SMICA
SERIOUS MENTAL ILLNESS
CALIFORNIA ADVISER

Antipsychotic Polypharmacy (APP): When does it make sense?

APP use is prevalent in a variety of settings

- In a survey of 204 psychiatrists on their choice of treatment for a patient who did not respond to 2 antipsychotics, APP was the second most popular choice (the most popular choice was an increase in the current antipsychotic dose) (Correll, 2019)
- In a retrospective study of APP utilization among publicly insured US adults, 11-19% of 397,533 antipsychotic users had some APP utilization (Horvitz-Lennon, 2021)
- In a meta-analysis of 517 studies reporting on 4,459,149 individuals, 24.8% of the populations received APP (Højlund, 2024)
- In a Canadian forensic sample of 142 patients, APP was prescribed to 54.9% of patients (Farrell, 2020)

APP is not recommended in the majority of cases

- In a systematic review of 14 studies, there was limited evidence for the efficacy of APP in the treatment of schizophrenia over the use of antipsychotic monotherapy at a standard dose (Lawrence, 2024)

APP has multiple disadvantages compared to antipsychotic monotherapy

- Was associated with a subsequent increased risk of hyperprolactinemia and a BMI > 25 (Yang, 2023)
- Was associated with more extrapyramidal symptoms, dystonia, anticholinergic use, and longer corrected QT interval (Højlund, 2024)
- Reduced the likelihood of adherence (Smith, 2020)

There are a few APP combinations with empirical support

- In a study of 62,250 patients, clozapine plus aripiprazole was associated with the lowest risk of psychiatric rehospitalization amongst 29 treatment options (Tiihonen, 2019)
- Out of the next 7 treatments associated with the lowest risk of psychiatric hospitalization, clozapine monotherapy and clozapine plus another antipsychotic (including a LAI) accounted for 6 of those treatment options. A long-acting injectable (LAI) plus an oral antipsychotic rounded out the top 10.

SMICA
SERIOUS MENTAL ILLNESS
CALIFORNIA ADVISER

Core principles when using polypharmacy

- The best combination implements antipsychotics with different types of receptor profiles (Guinart, 2020)
- Clozapine plus almost any other antipsychotic (except olanzapine and quetiapine, which should not be utilized due to the increased anticholinergic burden) has been shown to be more effective than monotherapy (Lähteenvuo, 2021)
- A LAI plus an oral agent has been shown to be more effective than monotherapy, with the exception of clozapine monotherapy (Lähteenvuo, 2021)
- There is limited evidence that adding a partial dopamine agonist (aripiprazole, brexpiprazole, cariprazine) to a strong dopamine antagonist (such as haloperidol or risperidone) will increase the chance for response or achieve a more rapid response (Lippi, 2022). The combination may exacerbate psychotic symptoms (Burke, 2006; Adan-Manes, 2009)

Treatment options to consider before using/instead of polypharmacy

Check antipsychotic plasma levels instead of relying on dosing

- Plasma levels are a more accurate method of measuring the amount of medication in a patient and can help detect factors that affect treatment response such as non-adherence, variability in metabolism (due to genetics, ethnic background, age, gender, and/or weight), co-morbid medical issues, and/or co-prescribed medications that affect metabolism (Meyer, 2021)

Use LAIs for adherence

- In one therapeutic drug monitoring (TDM) study of 99 patients diagnosed with treatment-resistant schizophrenia who prescribed an oral non-clozapine antipsychotic, 35% of plasma levels were subtherapeutic and 34% of those were nondetectable (McCutcheon, 2017)

Consider a mood stabilizer if the patient has a history of mood disorder, as "treatment-resistant psychotic symptoms" might represent inadequate mood stabilization in a patient whose bipolar diathesis was overlooked due to the fact that the antipsychotic addressed the more florid aspects of mania" (Cummings, 2021).

Clozapine is the treatment of choice for treatment-resistant schizophrenia, which is defined for clinical purposes as 2 failed prior treatment episodes > 6 weeks with different antipsychotics at dosages equivalent to > 600 mg/d of chlorpromazine and at least one utilizing an LAI antipsychotic for at least 4 months" (Howes, 2017). Studies have shown that for treatment-resistant schizophrenia, the response rate to most antipsychotics is less than 5%, 7% with olanzapine, and between 40-60% for clozapine (Conley, 1998; Siskind, 2017)

References

Adan-Manes J, Garcia-Parajua P. Aripiprazole in combination with other antipsychotic drugs may worsen psychosis. J Clin Pharm Ther. 2009 Apr;34(2):245-6. doi: 10.1111/j.1365-2710.2008.00996.x.

Burke MJ and Lincoln J. Aripiprazole and haloperidol: a clinically relevant interaction with a dopamine antagonist and partial agonist. Ann Clin Psychiatry. 2006 Apr-Jun;18(2):129-30. doi: 10.1080/10401230600614678.

Conley, RR, et al. (1998). Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. American Journal of Psychiatry, 1998;155: 914–920.

Correll CU, et al. Patient characteristics, burden and pharmacotherapy of treatment-resistant schizophrenia: results from a survey of 204 US psychiatrists. BMC Psychiatry. 2019;19(1):362. doi: 10.1186/s12888-019-2318-x.

Cummings, MA, Stahl SM. Management of Complex Treatment-Resistant Psychotic Disorders, Chapter 1.07 Approach to Bipolar Diathesis in Schizophrenia Spectrum Patients. Stahl's Handbooks. Cambridge University Press; 2021

Farrell C and Brink J. The Prevalence and Factors Associated With Antipsychotic Polypharmacy in a Forensic Psychiatric Sample. Front Psychiatry. 2020 Apr 17;11:263. doi: 10.3389/fpsyt.2020.00263.

Guinart D and Correll CU. Antipsychotic Polypharmacy in Schizophrenia: Why Not? J Clin Psychiatry. 2020 Apr 28;81(3):19ac13118. doi: 10.4088/JCP.19ac13118.

Horvitz-Lennon M, et al. Significance and Factors Associated with Antipsychotic Polypharmacy Utilization Among Publicly Insured US Adults. Adm Policy Ment Health. 2022 Jan;49(1):59-70. doi: 10.1007/s10488-021-01141-7.

Howes, OD, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. AmJ Psychiatry 2017;174:216–229; doi: 10.1176/appi.ajp.2016.16050503

Højlund M, et al. Prevalence, correlates, tolerability-related outcomes, and efficacy-related outcomes of antipsychotic polypharmacy: a systematic review and meta-analysis. Lancet Psychiatry. 2024 Dec;11(12):975-989. doi: 10.1016/S2215-0366(24)00314-6.

Lawrence C, et al. Antipsychotic polypharmacy and high-dose antipsychotic therapy compared to antipsychotic monotherapy at standard doses in schizophrenia - a systematic review. J Psychopharmacol. 2025 Feb;39(2):132-140. doi: 10.1177/02698811241303652.

Lähteenvuo M and Tiihonen J. Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations. Drugs. 2021 Jul;81(11):1273-1284. doi: 10.1007/s40265-021-01556-4.

Lippi M, et al. The dilemma of polypharmacy in psychosis: is it worth combining partial and full dopamine modulation? Int Clin Psychopharmacol. 2022 Nov 1;37(6):263-275. doi: 10.1097/YIC.0000000000000417.

Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels Introduction. Stahl's Handbooks. Cambridge University Press; 2021

McCutcheon R, et al. Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. Acta Psychiatr Scand. 2018 Jan;137(1):39-46. doi: 10.1111/acps.12825.

Siskind, D., et al. Clozapine response rates among people with treatment-resistant schizophrenia: Data from a systematic review and meta-analysis. Canadian Journal of Psychiatry. 2017;62:772–777.

Smith RL, et al. Impact of antipsychotic polypharmacy on nonadherence of oral antipsychotic drugs - A study based on blood sample analyses from 24,239 patients. Eur Neuropsychopharmacol. 2020 Aug;37:64-69. doi: 10.1016/j.euroneuro.2020.06.007.

Tiihonen J, et al. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. JAMA Psychiatry. 2019 May 1;76(5):499-507. doi: 10.1001/jamapsychiatry.2018.4320.

Yang JC, et al. Antipsychotic polypharmacy and adverse drug reactions among adults in a London mental health service, 2008-2018. Psychol Med. 2023 Jul;53(9):4220-4227. doi: 10.1017/S0033291722000952.

Funding for SMI CalAdviser was made possible by the State of California Department of State Hospitals (DSH) (the Department), but does not necessarily represent the views of the Department or any of its employees except to the extent, if any, that it has formally been approved by the Department.