Welcome to the 11th issue of Schizophrenia Research Review

Pooled data from two phase 2 trials was used to assess efficacy and safety of a glycine transporter type-1 inhibitor for schizophrenia. The study showed a therapeutic benefit at a moderate dose level. The studies were terminated due to the development of a severe adverse reaction to drug in one patient. However, the results provide support that this therapeutic target is worth further attention. A meta-analysis of randomised controlled trials investigating the use of antiepileptic drugs as augmentation agents for treatment resistant schizophrenia concluded sodium valproate augmentation was efficacious and safe. A large trial in severely decompensated postmenopausal women with schizophrenia showed no benefit of antipsychotics plus raloxifene versus antipsychotics plus placebo.

Findings from a study mapping grey matter volume and fractional anisotropy suggest that schizophrenia is characterised by an initial, rapid rate of grey matter loss that slows in middle life, followed by the emergence of a deficit in white matter that progressively worsens with age at a constant rate. We conclude this issue with a study of long term effects of smoking cessation in schizophrenia patients. The results suggest that smoking reduces both autonomic nervous system activity and the effectiveness of drug therapy with antipsychotics and antiparkinsonian drugs in patients with schizophrenia. The authors highlight that both factors could be ameliorated over the long term by smoking cessation.

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,
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Personality traits predicting quality of life and overall functioning in schizophrenia

Authors: Ridgewell C, et al

Summary: The aim of this study was to examine the effects of neuroticism and extraversion on quality of life and functioning. Patients with schizophrenia-spectrum disorders (n=153) and healthy controls (n=125) completed personality and quality of life questionnaires. Global functioning was assessed by structured interview administered by a clinician. The authors concluded quality of life was significantly associated with neuroticism and extraversion. For overall functioning, only diagnosis had a significant effect.

Comment: Due to the at times overwhelming nature of the psychotic symptoms experienced by patients with schizophrenia, these frequently preoccupy those treating patients with this disorder at the expense of consideration and management of other psychological factors that may have a major impact on patients functioning and quality of life. In this study, the authors explored the relationship between personality traits and quality of life in patients with schizophrenia. They found that patients with lower neuroticism scores actually described quality of life similar to that seen in healthy individuals whereas high neuroticism was substantially associated with poorer quality of life. A major limitation of this research is that the authors have not comprehensively controlled for the effect of depression, which has been demonstrated to be both associated with neuroticism and poor quality of life in patients with schizophrenia. However, it is a timely reminder that a patient’s psychological state beyond their immediate primary diagnosis should be taken account of in formulation and management of patients with psychotic disorders.

Reference: Schizophr Res 2017 Apr;182:19-23

Abstract

In this issue:

- Personality traits predicting quality of life and functioning
- Efficacy and safety of a glycine transporter type-1 inhibitor for schizophrenia
- Gestational weight gain and risk for nonaffective psychosis in offspring
- Risk calculator for the transdiagnostic prediction of psychosis
- Magnocellular and parvocellular visual pathways in facial emotion perception in schizophrenia
- Clozapine augmentation with antiepileptic treatments for treatment-resistant schizophrenia
- Raloxifene + antipsychotics vs placebo + antipsychotics in severely ill decompensated postmenopausal women with schizophrenia
- Accelerated grey and white matter deterioration with age in schizophrenia
- Meta-analysis of placebo-controlled antipsychotic drug trials in acute schizophrenia over sixty years
- Long term effects of smoking cessation in schizophrenia patients

Abbreviations used in this issue:

BMI = body mass index; GlyT1 = glycine transporter type-1; NSFS = Negative Symptom Factor Score; PANSS = Positive and Negative Syndrome Scale; SMD = standardised mean difference.

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Efficacy and safety of the glycine transporter type-1 inhibitor AMG 747 for the treatment of negative symptoms associated with schizophrenia

Authors: Dunayevich E, et al

Summary: This paper analysed pooled data from two phase 2 trials to determine the safety and efficacy of AMG 747, an oral inhibitor of glycine transporter type-1 (GlyT1), as an antipsychotic therapy in schizophrenia. The study cohort included adults with schizophrenia stabilised on antipsychotic medication randomised to receive daily AMG 747 (5mg, 15mg, or 40mg) or placebo. Studies were terminated early after one case of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. At termination, 232 participants had enrolled and 153 completed 12 weeks of treatment. The primary endpoint, change from baseline Negative Symptom Assessment (NSA)-16 total score, showed no differences between groups. Mean decreases in Positive and Negative Syndrome Scale (PANSS), Negative Symptom Factor Score (NSFS) and NSA-16 global score were greater with 15-mg AMG 747 than placebo. Changes in patient-reported outcomes showed trends consistent with greater efficacy of 15-mg AMG 747 compared with placebo. Adverse event rates were similar among all groups.

Comment: Modulation of glycine levels or activity at the glycine receptor has been of considerable interest as a way of potentially treating the often intractable negative symptoms associated with schizophrenia. Investigator initiated studies have suggested that oral glycine at sufficient dose can reduce negative symptoms although the dose required to achieve therapeutic effects is often difficult for subjects to tolerate and there is no incentive for the pharmaceutical industry to develop glycine as stand-alone intervention. However, there have been attempts by industry to develop glycine receptor modulators with the current study reporting the outcome of two phase 2 trials. The study showed a therapeutic benefit at a moderate dose level of a novel drug, which inhibits the glycine transporter. Unfortunately, the studies were terminated due to the development of a severe adverse reaction to drug in one patient. However, the results do provide further support that this is a therapeutic target worth further attention, especially given the poor outcomes with other treatments for negative symptoms in schizophrenia.

Reference: Schizophr Res 2017 Apr;182:90-97

Association of gestational weight gain and maternal body mass index in early pregnancy with risk for nonaffective psychosis in offspring

Authors: Mackay E, et al

Summary: This population-based cohort study used data from Swedish registers to follow up 526,042 individuals including 2,910 persons with nonaffective psychoses at the end of follow-up. Among individuals with nonaffective psychosis, 184 (6.32%) had mothers with extremely inadequate gestational weight gain (<8 kg for mothers with normal baseline BMI), compared with 23,627 (4.52%) of unaffected individuals. Maternal mild thinness in early pregnancy was weakly associated with an increased risk for nonaffective psychosis in offspring, as was paternal severe thinness. In matched-sibling analysis, no association was observed between maternal underweight, overweight, or obesity and risk for nonaffective psychosis in offspring.

Comment: A variety of previous studies have identified an association between poor maternal nutrition during pregnancy and an increased risk of the development of schizophrenia related psychosis later in life, usually associated with exposure to famine. This current large cohort study explored whether there is a relationship between the weight gain experienced by mothers and the risk of nonaffective psychosis in their children. The authors found a significant association between inadequate weight gain during pregnancy and a high risk of the development of psychosis in the offspring of affected individuals. This association was found for nonaffective psychosis as a broad diagnosis, or schizophrenia more narrowly defined. It supports the contention that maternal nutrition plays a significant role in determining the risk of schizophrenia or related psychotic disorders.

Reference: JAMA Psychiatry 2017 Apr 1;74(4):339-349

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Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis

Authors: Fusar-Poli P, et al.

Summary: This clinical register-based cohort study included patients (n=91,199) receiving a first index diagnosis of nonorganic and nonpsychotic mental disorder. The mean follow-up was 1,588 days. The researchers reported the overall 6-year risk of psychosis in secondary mental health care was 3.02 (95% CI, 2.86-3.15), higher than the 6-year risk in the local general population (0.62). The At Risk Mental State designation accounted only for a small proportion of transitions to psychosis (5.19%). The researchers developed an online risk calculator based on preselected variables, including index diagnosis, age, sex and race/ethnicity. The model was externally validated, showing good performance and potential clinical usefulness.

Comment: There has been considerable interest in the implementation of services for patients considered to be at risk of the development of subsequent psychosis. However, the implementation of programs to adequately detect these patients is problematic and is not clear whether standard approaches can be translated into widespread clinical settings. In this current research, the authors investigated whether there was a significant risk of progression to psychosis in all patients presenting for the management of non-organic/non-psychotic mental disorders and what characteristics might be associated with a greater risk of progression. They found that patients considered de novo to be at risk of progression only constituted about 5% of patients who went on to be diagnosed with a psychotic disorder and that most patients who did progress to psychosis had a primary initial diagnosis across the diagnostic spectrum. They then went ahead and developed a risk model and calculator based upon a range of demographic and clinical variables and present data suggesting that this can have value in predicting progression to psychosis. This may well have clinical value but its utility will need to be demonstrated across a variety of service settings.

Reference: JAMA Psychiatry 2017 May 1;74(5):493-500

Probing the magnocellular and parvocellular visual pathways in facial emotion perception in schizophrenia

Authors: Jahshan C, et al

Summary: Schizophrenia patients (n=35) and healthy individuals (n=35) were assessed on an emotion identification task, in which facial stimuli were either unattentive or manipulated to contain only high or low spatial frequencies, thereby respectively biasing the visual system toward the parvocellular or magnocellular pathways. Schizophrenia patients were less accurate and slower in recognising emotions across all conditions, relative to parvocellular or magnocellular pathways. These results support differential magnocellular frequency condition. A significant group by spatial frequency interaction was observed for topiramate (P = 0.04 and P = 0.02, respectively) and sodium valproate (P = 0.009 and P = 0.003, respectively). There were no significant differences in adverse drug reactions and all-cause discontinuations except for topiramate, which was associated with more all-cause discontinuations.

Comment: How to manage patients who are poorly responsive or only partially responsive to clozapine therapy for treatment resistant schizophrenia is a common day-to-day issue in clinical management. In this study, the authors meta-analysed randomised controlled trials investigating the use of antiepileptic drugs as augmentation agents in this patient group. Sodium valproate therapy was shown to be associated with overall improvements in positive and general symptoms to a significant degree. A positive effect of lamotrigine in the initial analysis did not hold up after the removal of some outliers from the analysis. Topiramate was also associated with improved positive and general symptoms but also with a higher rate of all-cause discontinuation.

Reference: J Clin Psychiatry 2017 May;78(5):e498-e505

Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: A meta-analysis of randomized controlled trials

Authors: Zheng W, et al

Summary: The meta-analysis included 22 randomised controlled trials (n=1,227) with 4 adjunctive antiepileptic drugs; topiramate, lamotrigine, sodium valproate and magnesium valproate. The mean treatment duration was 12.1 weeks. The authors concluded significant superiority in total psychopathology for topiramate (P < 0.0001), lamotrigine (P = 0.05), and sodium valproate (P = 0.002), compared to clozapine monotherapy. They noted after removing outliers, the positive effect of sodium valproate remained, but the positive effect of lamotrigine disappeared (P = 0.40). Significantly improved efficacy in positive and general symptom severity was observed for topiramate (P = 0.04 and P = 0.02, respectively) and sodium valproate (P = 0.009 and P = 0.003, respectively). Given well established differences in the epidemiology of psychosis between men and women, there has been increasing interest in recent decades in the use of hormonal based interventions, especially for women with schizophrenia. This study was a multicentre study exploring the use of raloxifene, a selective oestrogen agonist, and whether it would have augmentation effects when added to antipsychotic therapy in patients with acute symptoms of schizophrenia. Unfortunately, no therapeutic benefits were seen in the raloxifene group, which actually had worse outcomes than patients receiving placebo. Notably, these were described as severely unwell patients, which may differ from patient groups included in previous single site oestrogen or raloxifene trials.

Reference: J Clin Psychiatry 2017 May 23; 78(6):15m10498

Raloxifene plus antipsychotics versus placebo plus antipsychotics in severely ill decompenesated postmenopausal women with schizophrenia or schizoaffective disorder: A randomised controlled trial

Authors: Weiser M, et al

Summary: A study cohort of 200 severely ill, decompenesated postmenopausal women with schizophrenia or schizoaffective disorder were randomised to receive either raloxifene 120 mg/d plus antipsychotics or placebo plus antipsychotics. The investigators found placebo plus antipsychotics group experienced statistically significant improvement in PANSS total score (P < 0.001) compared to the raloxifene plus antipsychotics group. This negative effect was more pronounced in patients who had more frequent relapses and in those with baseline PANSS scores of 100 or higher.

Comment: The pattern of changes in brain structure and function across time in patients with schizophrenia has remained unclear despite many decades of research. This study attempted to explore these questions by analysing grey matter volume and white matter integrity in over 300 patients with schizophrenia between the ages of 20 and 65 and matched controls. The authors found that grey matter volume loss was significantly accelerated in schizophrenia up to middle age and then plateaued. They also reported significant reductions in fractional anisotropy emerged in schizophrenia only after age 35, and the rate of fractional anisotropy deterioration with age was constant. Accelerated gray and white matter deterioration with age in schizophrenia

Authors: Cropley VL, et al

Summary: Grey matter volume and fractional anisotropy were mapped in subjects with schizophrenia or schizoaffective disorder (n=526) and in healthy comparison subjects (n=197). The team reported significant loss of grey matter volume in schizophrenia, progressively worsening with age to a maximal loss of 6% in the seventh decade of life. The rate of grey matter volume loss was significantly accelerated in schizophrenia up to middle age and then plateaued. They also reported significant reductions in fractional anisotropy emerged in schizophrenia only after age 35, and the rate of fractional anisotropy deterioration with age was constant. Notably the slope of this line was 60% steeper in schizophrenia relative to comparison subjects.

Comment: This is a rather technical report exploring the way in which patients with schizophrenia process emotion in faces that they perceive. Facial emotional processing occurs through two separate visual pathways: the magnocellular and parvocellular. Using manipulations of the facial stimuli presented, the authors explored whether dysfunctional facial emotional processing was related to difficulties mediated through one or both of these pathways. They found a significantly greater dysfunction in processing through the magnocellular pathway. The overall importance of this research, is that it confirms other studies both in the visual and other domains that suggest that higher order cognitive functions in patients with schizophrenia may in part be determined by difficulties in processing at relatively early stages of cognitive function. Cognitive remediation is likely to require approaches that address processing from very early stages upwards rather than concentrating on higher order cognitive activity.
Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: Systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors

Authors: Leucht S, et al

Summary: This meta-analysis included 167 randomised controlled trials with 28,102 patients with mainly chronic schizophrenia. The standardised mean difference (SMD) for overall efficacy was 0.47; accounting for small-trial effects and publication bias reduced this to 0.38. At least a minimal response occurred in 51% of the antipsychotic group versus 30% in the placebo group, and 23% versus 14% had a good response. The authors highlight effect sizes were reduced by industry sponsorship and increasing placebo response, not decreasing drug response.

Comment: This was an interesting report describing outcomes from 167 randomised trials of drugs in schizophrenia conducted over six decades. The authors found a consistent pattern of differences in response to antipsychotic drugs across time between active drug and placebo. Positively, some degree of response was seen consistently in about half of patients receiving an active drug compared to about 30% of patients receiving placebo. However, a substantial or good response was consistently only seen in slightly less than a quarter of patients receiving active drug (compared to 14% on placebo). Interestingly, smaller effect sizes were seen in industry sponsored trials. Although this analysis supports the overall efficacy of antipsychotic drugs, it also suggests that we should be exploring substantially novel treatment targets to try and achieve better overall clinical responses, as these are likely to be sufficient in only a minority of patients receiving existing antipsychotic treatments.


Abstract

Authors: Miyauchi M, et al

Summary: Clinical parameters in a cohort of 70 Japanese patients with schizophrenia (38 smokers, 32 non-smokers) were assessed at baseline (before smoking cessation) and at three years after smoking cessation. The group concluded parasympathetic nervous system activity and the doses of antiparkinsonian drugs in smokers were significantly higher than those in non-smokers at baseline. They also reported smoking cessation was associated with significantly decreased sympathetic nervous system activity and decreased doses of antipsychotics and antiparkinsonian drugs at three years after smoking cessation.

Comment: The physical benefits of smoking cessation are clearly apparent to all and are motivating attempts to encourage and aid patients with schizophrenia to reduce or give up smoking. This research provides additional impetus for these activities as it explores the impact of successful smoking cessation on additional health-related benefits. In the study, successful smoking cessation was associated with a reduction in sympathetic nervous system activity and importantly decreased doses of antipsychotic and anti-parkinsonism drugs required three years after successful smoking cessation. The reduction in required drug doses may reflect metabolic changes and/or improvements in efficacy. Regardless, lower doses of medication are likely to be associated with fewer side effects and be of substantial importance longer term for patients.

Reference: BMC Psychiatry 2017 Mar 7;17(1):87

Abstract

Long term effects of smoking cessation in hospitalized schizophrenia patients