Abstracts

SCHIZOPHRENIA

Given space limitations and varying reprint permission policies, not all of the influential publications the editors considered reprinting in this issue could be included. This section contains abstracts from additional articles the editors deemed well worth reviewing.

Genome-Wide Association Study Identifies Five New Schizophrenia Loci.

Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, Lin DY, Duan J, Ophoff RA, Andreassen OA, Scolnick E, Cichon S, St Clair D, Corvin A, Gurling H, Werge T, Rujescu D, Blackwood DH, Pato CN, Malhotra AK, Purcell S, Dudbridge F, Neale BM, Rossin L, Visscher PM, Posthuma D, Ruderfer DM, Fanous A, Stefansson H, Steinberg S, Mowry BJ, Golimbet V, De Hert M, Jönsson EG, Bitter I, Pietiläinen OP, Collier DA, Tosato S, Agartz I, Albus M, Alexander M, Amdur RL, Amin F, Bass N, Bergen SE, Black DW, Børglum AD, Brown MA, Bruggeman R, Buccola NG, Byerley WF, Cahn W, Cantor RM, Carr VJ, Catts SV, Choudhury K, Cloninger CR, Cormican P, Craddock N, Danoy PA, Datta S, de Haan L, Demontis D, Dikeos D, Djurovic S, Donnelly P, Donohoe G, Duong L, Dwyer S, Fink-Jensen A, Freedman R, Freimer NB, Friedl M, Georgieva L, Giegling I, Gill M, Glenthøj B, Godard S, Hamshere M, Hansen M, Hansen T, Hartmann AM, Henskens FA, Hougaard DM, Hultman CM, Ingason A, Jablensky AV, Jakobsen KD, Jay M, Jürgens G, Kahn RS, Keller MC, Kenis G, Kenny E, Kim Y, Kirov GK, Konnerth H, Konte B, Krabbendam L, Krasucki R, Lasseter VK, Laurent C, Lawrence J, Lencz T, Lerer FB, Liang KY, Lichtenstein P, Lieberman JA, Linszen DH, Lönnqvist J, Loughland CM, Maclean AW, Maher BS, Maier W, Mallet J, Malloy P, Mattheisen M, Mattingsdal M, McGhee KA, McGrath JJ, McIntosh A, McLean DE, McQuillin A, Melle I, Michie PT, Milanova V, Morris DW, Mors O, Mortensen PB, Moskvina V, Muglia P, Myin-Germeys I, Nertney DA, Nestadt G, Nielsen J, Nikolov I, Nordentoft M, Norton N, Nöthen MM, O'Dushlaine CT, Olincy A, Olsen L, O'Neill FA, Orntoft TF, Owen MJ, Pantelis C, Papadimitriou G, Pato MT, Peltonen L, Petursson H, Pickard B, Pimm J, Pulver AE, Puri V, Quested D, Quinn EM, Rasmussen HB, Réthelyi JM, Ribble R, Rietschel M, Riley BP, Ruggeri M, Schall U, Schulze TG, Schwab SG, Scott RJ, Shi J, Sigurdsson E, Silverman JM, Spencer CC, Stefansson K, Strange A, Strengman E, Stroup TS, Suvisaari J, Terenius L, Thirumalai S, Thygesen JH, Timm S, Toncheva D, van den Oord E, van Os J, van Winkel R, Veldink J, Walsh D, Wang AG, Wiersma D, Wildenauer DB, Williams HJ, Williams NM, Wormley B, Zammit S, Sullivan PF, O'Donovan MC, Daly MJ, Gejman PV; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium.

Nat Genet. 2011 Sep 18;43(10):969–76. doi: 10.1038/ng.940.

We examined the role of common genetic variation in schizophrenia in a genome-wide association study of substantial size: a stage 1 discovery sample of 21,856 individuals of European ancestry and a stage 2 replication sample of 29,839 independent subjects. The combined stage 1 and 2 analysis yielded genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest new finding ($P = 1.6 \times 10(-11)$) was with rs1625579 within an intron of a putative primary transcript for MIR137 (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci achieving genome-wide significance contain predicted targets of MIR137, suggesting MIR137-mediated dysregulation as a previously unknown etiologic mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance: CACNA1C (rs4765905, $P = 7.0 \times 10(-9)$), ANK3 (rs10994359, $P = 2.5 \times 10(-8)$) and the ITIH3-ITIH4 region (rs2239547, $P = 7.8 \times 10(-9)$).

Relapse Prevention in Schizophrenia: A Systematic Review and Meta-Analysis of Second-Generation Antipsychotics Versus First-Generation Antipsychotics

Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU.
Mol Psychiatry. 2011 Nov 29. doi: 10.1038/mp.2011.143. [Epub ahead of print]

Few controlled trials compared second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) regarding relapse prevention in schizophrenia. We conducted a systematic review/meta-analysis of randomized trials, lasting ≥6 months comparing SGAs with FGAs in schizophrenia. Primary outcome was study-defined relapse; secondary outcomes included relapse at 3, 6 and 12 months; treatment failure; hospitalization; and dropout owing to any cause, non-adherence and intolerability. Pooled relative risk (RR) (±95% confidence intervals (CIs)) was calculated using random-effects model, with numbers-needed-to-treat (NNT) calculations where appropriate. Across 23 studies (n=4504, mean duration=61.9±22.4 weeks), none of the individual SGAs outperformed FGAs (mainly haloperidol) regarding study-defined relapse, except for isolated, single trial-based superiority, and except for risperidone's superiority at 3 and 6 months when requiring ≥3 trials. Grouped together, however, SGAs prevented relapse more than FGAs (29.0 versus 37.5%, RR=0.80, CI: 0.70-0.91, P=0.0007, I(2)=37%; NNT=17, CI: 10-50, P=0.003). SGAs were also superior regarding relapse at 3, 6 and 12 months (P=0.04, P<0.0001, P=0.0001), treatment failure (P=0.003) and hospitalization (P=0.004). SGAs showed trend-level superiority for dropout owing to intolerability (P=0.05). Superiority of SGAs regarding relapse was modest (NNT=17), but confirmed in double-blind trials, first- and multi-episode patients, using preferentially or exclusively raw or estimated relapse rates, and for different haloperidol equivalent comparator doses. There was no significant heterogeneity or publication bias. The relevance of the somewhat greater efficacy of SGAs over FGAs on several key outcomes depends on whether SGAs form a meaningful group and whether mid- or low-potency FGAs differ from haloperidol. Regardless, treatment selection needs to be individualized considering patient- and medication-related factors. Molecular Psychiatry advance online publication, 29 November 2011; doi:10.1038/mp.2011.143.

A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia.

Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P.
Am J Psychiatry. 2011 Jun;168(6):603–9. Epub 2011 Mar 1.

OBJECTIVE: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. The authors examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland. METHOD: The authors linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient. RESULTS: Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%, 95% confidence interval [CI]=43.7-47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17-0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI=0.31-0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI=0.40-0.73) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI=0.31-0.67). CONCLUSIONS: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

Evaluation of Functionally Meaningful Measures for Clinical Trials of Cognition Enhancement in Schizophrenia.
Green MF, Schooler NR, Kern RS, Frese FJ, Granberry W, Harvey PD, Karson CN, Peters N, Stewart M, Seidman LJ, Sonnenberg J, Stone WS, Walling D, Stover E, Marder SR.
Am J Psychiatry. 2011 Apr;168(4):400–7.

OBJECTIVE: Because reduction of psychotic symptoms in schizophrenia does not result in adequate community functioning, efforts have shifted to other areas, such as cognitive impairment. The U.S. Food and Drug Administration requires that drugs for cognition enhancement in schizophrenia show improvement on two distinct outcome measures in clinical trials: an accepted cognitive performance battery and a functionally meaningful coprimary measure. The authors examined the reliability, validity, and practicality of functionally meaningful measures. METHOD: In this four-site validation study, schizophrenia patients were assessed at baseline (N=166) and 4 weeks later (N=144) on performance-based (Independent Living Scales, Test of Adaptive Behavior in Schizophrenia [TABS], and UCSD Performance-based Skills Assessment [UPSA]) and interview-based (Cognitive Assessment Interview and Clinical Global Impression Scale for Cognition) candidate coprimary measures. In addition, cognitive performance, community functioning, and clinical symptoms were assessed. Both full and short forms of the performance-based measures were evaluated. RESULTS: All measures were well tolerated by patients, had adequate test-retest reliability, and showed good utility as a repeated measure. Measures differed in their correlation with cognitive performance, with performance-based measures having stronger correlations than interview-based measures. None of the measures had notable floor or ceiling effects or missing data. CONCLUSIONS: Among the full-form measures, the UPSA was judged to have the strongest overall properties. Among the short forms, the TABS and UPSA appeared to have the strongest features. Use of the short forms saves time, but at the cost of lower test-retest reliability and weaker correlations with cognitive performance.

Rethinking Schizophrenia
Insel TR.
Nature. 2010 Nov 11;468(7321):187–93.

How will we view schizophrenia in 2030? Schizophrenia today is a chronic, frequently disabling mental disorder that affects about one per cent of the world's population. After a century of studying schizophrenia, the cause of the disorder remains unknown. Treatments, especially pharmacological treatments, have been in wide use for nearly half a century, yet there is little evidence that these treatments have substantially improved outcomes for most people with schizophrenia. These current unsatisfactory outcomes may change as we approach schizophrenia as a neurodevelopmental disorder with psychosis as a late, potentially preventable stage of the illness. This 'rethinking' of schizophrenia as a neurodevelopmental disorder, which is profoundly different from the way we have seen this illness for the past century, yields new hope for prevention and cure over the next two decades.

Advances in the Management of Treatment- Resistant Schizophrenia
Ballon JS, Lieberman JA.
FOCUS 2010;8:475–487.

Schizophrenia is a serious mental illness responsible for tremendous morbidity and decreases in quality of life and productivity. It is the eighth leading cause of disability-associated life years lost (1) and accounts for nearly 1.1% of overall losses according to the World Health Organization (2). Although there are several treatments for schizophrenia, numerous individuals continue to experience the wide range of symptoms with which many patients present. Current medications target positive symptoms, i.e., hallucinations and delusions, but are not effective for negative symptoms, i.e., apathy, social dysfunction, and flat affect, or cognitive symptoms, such as deficits in executive function and working memory.

Cannabis Use and the Course of Schizophrenia: 10-Year Follow-Up After First Hospitalization.
Foti DJ, Kotov R, Guey LT, Bromet EJ.
Am J Psychiatry. 2010 Aug;167(8):987–93.

OBJECTIVE: The authors examined the relationship between cannabis use and the course of illness in schizophrenia over 10 years of follow-up after first psychiatric hospitalization. METHOD: The authors assessed 229 patients with a schizophrenia spectrum disorder five times: during the first admission and 6 months, 2 years, 4 years, and 10 years later. Ratings of cannabis use and psychiatric symptoms (psychotic, negative, disorganized, and depressive) were made at each assessment. RESULTS: The lifetime rate of cannabis use was 66.2%, and survival analysis revealed that lifetime use was associated with an earlier onset of psychosis. The rates of current use ranged from 10% to 18% across assessments. Cannabis status was moderately stable, with tetrachoric correlation coefficients between waves ranging from 0.48 to 0.78. Mixed-effects logistic regression revealed that changes in cannabis use were associated with changes in psychotic symptoms over time even after gender, age, socioeconomic status, other drug use, antipsychotic medication use, and other symptoms were controlled for. Structural equation modeling indicated that the association with psychotic symptoms was bidirectional. CONCLUSIONS: Cannabis use is associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after taking into account other clinical, substance use, and demographic variables.

The 2009 Schizophrenia PORT Psychosocial Treatment Recommendations And Summary Statements.
Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, Lehman A, Tenhula WN, Calmes C, Pasillas RM, Peer J, Kreyenbuhl J; Schizophrenia Patient Outcomes Research Team (PORT).
Schizophr Bull. 2010 Jan;36(1):48–70.

The Schizophrenia Patient Outcomes Research Team (PORT) psychosocial treatment recommendations provide a comprehensive summary of current evidence-based psychosocial treatment interventions for persons with schizophrenia. There have been 2 previous sets of psychosocial treatment recommendations (Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull. 1998;24:1-10 and Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull. 2004;30:193-217). This article reports the third set of PORT recommendations that includes updated reviews in 7 areas as well as adding 5 new areas of review. Members of the psychosocial Evidence Review Group conducted reviews of the literature in each intervention area and drafted the recommendation or summary statement with supporting discussion. A Psychosocial Advisory Committee was consulted in all aspects of the review, and an expert panel commented on draft recommendations and summary statements. Our review process produced 8 treatment recommendations in the following areas: assertive community treatment, supported employment, cognitive behavioral therapy, family-based services, token economy, skills training, psychosocial interventions for alcohol and substance use disorders, and psychosocial interventions for weight management. Reviews of treatments focused on medication adherence, cognitive remediation, psychosocial treatments for recent onset schizophrenia, and peer support and peer-delivered services indicated that none of these treatment areas yet have enough evidence to merit a treatment recommendation, though each is an emerging area of interest. This update of PORT psychosocial treatment recommendations underscores both the expansion of knowledge regarding psychosocial treatments for persons with schizophrenia at the same time as the limitations in their implementation in clinical practice settings.

Risperidone Maintenance Treatment in Schizophrenia: A Randomized, Controlled Trial
Wang CY, Xiang YT, Cai ZJ, Weng YZ, Bo QJ, Zhao JP, Liu TQ, Wang GH, Weng SM, Zhang HY, Chen DF, Tang WK, Ungvari GS; Risperidone Maintenance Treatment in Schizophrenia (RMTS) investigators.
Am J Psychiatry 2010;167:676–685.

Objective Prevention of relapse is the crucial task in the maintenance treatment of schizophrenia. The investigators in this study sought to determine the duration of maintenance treatment needed with the initial therapeutic dose, in contrast to a reduced dose. Method In a multicenter open-label, randomized, controlled study, patients with schizophrenia who were clinically stabilized following an acute episode were randomly assigned to a no-dose-reduction group (initial optimal therapeutic dose continued throughout the study), a 4-week group (initial optimal therapeutic dose continued for 4 weeks, followed by a 50% dose reduction that was maintained until the end of the study), or a 26-week group (initial optimal therapeutic dose continued for 26 weeks, followed by a 50% dose reduction until the end of the study). All patients continued until the last recruited patient completed the 1-year follow-up. Results Of the 404 patients who met the entry criteria and were randomly assigned, 374 completed the study. The estimated mean time from entry to relapse was 571 days in the 4-week group, 615 days in the 26-week group, and 683 days in the no-dose-reduction group, with estimated relapse rates of 30.5%, 19.5%, and 9.4%, respectively. Patients in the no-dose-reduction group experienced greater reduction in the severity of psychotic symptoms. Conclusions Patients who continued to receive the full risperidone dose used for their acute episode had fewer relapses than those who had dose reductions after 4 weeks or 26 weeks during the maintenance period. There was negligible difference in side effects among the three groups.

A Genome-Wide Investigation of SNPs and CNVs in Schizophrenia
Need AC, Ge D, Weale ME, Maia J, Feng S, Heinzen EL, Shianna KV, Yoon W, Kasperaviciūte D, Gennarelli M, Strittmatter WJ, Bonvicini C, Rossi G, Jayathilake K, Cola PA, McEvoy JP, Keefe RS, Fisher EM, St Jean PL, Giegling I, Hartmann AM, Möller HJ, Ruppert A, Fraser G, Crombie C, Middleton LT, St Clair D, Roses AD, Muglia P, Francks C, Rujescu D, Meltzer HY, Goldstein DB.
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Open Access at http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000373

We report a genome-wide assessment of single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) in schizophrenia. We investigated SNPs using 871 patients and 863 controls, following up the top hits in four independent cohorts comprising 1,460 patients and 12,995 controls, all of European origin. We found no genome-wide significant associations, nor could we provide support for any previously reported candidate gene or genome-wide associations. We went on to examine CNVs using a subset of 1,013 cases and 1,084 controls of European ancestry, and a further set of 60 cases and 64 controls of African ancestry. We found that eight cases and zero controls carried deletions greater than 2 Mb, of which two, at 8p22 and 16p13.11-p12.4, are newly reported here. A further evaluation of 1,378 controls identified no deletions greater than 2 Mb, suggesting a high prior probability of disease involvement when such deletions are observed in cases. We also provide further evidence for some smaller, previously reported, schizophrenia-associated CNVs, such as those in NRXN1 and APBA2. We could not provide strong support for the hypothesis that schizophrenia patients have a significantly greater "load" of large (>100 kb), rare CNVs, nor could we find common CNVs that associate with schizophrenia. Finally, we did not provide support for the suggestion that schizophrenia-associated CNVs may preferentially disrupt genes in neurodevelopmental pathways. Collectively, these analyses provide the first integrated study of SNPs and CNVs in schizophrenia and support the emerging view that rare deleterious variants may be more important in schizophrenia predisposition than common polymorphisms. While our analyses do not suggest that implicated CNVs impinge on particular key pathways, we do support the contribution of specific genomic regions in schizophrenia, presumably due to recurrent mutation. On balance, these data suggest that very few schizophrenia patients share identical genomic causation, potentially complicating efforts to personalize treatment regimens.