University of Southampton

Medicine

What is the relative efficacy and tolerability of Antipsychotic Polypharmacy and High Dose Antipsychotic Therapy compared to the use of Antipsychotic Monotherapy at standard doses in the treatment of Schizophrenia? – A Systematic Review Protocol

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BACKGROUND

Schizophrenia is a severe, lifelong mental disorder, characterised by symptoms such as delusions, hallucinations, and interference of the flow of thought. It can have significant impacts upon cognitive, behavioural and emotional function and the mean lifetime prevalence is felt to be just under 1% (Kahn et al., 2015). A significant proportion of patients diagnosed with Schizophrenia are subsequently categorised as being treatment resistant (Siskind et al., 2022). Treatment resistant schizophrenia is broadly defined as patients who have not responded to at least 2 sequential trials of an antipsychotic at an effective dose, duration and degree of concordance (Correll & Howes, 2021).

Current practice is that patients who are deemed treatment resistant, should undergo a trial of treatment with Clozapine, however a significant number of patients are treated instead with Antipsychotic Polypharmacy (APP) or High Dose Antipsychotic Therapy (HDAT) (Burness et al., 2021; Paton et al., 2008; Rajan & Clarke, 2013; Takahashi et al., 2020).

OBJECTIVES

Current national and local guidance advise against the use of APP and HDAT (NICE, 2014; RCPsych, 2023). Previous reviews have suggested, at the time of their publication, that there was insufficient evidence to support these treatment approaches ("CADTH Optimal Use Reports," 2011).

This review aims to evaluate whether progress has been made and if there is sufficient evidence of the efficacy and tolerability of APP and HDAT to suggest either approach as a viable alternative to antipsychotic monotherapy at standard dose in the treatment of schizophrenia.

METHODS

Searches were completed of the PubMed, PsycINFO and EMBASE databases.

Studies will be assessed for quality using the Joanna Briggs Institute Checklist for Randomised Controlled Trials.

Results will be collated and findings summarised descriptively.

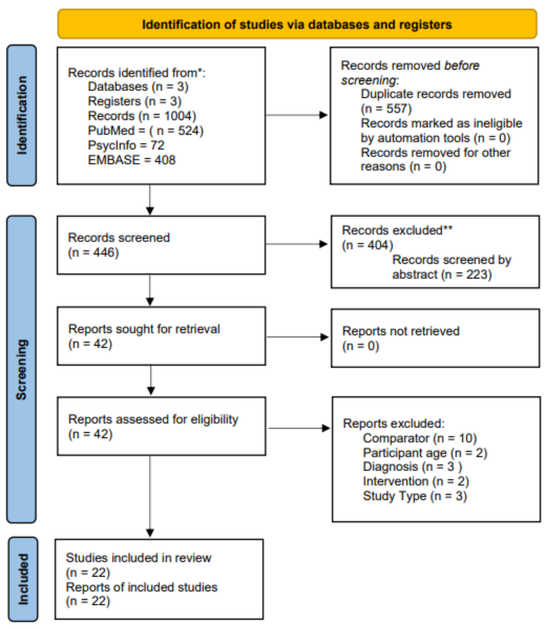
Where possible, meta-analysis of the primary outcomes, efficacy and tolerability of HDAT and APP compared to treatment with antipsychotic monotherapy at a standard dose, will be completed using either random or fixed effects model based upon the results of heterogeneity testing. Depending on the availability of data we may include secondary sub-group analysis where specific antipsychotics at high doses and / or specific combinations of antipsychotic agents will be compared to antipsychotic monotherapy at a standard dose.

ELIGIBILITY CRITERIA

PICO	Inclusion Criteria	Exclusion Criteria
Population	• Adults (>18 years of age) • ICD10 Diagnosis of F20-F29 (Schizophrenia, schizotypal and delusional disorders). ICD11 Diagnosis of Schizophrenia or other primary psychotic disorder (6A20-6A2Z). DSM-IV Diagnosis of Schizophrenia Spectrum and Other Psychotic Disorders. DSM-V Diagnosis of Schizophrenia Spectrum and Other Psychotic Disorders.	• Children (<18 years of age) • Primary diagnosis of an affective disorder and not Schizophrenia spectrum or other psychotic disorder.
Intervention	• Treatment with High Dose Antipsychotic Therapy • AND / OR Treatment with Antipsychotic Polypharmacy	• No antipsychotic treatment
Comparison	• Treatment with a single antipsychotic agent at a standard dose	• No valid comparator
Outcomes	• Change in Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) or other quantitative measure of psychiatric symptoms as defined by individual study. • Change in Glasgow Antipsychotic Side-Effect Scale (GASS) • Changes in markers of metabolic syndrome including weight, prolactin and HbA1c.	• No quantitative measure of psychiatric symptoms
Study Type	• Randomised Controlled Trial	• Not Randomised Control Trial

CURRENT PROGRESS

Searches were initially ran for this systematic review following the registration of the protocol on PROSPERO in March 2023. Data extraction is ongoing at the time of the presentation of this poster. The current PRISMA diagram can be seen below:



REFERENCES

Burness, C., Corbet, C., Beyene, K., Webby, C., Nankivell, C., Cabasag, P., Hari, K., Fraser, A., Gray, S., Harrison, J., & Chan, A. H. Y. (2021). Factors predicting high-dose and combined antipsychotic prescribing in New Zealand: High-dose antipsychotic prescribing. Psychiatry Res, 302, 113996. https://doi.org/10.1016/j.psychres.2021.113996

CADTH Optimal Use Reports. (2011). In A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia. Canadian Agency for Drugs and Technologies in Health
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Correll, C. U., & Howes, O. D. (2021). Treatment-Resistant Schizophrenia: Definition, Predictors, and Therapy Options. J Clin Psychiatry, 82(5). https://doi.org/10.4088/jcp.My20096ah1c

Insititute, J. B. (2020). Checklist for Randomised Controlled Trials. https://jbi.global/critical-appraisal-tools

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., O'Donovan, M., Correll, C. U., Kane, J. M., van Os, J., & Insel, T. R. (2015). Schizophrenia. Nat Rev Dis Primers, 1, 15067. https://doi.org/10.1038/nrdp.2015.67

NICE. (2014). Psychosis and schizophrenia in adults: prevention and management [cg178]. https://www.nice.org.uk/guidance/cg178

Paton, C., Barnes, T. R., Cavanagh, M. R., Taylor, D., & Lelliott, P. (2008). High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry, 192(6), 435-439. https://doi.org/10.1192/bjp.bp.107.042895

Rajan, L., & Clarke, I. (2013). Audit of combination and high-dose antipsychotic treatment in the community. The Psychiatrist, 37(9), 302-307. https://doi.org/10.1192/pb.bp.112.039750

RCPsych. (2023). The risks and benefits of highdose antipsychotic medication [CR190]. https://www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/college-reports/college-report-cr190.pdf?sfvrsn=54f5d9a2_11

Siskind, D., Orr, S., Sinha, S., Yu, O., Brijball, B., Warren, N., MacCabe, J. H., Smart, S. E., & Kisely, S. (2022). Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. Br J Psychiatry, 220(3), 115-120. https://doi.org/10.1192/bjp.2021.61

Takahashi, T., Otsubo, T., Kunisawa, S., Sasaki, N., & Imanaka, Y. (2020). Factors associated with high-dose antipsychotic prescriptions in outpatients with schizophrenia: An analysis of claims data from a Japanese prefecture. Neuropsychopharmacol Rep, 40(3), 224-231. https://doi.org/10.1002/npr2.12109

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