Antipsychotic Polypharmacy and Adjunct Agents for Treatment Resistant Schizophrenia and Schizoaffective Disorder: A Case Report and Review of Literature

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Introduction

- Schizoaffective disorder is more common in women and one-third as common as schizophrenia, with a lifetime prevalence of approximately 0.3% [1,2].
- Diagnostic criteria requires a mood component with patients experiencing positive and/or negative symptoms [3].
  - Positive symptoms: hallucinations, delusions, disorganized thinking or speech, and disorganized or abnormal movement [1].
  - Negative symptoms, including difficulty in creating plans, speaking, expressing emotions, or finding pleasure [1].
- This case presents a patient with treatment-resistant schizoaffective disorder who is unable to trial clozapine due to concerns for monitoring adherence.
- Treatment-resistant schizophrenia (TRS): Patients who fail two different adequate trials of antipsychotic drug therapy [4].
  - TRS occurs in one-fifth to one-half of patients diagnosed with schizophrenia [4].
  - Randomized trials have demonstrated clozapine is more efficacious compared to first- and other second-generation antipsychotics in treating TRS [5].
  - Clozapine is considered first-line therapy for TRS patients [4].

Case Presentation

A male military veteran in his 20s presenting with acute exacerbation of psychosis in the context of daily cannabis use.

- HPI:
  - Direct transfer from outside hospital
  - Symptoms
    - Visual hallucinations
    - Engaged in hyper-religious behavior
    - Mood lability with episodes of agitation and aggression
- PMHx: Schizoaffective Disorder, Cannabis Use Disorder
  - Discharged from the military 6.5 months earlier, after two years of service
  - Symptoms were noted to have started soon after discharge from the military and preceded but were further exacerbated after smoking *Cannabis sativa* following his first hospitalization
  - One previous psychiatric hospitalization at another facility two months prior to the current hospitalization
  - During his past hospitalization, he was diagnosed with schizoaffective disorder
  - Previous trials of lithium, valproic acid (VPA), risperidone, and olanzapine without adequate control of his psychotic symptoms
- FamHx: 1st degree relative (mother) with bipolar disorder
- Medications: Prior to admission - Loading doses of paliperidone long-acting injectable (LAI), VPA 1000 mg twice per day (BID).

Treatment and Outcome

Admission
- VPA was decreased to 750 mg BID to bring VPA level within the therapeutic range at 99 mcg/ml (reference range: 50 – 100 mcg/ml), and he received the first maintenance dose of paliperidone 234 mg.

During Hospitalization
- Mood continued to fluctuate, and residual psychosis persisted beyond that compatible with his stated goals.
- Haloperidol was initiated and titrated to 2 mg BID over a 3 day period.
- Responded well to this dosage of haloperidol and continued improving over a 9 day period.

Results on Discharge
- Resolution of distressing psychotic and mood symptoms with return to premorbid levels of functioning.
- He felt better equipped to pursue his goal of completing higher education with his GI bill.
- Declined specific substance use disorder treatment, he planned to abstain from cannabis.
- Abnormal Involuntary Movement Scale (AIMS) completed prior to discharge was 0.
- Paliperidone LAI 234 mg every 4 weeks, haloperidol 2 mg BID, and VPA 750 mg BID with plan for outpatient follow-up

Differential Diagnosis and Discussion

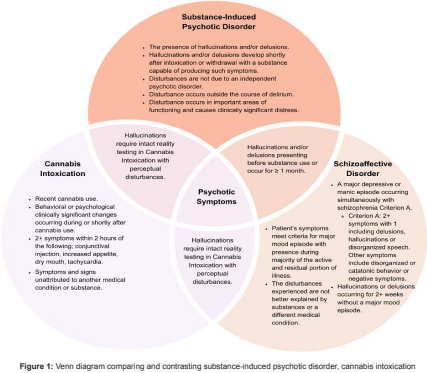

Figure 1: Venn diagram comparing and contrasting substance-induced psychotic disorder, cannabis intoxication and schizoaffective disorder [1]

- American Psychiatric Association (APA) guidelines: 1A recommendation: Patients with schizophrenia to be treated with antipsychotic medications and monitored for effectiveness and continue treatment if responsive [6].
- Current treatment guidelines recommend against antipsychotic polypharmacy (APP)
- Recent studies have demonstrated utility in APP and frequency ranging from 19.6% to 40% [7, 8, 9].
- A systematic review and meta-regression - most common combination was a first- generation antipsychotic and second-generation antipsychotic at 42.4% [9].
- Research has shown a decreased risk for psychiatric hospitalization in patients on low-dose and high-dose APP [7].

- Lamotrigine
  - Superior to placebo in clozapine augmentation [10]
  - Titration time approx 8 weeks [11]
  - Titration to 200 mg within 11 days - limitations: small cohort and study design [11]
    - Needed rapid symptom reduction
    - Results found were evaluating the augmentation of clozapine
- Minocycline
  - Adjunctive medication for schizophrenia [12]
  - Meta-analysis - greater efficacy in treatment with minocycline adjunctively versus placebo [13]
  - Reducing total symptoms, negative symptoms, and general symptoms, without improvement in positive symptoms or cognitive domains [13]
    - Primarily experiencing positive symptoms
- Topiramate
  - Meta- analysis - topiramate-augmentation therapy superior in decreasing overall symptoms when compared to antipsychotic alone or placebo plus antipsychotic [14]
  - Superior in reducing positive and negative symptoms - limitations: small overall cohort, short follow-up period and lack of investigation of optimal dosage [14]
    - Current therapy of VPA
- Amisulpride
  - Benzamide antipsychotic with D2 and D3 dopamine receptor [15]
  - Open-label trial - 34.5% had greater than 50% response to the add-on therapy of amisulpride [15]
  - Research has explored combinations of amisulpride add-on to an antipsychotic demonstrating statistical significance [16,17]
    - Studies excluded patients on LAIs or different medication combination

Conclusion

Our case demonstrates rapid and adequate treatment of psychosis through the utility of a second antipsychotic agent in a patient with treatment resistance. This case also highlights the importance of examining whether the patient is experiencing primarily positive or negative symptoms when considering adjunctive treatment options in TRS. We also reviewed the evidence for and against antipsychotic polypharmacy and non-antipsychotic agents as adjunct treatment for treatment-resistant schizophrenia and discussed applicability to our patient's treatment. Our patient showed rapid improvement in both positive and negative symptoms in the absence of reported adverse effects with the regimen of paliperidone LAI 234 mg every 4 weeks and VPA 750 mg BID, with the initiation and titration of haloperidol to 2 mg BID.