Welcome to the 12th issue of Schizophrenia Research Review

A meta-analysis comparing immediate versus gradual discontinuation in antipsychotic switching found no significant differences in any clinical outcomes between the two approaches. The authors advise clinicians to choose an antipsychotic switching strategy according to individual patient needs. Another interesting study investigated an integrated care model, which included antipsychotics plus cognitive behavior therapy and rehabilitation treatment for patients with schizophrenia. The model resulted in lower post-discharge relapse rates and significantly improved reductions in positive symptoms and self-care compared to standard antipsychotic medication alone. A study of computer-assisted cognitive remediation therapy in schizophrenia found a decrease in acute psychiatric admissions at 12, 24 and 36 months post-therapy, which may help to reduce health care costs.

We also include a post hoc analysis on data from three similarly designed, randomised controlled withdrawal studies of paliperidone in adults with schizophrenia. The authors concluded patients who had been taking oral medication experienced relapse more rapidly than patients who had been receiving injectable versions of the medication. Importantly, patients receiving the injectable medication had improved adherence and lower overall use of medication. A study comparing once-monthly paliperidone palmitate versus oral atypical antipsychotic treatment among adults recently diagnosed with schizophrenia found paliperidone palmitate was associated with better adherence and less use of other psychiatric medications. Total healthcare costs were similar across groups.

We conclude this issue with an interesting study assessing treatment effect of antipsychotics in combination with horticultural therapy in patients with schizophrenia. The horticultural therapy produced significant benefits for both positive and negative symptoms of schizophrenia, highlighting the psychological value of actively engaging patients in meaningful activities.

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 Paul Fitzgerald
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Immediate vs gradual discontinuation in antipsychotic switching: A systematic review and meta-analysis

Authors: Takeuchi H, et al

Summary: This meta-analysis included a total of nine randomised controlled trials examining immediate vs gradual antipsychotic discontinuation in antipsychotic switching in 1,416 patients with schizophrenia and/or schizoaffective disorder. Clinical outcomes assessed included study discontinuation, psychopathology, extrapyramidal symptoms, and treatment-emergent adverse events. The authors concluded there were no significant differences in any clinical outcomes between the 2 approaches (all Ps > 0.05).

Comment: How to stop antipsychotic medication when changing to new treatments is a fundamental clinical question faced by psychiatrists every day. As with many of these really basic questions however, there is relatively limited research data that informs how clinicians should make decisions about how to discontinue medication. In the current report, the authors reviewed nine studies that explored whether there were differences between a gradual approach to stopping medication or immediate discontinuation. Interestingly, in a meta-analysis of these nine studies, the authors found no differences in clinical outcomes between patients who had medication ceased immediately or gradually tapered. This did not appear to be related to the medication type that was being ceased. Although clearly decisions about how to switch medications need to be determined on an individual patient basis, this review suggests that highly cautious cross tapering may not be as valuable as some might think and potentially not worth the risk of cessation not going ahead and patients remaining long-term on polypharmacy.

Reference: Schizophr Bull 2017 Jan 1. pii: sbw171

Abstract

Independent commentary by Professor Paul Fitzgerald, Professor of Psychiatry at Epworth Clinic/Epworth Hospital and Deputy Director at the Monash Alfred Psychiatry Research Centre, a joint research centre of Monash University and the Alfred Hospital in Melbourne, Australia. He runs a research program focussed on the conduct of investigative studies of brain function & dysfunction as well as the conduct of a variety of novel clinical trials in Mood, Anxiety, Psychotic and Developmental Disorders. He has published over 350 papers and received grant funding from a range of Australian and international organisations.
Does half-life matter after antipsychotic discontinuation? A relapse comparison in schizophrenia with 3 different formulations of paliperidone.

Authors: Weiden PJ, et al

Summary: The researchers performed post hoc analysis on data from three similarly designed, multicentre, double-blind, placebo-controlled, randomised-withdrawal studies of paliperidone in adults with schizophrenia. Of the study cohort of 449 adults withdrawn from 3 paliperidone formulations, 101 were taking once-daily extended-release oral paliperidone, 203 once monthly paliperidone palmitate and 145 once every-3-months paliperidone palmitate. Postwithdrawal median days to relapse were 56 days (42-114 days) for oral paliperidone, 172 days (134-222 days) for once-monthly paliperidone palmitate, and 395 days (274 days-not reached) for once-every-3-months. Relapse risk was significantly lower (P < .001) for patients who withdrew from either injectable paliperidone palmitate formulation relative to oral paliperidone. In addition they noted relapse risk was significantly lower for patients who withdrew from and once-every-3-months paliperidone palmitate relative to once-monthly paliperidone palmitate.

Comment: This study explored the median time to relapse in patients who had discontinued treatment with paliperidone, either from oral medication, one monthly or three monthly injectable versions. Patients who had been taking oral medication experienced relapse more rapidly than patients who had been receiving injectable versions of the medication and was slowed in patients receiving the once every three months depot formulation. Whilst this is in many ways not surprising given that the long half-life of injectable medication will ensure that it has a lasting direct effect much longer than oral medication on discontinuation, it is noteworthy that the median time to relapse for the three monthly injection was quite long (over one year). It is also worthy of noting that 50% of patients in all three groups experienced relapse in the follow-up time, clearly a highly significant percentage.


Abstract

Sun exposure and psychotic experiences

Authors: Pilecka I, et al

Summary: This study assessed a Swedish population-based cohort of 34,297 women aged between 30 and 50. Psychotic experiences were established using the 20-item community assessment of psychotic experiences (CAPEs) and sun exposure measured by history of sunburn and sunbathing holidays. The group found women who reported no sunbathing holidays and 2 or more weeks of sunbathing holidays scored higher on the CAPE scale than women exposed to 1 week of sunbathing holidays. In addition, women with none or two or more sunburns showed higher scores on the CAPE scale, compared with women who reported a history of one sunburn.

Comment: There has been increasing interest in the potential role of vitamin D as a risk factor for the development of psychiatric disorders such as schizophrenia. In this current report, investigators studied the relationship between unusual experiences (using a psychotic experiences rating scale) and sun exposure (as assessed by how often individuals had sunbathing holidays or had exposure to sunburn). Interestingly, both high and low levels of exposure to sun based on this assessment method were associated with higher rates of experiencing so-called psychotic experiences. Clearly there are major limitations in the use of this form of assessment tool to assess factors related to psychotic disorders, and the sun exposure methods are relatively crude, but this provides interesting supporting evidence that vitamin D may have some relevance in moderating vulnerability to psychotic illnesses.

Reference: Front Psychiatry 2017 Jun 19:8107

Abstract

The associations between quality of life and clinical symptoms in individuals with an at-risk mental state and first-episode psychosis

Authors: O'murro N, et al

Summary: These researchers investigated what specific clinical symptoms relate to a decreased quality of life in 104 individuals with an at-risk mental state and 53 with first-episode psychosis. Quality of life was assessed using World Health Organization’s WHOQOL-BREF and clinical symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) and the Beck Depression Inventory-II. They reported significant correlations between poor quality of life and severity of depressive symptoms in both the first-episode psychosis and at-risk mental state group. They also noted no between-group differences in any correlation coefficients between quality of life and clinical symptoms.

Comment: Quality of life and its determinants has been extensively investigated in patients with schizophrenia and related disorders. Generally speaking, quality of life in patients with established illness is predominantly determined by rates of mood symptoms and to a lesser degree negative symptoms, with the severity of positive symptoms of the disorder playing a very limited role. In the current report the investigators focused on rates of quality of life in patients with first episode psychosis and those judged to be at high risk of transition to psychosis. They found no differences across the two groups in the factors determining poor quality of life. They found, like in established illness groups, that depression was by far and away the major determinant of quality of life in this population. Clearly, treatment approaches in patients with schizophrenia need to focus on moderating positive symptoms but depression should also be a major focus of active treatment to improve patient quality of life.


Abstract

Two-stage integrated care versus antipsychotic medication alone on outcomes of schizophrenia: One-year randomized controlled trial and follow-up

Authors: She S, et al

Summary: Chinese inpatients with schizophrenia were randomly assigned to antipsychotic medication-alone (n=84) or two-stage integrated care (n=86), which included antipsychotics plus cognitive-behavioural therapy and rehabilitation treatment. The authors reported rates of relapse were significantly lower in the integrated care group compared with medication-alone group (p=0.012). They also observed the integrated care group significantly improved in positive symptoms and had greater improvement in self-care and less aggressive behaviors over time (all p<0.008).

Comment: This interesting study investigated a new model for the provision of intensive multimodal care for patients with schizophrenia. In the study, the investigators randomised patients to receive antipsychotic medication alone or so-called integrated care which was provided intensely whilst patients were hospitalised and then on three occasions at three month intervals in clinic settings. This is significantly different from most approaches to integrated psychosocial rehabilitation and treatment where approaches have been provided on an outpatient basis and is described by the authors as being suitable for application in settings where medical resources are concentrated, presumably in hospital based programs. The integrated care model required patients to engage in intensive cognitive-behavioural therapy and rehabilitation. This model of care resulted in lower post discharge relapse rates and significantly improved reductions in positive symptoms and self-care compared to standard antipsychotic medication alone. Clearly integrated models of care need to be developed that suit a variety of different treatment settings and research such as this evaluating these innovative programs is critical going forward.


Abstract

Computer-assisted cognitive remediation therapy in schizophrenia: Durability of the effects and cost-utility analysis

Authors: Garetto G, et al

Summary: From a total of 67 participants initially recruited 33 were enrolled in the follow-up study; 20 to the computer-assisted cognitive remediation (CACR) condition group and 13 to the active control condition group. Participants were assessed at baseline, post-therapy and 12 months post-therapy on neuropsychology, quality of life and self-esteem measures. Treatment effectiveness persisted in the CACR group one year post-therapy on neuropsychology, quality of life and self-esteem measures. They also found that the CACR group had a decrease in acute psychiatric admissions at 12, 24 and 36 months post-therapy, helping to reduce health care costs.

Comment: Impaired cognition is increasingly understood substantive part of the symptomatology of schizophrenia and an element of the disorder that significantly contributes to disability and impaired quality of life. As traditional antipsychotic medications have limited impacts on cognition, there has been increasing interest in the use of various forms of cognitive remediation therapy including those using technologically-based solutions. This study described the persistence of effects and cost utility of a computer-based cognitive remediation program. The authors found that cognitive remediation produced decreases in psychiatric hospital admissions for several years post treatment with a significant reduction in treatment costs. It also had clinical outcome benefits at 12 months post treatment. The major limitation of this report is that this follow-up analysis only assessed a subset of patients included in the initial therapy raising the possibility that selection biases may have significantly impacted on the outcomes. However, it is certainly highly promising data that justifies further exploration and evaluation of this type of novel treatment.


Abstract
Abilify Maintena® (aripiprazole)

For the acute and maintenance treatment of schizophrenia in adults,1 and for reduced relapse:2

- Over 90% of patients remained relapse-free over 38 weeks2
- Significantly reduced hospitalisation rates vs. oral standard-of-care antipsychotics in a naturalistic, open-label study3

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Minimum Product Information*: Abilify Maintena® (aripiprazole). Powder and solvent for reconstitution to give a prolonged release suspension for intramuscular injection (400 mg or 300 mg). Indications: For acute and maintenance treatment of schizophrenia in adults. Dosage & Administration: For deltoid and gluteal intramuscular injection only. Prior to initiating treatment with Abilify Maintena tolerability with oral aripiprazole should be established in patients who have never taken aripiprazole. Adults: The recommended starting and maintenance dose is 400 mg once monthly. For CYP2D6 poor metabolisers, the starting and maintenance dose is 300 mg and if taken with strong CYP3A4 inhibitors, reduce the dose to 200 mg. Consider reducing the dose to 300 mg for patients experiencing adverse reactions. Adjust dose if strong CYP2D6/CYP3A4 inhibitors are used for >14 days (refer to full PI). Avoid the use of CYP3A4 inducers and Abilify Maintena for >14 days. After the first injection, continue treatment with oral aripiprazole (10 mg to 20 mg) or other oral antipsychotic for 14 consecutive days. When switching from oral antipsychotics, continue the current antipsychotic (oral aripiprazole 10-20 mg or prescribed dose of other oral antipsychotic) for 14 days following the first injection of Abilify Maintena. When switching from other long-acting injectable antipsychotics, start treatment with Abilify Maintena in place of the next injection with 14 consecutive days of oral aripiprazole. If the dose of Abilify Maintena is discontinued, its prolonged-release characteristics must be considered. See full PI for further details of dosing in special populations, missed doses and detailed instructions on the preparation and administration of Abilify Maintena. Contraindications: Hypersensitivity to aripiprazole or any of the excipients in Abilify Maintena. Precautions: Elderly patients with dementia-related psychosis; suicide; tardive dyskinesia; Neuroleptic Malignant Syndrome; seizures; hyperglycaemia; diabetes mellitus; cardiovascular disorders; orthostatic hypotension; venous thromboembolism; body temperature dysregulation; dysphagia; akathisia; leukopenia; neutropenia; agranulocytosis; pregnancy (Category C); breastfeeding is not recommended; impaired judgement, thinking or motor skills; pathological gambling and impulse control disorders; alcohol. Interactions: strong CYP2D6 inhibitors or inducers; strong CYP3A4 inhibitors; CYP3A4 inducers (e.g. carbamazepine); CNS drugs or alcohol; medicines prolonging QT interval or causing electrolyte imbalance. Adverse Effects: agitation; anxiety; restlessness; insomnia; akathisia; extrapyramidal disorder; tremor; sedation; somnolence; dizziness; headache; dry mouth; musculoskeletal stiffness; fatigue; weight increase; weight decrease; elevated CPK; injection site pain; leukopenia. For all other adverse events see full PI. Presentation: Each one-month therapeutic kit is intended for single use and contains one vial of powder (400 mg or 300 mg aripiprazole); 2 mL vial of water for injections; one 3 mL sterile syringe with 21G needle attached for reconstitution; one 3 mL sterile syringe without a needle; one vial adapter; one 23G, 1-inch (25 mm), one 22G, 1.5-inch (38 mm) and one 21G, 2-inch (51 mm) sterile safety needle. Date of TGA approval: 25 July 2014. Date of Amendment: 11 October 2016. Date of Minimum PI: 17 October 2016. *Updated information in bold italics.


Abilify Maintena is a registered trademark of Otsuka Pharmaceutical Co., Ltd. ABN: 20 601 768 754. Level 2, 9 Help Street Chatswood NSW 2067. Lundbeck Australia Pty Ltd. ABN: 86 070 094 290. Ground Floor, 1 Innovation Road, North Ryde NSW 2113. For expert medical information on Abilify Maintena please call medical services on 1300 721 277. July 2017. SM_LUN757.

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Otsuka

PBS Information: Authority required (STREAMLINED) 4246 Schizophrenia.
Prescribing of clozapine and antipsychotic polypharmacy for schizophrenia in a large medicaid program

Authors: Tang Y, et al.

Summary: This study used Pennsylvania Medicaid data to examine variation in prescribing clozapine and antipsychotic polypharmacy for patients with adult schizophrenia. The study found that clozapine was used in about 7% of patients although there was considerable heterogeneity in the rates of clozapine prescription by prescriber. Average antipsychotic polypharmacy rates were also 7% with considerable variability between prescribers. The authors concluded that generally clozapine prescribing is under utilised and the opposite occurs for antipsychotic polypharmacy. However, without understanding the details of the practices of individual prescribers, it is very hard to draw these conclusions. Although clozapine does appear to be under-utilised in this overall sample, clearly there are substantial barriers to the use of this medication in community settings and perhaps efforts would be better oriented towards addressing and lowering some of these than providing education in evidence-based prescribing which appears to be the conclusion of the authors.


Effectiveness of electroconvulsive therapy and associated cognitive change in schizophrenia: A naturalistic, comparative study of treating schizophrenia with electroconvulsive therapy

Authors: Tor PC, et al

Summary: These investigators compared the symptomatic and cognitive outcomes of patients with schizophrenia who received different modalities of electroconvulsive therapy (ECT). The study cohort of 62 patients received 1 of 4 ECT modalities: bitemporal ECT with age-based dosing, right unilateral ECT with seizure threshold-based dosing, bitemporal ECT with seizure threshold-based dosing, and bifrontal ECT with seizure threshold-based dosing ECT. Patients were assessed before and after the ECT course using the Brief Psychiatric Rating Scale (BPRS) and Montreal Cognitive Assessment (MoCA). The investigators concluded there was a significant improvement in both the total and psychotic subscales of BPRS and MoCA scores across the patients after the course of ECT. In addition, they found global improvements in both scores were not influenced by the type of ECT administered. It was noted that age-based dosing was associated with poorer memory outcomes.

Reference: J ECT 2017 Jun 15 [Epub ahead of print]

Treatment effect of antipsychotics in combination with horticultural therapy: A randomized, double-blind, placebo-controlled study.

Authors: Zhu S, et al

Summary: The study cohort of 110 schizophrenia patients were randomised into either the intervention group or the control group. Both groups received normal medications and the intervention group also attended horticultural therapy. The 90 minute sessions held 3 times every week for 12 weeks included planting, watering, fertilizing, pruning, weeding, collecting vegetables and cooking. The two groups were measured by the PANSS score in the intervention group was significantly lower than in the control group both at the end of the 4th week (p=0.04), the 8th week (p=0.004) and at the end of the 12th week (p=0.057, p<0.001).

Comment: This interesting study, in a western context, appears to hark back to the days of asylum treatment for patients with serious mental health problems. However, I suspect that it has considerable relevance to considerations of management of modern day patients regardless of cultural situation. In the study, 110 patients were randomised to receive ‘horticultural therapy’ or not. The horticultural therapy appears to have involved rehabilitation therapist supervised horticultural activities across the spectrum of activities from planting to cooking vegetables. Interestingly, the horticultural therapy produced significant benefits in terms of general and positive symptoms of schizophrenia. The study doesn’t really allow us to draw many conclusions about the specific values of horticultural activities themselves but I think certainly speaks to the psychological value of actively engaging patients in meaningful activities. This is something that has been lost in the context of Western psychiatric facilities which are frequently now designed to house ‘at risk’ patients and to protect them from themselves over short periods of time before they are discharged rather than truly therapeutic environments. I also wonder whether this study says something about the potentially fundamentally therapeutic nature of being engaged in outdoor activities, especially those that are generative and nature-based.


Adherence, healthcare resource utilization and medicaid spending associated with once-monthly paliperidone palmitate versus oral atypical antipsychotic treatment among adults recently diagnosed with schizophrenia

Authors: Pilon D, et al

Summary: This group investigated the impact of paliperidone palmitate in patients recently diagnosed with schizophrenia. They reported overall, patients initiated on paliperidone palmitate (N = 2053) were younger (mean age: 41 vs. 44 years) and had more baseline antipsychotic use (68% vs. 62%) compared to oral atypical antipsychotics patients (N = 22,347). Paliperidone palmitate was also associated with better adherence and less use of other psychiatric medications. Total healthcare costs were similar across groups.

Comment: Clearly motivated by the recent approvals of several new long-acting injectable antipsychotic medications, there has been a significant upswing in research focusing on the benefits and impacts of these treatment options in patients with psychiatric disorders. The current report examined healthcare costs in patients commencing medication on paliperidone palmitate as compared to those accumulated by patients on standard oral antipsychotic medications. The study found that the use of paliperidone palmitate was associated with higher direct medication costs but that this was offset by a reduction in overall medical costs resulting in a similar cost for each treatment group. The reduction in medical costs was attributable mostly to reductions in inpatient treatment. Importantly, patients receiving the injectable medication had improved adherence and lower overall use of medication.


Treatment of patients with schizophrenia on clozapine and their adherence in a real-world setting

Authors: Gaffney C, et al

Summary: This study used a retrospective cohort design to examine adherence to clozapine treatment and its association with factors such as age, gender, and length of illness. The study included 211 patients with schizophrenia who were prescribed clozapine in a real-world setting. The primary outcome was adherence to clozapine treatment measured by the number of days patients took their medication. The results showed that patients who were prescribed clozapine had a higher level of adherence compared to those who were not prescribed. The study also found that patients who were prescribed clozapine were more likely to be adherent to their medication regimen and this was associated with better outcomes in terms of symptom control. In conclusion, the study highlights the importance of prescribing clozapine to patients with schizophrenia as it is associated with better adherence and better outcomes.