# Schizophrenia Research Review™

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Issue 26 - 2021


## In this issue:



**Abbreviations used in this issue:**

**AE** = adverse event; **aHR** = adjusted hazard ratio; **AUD** = alcohol use disorder; **CGI-S** = Clinical Global Impression-Severity; **LAI** = long-acting injectable; **OAP** = oral antipsychotic; **PANSS** = Positive and Negative Syndrome Scale; **SMR** = standardised mortality ratio.

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# Welcome to the 26th issue of Schizophrenia Research Review.

The lead article, from The Lancet, is a meta-analysis of randomised controlled trials comparing standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia. The authors conclude during maintenance treatment antipsychotic doses should not be reduced below the standard dose range due to increased risk of both relapse and all-cause discontinuation. A network meta-analysis investigated maintenance treatment with LAI antipsychotics for people with nonaffective psychoses. The researchers found paliperidone (3-month formulation), aripiprazole, olanzapine, and paliperidone (1-month formulation) showed the highest effect sizes for both relapse prevention and acceptability. Results from another meta-analysis show almost a quarter of people with first-episode psychosis or schizophrenia will develop treatment-resistant schizophrenia in the early stages of treatment. A study from Taiwan comparing LAI with oral antipsychotics reports LAI use in patients with newly diagnosed schizophrenia is associated with decreased all-cause mortality and suicide risk. Another study using US Medicare data found suicide risk was elevated in adult patients with schizophrenia, with the highest absolute and relative risk among young adults. The authors suggest suicide prevention efforts should focus on young adults with schizophrenia, especially those with suicidal symptoms and substance use.

Other interesting research reported in this issue include the influence of prenatal and infant exposure to viral infectious diseases on incidence of schizophrenia and functional connectivity of cerebellar dentate nucleus and cognitive impairments in patients with drug-naïve and first-episode schizophrenia

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,


**Professor Bruce Singh**

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## Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: A systematic review and meta-analysis of randomised controlled trials

**Authors:** Højlund M, et al


**Summary:** The meta-analysis included 24 randomised trials (n = 3,282) in adults with schizophrenia or schizoaffective disorder lasting at least 24 weeks; including individuals clinically stable at baseline and excluding first-episode psychosis or treatment-resistant schizophrenia. The authors compared low-dose (within 50-99% of the lower limit of the standard dose) and very-low dose (less than 50% of the lower limit) with standard dose. Compared with standard dose, low dose increased the risk of relapse by 44% (16 trials, n = 1,920 participants; RR 1.44; p=0.0076) and the risk of all-cause discontinuation by 12% (16 trials, n= 932; RR 1.12; p=0.0085). Very low dose increased the risk of relapse by 72% (13 trials, n= 2,058; RR 1.72; p=0.0002) and all-cause discontinuation by 31% (11 trials, n = 1,866; RR 1.31; p=0.0011). Compared with low dose, very low dose did not significantly increase the risk of relapse (five trials, n = 686; RR 1.31; p=0.092) or all-cause discontinuation (five trials, n = 686; RR 1.11; p=0.18). The authors noted most studies had some concerns in the risk of bias assessment.


**Comment:** This paper from the Lancet demonstrates again the risk of dose reduction of antipsychotic maintenance treatment in patients with schizophrenia in order to minimise adverse effects of these drugs. It is a large meta-analysis and the findings are consistent with current thinking, namely that during maintenance treatment in multi-episode schizophrenia antipsychotic doses should probably not be reduced below the standard dose range required for acute stabilisation because of an increased risk of relapse and/or discontinuation.

***Reference: Lancet Psychiatry 2021 Jun;8(6):471-486***
Abstract

## Functional connectivity of cerebellar dentate nucleus and cognitive impairments in patients with drug-naïve and first-episode schizophrenia

**Authors:** Xie YJ, et al

**Summary:** The researchers investigated the abnormal functional connectivity of the cerebellar dentate nucleus and its correlation with cognitive impairments in 47 patients with schizophrenia and 43 healthy controls. Functional connectivity was assessed by MRI and cognitive functions by number sequence span, verbal category fluency and digit-symbol coding tests. They found patients had deficits in all three cognitive tests compared to the controls. In addition, the increased functional connectivity of the cerebellar dentate nucleus with the bilateral postcentral gyrus and decreased functional connectivity of the dentate nucleus with the right inferior temporal gyrus and regional cerebellum were observed in the patient group compared to the control group. They noted the abnormal functional connectivity significantly correlated with cognitive tests and clinical symptoms in the patient group.

**Comment:** This study from China looks at both cognitive functions using a number of tests and showed deficits as compared to controls. They were able to relate abnormal functional connectivity of the cerebella dentate nucleus with these impairments, showing again, that schizophrenia is clearly a disorder of brain connectivity as a number of other studies from China have also demonstrated.

***Reference: Psychiatry Res 2021 Jun;300:113937***
Abstract



## Maintenance treatment with long-acting injectable antipsychotics for people with nonaffective psychoses: A network meta-analysis

**Authors:** Ostuzzi G, et al

**Summary:** The meta-analysis compared 78 randomised controlled trials (n = 11,505) of long-acting injectable (LAI) antipsychotics in the maintenance treatment of adults with nonaffective psychoses. The primary outcomes were relapse rate and all-cause discontinuation. The authors reported most of the 12 LAIs included outperformed placebo in regard to relapse prevention with the best rankings for paliperidone (3-month formulation) and aripiprazole. Moderate to high grade certainty for superior relapse prevention compared with placebo was also found for risperidone, pipothiazine, olanzapine, and paliperidone (1-month formulation). In head-to-head comparisons only haloperidol was inferior to aripiprazole, fluphenazine, and paliperidone. For acceptability, most LAIs outperformed placebo, with moderate to high grade certainty for zuclopenthixol, aripiprazole, paliperidone (3-month formulation), olanzapine, flupenthixol, fluphenazine, and paliperidone (1-month formulation). In head-to-head comparisons, only aripiprazole had superior acceptability to other LAIs.

**Comment:** This meta-analysis of 86 eligible trials showed that LAIs were significantly better for the long acting paliperidone 3-month formulation than for placebo with comparable aripiprazole, olanzapine and the paliperidone 1-month formulation being comparable. For acceptability most LAIs outperform placebo. In head-to-head comparisons, only aripiprazole 1 month formulation has superior acceptability over other LAIs.

***Reference: Am J Psychiatry 2021 May 1;178(5):424-436***
Abstract

## Rates of treatment-resistant schizophrenia from first-episode cohorts: Systematic review and meta-analysis

**Authors:** Siskind D, et al

**Summary:** The researchers conducted a systematic review of treatment-resistant schizophrenia rates among people with first-episode psychosis and schizophrenia, with a minimum follow-up of 8 weeks. The meta-analysis included 12 studies with a total of 11,958 participants. The rate of treatment-resistant schizophrenia was 22.8% (95% CI 19.1–27.0%, P < 0.001) among all first-episode cohorts and 24.4% (95% CI 19.5–30.0%, P < 0.001) among first-episode schizophrenia cohorts. The researchers noted men were 1.57 times more likely to develop treatment-resistant schizophrenia than women (95% CI 1.11–2.21, P = 0.010).

**Comment:** This study from Queensland confirmed the clinical observation that almost a quarter of people with first episode psychosis or schizophrenia will develop treatment resistance in the early stages of treatment. These findings of an increased percentage of resistance appears to have increased over time and is possibly due to comorbidity with drug and alcohol use. It does suggest that early clozapine treatment may need to be initiated in such patients.

***Reference: Br J Psychiatry. 11 May 2021. Online ahead of print.***
Abstract

## Comparative safety of antipsychotic medications in elderly stroke survivors: A nationwide claim data and stroke registry linkage cohort study

**Authors:** Su CC, et al

**Summary:** The retrospective cohort study used health insurance data to identify stroke patients aged above 65 years who were prescribed haloperidol (n = 22,235), quetiapine (n = 28,702) and risperidone (n = 8,663). The authors found haloperidol (adjusted hazard ratio (aHR) = 1.22) and risperidone (aHR = 1.31) users had a higher mortality risk than quetiapine users. Furthermore, when dosage was higher than 0.5 defined daily dose, haloperidol and risperidone users had a significant mortality risk as compared with those taking a lower dose.

**Comment:** This study from Taiwan demonstrated that antipsychotics remain the first choice of treatment for post stroke psychosis and that in these patients, quetiapine has less mortality risk than risperidone and haloperidol. When haloperidol or risperidone is indicated starting with the lowest effective dose is suggested.

***Reference: J Psychiatr Res 2021 Jul;139:159-166***
Abstract

## Incidence of schizophrenia and influence of prenatal and infant exposure to viral infectious diseases

**Authors:** Tanskanen A, et al

**Summary:** The investigators examined the incidence of schizophrenia over a 30-year period in Finland. They found cumulative incidence of schizophrenia among individuals born 1956-1989 decreased by 23% (from 13 to 10 cases per 1,000 live births). It was noted the decline was the most prominent in those with onset of schizophrenia diagnosed 16-25 years of age (-41%). The investigators also reported the incidence of catatonic schizophrenia declined by 90% over three decades, and there was a significant association between annual polio incidence during the birth year and incidence of catatonic schizophrenia.

**Comment:** This study from Sweden deals with the conflicting evidence about whether the incidence of schizophrenia is increasing or decreasing in the west and the role of prenatal and early childhood viral infections in the aetiology. Researchers show that over a 30-year period in Finland the incidence of schizophrenia had declined and they believe that this may be partly attributable to eradication of polio and reduction in exposure to other viral conditions during the prenatal and infant period.

***Reference: Acta Psychiatr Scand 2021 Jun;143(6):487-494***
Abstract

## Effects of comorbid alcohol use disorder on the clinical outcomes of first-episode schizophrenia: A nationwide population-based study

**Authors:** Ahn S, et al

**Summary:** This study investigated the impact of alcohol use disorder (AUD) on clinical outcomes of schizophrenia. Of the study cohort of 64,442 patients with first-episode schizophrenia 1,598 patients had comorbid AUD. The rates of psychiatric admissions, emergency department visits, and medication possession ratio were worse in the comorbid AUD group both before and after the diagnosis of AUD.

**Comment:** This study from South Korea looked at alcohol use disorder as a common psychiatric comorbidity in schizophrenia associated with poorer clinical outcomes and medication noncompliance. This study essentially confirms what is already known but is useful because of the sample size which essentially used health insurance data of the whole nation of south Korea for 9 years (2007 – 2016).

***Reference: Ann Gen Psychiatry 2021 May 29;20(1):32***
Abstract

## A phase 3, multicenter study to assess the 1-year safety and tolerability of a combination of olanzapine and samidorphan in patients with schizophrenia: Results from the ENLIGHTEN-2 long-term extension

**Authors:** Kahn RS, et al

**Summary:** The ENLIGHTEN-2 study was a randomised, double-blind, phase 3 trial comparing weight change from baseline to week 24 with olanzapine and samidorphan versus olanzapine. This open-label extension study enrolled 265 patients to olanzapine and samidorphan for 52-weeks; 63.0% completed the 52-week treatment. The team reported common adverse events (≥5%) were weight decreased (8.7%), extra dose administered (7.9%), headache (6.8%), and weight increased (6.0%). At week 52, the mean change from baseline for weight and waist circumference was -0.03 (6.17) kg and - 0.35 (6.12) cm, respectively. Positive and Negative Syndrome Scale (PANSS) total scores remained stable, and at week 52, 81.3% of patients had Clinical Global Impression-Severity (CGI-S) scores of 3 or less, reflecting mild illness severity. They also noted metabolic laboratory parameters remained stable over 52 weeks.

**Comment:** A combination of olanzapine and samidorphan, an antiobesity agent, is being trialled for treatment for patients with schizophrenia or bipolar 1. This 1-year study assessed the long term safety, comparability and tolerability of the combination demonstrating that it was well tolerated over 52 weeks and that weight, waist circumference, metabolic laboratory parameters and schizophrenic symptoms all remain stable throughout the study.

***Reference: Schizophr Res 2021 May 17;232:45-53***
Abstract

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## Comparison of long-acting injectable antipsychotics with oral antipsychotics and suicide and all-cause mortality in patients with newly diagnosed schizophrenia

**Authors:** Huang CY, et al

**Summary:** This study included a population-based cohort of patients with schizophrenia who received oral antipsychotics (OAPs). Within this cohort, the LAI antipsychotics group was defined as patients who switched to LAIs and were prescribed LAIs at least 4 times within 1 year. The LAI group (n = 2,614) was propensity matched 1:1 to patients who continued receiving OAPs (n = 2,614) of the same compounds. The authors reported during the 16-year follow-up period patients who switched to LAIs had lower risks of all-cause mortality (aHR, 0.66), natural-cause mortality (aHR, 0.63), and suicide attempts (incidence rate ratio, 0.72) compared with patients who received the corresponding OAPs. Moreover, there was a 47% lower suicide mortality risk (aHR, 0.53) in patients who switched to LAIs within the first 2 years of OAP initiation.

**Comment:** This study from Taiwan again confirmed that LAI use in patients with newly diagnosed schizophrenia is associated with decreased all-cause mortality and suicide risk. It's another reason for the offering of LAI to people in the early phases of schizophrenia despite their reticence to use them.

***Reference: JAMA Netw Open 2021 May 3;4(5):e218810***
Abstract

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## Suicide risk in Medicare patients with schizophrenia across the life span

**Authors:** Olfson M, et al

**Summary:** The researchers explored suicide mortality rates among adults with schizophrenia across the life span and standardised mortality ratios (SMRs) for suicide compared with the general US population. The study cohort included 668,836 US Medicare patients with schizophrenia, 2,997,308 years of follow-up, and 2,218 suicide deaths. The total suicide rate per 100,000 person-years was 74.00, which is 4.5 times higher than that for the general US population (SMR, 4.54) and included a rate of 88.96 for men and 56.33 for women, which are 3.4 (SMR, 3.39) and 8.2 (SMR, 8.16) times higher, respectively, than the rates for the general US population. The researchers noted suicide rates were significantly higher for men (aHR, 1.44) and those with depressive (aHR, 1.32), anxiety (aHR, 1.15), drug use (aHR, 1.55), and sleep disorders (aHR, 1.22), suicidal ideation (aHR, 1.41), and suicide attempts or self-injury (aHR, 2.48). The suicide rate declined with age, from 141.95 (SMR, 10.19) for patients aged 18 to 34 years to 24.01 (SMR, 1.53) for patients 65 years or older. The corresponding declines per 100,000 person-years were from 153.80 (18-34 years of age) to 34.17 (65 years or older) for men and from 115.70 (18-34 years of age) to 18.66 (65 years or older) for women.

**Comment:** This study from the US used 5 national retrospective longitudinal cohorts of patients with schizophrenia in the Medicare program from 2007 to 2016. Suicide risk was elevated with the highest and absolute and relative risk among young adults. This study reinforces that suicide risk is highest early in the course of the illness perhaps as its devastating effects start to become appreciated by patients.

***Reference: JAMA Psychiatry 2021 May 26;e210841***
Abstract

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**Independent commentary by Professor Bruce Singh**

Bruce Singh is currently Emeritus Professor of Psychiatry at University of Melbourne. He was Assistant Vice-Chancellor (Medicine Dentistry & Health Sciences Projects), University of Melbourne prior to retirement in 2013. He was previously Deputy Dean of the Faculty of Medicine Dentistry & Health Sciences for 3 years and before that Cato Professor and Head, Department of Psychiatry, University of Melbourne and Clinical Director of North Western Mental Health for 17 years. He has previously held a professorial position at Monash University, a senior lectureship at the University of Newcastle and been an NH&MRC Travelling Fellow in the Clinical Sciences in Rochester NY and London. He is a graduate of the University of Sydney and trained in Medicine and Psychiatry at the Royal Prince Alfred Hospital in Sydney. He has received the Centenary Medal of Federation, the Victorian Minister for Health's Award for Contribution to Mental Healthcare in Victoria and has recently retired as Foundation Chair of the Victorian Responsible Gambling Foundation. In 2007 he was awarded Membership of the Order of Australia for his contribution to psychiatric education and the development of clinical mental health services. In 2014 The University of Melbourne awarded him an Honorary Doctorate of Medical Science as recognition of his service to the University and the speciality of Psychiatry.









 