–292.