Snips from the journals Update on bipolar disorder

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Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey

A cross-sectional, face-to-face household survey conducted among 61,392 community adults in 11 countries in the Americas, Europe and Asia indicates that the severity, impact, and patterns of co-morbidity of bipolar spectrum disorder (BPS) are remarkably similar internationally. The lifetime prevalence rates of bipolar I, bipolar II and sub-threshold bipolar disorder in a pooled sample of 11 countries was 0.6%, 0.4% and 1.4% respectively. The mean age of onset increased as the severity of the disorder decreased; the mean age of onset was 18.4 years for bipolar-I, 20.0 years for bipolar-II and 21.9 years for sub-threshold bipolar disorder.

A striking finding of this study was that about three fourths of those with BPS also met diagnostic criteria for another life time disorder. The most common co-morbid condition was anxiety disorders (62.9%), followed by behavioural disorders (44.8%) and substance use disorders (36.6%). In particular, patterns of co-morbidity that BPS displayed with both anxiety disorders and substance use disorders were similar across countries. The authors also suggest that BPS could be considered a risk factor for the development of substance use disorders, which would have implications for prevention strategies.

A significant degree of role impairment (measured by the Sheehan Disability Scale) was present in patients with BPS, with the role impairment being greater for depression (74.0%) than for mania (50.9%).

Despite the above findings, only one third or less patients from middle income countries (33.9%) and low income countries (25.9%) reported a life time history of the use of mental health services, compared to 50.2% from high income countries – indicating that treatment needs for BPS patients are often unmet, particularly in low-income countries.

Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA et al. Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative. Archives G Psychiatry 2011; 68(3): 241-251.

Bipolar Disorder and Violent Crime

In this longitudinal study in Sweden, patients over 15 years with a minimum of two hospital discharge diagnoses of bipolar disorder (BPD) during 1973-2004 (n=3743) were compared with population controls (n=37,429) for rates of conviction for violent crime, as listed in the Swedish crime register during the same period. A similar comparison was also made between those with bipolar disorder and their unaffected siblings (n=4059). The authors also conducted a meta-analysis and systematic review of publications relevant to violent crime in patients with BPD.

Patients with BPD without substance abuse co-morbidity had only a minimally elevated risk of violent crime compared to the general population (adjusted Odds Ratio, OR, 1.3; 95% Confidence Interval, CI, 1.0-1.5). This risk was not significantly elevated compared with that of unaffected siblings (adjusted OR, 1.1; 95% CI, 0.7-1.6). However patients with BPD who had co-morbid substance abuse showed a significantly higher risk of violent crime than general population controls (OR 6.4; 95% CI, 5.1-8.1). When patients with BPD with co-morbid substance use were compared with unaffected siblings, the risk of violence was again increased, but to a lesser degree (adjusted OR, 2.8; 95% CI, 1.8-4.3). BPD severity (measured by the presence of psychotic symptoms) and diagnostic subgroups (manic episodes compared to depressive episodes) were not associated with an increase in risk of violent crime. Interestingly, the authors also report an increased risk for violent crime among unaffected siblings of patients with BPD.

This study indicates there was an increased risk for violent crime among those with BPD and co-morbid substance abuse. There was no increased risk of violence in patients with BPD without substance abuse compared to general population controls.

Findings of this study can be explained in several ways. One possible explanation is that BPD (with a predominantly genetic cause) leads to substance abuse, which in turn leads to increased risk of violent crime. Another possible explanation is a shared genetic aetiology for BPD, substance abuse and violent crime. At present available data is too limited to make a definitive conclusion.

Fazel S, Lichtenstein P, Grann M, Goodwin GM and Langstrom N. Bipolar Disorder and Violent Crime: new evidence from population-based longitudinal studies and systematic review. Arch Gen Psychiatry 2010; 67(9): 931-938.

Cognitive functions among euthymic bipolar I patients after a single manic episode versus recurrent episodes.

Examination of cognitive functions (executive function, memory, intelligence, attention and concentration) of a group of euthymic patients with bipolar affective disorder (n=100) showed that patients after a single manic episode have impairment in attention, executive functions and total memory score compared to healthy control subjects. However euthymic patients after a single manic episode performed better on attention and cognitive function compared with euthymic patients with more than one recurrence. The duration of the illness, and the age of onset of the illness were inversely proportionate to attention and executive function.

The findings of this study support the hypothesis that bipolar disorder is associated with deterioration of cognitive functions which worsen with each recurrence. Stress induced hypercortisolaemia during affective episodes causing hippocampal cell toxicity and structural changes in prefrontal and temporal (hippocampal) areas of the brain have been suggested as possible mechanisms.

Elshahwi HH, Essawi H and Rable MA. Cognitive functions among euthymic bipolar I patients after a single manic episode versus recurrent episodes. J Affect Disord 2011; 130(1-2): 180-191.

Randomized Add-on Trial of an N-methyl-D-Aspartate (NMDA) Antagonist in Treatment-Resistant Bipolar Depression

A randomized placebo controlled, double-blind crossover, add-on study was conducted to determine whether a single intravenous infusion of an NMDA antagonist (ketamine) in patients with treatment-resistant bipolar depression would result in a rapid antidepressant response. The Sample included 18 patients who met DSM-IV criteria for bipolar depression. During the trial period and the preceding two weeks, the patients received either lithium or valproate treatment within the specified range, but were not prescribed any other psychotropic medication. During the trial, patients received intravenous infusions of 0.9ml saline, and 0.5mg/kg ketamine hydrochloride, two weeks apart, in a randomly assigned order. Patients and all administering staff were blinded as to whether ketamine or saline was being administered. The primary outcome was the severity of depression as rated by the Montgomery-Ashberg Depression Rating Scale, at baseline, and at 40, 80, 110, and 230 minutes and on days 1, 2, 3, 7, 10, and 14 post-infusion. Within 40 minutes, depressive symptoms significantly improved in subjects receiving ketamine compared with placebo (d=0.52, 95% CI, 0.28-0.76); this improvement remained significant through day 3. The drug difference effect size was largest at day 2 (d=0.80, 95% CI, 0.55-1.04). Ketamine was generally

well tolerated; the most common adverse effect was mild dissociative symptoms, only at the 40-minute point.

These findings suggest that a single dose of an intravenous NMDA antagonist may result in an antidepressant effect in treatment resistant bipolar depression. However these are preliminary results which require cautious interpretation and further trials are needed to confirm these findings.

Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P and Khalife S. A Randomized Add-on Trial of an N-methyl-D-Aspartate Antagonist in Treatment-Resistant Bipolar Depression. Arch Gen Psychiatry 2010; 76(8): 793-802.

Pharmacological interventions for people with depression and chronic physical health problems

This paper reports on a meta-analysis of randomized controlled efficacy trials of antidepressants for depression in patients with chronic physical health conditions, and a systematic review of safety studies. In the meta-analysis, in placebo-controlled studies, antidepressants showed a significant advantage with respect to remission and response. For selective serotonin reuptake inhibitors (SSRIs) the risk ratio (RR) for remission was 0.81 (95% CI, 0.73-0.91) and the RR for response was 0.83 (95% CI, 0.71-0.97). For tricyclic antidepressants (TCADs), the RR for remission was 0.70 (95% CI, 0.40-1.25) which was not significant and the RR for response was 0.55 (CI, 95% 0.43-0.70). Both groups were less well tolerated than placebo in the context of leaving the study early due to adverse effects for which, for SSRIs the RR was 1.80 (95% CI, 1.16-2.78), and for TCADs the RR was 2.00 (95% CI, 0.99-3.57). Only SSRIs were shown to improve quality of life. Comparisons of SSRIs and TCADs revealed no advantage for either group for remission, response, effect size or tolerability.

Antidepressants of all types appear to be effective in depression in chronic physical conditions, but no particular drug or group of drugs was shown to have superiority in efficacy or tolerability. The authors suggest that SSRIs may be better tolerated, since they are less likely to be involved in pharmacodynamic interactions, and because of the absence of sedative and anti-muscarinic properties.

For treatment of depression in post-myocardial infarction, sertraline, mirtazapine and possibly other SSRIs (such as citalopram) appear to be safe to use, but results regarding efficacy are more conflicting - for example, the MIND-IT study found no advantage for antidepressant (mirtazapine) over controls, whereas in the SADHART study sertraline was more effective than placebo in treating depression

Taylor D, Meader N, Bird V, Pilling S, Creed F, Goldberg D; Pharmacological interventions for people with depression and chronic physical health problems: systematic review and meta-analyses of safety and efficacy. British J Psychiatry 2011; 198: 179-188.

Differences between bipolar I and bipolar II disorders in clinical features, comorbidity and family history

According to the DSM-IV classification, bipolar I disorder (BP-I) and bipolar II disorder (BP-II) are distinguished only by the presence of a manic or hypomanic episode, respectively. However, whether BP-I and BP-II differ only in the severity of manic episodes, or whether they also differ in other clinically and biologically meaningful ways remains controversial. This study, conducted in Korea, attempts to compare the clinical characteristics of BP-I and BP-II patients, based on information available in an ordinary clinical setting.

Patients aged 18-60 years, who met the diagnostic criteria of DSM-IV BP-I (n 71) or BP-II (n 34), who were currently stable, were interviewed using a semi-structured clinical interview schedule (Diagnostic interview for Genetic Studies). Further information was also collected from care-givers, physicians and medical records.

Results showed no significant difference in the socio-demographic characteristics of the two patient groups. Polarity of onset was predominantly depressive episodes in both groups. Compared to the BP-I group, BP-II patients showed a higher frequency of depressive episodes after the disease onset ($p=0.009$) and were more likely to have a history of seasonality ($p=0.035$) and rapid cycling ($p=0.062$). Compared to BP-I patients, BP-II patients also had a higher lifetime comorbidity of an axis I diagnosis ($p=0.09$). Specifically, BP-II patients had a higher lifetime incidence of phobia and eating disorders. With regards to family history, as expected, bipolar affective disorder was the most commonly detected illness in relatives of BP-I probands. In contrast, major depression and substance use disorders were the most prevalent disorders reported in relatives of BP-II probands.

Based on the findings of this study, the authors suggest that BP-II is qualitatively different from BP-I, and not merely an attenuated form of BP-I. While this is an interesting concept, a definitive conclusion cannot be made from the findings of a single study. The limitations of the study include a small sample size and a possible recall bias - as the lifetime history of clinical features was based on a retrospective assessment.

Baek JH, Park DY, Choi J, Kim JS, Choi JS, Ha K, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity and family history. J Affective Disord 2011; 131: 59-67.

Lithium in drinking water and suicide mortality

In Austria, a nationwide sample of 6460 lithium measurements was examined for association with suicide rates per 100,000 population and suicide standardised mortality ratios across all 99 Austrian districts. Results of adjusted multivariate regression models showed that the overall suicide rate ($R(2) = 0.15$, $\beta = -0.39$, $t = -4.14$, $P = 0.000073$) as well as the suicide mortality ratio ($R(2) = 0.17$, $\beta = -0.41$, $t = -4.38$, $P = 0.000030$) were inversely associated with lithium levels in drinking water and remained significant after sensitivity analyses and adjustment for socioeconomic factors.

These are interesting findings, which further replicate and extend previous studies (5, 6), and strongly indicate that geographic regions with higher natural lithium concentrations in drinking water are associated with lower suicide mortality rates. However it should be noted that results of this study are based on statistical modeling of aggregated data and therefore need cautious interpretation. There is a considerable amount of unexplained variance. Furthermore, the findings cannot be applied to individual cases and do not prove causation.

Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M, Praschak-Rieder N, Sonneck G, Leithner-Dziubas K. Lithium in drinking water and suicide mortality. Br J Psychiatry. 2011 May;198:346-50.

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