Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

In this article we discuss, with Dr. Michael Cummings, a new book he co-authored with Steven M. Stahl on the management of treatment-resistant psychosis. An increasing number of individuals with psychotic illnesses deal with homelessness, repeated incarceration, and associated trauma. There is limited access to care for these individuals, leading to poor prognosis. Also, there are many comorbid conditions including mood disorders and substance use. This book provides prescribers with information regarding treatment of the most challenging, treatment-resistant, severely psychotic patients.

Dr. David Puder, Dr. Kat Woo and Dr. Michael Cummings have no conflicts of interest to report.

This article is further discussed in the podcast "Psychiatry & Psychotherapy" **Episode 129** found on **iTunes**, **Google Play**, **Stitcher**, **Overcast**, **PlayerFM**, **PodBean**, **TuneIn**, **Podtail**, **Blubrry**, **Podfanatic**

Positive symptoms of psychosis

Positive symptoms of schizophrenia are hypothesized to be due to increased dopamine and decreased top-down glutamate modulation of dopamine signaling in the meso-limbic pathway. These positive symptoms dominate in severely mentally ill patients (i.e., chronically institutionalized) suffering from schizophrenia spectrum disorders. By contrast, in the community, the most difficult symptoms that keep them from working or living independently are the cognitive and negative symptoms. Antipsychotics are the most common medication seen in complex treatment-resistant populations.

Acute Agitation

For acute agitation there is often a PRN or STAT order, which a provider can determine is mild, moderate or severe. Severity is based on observation of physical level of activity: if they can sit still, if they are making threats or attacking people. An example of psychomotor agitation can be seen in a cat fighting going into a cat carrier. In a similar

way, humans can get agitated physically in response to psychotic internal thoughts and paranoia.

- For mild agitation psychosis give 1-2mg lorazepam or 25-50mg hydroxyzine PO or IM every 2 hours, a maximum of four times.
- For moderate or severe agitation, a provider can give oral or IM antipsychotic with 2mg of lorazepam and 25-50mg of diphenhydramine. This can be repeated 4 times every 2 hours in a 24-hour period, if needed. Ideally, this antipsychotic is the same as the one that will be given as the primary treatment.
- Antipsychotic options include:
    - IM haloperidol & fluphenazine (both have acute neurological adverse effects)
    - Chlorpromazine (orthostasis risk)
    - Ziprasidone
    - Olanzapine oral is not a good option for STAT use because it takes 6-9 hours to get to peak plasma concentration. IM olanzapine should not be mixed with lorazepam because of the increased risk of orthostasis.

How To Determine Treatment-Resistance

About 20-30% of those diagnosed with schizophrenia are treatment-resistant. There is not one unified criteria for treatment-resistant schizophrenia. But, according to the Consensus Criteria for Treatment-Resistance, it is defined as (Howes, et al 2016):

A) Failure to achieve 20-30% reduction in psychotic symptoms after two different antipsychotics trials of at least 6 weeks (if long-acting injectable, at least 4 months) at therapeutic dosages (dose equivalent of at least 600mg chlorpromazine).
B) Patient must have taken at least 80% of prescribed doses, determined by checking at least two sources of adherence (example: pill counts, medication administration record, patient/caregiver report)
C) Minimum of at least one measured antipsychotic plasma level to ascertain for treatment adherence
    a) Optimally, serum levels should be obtained without notifying the patient prior to blood draws on at least two occasions, separated by at least two weeks

Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

If a patient has an inadequate response on an antipsychotic and no adverse effects, titrate up the medication until one of the following three endpoints is reached:

- Intolerability ("*tolerability threshold*" - level at which 80% of patients have intolerable adverse effects)
- Maximum level ("point of futility"), at which further increases in dose doesn't produce any more benefit
- Positive treatment response

The table below outlines expected plasma levels (ng/ml) based on dose of antipsychotic (oral) and optimal antipsychotic plasma concentration ranges. This can help guide our treatment. But remember, there are always exceptions to this, as some patients may be slow/fast metabolizers or may be on other medications that can interact/affect antipsychotic metabolism. "Therapeutic threshold" is the minimum level of the drug at which below that, one is unlikely to find adequate response.

Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

MEDICATION	MINIMUM Response Threshold	POINT OF FUTILITY
Aripiprazole Average Expected Level = 11 x oral dose (mg/d)	110 ng/mL	500 ng/mL
Clozapine Nonsmokers: • Male: Average Expected Level = 1.08 x oral dose (mg/d) • Female: Average Expected Level = 1.32 x oral dose (mg/d)	350 ng/mL	1000 ng/mL
Fluphenazine Nonsmokers: Average Expected Level = 0.08 to 0.10 x oral dose (mg/d)	0.8 ng/mL	4.0 ng/mL
Haloperidol Average Expected Level = 0.78 x oral dose (mg/d)	2.0 ng/mL	18 ng/mL
Olanzapine Nonsmokers Average Expected Level = 2.0 x oral dose (mg/d)	23 ng/mL	150 ng/mL
Paliperidone Average Expected Level = 4.09 x oral dose (mg/d)	20 ng/mL	90 ng/mL
Risperidone + 9-OH Risperidone Average Expected Level = 7.0 x oral dose (mg/d)	15 ng/mL	112 ng/mL
Perphenazine Average Expected Level = 0.04 x oral dose (mg/d) Average Expected Level = 0.08 x oral dose (mg/d) (CYP 2D6 Poor Metabolizers)	0.81 ng/mL	5.0 ng/mL

Reference: Meyer JM, Stahl SM. Chapter 18: Therapeutic threshold, point of futility, oral concentration-dose relationships. **The Clinical Use of Antipsychotic Plasma Levels - Stahl's Handbooks.** New York, NY: Cambridge University Press, 2021.

Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

Mood stabilizers as adjunct treatment for treatment-resistant schizophrenia psychomotor agitation

At times, mood stabilizers can be used as adjunctive treatment for treatment-resistant schizophrenia. As mentioned above, we can also use serum levels of mood stabilizers to help guide treatment. The most common mood stabilizers used are lithium and valproic acid.

- For lithium, optimal serum concentration of the drug is between 0.8-1.2 meq/l.
    - Maintenance levels > 1.0 meq/l pose high risk of renal dysfunction and should not be used chronically (ok for acute mania, but afterwards should be gradually decreased).
- For valproic acid, the optimal serum concentration range is between 80-120 mcg/ml.
- Avoid carbamazepine (auto-inducer) and oxcarbazepine (literature doesn't support its efficacy, higher risk of hyponatremia).

Long-acting injectable (LAI) formulations of antipsychotics

Medication adherence to oral antipsychotics is <50% in outpatient settings. Long-acting injectables offer better adherence, which subsequently reduces crime/violence, decreases number of hospitailzations, increases longevity by decreasing rates of suicide. They are, nevertheless, still very underutilized, and should be considered more often because of these reasons.

These are the options for long-acting injectable formulations:

- aripiprazole (Abilify Maintena, Aristada Q4wks)
- fluphenazine Q2wks
- haloperidol Q4wks
- olanzapine (Relprevv Q2-4wks)
- paliperidone (Invega Sustenna -Q4wks, Invega Trinza -Q3mo, Invega Hafyera Q 6 months)

- risperidone (Risperdal consta -Q2ks, Perseris -Q4wks)

Clozapine: the gold standard for treatment-resistant schizophrenia

After a patient is determined to have treatment-resistant schizophrenia by said criteria mentioned earlier, it is imperative that the patient is started on clozapine promptly. Clozapine has a 40-60% response rate in those with treatment-resistant schizophrenia (compared to 0-7% response rates of other antipsychotics), but after ~2.8 years of treatment resistance, its superior efficacy begins to decline.

- Clozapine has additional effects independent of its antipsychotic effects:
    - Decreases suicidality
        - There is an estimated 10% overall suicide rate in schizophrenic patients.
        - InterSePT study showed that clozapine when compared to olanzapine, decreased time to suicidal event for both Type 1 (suicide attempt/hospitalization) and Type 2 (worsening suicidality). (Meltzer et al, 2003)
        - Clozapine has 5-fold reduction in suicide risk in schizophrenia, independent of its antipsychotic effects. Also, it reduces all-cause mortality despite its adverse effect profile.

    - Decreases aggression/violence/impulsivity
        - Possibly due to improvement in executive function from glutamate modulation in the prefrontal cortex.
        - A 12-week randomized double blind trial comparing treatment (clozapine vs. olanzapine vs. haloperidol) of chronically, physically assaultive male inpatients with schizophrenia/schizoaffective disorder in NY state hospital showed favorable decrease in aggression in those treated with clozapine (Krakowski et al, 2006).

- For those with persistent aggression and violence, underlying etiology of violence may stem from multiple factors, so consider other variables (environment, psychosocial stressors, inpatient staffing ratio/expertise, etc.) in addition to medications.
- 3 types of aggression:
    - Psychotic aggression
        - Stems from underlying positive symptoms of schizophrenia. Example: command hallucinations and/or persecutory/paranoid delusions. Unpredictable, but the most treatable type.
    - Impulsive aggression
        - Most common among inpatient psychiatric units. Example: Patient acts out due to something that causes them distress, such as after an argument. They do not think of the consequences associated with aroused emotional states (excited, angry, agitated).
    - Predatory aggression
        - Pre-planned, goal-oriented. 2nd most common type. Least responsive to psychopharmacological interventions.

Alternative treatment options

There is also some evidence to support effectiveness of adjunctive agents to clozapine for treatment-resistant schizophrenia. These agents include: other antipsychotics, Abilify (dopamine partial agonist), other dopamine (D2) agonists, valproic acid, beta-blockers (propranolol), SSRIs, stimulants, ECT. Motivational interviewing is not effective in this subset of the population so it should not be considered first-line therapy in patients with schizophrenia. Non-pharmacologic options to consider (limited data, but promising) for treatment-resistant schizophrenia includes ECT, rTMS, transcranial direct current stimulation, vagal nerve stimulation, and deep brain stimulation. A good therapeutic alliance helps to increase compliance.

Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

Negative symptoms of schizophrenia

The main goal of patients who display primarily negative symptoms and cognitive deficits is to target the dysphoric mood states and suicidality, as these are the most common reasons for decreased life expectancy among these patients.

- Consider long-acting injectable formulations for better adherence, decrease in hospitalizations, decreased suicidality by unpairing psychotic symptoms with emotional dysregulation & impulsivity.
- Do not delay treatment with Clozapine, as it significantly reduces suicide risk in schizophrenia, independent of its antipsychotic effects.
- Lithium reduces risk of suicide independent of its mood stabilizer properties. Plasma levels do not necessarily correlate with effectiveness in decreasing suicidality, but higher concentrations appear to be more protective.
- Consider antidepressants (if not vulnerable to bipolar disorder). Reduces suicidality and overall mortality.
- Other options: lamotrigine, lurasidone, quetiapine, pramipexole
- Get patient off anticholinergic medications and benzodiazepines

Targeting other comorbid conditions

Many patients with schizophrenia/treatment-resistant schizophrenia have underlying comorbid psychiatric conditions, including anxiety, obsessive-compulsive disorder, substance use disorders, insomnia, PTSD, and other medical comorbidities. Be a good psychiatrist and figure out the underlying cause of their symptoms before adding on medications.

- Insomnia
    - Sleep abnormalities and insomnia are common comorbid conditions seen in schizophrenia.
    - A recent meta-analysis that looked at sleep studies of schizophrenic patients vs. controls conducted between 1968 and 2014, found that schizophrenic patients have significantly shorter total sleep time, longer sleep onset latency, more wake time after sleep onset, lower sleep

efficiency, decreased stage 4 sleep, decreased slow wave sleep, and decreased duration/latency of REM sleep compared to controls.
    - Chan, M. S., Chung, K. F., Yung, K. P., & Yeung, W. F. (2017). Sleep in schizophrenia: A systematic review and meta-analysis of polysomnographic findings in case-control studies. *Sleep medicine reviews*, *32*, 69–84. https://doi.org/10.1016/j.smrv.2016.03.001
  - Good treatment options include: Z drugs (eszopiclone), circadian modulators (melatonin, ramelteon), low-dose doxepin, orexin receptor antagonists or lemvorexant suvorexant
- Substance use
  - Schizophrenic patients tend to be externally motivated, so use a flexible approach and focus on engagement, harm reduction, and contingency management.
  - Options include medication-assisted treatment (same as that for the general population) including naltrexone, acamprosate, suboxone, methadone, topiramate, etc.
  - Keep in mind that smoking tobacco (1A2 inducer) affects metabolism of certain psychotropics (clozapine, olanzapine, chlorpromazine, fluvoxamine).
  - Pearl: Amphetamines detection time is 48 hours, and false positives could include bupropion or nasal decongestants.

Childhood Schizophrenia Work Up

- Childhood schizophrenia is uncommon, so consider other causes of psychosis, including substance use. Urine drug screens will pick up some things like THC and meth that can cause psychosis, but there are substances that a urine drug screen will not pick up including spice or bath salts!

Psychosis: Management of Complex Treatment-Resistant Psychotic Disorders

Kat Woo, M.D., Michael Cummings, M.D., David Puder, M.D.

Cummings, M. A., & Stahl, S. M. (2021). *Management of complex treatment-resistant psychotic disorders*. Cambridge University Press.

Acknowledgments:
This article was supported by "Mental Health Education & Research".

Other citations:

Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical Antipsychotic Agents in the Treatment of Violent Patients With Schizophrenia and Schizoaffective Disorder. *Arch Gen Psychiatry.* 2006;63(6):622–629. doi:10.1001/archpsyc.63.6.622

Meltzer, H. Y., Alphs, L., Green, A. I., Altamura, A. C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M. Z., Kane, J., Krishnan, R., Lindenmayer, J. P., Potkin, S., & International Suicide Prevention Trial Study Group (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Archives of general psychiatry*, *60*(1), 82–91. https://doi.org/10.1001/archpsyc.60.1.82

Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., Bloomfield, M. A., Bressan, R. A., Buchanan, R. W., Carpenter, W. T., Castle, D. J., Citrome, L., Daskalakis, Z. J., Davidson, M., Drake, R. J., Dursun, S., Ebdrup, B. H., Elkis, H., Falkai, P., Fleischacker, W. W., … Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *The American journal of psychiatry*, *174*(3), 216–229. https://doi.org/10.1176/appi.ajp.2016.16050503