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on schizophrenia and bipolar disorders

Polypharmacy with antipsychotics, antidepressants, or benzodiazepines
and mortality in schizophrenia

Archives of General Psychiatry, 2012 May; 69(5):476–83

Occupational outcome in bipolar disorder is not predicted
by premorbid functioning and intelligence

Bipolar Disorders, 2013 May; 15(3):294–305

Brain effects of cognitive remediation therapy in schizophrenia:
a structural and functional neuroimaging study

Biological Psychiatry, 2013 May 15; 73(10):1015–23

Abnormal rich club organization and functional brain dynamics in schizophrenia

JAMA Psychiatry, 2013 August 1; 70(8):783–92

A systematic review of psychostimulant treatment of negative symptoms
of schizophrenia: challenges and therapeutic opportunities

Schizophrenia Research, 2013 July; 147(2–3):241–52

Hippocampal shape abnormalities of patients with childhood-onset schizophrenia
and their unaffected siblings

Journal of the American Academy of Child & Adolescent Psychiatry, 2013 May; 52(5):527–536.e2

Bipolar disorder diagnosis: challenges and future directions

The Lancet, 2013 May 11; 381(9878):1663–71

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The American Journal of Psychiatry, 2013 June 1; 170(6):609–15

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ANTIPSYCHOTICS AND MORTALITY IN FIRST-ONSET SCHIZOPHRENIA: PROSPECTIVE FINNISH REGISTER STUDY WITH 5-YEAR FOLLOW-UP

Schizophrenia Research, 2013 October; 150(1):274–80

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BACKGROUND & AIM: Compared with the general population, people with schizophrenia have an increased risk of mortality. However, there is a reduction in mortality in patients using antipsychotic medications, albeit that the concurrent use of more than one antipsychotic is associated with a risk of premature death. While findings across studies are inconsistent, increased mortality is particularly associated with the use of first-generation antipsychotics (FGAs). The aim of this study was to evaluate the impact of the most commonly prescribed FGAs, second-generation antipsychotics (SGAs) and antidepressants on mortality in patients with first-onset schizophrenia.

STUDY DESIGN: Population-based study.

ENDPOINTS: All-cause mortality, suicide, and cardiovascular death.

METHOD: The study included 6987 patients (mean age 33.8 years, 42.2% women) presenting with first-onset schizophrenia

between January 1998 and December 2003, identified from 4 national patient registers in Finland. Information on reimbursed medicines was obtained from the register of Social Insurance Institution, and cause of death was obtained from the Finnish register which records cause-of-death ICD-10 criteria.

RESULTS: A total of 357 patients died during the 5-year follow-up. Mortality was significantly higher in men than in women (6.2 versus 3.6%, respectively; $p < 0.001$). Of all deaths, 34.2% were suicides and 23.2% were from cardiovascular disease. FGAs (specifically, levomepromazine, thioridazine or clorprothixene) were associated with an increased risk of all-cause mortality, while SGAs (in particular, clozapine, olanzapine and quetiapine) were associated with a reduced risk of all-cause mortality. The use of the SGA clozapine reduced the likelihood of suicide in patients with schizophrenia, while FGAs were associated with an increased risk of suicide compared with non-users of antipsychotics. The results of additional analyses for polypharmacy (Table) supported these findings. As regards antidepressant medications, mirtazapine was associated with an increased risk of suicide and venlafaxine with an increased risk of all-cause mortality.

CONCLUSIONS: First-onset schizophrenia patients who used SGAs had a reduced risk of premature death, while FGAs increased the risk of all-cause premature deaths and deaths by suicide.

Antipsychotic polypharmacy and mortality in first-onset schizophrenia

Cause of death	Antipsychotic medication	Mortality risk	
		Adjusted odds ratio (95% confidence interval)	p-value
Overall mortality	No antipsychotics	Reference	
	FGAs only	1.76 (1.28–2.42)	0.001
	SGAs only	0.61 (0.46–0.79)	<0.001
	Both FGAs and SGAs	1.01 (0.72–1.43)	0.940
Suicide	No antipsychotics	Reference	
	FGAs only	2.41 (1.40–4.13)	0.001
	SGAs only	0.59 (0.38–0.94)	0.026
	Both FGAs and SGAs	1.13 (0.64–2.00)	0.663

POLYPHARMACY WITH ANTIPSYCHOTICS, ANTIDEPRESSANTS, OR BENZODIAZEPINES AND MORTALITY IN SCHIZOPHRENIA

Archives of General Psychiatry, 2012 May; 69(5):476–83

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BACKGROUND & AIM: Although current guidelines for the treatment of schizophrenia recommend antipsychotic monotherapy, polypharmacy is commonly practiced, despite the potential adverse effects on patients' well-being. As little is known about the association between the use of benzodiazepines, antidepressants or multiple concomitant antipsychotic medications and mortality risk in patients with schizophrenia, the aim of this study was to investigate the relationship between polypharmacy and mortality in Finnish patients.

STUDY DESIGN: Registry-based, case linkage study.

ENDPOINT: All-cause mortality.

METHOD: A complete nationwide cohort of 2588 patients with a defined diagnosis of schizophrenia during their first hospitalization between January 1, 2000 and December 31, 2007 was included in the study. Patients were identified from the Finnish National Hospital Discharge Register. After adjusting for sociodemographic and clinical variables, geographic location, and current

and past pharmacological treatments, hazard ratios were calculated for all-cause mortality during the use of antipsychotics, antidepressants or benzodiazepines in outpatient care.

RESULTS: Compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotic medications was not associated with an increased risk of mortality ($p=0.56$; Table). However, a significantly higher risk of mortality was found when no antipsychotics were used (HR 2.09, 95% confidence interval 1.34–3.26). Current antidepressant use was not associated with a higher risk of mortality (Table), but it was associated with a markedly decreased risk of death from suicide (HR 0.15, 95% CI 0.03–0.77). Compared with no benzodiazepine use, mortality risk during benzodiazepine use was increased, a result of both suicidal (HR 3.83, 95% CI 1.45–10.12) and non-suicidal deaths (HR 1.60, 95% CI 0.86–2.97). Of the patients who used benzodiazepines, 91.4% acquired prescriptions with more than 28 defined daily doses, a violation of normal treatment guidelines.

CONCLUSIONS: Benzodiazepine use among patients with schizophrenia was associated with a substantial increase in mortality. Neither antidepressants nor the use of several concomitant antipsychotics were associated with increased mortality.

All-cause mortality risk: primary comparisons of interest

Comparison	Hazard ratio (95% CI)	<i>p</i> -value
Current use of ≥ 2 antipsychotics versus antipsychotic monotherapy	0.86 (0.51–1.44)	0.56
Current benzodiazepine use versus no benzodiazepine use	1.91 (1.13–3.22)	0.02
Current antidepressant use versus no antidepressant use	0.57 (0.28–1.16)	0.12

OCCUPATIONAL OUTCOME IN BIPOLAR DISORDER IS NOT PREDICTED BY PREMORBID FUNCTIONING AND INTELLIGENCE

Bipolar Disorders, 2013 May; 15(3):294–305

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BACKGROUND & AIM: The reasons for the reduced occupational capacity observed in patients with bipolar I disorder (BD) have yet to be elucidated, and there is a need to identify preventive factors and predictors of disability. Recent studies suggest that educational attainment may not protect patients with BD from unemployment; indeed, other factors intrinsic to BD, such as premorbid functioning, general intelligence or clinical characteristics, might explain occupational dysfunction. The aim of this study was to investigate the role of these factors on occupational outcome in BD patients.

STUDY DESIGN: Cross-sectional study.

ENDPOINTS: Premorbid intelligence quotient (IQ), decline in IQ, premorbid function, course of illness, and demographic characteristics.

METHOD: A total of 226 patients with bipolar I disorder ($n=144$), bipolar II disorder ($n=70$), or bipolar disorder not otherwise specified ($n=12$) were recruited

consecutively from October 2002 to December 2009 from 4 major hospitals in Oslo, Norway. Current IQ was assessed using the Wechsler Abbreviated Scale of Intelligence, and premorbid intellectual functioning was estimated using the National Adult Reading Test. Premorbid function was assessed using the Premorbid Adjustment Scale across 4 age ranges: childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years) and adulthood (≥ 19 years).

RESULTS: In total, 31.4% of the cohort received disability benefit, 53.3% had a history of psychosis and 14.2% were hospitalized at the time of inclusion. Premorbid adjustment scale values were similar for the 4 age groups, indicating stable premorbid function across different life stages. The number of hospitalizations for depressive episodes, illness duration and age at inclusion were significantly associated with receipt of disability benefit (Table). No significant associations between receipt of disability benefit and Premorbid Adjustment Scale scores, premorbid or current IQ, decline in IQ, or any of the other demographic and clinical variables were observed.

CONCLUSIONS: Occupational disability in patients with BD was significantly associated with the severity of the clinical course, but was unrelated to poor premorbid functioning or premorbid or current IQ.

Association between disability benefit and demographic and clinical variables

Variable	Disability benefit		<i>p</i> -value
	No ($n=142$)	Yes ($n=65$)	
Age at inclusion; mean (SD)	33.2 (10.5)	36.7 (11.8)	0.035
IQ decline; n (%)	18 (12.7)	7 (11.1)	0.821
Illness duration, years; mean (SD)	11.4 (9.0)	14.8 (12.1)	0.048
Number of hospitalizations for depressive episodes; mean (SD)	0.5 (1.1)	1.1 (1.8)	0.014

BRAIN EFFECTS OF COGNITIVE REMEDIATION THERAPY IN SCHIZOPHRENIA:

A STRUCTURAL AND FUNCTIONAL NEUROIMAGING STUDY

Biological Psychiatry, 2013 May 15; 73(10):1015–23

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BACKGROUND & AIM: Cognitive remediation therapy (CRT) has been associated with improvement in neurocognition and daily functioning in patients with schizophrenia. Although a few studies have evaluated concomitant changes in brain activity with CRT, no studies have fully explored the impact of CRT on brain connectivity using structural and functional magnetic resonance imaging (MRI) techniques. The aim of this study was to investigate changes in brain functional and structural connectivity using functional MRI and diffusion tensor imaging after CRT in patients with schizophrenia.

STUDY DESIGN: Randomized controlled trial.

ENDPOINTS: Functional and structural MRI data.

METHOD: The study included a group of patients with schizophrenia receiving CRT ($n=17$), an active control group of schizophrenia patients receiving social skills training (SST, $n=18$), and a control group of healthy individuals ($n=15$). The interventions were administered for 4 months. Individuals randomized to CRT received a strategy-learning-based treatment, whereas those assigned to SST received information about illness management. Functional and structural imaging, performed using a 3-tesla MRI scanner, and

neuropsychological evaluations were performed 2–3 days before and after treatment. Assessment was made of changes in the pattern of functional connectivity assessed during an n-back task, and in the fractional anisotropy (FA) index of white matter integrity using tract-based spatial statistics.

RESULTS: After treatment, CRT patients showed during task-related responses decreased activation in the central executive network in regions that had shown overactivation at baseline, and decreased activation of its anticorrelated default mode network, suggesting an improvement in the efficiency of both networks. No significant changes were observed for the SST and control groups. Patients in the CRT group also exhibited an increase in white matter integrity, reflected by an increase in FA index in the genu and body of the corpus callosum, and in the right posterior thalamic radiation. In contrast, SST patients showed decreased FA in bilateral superior longitudinal fasciculus and left inferior longitudinal fasciculus, whereas no significant changes in FA emerged in the control group. There was a correlation between functional and structural changes in CRT patients.

CONCLUSIONS: There were detectable effects on functional and structural connectivity in patients with schizophrenia treated with CRT, suggestive of an improvement in the efficiency of functional networks.

ABNORMAL RICH CLUB ORGANIZATION AND FUNCTIONAL BRAIN DYNAMICS IN SCHIZOPHRENIA

JAMA Psychiatry, 2013 August 1; 70(8):783–92

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BACKGROUND & AIM: The normal function of the brain is reliant on the organization of connections between its different regions, and recent studies suggest the existence of a set of highly-connected hub regions that play a key role in the whole network. These hubs form a central core or so-called rich club. The pathophysiology of schizophrenia is thought to be due to a loss of brain connectivity, and imaging studies have shown reduced integrity of frontal and temporal white matter connections, while network studies have indicated disruptions in the organization of structural and functional connectivity. The aim of this study was to investigate whether schizophrenia was associated with abnormal connectivity within the brain's rich club.

STUDY DESIGN: Cross-sectional study.

ENDPOINTS: Rich club organization, connectivity density, global brain network efficiency, and coupling between structural and functional connectivity.

METHOD: A total of 48 patients with schizophrenia and 45 healthy control subjects (principal dataset) underwent structural diffusion tensor imaging and resting-state functional magnetic resonance imaging. After preprocessing of the imaging data to parcellate distinct cortical and sub-cortical regions, and to reconstruct white matter fibre tracts, structural and functional

brain networks were created for each participant. Rich club regions were identified, and the nodes of each network were classified according to their class as rich club, feeder or local connections. Functional networks were analysed for their node-specific connectivity strength and level of modularity. The assessments were repeated in 41 patients and 51 controls (replication dataset).

RESULTS: Patients with schizophrenia had a reduced level of rich club organization compared with healthy control subjects, with a lower connectivity between the central hubs of the brain. This was most pronounced in the cortical networks. Schizophrenia was also associated with a reduced density of rich club connections between the midline frontal, parietal and insular hub regions, and this led to a lower global communication capacity in these white matter pathways. Compared with controls, patients with schizophrenia had a reduced level of overall functional connectivity strength, and an increase in the strength of coupling between structural and functional connectivity.

CONCLUSION: Schizophrenia was associated with a disruption in connectivity between the central hub regions of the brain, which may lead to abnormal functional brain dynamics.

COMPARATIVE EFFICACY AND TOLERABILITY OF 15 ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA: A MULTIPLE-TREATMENTS META-ANALYSIS

The Lancet, 2013 September 14; 382(9896):951–62

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BACKGROUND & AIM: The antipsychotic drug of choice for the treatment of patients with schizophrenia has yet to be identified. Newer second-generation antipsychotic drugs (e.g. aripiprazole, iloperidone, lurasidone and paliperidone) continue to be approved, despite the fact that their cost-effectiveness remains to be determined. Previous conventional meta-analyses have been unable to generate clear efficacy and tolerability hierarchies for the drugs currently available, partly because of a lack of comparative head-to-head studies. The aim of this study was to provide evidence-based hierarchies of the comparative efficacy and tolerability of first-generation (haloperidol and chlorpromazine) and 13 second-generation antipsychotic drugs.

STUDY DESIGN: Multiple-treatments meta-analysis.

ENDPOINT: The primary outcome was efficacy, assessed as mean overall change in symptoms.

METHOD: A search of the Cochrane Schizophrenia Group's specialized register, Medline, Embase, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov identified 212 blinded, randomized, placebo-controlled trials of 15 orally administered antipsychotic drugs used as monotherapy in the acute treatment of 43,049 patients with schizophrenia.

Bayesian-framework, multiple-treatments meta-analyses were conducted, and drugs were ranked according to surface under the cumulative ranking probabilities.

RESULTS: All drugs were significantly more effective than placebo. Standardized mean differences versus placebo ranged from -0.33 with iloperidone (worst) to -0.88 with clozapine (best); clozapine was significantly more effective than all other drugs. All but zotepine were significantly superior to placebo for all-cause discontinuation: odds ratios versus placebo ranged from 0.80 for haloperidol (worst) to 0.43 for amisulpride (best). Ziprasidone, paliperidone, risperidone, lurasidone, chlorpromazine, zotepine and haloperidol were associated with a higher rate of extrapyramidal adverse events than placebo. All drugs except amisulpride, paliperidone, sertindole and iloperidone were associated with larger effects on sedation than placebo (ORs ranged from 1.42 with amisulpride to 8.82 with clozapine). All drugs except haloperidol, ziprasidone and lurasidone produced more weight gain than placebo (SMDs ranged from -0.09 with haloperidol to -0.74 with olanzapine). Efficacy outcomes were robust under meta-regressions and sensitivity analyses.

CONCLUSION: Small but robust differences in efficacy were observed between antipsychotics, but adverse events varied substantially.

A SYSTEMATIC REVIEW OF PSYCHOSTIMULANT TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: CHALLENGES AND THERAPEUTIC OPPORTUNITIES

Schizophrenia Research, 2013 July; 147(2–3):241–52

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BACKGROUND & AIM: Compared with positive symptoms of schizophrenia, which can often be managed adequately using antipsychotic medications, the treatment of negative symptoms (e.g. flattened/blunted affect, alogia, asociality, avolition/amotivation, anergia and anhedonia) continues to be a challenge. Such symptoms contribute to poor global psychosocial functioning, to greater impairments in relationships, recreational and work activities, and to a reduction in quality of life and social functioning in patients. There is therefore a need for alternative pharmacological agents beyond the traditional dopaminergic and serotonergic antagonists currently used as treatments, and the aim of this article was to review evidence suggesting that psychostimulants may have a role in the treatment of patients with negative symptoms of schizophrenia.

ARTICLE TYPE: Review.

FINDINGS: The modified dopamine hypothesis suggests that positive symptoms of schizophrenia are associated with increased dopamine activity in the mesolimbic tract whereas negative and cognitive symptoms are associated with a decrease in dopamine activity in the mesocortical (frontal) region. Dopamine agonists that either directly or indirectly activate dopamine receptors could therefore improve negative symptoms. A number of psychostimulants act as indirect dopamine agonists, and these include methylphenidate, amphetamine, modafinil and armodafinil.

The authors reviewed both non-therapeutic psychostimulant challenge studies and those investigating the therapeutic effects of various psychostimulants on symptoms, function and cognition in patients with schizophrenia. Many of the clinical studies identified had small sample sizes, and varied in the control of bias, and in the doses and duration of adjunctive psychostimulant administration. The short-term nature of most studies precluded the drawing of conclusions regarding the potential for the development of tolerance, an important consideration with long-term use of psychostimulants. Despite a lack of well-controlled clinical trials investigating the safety and efficacy of prolonged treatment with psychostimulants, the authors were of the opinion that dopamine agonists, used adjunctively, can improve negative symptoms of schizophrenia without worsening of positive symptoms in selected patients who are stable and receiving effective antipsychotic medications. However, psychostimulant therapy was associated with a risk of triggering psychotic symptoms, especially in the absence of concurrent antipsychotic drug treatment. Large, controlled clinical trials are required to further characterize the effects of psychostimulants on negative symptoms in patients with schizophrenia.

CONCLUSION: Psychostimulants, used adjunctively, may improve negative symptoms of schizophrenia without worsening positive symptoms in selected patients who are stable and receiving effective antipsychotic therapy.

METABOLIC RISK FACTORS IN FIRST-EPISODE SCHIZOPHRENIA: BASELINE PREVALENCE AND COURSE ANALYSED FROM THE EUROPEAN FIRST-EPISODE SCHIZOPHRENIA TRIAL

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BACKGROUND & AIM: A recent systematic review has suggested that the prevalence of metabolic syndrome is 35.3% in medicated schizophrenic patients compared with 9.8% in those who are not medicated. However, data on the metabolic risks of antipsychotic treatment is potentially confounded by the effects of previous therapy. The aim of this study was to investigate the prevalence of metabolic abnormalities during antipsychotic treatment in partially antipsychotic-naïve patients with first-episode schizophrenia.

STUDY DESIGN: Randomized, open-label trial.

ENDPOINTS: Metabolic risk factors and metabolic syndrome.

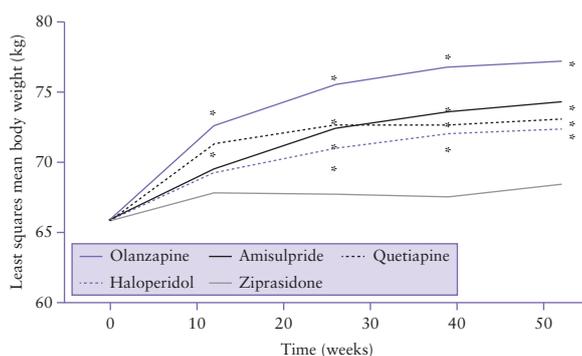
METHOD: The study included 440 patients with a diagnosis of first-episode

schizophrenia, schizophreniform disorder or schizo-affective disorder. All were participants in the European First-Episode Schizophrenia Trial (EUFEST) during which they were treated with one of 5 commonly-used antipsychotic drugs (haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone). Metabolic risk factors including body weight, waist circumference, glucose, lipids and insulin were assessed at baseline and throughout the trial. The least squares mean body weight was derived from a mixed model for repeated measures.

RESULTS: A total of 28.5% of patients had a suboptimal high-density lipoprotein cholesterol level, 24.2% had hypertension, 17.7% had hypertriglyceridaemia, 8.2% had abdominal obesity and 7.3% had hyperglycaemia. Treatment with haloperidol, amisulpride, olanzapine or quetiapine was associated with an increase in body weight (0.62, 0.76, 0.98 or 0.58 kg/month, respectively), while the increase with ziprasidone was significantly less (0.18 kg/month; Figure). All 5 antipsychotic treatments were associated with worsening of hypertriglyceridaemia or hyperglycaemia, while the incidence of new cases of diabetes was 0.82% over one year of treatment.

CONCLUSIONS: The increase in metabolic risk in patients with schizophrenia can be attributed mainly to the adverse effects of antipsychotic treatment and/or the effects of the illness itself.

Change in body weight over 52 weeks (* $p < 0.05$ versus ziprasidone)



HIPPOCAMPAL SHAPE ABNORMALITIES OF PATIENTS WITH CHILDHOOD-ONSET SCHIZOPHRENIA AND THEIR UNAFFECTED SIBLINGS

Journal of the American Academy of Child & Adolescent Psychiatry, 2013 May; 52(5):527–536.e2

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BACKGROUND & AIM: Hippocampal volume deficits have been consistently reported in schizophrenia. Although the subregional specificity of these deficits is unclear, hippocampal shape analysis could reveal subtle alterations at a subregional level. The main aim of this study was to explore subregional shape abnormalities of the hippocampus in patients with childhood-onset schizophrenia (COS), their healthy siblings and healthy controls.

STUDY DESIGN: Cohort study.

ENDPOINTS: Hippocampal shape and volume.

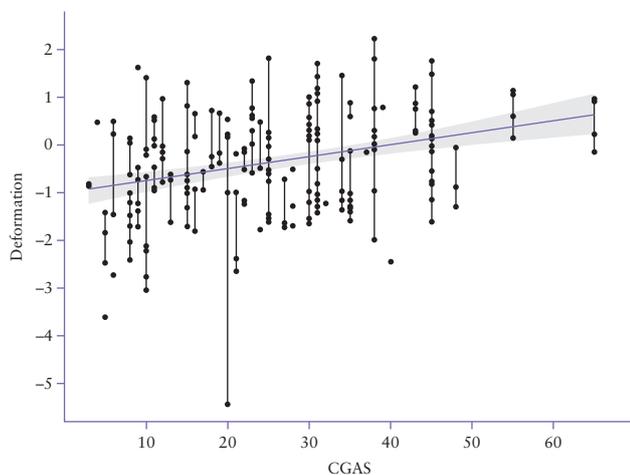
METHOD: The cohort consisted of 103 patients with COS, 79 healthy siblings and

101 age- and sex-matched healthy controls, and the numbers of magnetic resonance imaging (MRI) scans available for analysis were 255, 169 and 255, respectively. Patients and their siblings were followed prospectively, and had anatomic rescans at 2-yearly intervals. Associations between hippocampal shape and scores on clinical measures, including the Children's Global Assessment Scale (CGAS), were determined in COS patients.

RESULTS: Compared with healthy controls and siblings at the average age of 17.4 years, COS patients exhibited significant differences in inward and outward hippocampal deformations. Inward deformation was most pronounced in the anterior hippocampus, the medial and lateral surfaces, and in the body, whereas outward deformation was more pronounced in the inferior anterior hippocampus bilaterally, and in smaller regions throughout the body and tail. Healthy siblings showed a trend for inward and outward deformation compared with controls. In COS patients, higher CGAS scores (indicating better overall functioning) were related to more outward deformation in the anterior and body of the hippocampus (Figure).

CONCLUSION: Compared with healthy siblings and controls, COS patients had anterior hippocampal abnormalities which correlated with clinical measurements.

Scatter plot of CGAS scores versus hippocampal surface deformations in COS patients



EPIDEMIOLOGICAL AND CLINICAL CHARACTERIZATION FOLLOWING A FIRST PSYCHOTIC EPISODE IN MAJOR DEPRESSIVE DISORDER:

COMPARISONS WITH SCHIZOPHRENIA AND BIPOLAR I DISORDER IN THE CAVAN-MONAGHAN FIRST EPISODE PSYCHOSIS STUDY (CAMFEPS)

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BACKGROUND & AIM: Most information about psychosis has come from studies of patients with schizophrenia or bipolar 1 disorder. However, the next most common psychotic diagnosis is major depressive disorder with psychotic features (MDDP), and this condition also has the potential to provide information about the nature of psychotic illness. Previous studies comparing first-episode MDDP with schizophrenia have reported similar symptom and cognitive profiles, with differences in severity and pervasiveness. The aim of this study was to compare the epidemiology and clinical characteristics of MDDP with those of schizophrenia and bipolar disorder.

STUDY DESIGN: Cohort study.

ENDPOINTS: Epidemiological and clinical characteristics.

METHOD: The study included 77 patients with a first psychotic episode of MDDP, 73 with schizophrenia and 73 with bipolar disorder, all of whom were participants in the

Cavan-Monaghan First Episode Psychosis Study which aimed to identify all incident cases of a first episode of any psychotic disorder within 2 Irish counties. All patients were evaluated using the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders, and all diagnoses were updated at 6 months. As soon as possible after presentation, psychopathology, neuropsychology, neurology, premorbid adjustment and quality of life were assessed using appropriate instruments, including the Positive and Negative Syndrome Scale (PANSS).

RESULTS: For patients with MDDP, the first psychotic episode was equally likely at any age during adulthood. By contrast, the first psychotic episode of schizophrenia or bipolar disorder was most likely to occur in young adulthood. The incidences of MDDP and bipolar disorder were similar between men and women, while schizophrenia was 3 times more common in men. MDDP and schizophrenia were characterized by a similar profile of executive dysfunction, neurological soft signs, premorbid intellectual function, premorbid adjustment and reduced quality of life, while bipolar disorder was associated with less evident negative symptoms, less severe executive dysfunction and neurological soft signs, and a better quality of life (Table).

CONCLUSION: MDDP and schizophrenia may be more closely related than previously thought.

Clinical features by diagnosis at 6 months
(* $p < 0.05$ versus schizophrenia; ** $p < 0.05$ versus MDDP)

Clinical Feature	Diagnosis		
	Schizophrenia	MDDP	Bipolar disorder
PANSS negative	21.7 (7.4)	17.3 (8.3)*	9.5 (4.0)*
Executive Interview	8.4 (4.5)	9.9 (4.2)	6.9 (5.3)**
Neurological Evaluation Scale	14.2 (8.1)	18.7 (11.0)	10.3 (8.0)*
Premorbid Adjustment Scale (total)	23.3 (7.0)	26.2 (10.9)	19.9 (8.2)**
Quality of Life Scale (total)	65.5 (20.6)	76.1 (28.0)	100.3 (22.3)*

BIPOLAR DISORDER DIAGNOSIS: CHALLENGES AND FUTURE DIRECTIONS

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BACKGROUND & AIMS: The diagnosis of a patient with a psychiatric illness is primarily based on an assessment of behaviour together with the patient's subjective reports of abnormal experiences. However, definitive and objective biomarkers of pathophysiological processes underlying behaviours associated with psychiatric illness are often lacking. In addition, behaviours can overlap considerably between illnesses. It can therefore be difficult to diagnose, and hence treat appropriately, many patients with psychiatric diseases. Bipolar disorder comprises a group of affective disorders that are characterized by depressive and manic/hypomanic episodes, and is an example of a group of psychiatric illnesses that are difficult to diagnose accurately. The aims of this article were to discuss the main reasons for the difficulty in diagnosing patients with bipolar disorder in clinical practice and to describe clinical and biological strategies for improving the accuracy of diagnosis.

ARTICLE TYPE: Review.

FINDINGS: One reason that bipolar disorder can be hard to diagnose is that the disorder comprises many subtypes: bipolar disorder type I (characterized by depressive and manic episodes), bipolar disorder type II (characterized by depressive and hypomanic episodes), cyclothymic disorder (characterized by hypomanic and depressive symptoms that do not meet criteria for depressive

episodes) and bipolar disorder not otherwise specified (characterized by depressive and hypomanic-like symptoms that do not meet the criteria for any of the aforementioned subtypes). The diagnosis of patients with bipolar disorder types I and II can be particularly difficult as the diagnostic criteria for depressive episodes in these subtypes are identical to those for unipolar depression.

Clinical strategies to improve the diagnosis of patients with bipolar disorder include changes to the classification criteria for bipolar disorder in the recently published fifth edition of the Diagnostic and Statistical Manual for Mental Disorders. In addition, promising findings suggest that neuroimaging could help identify biomarkers differentiating bipolar disorder from unipolar depression; however, the difficulty in finding a clear distinction between the two disorders suggests that they might be better represented as a spectrum of affective disorders. Ultimately, it is thought that an integrative approach, using genetic, molecular, cellular, neural circuitry and behavioural factors, might identify patterns of biomarkers that could be used to identify biological targets for the development of new and personalized treatments.

CONCLUSION: The diagnosis of patients with bipolar disorder remains a challenge, but a number of clinical and biological strategies might help improve the accuracy of diagnosis.

RELAPSE DURATION, TREATMENT INTENSITY, AND BRAIN TISSUE LOSS IN SCHIZOPHRENIA: A PROSPECTIVE LONGITUDINAL MRI STUDY

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BACKGROUND & AIM: Longitudinal studies have revealed that brain tissue loss in patients with schizophrenia progresses over time and is related to severity of psychotic symptoms and cognitive impairments. Although recurrent relapses are believed to play a role in this loss, no study has analysed the relationship between relapse and brain tissue loss longitudinally using structural magnetic resonance imaging (MRI) brain measures. Since relapse typically triggers an increase in treatment intensity, it is also important to determine whether any observed brain volume changes may be a medication effect. The aim of this study was to analyse the association between duration and number of relapses, treatment intensity, and brain tissue loss assessed by structural MRI in schizophrenia patients.

STUDY DESIGN: Retrospective analysis of a longitudinal imaging study.

ENDPOINTS: Number and duration of relapses, and brain volume.

METHOD: The analysis included 202 schizophrenia patients who had participated in the Iowa Longitudinal Study of first-episode schizophrenia. Clinical follow-up data were obtained at 6-month intervals, whereas MRI scans ($n=659$) were obtained at regular intervals over an average of 7 years. A repeated-measures linear model was used to model changes in brain volume over time. Covariates included in the model were time elapsed between two consecutive MRI scans, relapse duration, sex and age.

RESULTS: In total, 157 patients experienced at least one relapse, 29 had no relapses and 16 remained at a persistently severe illness level. For patients who relapsed, the average number of relapses was 1.64 (range 1–4). Mean duration of relapse was 1.34 ± 1.40 years, and the maximum was 7.09 years. Greater relapse duration was significantly associated with tissue loss in total cerebral volume, and with more specific measures, such as frontal and temporal lobe white matter (Table). In addition, treatment intensity was related to brain volume changes. By contrast, there was no association between number of relapses and brain measures.

CONCLUSION: In patients with schizophrenia, duration of relapse and treatment intensity were closely related to loss of brain tissue over time in multiple brain regions.

Effect of interscan interval relapse duration on brain volume measures
(β_2 = tissue decrease during interscan intervals due to relapse duration)

Brain volume measure	β_2 (cc/year)	Z	p-value
Cerebral			
Total	-1.55	-2.53	0.01
Grey matter	-0.78	-1.48	0.14
White matter	-0.95	-1.77	0.07
Frontal lobe			
Total	-0.99	-2.91	0.004
Grey matter	-0.37	-1.42	0.16
White matter	-0.48	-2.02	0.04
Temporal lobe			
Total	-0.14	-1.21	0.23
Grey matter	-0.10	-1.00	0.32
White matter	-0.17	-2.12	0.03

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: 2013-02-21

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