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on schizophrenia and bipolar disorders

Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS®) in the Swedish COAST-study

European Neuropsychopharmacology, 2013 December; 23(12):1754–62

The role of the major histocompatibility complex region in cognition and brain structure: a schizophrenia GWAS follow-up

American Journal of Psychiatry, 2013 August 1; 170(8):877–85

Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network

Cell, 2013 August 1; 154(3):518–29

Neural primacy of the salience processing system in schizophrenia

Neuron, 2013 August 21; 79(4):814–28

Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder

American Journal of Psychiatry, 2013 September 1; 170(9):1032–40

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European Journal of Clinical Pharmacology, 2013 August; 69(8):1497–509

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Framingham's team of medical writers prepares original abstracts of these articles, in a structured format that presents the main points at a glance. Our aim is to convey the essence of each article in a concise but readable style.
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DRUG ATTITUDE AND OTHER PREDICTORS OF MEDICATION ADHERENCE IN SCHIZOPHRENIA:

12 MONTHS OF ELECTRONIC MONITORING (MEMS®) IN THE SWEDISH COAST-STUDY

European Neuropsychopharmacology, 2013 December; 23(12):1754–62

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CENTRE FOR CORRESPONDENCE: Psychosis Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden

BACKGROUND & AIM: Long-term treatment is recommended for schizophrenia patients, but adherence to medication is poor for a variety of reasons, which include the tolerability and side-effects of medication, the perception of drug efficacy (and effectiveness in the clinical setting), and a lack of insight and a negative drug attitude among patients. The aim of this study was to investigate baseline predictors of medication non-adherence over 12 months in patients with schizophrenia.

STUDY DESIGN: Cohort study.

ENDPOINT: Adherence to medication.

METHOD: Outpatients with schizophrenia or schizophrenia-like psychosis were recruited. Outcomes recorded at baseline from psychiatrist-rated, neuropsychological and self-rated tests including the Positive and Negative Syndrome Scale (PANSS), Personal and Social Performance scale (PSP), the Udvalg for Kliniske Undersøgelser Side-Effect Self-Rating Scale (UKU-SERS-Pat), and Drug Attitude Inventory-10 Items (DAI-10) for patients and informants. The Medication Event Monitoring system (MEMS) was used to measure medication adherence at 12 months. For analysis, mean MEMS adherence was dichotomised into 2 categories: adherent (>0.80) and non-adherent (≤0.80).

RESULTS: Of the 112 participants, 31 (27.7%) were classified as non-adherent according to MEMS. On univariate analysis, higher scores on the PANSS positive subscale and the insight item (G12) were associated with non-adherence. In addition, there was a relationship between non-adherence and psychiatric side effects (UKU-SERS-Pat) and lower level of functioning (PSP). Also, a more negative drug attitude (DAI-10) was associated with medication non-adherence. On multivariate regression analysis, low scores on the DAI-10 and PSP were associated with non-adherence. Receiver operating characteristic (ROC) analysis gave an area-under-the-curve (AUC) of 0.73 ($p<0.001$) for the ability of the DAI-10–patient instrument to correctly predict adherence. A cut-off DAI-10 score of 4 gave a sensitivity for prediction of non-adherence of 0.68 and a specificity of 0.32. Application of the ROC procedure to the final multivariate regression model including DAI-10, PSP, age and sex achieved a larger AUC (0.78, $p<0.001$) and an improved specificity (0.94), but sensitivity remained low at 0.52.

CONCLUSION: Drug attitude, as assessed by the DAI-10, was the best predictor of adherence to antipsychotic treatment over the 12-month study period. However, at the DAI-10 cut-off value of 4, one-third of the adherent patients would be falsely identified as non-adherent.

THE ROLE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX REGION IN COGNITION AND BRAIN STRUCTURE:

A SCHIZOPHRENIA GWAS FOLLOW-UP

American Journal of Psychiatry, 2013 August 1; 170(8):877–85

AUTHORS: Walters JT, Rujescu D, Franke B, Giegling I, Vásquez AA, Hargreaves A, Russo G, Morris DW, Hoogman M, Da Costa A, Moskvina V, Fernández G, Gill M, Corvin A, O'Donovan MC, Donohoe G, Owen MJ
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BACKGROUND & AIM: Three recent genome-wide association studies (GWAS) have identified significant genetic risk variants in patients with schizophrenia. Although these findings support the association of genomic regions rather than specific genes, the identification of single nucleotide polymorphisms (SNPs) may help elucidate the neurobiological pathways involved in the disease. The aim of this study was to investigate the effects of recently identified genome-wide significant schizophrenia genetic risk variants on cognition and brain structure in patients with schizophrenia.

STUDY DESIGN: Cross-sectional study.

ENDPOINTS: Neurocognitive measures, including IQ, episodic memory, verbal and spatial working memory and attention/vigilance; brain structural volumes, including total grey matter volume and total hippocampal volume.

METHOD: In a discovery sample of 346 schizophrenia patients and 2342 healthy controls, associations with cognition were tested for a panel of 6 SNPs representing all genome-wide significant signals from three GWAS for schizophrenia, namely the International Schizophrenia Consortium, Molecular Genetics of Schizophrenia, and SGENE-plus studies. Nominally significant marker-phenotype combinations were evaluated for replication in an independent cohort of 377 schizophrenia patients and 145 controls. The SNPs demonstrating a replicated association with cognition were assessed for association with brain structural volumes (assessed by structural magnetic resonance imaging) in a large independent sample of healthy comparison subjects.

RESULTS: Of the 6 SNPs, only rs6904071, a marker in the major histocompatibility complex region, showed a nominally significant association with cognition, in particular with IQ, spatial working memory, delayed episodic memory and attention. In the replication cohort, rs6904071 was associated with delayed episodic memory and remained significant in both samples combined. Although rs6904071 was associated with widespread effects across cognitive domains in both samples combined, these associations were not significant after adjustment for delayed episodic memory. Occurrence of rs6904071 was also associated with increased grey matter volume (β= –5.93, 95% confidence interval –0.37 to –11.49, p=0.036) and decreased total hippocampal volume (β=0.080, 95% CI 0.006–0.154, p=0.035).

CONCLUSIONS: In patients with schizophrenia, occurrence of the SNP rs6904071 was associated with poorer cognition and decreased hippocampal volume, but with increased grey matter volume.

SPATIAL AND TEMPORAL MAPPING OF DE NOVO MUTATIONS IN SCHIZOPHRENIA TO A FETAL PREFRONTAL CORTICAL NETWORK

Cell, 2013 August 1; 154(3):518–29

AUTHORS: Gulsuner S, Walsh T, Watts AC, Lee MK, Thornton AM, Casadei S, Rippey C, Shahin H, for the Consortium on the Genetics of Schizophrenia (COGS); Nimgaonkar VL, Go RC, Savage RM, Swerdlow NR, Gur RE, Braff DL, King MC, McClellan JM, for the PAARTNERS Study Group
CENTRE FOR CORRESPONDENCE: Department of Medicine and Department of Genome Sciences, University of Washington, Seattle, Washington, USA

BACKGROUND & AIMS: Patients with sporadic schizophrenia often bear *de novo* mutations that disrupt genes involved with signalling, synaptic plasticity and neurodevelopmental processes. The aims of this study were to identify *de novo* damaging mutations in patients with sporadic schizophrenia and to characterize functional brain networks of the genes harbouring these mutations using transcriptome profiles of normal human brain tissues across different developmental stages.

STUDY DESIGN: Genomic and computational study.

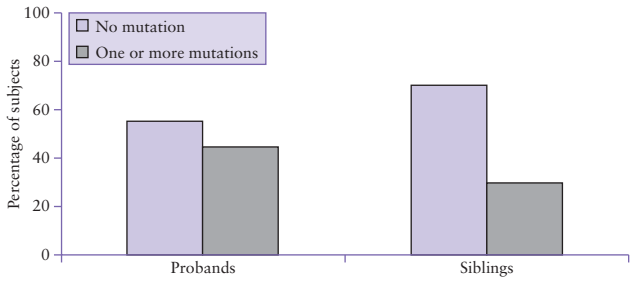
ENDPOINTS: *De novo* damaging mutations; transcriptome profiles.

METHOD: Exome sequencing identified *de novo* mutations in 105 probands with schizophrenia, their 210 unaffected parents and 84 unaffected siblings. *De novo* variants were identified by comparing exome sequences of each child with his/her parents and were further classified as damaging or not damaging to protein function. Each gene harbouring *de novo* damaging mutations was included in protein interaction and coexpression analyses, and compared with genes carrying *de novo* damaging mutations in unaffected siblings and with data from previous exome studies of schizophrenia and autism. Transcriptional coexpression across different brain regions at different developmental periods for genes harbouring *de novo* mutations were analysed in patients with schizophrenia and their unaffected siblings.

RESULTS: *De novo* damaging mutations were identified in 47 probands with schizophrenia (45%, 0.54 damaging mutations/individual) and in 25 unaffected siblings (30%, 0.42 damaging mutations/individual; Figure). In probands, these *de novo* damaging mutations were harboured by 54 different genes which formed a network significantly enriched for transcriptional coexpression and protein interaction in the dorsolateral and ventrolateral prefrontal cortex during foetal development. Of the 54 genes identified, 50 function in neuronal migration, synaptic transmission, signalling, transcriptional regulation and transport.

CONCLUSIONS: In patients with schizophrenia, damaging *de novo* mutations disrupt the development of prefrontal cortical networks which are involved in organizing input from other cortical and subcortical brain regions to plan and direct motor, cognitive, affective and social behaviours.

Presence of at least one *de novo* putatively damaging mutation



NEURAL PRIMACY OF THE SALIENCE PROCESSING SYSTEM IN SCHIZOPHRENIA

Neuron, 2013 August 21; 79(4):814–28

AUTHORS: Palaniyappan L, Simmonite M, White TP, Liddle EB, Liddle PF
CENTRES: Centre for Translational Neuroimaging in Mental Health, Division of Psychiatry, University of Nottingham; Nottinghamshire Healthcare NHS Trust, Nottingham; Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

BACKGROUND & AIMS: There is evidence for the existence of 2 "task-positive" brain systems that facilitate the performance of tasks requiring focused attention. One of these is the salience network (SN), which is anchored in the right anterior insula (rAI) and dorsal ACC (dACC), and is believed to be involved in integrating external stimuli with internal homeostatic context to mark objects that require further processing. The other is the central executive network (CEN), comprised of the dorsolateral prefrontal cortex (DLPFC) and lateral parietal regions, which works on the identified salient stimuli to enable task performance. Structural and functional neuroimaging studies suggest that the rAI and the DLPFC are involved in the pathophysiology of schizophrenia. The aims of this study were to investigate the causal influences between the SN and CEN and to determine whether causal processing between these networks are disrupted in schizophrenia.

STUDY DESIGN: Cross-sectional study.

ENDPOINT: Functional connectivity.

METHOD: Patients with DSM-IV-defined schizophrenia or schizoaffective disorder who were in a stable phase of illness underwent functional magnetic resonance imaging (fMRI), and the results were compared with those of healthy controls. Granger causal connectivity is a measure of effective connectivity, and so whole-brain Granger causality analysis was performed in task-free resting-state fMRI to elucidate the causal relationships existing across networks.

RESULTS: Thirty-eight patients with schizophrenia or schizoaffective disorder and 35 healthy controls underwent fMRI. rAI exerted a significant excitatory influence on the bilateral DLPFC and, in turn, the bilateral DLPFC had a significant inhibitory influence on the rAI. The excitatory neural influence from the rAI to the DLPFC was weaker in patients with schizophrenia than in healthy controls, and patients had a significant loss of inhibitory effect of the right DLPFC on the bilateral anterior insula and dorsal ACC. Schizophrenia patients also showed a significant reduction in the causal influence from bilateral visual cortex and right hippocampal formation to the insula when compared with controls. Further, the severity of schizophrenia was predicted by both reduced integrity of the salience-execution loop and reduced integrity of the visual inflow to the rAI.

CONCLUSION: Feed-forward and feedback processing between the SN and the CEN are disrupted in patients with schizophrenia.

METFORMIN FOR WEIGHT LOSS AND METABOLIC CONTROL IN OVERWEIGHT OUTPATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

American Journal of Psychiatry, 2013 September 1; 170(9):1032–40

AUTHORS: Jarskog LF, Hamer RM, Catellier DJ, Stewart DD, Lavange L, Ray N, Golden LH, Lieberman JA, Stroup TS; for the METS Investigators
CENTRES: Departments of Psychiatry and Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill; North Carolina Psychiatric Research Center, Raleigh, North Carolina; Departments of Psychiatry and Medicine, Columbia University, College of Physicians and Surgeons; New York State Psychiatric Institute, New York, New York, USA

BACKGROUND & AIM: There are a number of adverse metabolic side effects of antipsychotic medications, including an increased risk of weight gain, hyperlipidaemia, and impaired glucose metabolism. Studies suggest that side effects such as these can increase mortality from cardiovascular diseases among patients, yet little information is available to guide the management of antipsychotic-induced weight gain and the related metabolic deficits. The aim of this study was to investigate the effectiveness of metformin as a weight-loss agent in overweight subjects with schizophrenia.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial.

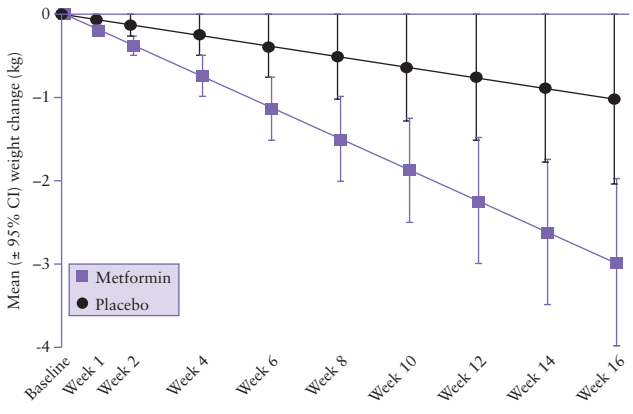
ENDPOINT: Change in body weight.

METHOD: Stable outpatients with schizophrenia or schizoaffective disorder with a body mass index ≥27 received 16 weeks of metformin (500 mg) or placebo twice daily in addition to antipsychotic medication. Metformin was titrated up as tolerated to a maximum dose of 2000 mg/day. All subjects received weekly advice on improving diet and exercise habits.

RESULTS: A total of 75 subjects were randomized to metformin and 71 to placebo. At week 16, the least-squares mean body weight change was –3.0 kg (95% confidence interval –4.0 to –2.0) for the metformin group and –1.0 kg (95% CI –2.0 to –0.0) for the placebo group. The between-group difference was –2.0 kg, 95% CI –3.4 to –0.6, p=0.007; Figure), which demonstrated a significant time-by-treatment interaction (p=0.007). The between-group difference in triglyceride levels was –20.2 mg/dL (95% CI –39.2 to –1.3, p=0.037) in favour of metformin with a time-by-treatment interaction of p=0.04. Changes in fasting glucose or insulin levels did not differ between groups. Metformin was well tolerated and side effects were mainly gastrointestinal.

CONCLUSION: Metformin significantly improved weight loss and other risk factors for cardiovascular disease compared with placebo over the 16-week study period. There was a significant time-by-treatment interaction for metformin, suggesting that benefits may accrue over the longer term.

Weight change across 16 weeks of treatment



ADDITIVE GENETIC VARIATION IN SCHIZOPHRENIA RISK IS SHARED BY POPULATIONS OF AFRICAN AND EUROPEAN DESCENT

American Journal of Human Genetics, 2013 September 5; 93(3):463–70

AUTHORS: de Candia TR, Lee SH, Yang J, Browning BL, Gejman PV, Levinson DF, Mowry BJ, Hewitt JK, Goddard ME, O'Donovan MC, Purcell SM, Posthuma D; International Schizophrenia Consortium; Molecular Genetics of Schizophrenia Collaboration, Visscher PM, Wray NR, Keller MC
CENTRE FOR CORRESPONDENCE: Department of Psychology and Neuroscience, University of Colorado, Boulder, Colorado, USA

BACKGROUND & AIM: Based on analysis of a large European case–control dataset, it has been shown that approximately one-third of the genetic variation in the liability to develop schizophrenia is captured by the additive effects of common single nucleotide polymorphisms (SNPs). However, it is not clear to what extent this genetic risk of schizophrenia extends to patients of other ethnicities. This study was carried out to investigate the extent to which additive genetic variation in the risk of schizophrenia is shared in populations of African descent (AD) and European descent (ED).

STUDY DESIGN: Pooled analysis of large case–control datasets.

ENDPOINT: The additive genetic correlation tagged by SNPs (SNP-rg) in populations of patients.

METHOD: The study analysed data from the large Molecular Genetics of Schizophrenia (MGS), the largest combined AD and ED schizophrenia case–control genome-wide association study dataset available. The dataset included data from a sample of 1223 cases of schizophrenia (AD) and 919 AD controls; plus 2571 cases of schizophrenia (ED) and 2419 ED controls. The analysis used a bivariate linear mixed-effects model to estimate the proportion of schizophrenia risk variation tagged by the additive effects of SNPs in the populations. This approach was then extended such that the SNP-rg between traits was used to estimate SNP-rg for the same trait between ethnicities. Findings in the MGS were validated by re-estimating SNP-rg in an independent dataset of patients/controls of ED, and comparing this with the AD sample from the MGS dataset.

RESULTS: The SNP-rg for schizophrenia between the MGS ED and MGS AD samples was estimated to be 0.66 (SE 0.23); this was significantly different from 0 ($p_{(SNP\text{-}rg=0)}$=0.0003), but not from 1 ($p_{(SNP\text{-}rg=1)}$=0.26). When SNP-rg was re-estimated between an independent ED data set (n=6665) and the MGS AD sample, it was found to be 0.61 (SE 0.21), which was also significantly different from 0 but not from 1 (Table).

CONCLUSIONS: Common genetic liability for schizophrenia appears to be largely shared across populations of African and European descent, suggesting that schizophrenia causal variants predate African–European racial divergence.

SNP-heritability and SNP-correlation estimates from bivariate models

Sample 1	Sample 2	SNP-rg (SE)	$p_{(SNP\text{-}rg=0)}$	$p_{(SNP\text{-}rg=1)}$
Across Ethnicity				
MGS AD (n=2142)	MGS ED (n=4990)	0.66 (0.23)	0.0003	0.26
MGS AD (n=2142)	ISC ED (n=6665)	0.61 (0.21)	0.0003	0.16
Within Ethnicity				
MGS ED (n=4990)	ISC ED (n=6665)	0.83 (0.09)	<0.0001	0.09

SCHIZOPHRENIA IS A COGNITIVE ILLNESS:
TIME FOR A CHANGE IN FOCUS

JAMA Psychiatry, 2013 October; 70(10):1107–12

AUTHORS: Kahn RS, Keefe RS
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BACKGROUND & AIM: The prognosis for people with schizophrenia remains substantially unchanged since the introduction of chlorpromazine more than 50 years ago. The authors of this article hypothesize that one of the reasons for this lack of progress is that schizophrenia is a cognitive illness that has for years been misclassified as a psychotic disorder. The emphasis on psychosis in schizophrenia has contributed to the lack of progress in our understanding of this illness and has hampered the development of adequate treatments.

ARTICLE TYPE: Review.

FINDINGS: The authors give a number of reasons why schizophrenia should be considered first and foremost a cognitive illness. Firstly, they point out that cognitive underperformance is a (genetically mediated) risk factor for schizophrenia. Cognitive and intellectual underperformance have consistently been shown to be risk factors for schizophrenia, and underperformance at school is associated with one of the highest risks for schizophrenia, second only to having a sibling with the illness.

In addition, several studies have found that a decline in cognitive functioning precedes the onset of psychosis in individuals with schizophrenia by almost a decade, a finding that can be used to distinguish schizophrenia from bipolar disorder. Hence, the age of a patient at the onset of the illness is probably a decade earlier than is currently assumed. Accordingly, the authors suggest that cognitive decline prior to the onset of psychosis should be included in the diagnostic criteria for schizophrenia.

Furthermore, there is evidence from a small number of studies that cognitive performance may continue to decline after the onset of psychosis in people with schizophrenia, and may possibly progress even further.

Finally, the authors point out that cognitive underperformance is an important predictor of general functional outcome in schizophrenia. Many studies have found that cognitive function is an independent predictor of global functional outcome, and is relatively unaffected by currently available antipsychotic therapies. Fortunately, new treatments specifically targeting cognitive impairment are under development. There is some evidence, for example, that combining cognitive interventions with rehabilitation programs results in clear, albeit modest, effects that may be translated into improved outcomes for patients.

CONCLUSION: Cognition should be recognized as the core component of schizophrenia, and emphasis should be placed on the early detection of developmental changes in cognitive function. The treatment of cognitive deficits, as well as the reduction of psychotic symptoms, should be key goals of therapy.

NEWER ANTIPSYCHOTICS AND UPCOMING MOLECULES FOR SCHIZOPHRENIA

European Journal of Clinical Pharmacology, 2013 August; 69(8):1497–509

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BACKGROUND & AIM: Symptoms of schizophrenia can be broadly classified into positive symptoms (delusions, hallucinations), negative symptoms (avolition, affective flattening, impoverishment of speech) and cognitive symptoms (attention deficits, impaired memory). Despite the introduction over the past few decades of an increasing number of antipsychotics, few of these drugs are effective against the cognitive and negative symptoms of the disease. The aim of this review was to assess the advantages, limitations and place in the pharmacotherapy of schizophrenia of the only antipsychotics to have been approved by regulatory agencies in the previous 4 years: iloperidone, asenapine, lurasidone and blonanserin.

ARTICLE TYPE: Review.

FINDINGS: The advantages and limitations of iloperidone, asenapine, lurasidone and blonanserin are summarized in the Table. All 4 antipsychotics have been shown to reduce total and positive Positive and Negative Syndrome Scale (PANSS) scores from baseline compared with placebo, whereas iloperidone, lurasidone and blonanserin have also been shown to improve negative PANSS scores.

The adverse event profile of iloperidone, asenapine and lurasidone is comparable to that of other second-generation antipsychotics; however, iloperidone appears to be free of extrapyramidal symptoms at therapeutic doses.

The small numbers of antipsychotic drugs being approved for use in patients with schizophrenia reflect certain difficulties specific to the disease, such as a lack of suitable animal models and a failure to understand the exact aetiology. Nevertheless, a number of promising therapeutic targets for new drugs are currently being explored, including glutamate receptors, GABAergic and cholinergic signalling pathways, phosphodiesterase, H3 receptors, neurokinin3 and adenosine.

CONCLUSION: Although regulatory bodies have approved only a few antipsychotics for the treatment of patients with schizophrenia in recent years, research on a wide spectrum of targets continues with the aim of developing antipsychotics with improved efficacy and acceptability.

Advantages and limitations of the antipsychotics

Drug	Advantages	Limitations
Iloperidone	Extrapyramidal side effects are almost absent at therapeutic doses.	Requires 4 days of titration to reach therapeutic dose range.
Asenapine	Does not cause as much weight gain as olanzapine. Metabolic adverse effects are minimum.	Requires twice daily dose dosing. Essential to avoid food at least 10 min after administration. Oral hypoesthesia is a specific ADR.
Lurasidone	Weight gain minimal. No clinically meaningful alterations in glucose, lipids, prolactin or the QT interval.	Drug must be taken with food (at least 350 calories) for adequate absorption. Dose-related EPS and akathisia known to occur.
Blonanserin	No specific advantage	Parkinson's syndrome, akathisia, insomnia, hyperprolactinaemia are common adverse effects. Profound CNS depression in the presence of alcohol and other CNS depressants.

EPIDEMIOLOGY OF SUICIDE IN BIPOLAR DISORDERS:
A SYSTEMATIC REVIEW OF THE LITERATURE

Bipolar Disorders, 2013 August; 15(5):457–90

AUTHORS: Pompili M, Gonda X, Serafini G, Innamorati M, Sher L, Amore M, Rihmer Z, Girardi P
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BACKGROUND & AIM: Suicide is an important worldwide public health problem; approximately one million deaths due to suicide are reported annually. The risk of suicide has been shown to be up to 20 times higher in patients with major affective disorders than in the general population. In patients with bipolar disorder, rates of both attempted and successful suicide are high, though suicide rates are inconsistent between studies. The aim of this investigation was to systematically review the published literature on the epidemiology of completed suicide in adults with bipolar disorder.

STUDY DESIGN: Systematic review.

ENDPOINT: Incidence of completed suicide.

METHOD: A search of the PubMed, Scopus, PsycLit, PsycInfo and Cochrane databases was carried out to identify all relevant papers published between 1980 and 2011 that met the search terms "suicide" and "bipolar disorder". The search was limited to papers published in peer-reviewed English-language journals that reported on adult patients with bipolar disorder. Studies that reported epidemiological data on completed suicides in patients with bipolar disorder were included; papers that focused exclusively on attempted suicide or suicidal ideation were excluded.

RESULTS: The study identified 34 papers that met the inclusion criteria from a total of 481 records that were screened for eligibility. The publications included prospective follow-up studies, retrospective studies, and a small number of autopsy studies that investigated the epidemiology of completed suicides in patients with bipolar disorder. Overall, the risk of suicide among patients with bipolar disorder was up to 20–30 times higher than that for the general population. Also, the risk of completed suicide was particularly high for younger patients in the first few years after their diagnosis. However, the rates of completed suicide varied considerably between the samples in the studies, and not all studies supported the view that the risk of suicide among patients with bipolar disorder was increased compared with the general population. Factors contributing to the variability of reported suicide rates included gender, previous history of suicide attempts, duration of psychiatric illness, and adherence to treatment.

CONCLUSIONS: The main findings were that suicide risk among people with bipolar disorder was up to 20–30 times higher than in the general population, and that it was particularly high for younger patients in the years following diagnosis.

http://onlinelibrary.wiley.com/doi/10.1111/bdi.12087/abstract

A FAMILY AFFAIR: BRAIN ABNORMALITIES IN SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA

Brain, 2013 November; 136(Pt 11):3215–26

AUTHORS: Moran ME, Hulshoff Pol H, Gogtay N
CENTRES: Child Psychiatry Branch, National Institute of Mental Health, NIH, Bethesda, Maryland, USA; Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre, Utrecht, the Netherlands

BACKGROUND & AIM: It is not yet known whether the anatomical brain abnormalities seen in schizophrenia are related to the illness itself or to the underlying genetic risk (endophenotype) of the individual. Endophenotypes are defined as being associated with the illness (though possibly not causing symptoms by themselves), heritable, and just as common in high-risk relatives as in the proband. They are potentially valuable in research because they allow the study of less complex biological precursors of highly genetic diseases, although there is always the possibility that they are not actually involved in the disease pathway. Structural brain abnormalities characteristic of schizophrenia patients are also seen in first-degree relatives, but it is not clear how they change over the course of development, or whether they are different in young and adult siblings. This article reviews the developmental changes in structural brain imaging findings in the siblings of schizophrenia patients.

ARTICLE TYPE: Review.

FINDINGS: Childhood-onset schizophrenia is characterized by progressive cortical grey matter loss, spreading in a parieto-frontal and parieto-temporal direction during adolescence, and localizing to prefrontal and temporal cortices in young adulthood. The healthy siblings of patients with this form of the illness have been shown to have a smaller total cerebellar volume, as well as smaller total, frontal and parietal grey matter volumes, compared with control subjects. While the progression of these abnormalities initially parallels that in probands, ultimately the deficits normalize, suggesting the existence of protective factors in the healthy siblings. By contrast, cerebellar volumes are no different between the siblings of patients with childhood-onset schizophrenia and control subjects, but the decline with age is greater (although not as abnormal as in the probands). Other potential endophenotypes may come from the genetic polymorphisms underlying these structural abnormalities, and one line of research has implicated a disruption in the pathway linking dopaminergic function to cortical maturation.

In adult-onset schizophrenia, a large number of sibling and twin studies have identified a range of structural brain abnormalities affecting probands and healthy siblings, and these include reductions in hippocampal, thalamic, whole brain and white matter volume, as well as an increase in third ventricle volume. Furthermore, twin studies have suggested that these abnormalities are due in part to genes implicated in schizophrenia.

CONCLUSION: The siblings of schizophrenia patients often have significant regional brain volume reductions, although not as severe as in patients and with a differing developmental trajectory.

NEUROPSYCHOLOGICAL TESTING OF COGNITIVE IMPAIRMENT IN EUTHYMIC BIPOLAR DISORDER:

AN INDIVIDUAL PATIENT DATA META-ANALYSIS

Acta Psychiatrica Scandinavica, 2013 September; 128(3):149–62

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BACKGROUND & AIM: Cognitive impairments (affecting executive control, verbal learning and memory, visual memory and attention) have been reported in patients with bipolar disorder, including euthymic patients. However, the findings of previous studies have varied considerably, due to small sample sizes and differences in the neuropsychological tests used. Furthermore, meta-analyses limited to purely euthymic patients have arrived at different conclusions as regards the cognitive areas involved. The aim of the current study was to conduct an individual patient data meta-analysis to arrive at a more definitive assessment of the link between bipolar disorder and cognitive impairment.

STUDY DESIGN: Individual patient data meta-analysis.

ENDPOINTS: Measures of cognitive impairment.

METHOD: The analysis was conducted using 31 primary data sets consisting, in total, of 2876 euthymic bipolar patients and healthy control subjects. Individual patient data were collected on 11 specific outcome measures from 4 common neuropsychological tests: the California or Rey Verbal Learning Task (VLT), the Trail Making Test (TMT), the Digit Span, and the Wisconsin Card Sorting Task (WCST). Demographic and clinical variables were also collected where possible, including current mood, previous manic and depressed episodes, hospitalizations and drug treatments. Euthymia was defined according to available mood score data, or when assessed by a qualified psychiatrist.

RESULTS: After adjusting for age, IQ and gender, all 11 test measures were found to be impaired in euthymic patients with bipolar disorder compared with healthy control subjects ($p<0.001$ in all cases). The overall effect size varied between 0.26 for the number of categories achieved on the WCST, and 0.63 for the time to complete the TMT B (Table). Residual mood symptoms had some effect on several of these test results, but not enough to account for the effect sizes found. Furthermore, the type of drug treatment had no effect on the performance of any of the tests.

CONCLUSION: Euthymic patients with bipolar disorder showed moderate yet significant cognitive impairments on a range of standard neuropsychological tests.

Overall effect size of group for the 11 outcome variables

Test	Outcome variable	Overall effect size (95% confidence interval)	*p*-value
VLT	Total 1–5	0.51 (0.42–0.60)	<0.001
VLT	Short Delay	0.48 (0.39–0.57)	<0.001
VLT	Long Delay	0.55 (0.47–0.64)	<0.001
VLT	Recognition	0.46 (0.36–0.57)	<0.001
VLT	Recog-FP	0.38 (0.26–0.50)	<0.001
TMT	A	−0.49 (−0.58 to −0.40)	<0.001
TMT	B	−0.63 (−0.72 to −0.55)	<0.001
Digit Span	Forward	0.30 (0.20–0.40)	<0.001
Digit Span	Reverse	0.60 (0.51–0.69)	<0.001
WCST	Categories	0.26 (0.15–0.37)	<0.001
WCST	Perseverations	−0.29 (−0.40 to −0.17)	<0.001

http://onlinelibrary.wiley.com/doi/10.1111/acps.12133/abstract

DIFFUSION TENSOR IMAGING WHITE MATTER ENDOPHENOTYPES IN PATIENTS WITH SCHIZOPHRENIA OR PSYCHOTIC BIPOLAR DISORDER AND THEIR RELATIVES

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BACKGROUND & AIM: Brain dysconnectivity has been hypothesized to be an underlying deficit in both schizophrenia and bipolar disorder. Studies have shown low white matter structure and integrity to be associated with schizophrenia but less consistently associated with bipolar disorder. The aim of this study was to investigate the disease specificity and endophenotypic status of white matter abnormalities by examining patients and their unaffected relatives using diffusion tensor imaging (DTI) imaging.

STUDY DESIGN: Cross-sectional study.

ENDPOINT: White matter integrity.

METHOD: The study recruited 513 participants, including 109 probands with schizophrenia, 35 probands with schizoaffective disorder, 63 probands with psychotic bipolar disorder, 95 relatives of the schizophrenia probands, 43 relatives of the probands with schizoaffective disorder and 64 relatives of the probands with psychotic bipolar disorder. In addition, 104 healthy control subjects were enrolled. Relatives were classified by the presence or absence of symptoms of DSM-IV-TR cluster A and cluster B personality. Individuals with cluster A or B personality characteristics were further examined. Fractional anisotropy was used to measure white matter integrity based on DTI images, collected as part of the Bipolar–Schizophrenia Network on Intermediate Phenotypes project.

RESULTS: The probands with schizophrenia and those with psychotic bipolar disorder had significantly lower fractional anisotropy than the healthy control subjects ($p<0.001$) in 29 white matter regions. There were no significant differences between the proband groups, but the differences were more marked in schizophrenia patients. Many white matter regions that were affected in schizophrenia probands showed similar but smaller deficits in relatives; a continuous decrease in fractional anisotropy was observed from healthy subjects to relatives to cluster A/B relatives to symptomatic probands. A similar pattern was observed for psychotic bipolar disorder, except that fewer brain regions were involved. In bipolar disorder, effects in relatives were only seen in younger subjects. Fractional anisotropy values decreased significantly with increasing age in all groups and most brain regions; this age-related decrease was significantly greater in schizophrenia but not psychotic bipolar disorder.

CONCLUSION: White matter integrity measured by fractional anisotropy was found to be highly heritable, indicating that it may have clinical value as an identifiable endophenotype.

Minimiinformation Sverige

ZYPADHERA 210 mg, 300 mg, 405 mg pulver och vätska till injektionsvätska, suspension (olanzapin)

ATC-kod: N05AH03
Indikationer: Underhållsbehandling av vuxna patienter med schizofreni som stabiliserats under akut behandling med oralt olanzapin.
Kontraindikationer: Känd risk för glaukom med trång kammarvinkel.
Varning: Ska endast ges som en djupt intramuskulär, gluteal injektion. Efter varje injektion ska patienten observeras med avseende på tecken och symtom tydande på olanzapinöverdos i minst 3 timmar av kvalificerad personal med tillgång till sjukvårdsresurser. Omedelbart innan patienten lämnar lokalen bör man förvissa sig om att patienten är klar och vaken och inte har några tecken eller symtom på överdos, och patienten ska observeras i 3 timmar efter injektionen. Observationstiden på 3 timmar bör förlängas, om kliniskt motiverat, för patienter som uppvisar tecken eller symtom på överdos.
Datum för översyn av produktresumén: 2013-08-26
För ytterligare information och priser se www.fass.se.
Rx, F

Eli Lilly Sweden AB, Box 721, 169 27 Solna. 08-737 88 00, www.lilly.se.