« La mémoire est une faculté qui oublie »

Cher rédacteur,

L’Association des psychiatres du Canada vient de publier un livre intitulé Psychiatry in Canada: 50 years (1), afin de célébrer les 50 ans de son organisation. L’ouvrage, composé de 16 chapitres, tente de tracer l’évolution de la pratique psychiatrique qui tient compte des différents mouvements de la discipline. Le chapitre 13 aborde la recherche en psychopharmacologie au Canada. Ce court chapitre qui relate 50 ans de progrès est surprenant : il récapitule dans un tableau (p. 205–208) un ensemble de recherches en psychopharmacologie liées à des programmes et à des chercheurs, université par université, en scotomisant complètement l’Université de Montréal, comme si elle n’avait pas d’existence dans le paysage de la psychopharmacologie au Canada. C’est pourtant dans cette université et par l’intermédiaire de ses hôpitaux, comme l’Hôpital Louis-H. Lafontaine, qu’ont été mis en évidence les premiers résultats concernant la potentialisation du traitement antidépresseur par le lithium. C’est aussi dans cette université qu’ont été étudiées de nombreuses molécules, au laboratoire du sommeil de l’Hôpital Sacré-Coeur de Montréal. C’est aussi dans les hôpitaux affiliés à cette université qu’ont été mis en évidence dès le début des années 90 les effets néfastes des benzodiazépines et des antidépresseurs. De nombreuses autres études, bien contrôlées et utilisant de très bonnes méthodes ont été réalisées et ont montré les effets bénéfiques et néfastes des benzodiazépines et des antidépresseurs. De plus, en collaboration avec le centre de recherche en sciences neurologiques de l’université et le département de pharmacologie, des chercheurs ont publié abondamment sur les récepteurs dopaminergiques et sérotoninergiques. Il est donc regrettable qu’un ouvrage aussi significatif de l’histoire de la psychiatrie au Canada omette l’Université de Montréal dans ce tableau synthétique. Oubli ou négligence? On dit souvent que la mémoire est une faculté qui oublie, mais dans ce cas-ci c’est la mémoire qui a oublié la faculté. I am waiting for a cognitive remediation.

Bibliographie


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Clinical and Family History
Markers of Bipolar II Disorder

Dear Editor:

This letter provides my comments with respect to the important and useful paper by Ghaemi and others (1). Bipolar spectrum disorder (BSD) is placed between unipolar disorder and bipolar disorders I and II (BD I, BD II). In their paper, they propose a definition: at least 1 major depressive episode (MDE), no spontaneous manic or hypomanic episodes, and signs of bipolarity. Of these signs, the most important are antidepressant-induced mania or hypomania and a family history of BD, with other criteria being > 3 MDEs, atypical features, and onset of first MDE at age < 25 years.

In recent studies, I have tested whether unipolar MDE that shows some of these features is linked to BD II, supporting this BSD definition. One study compared patients with unipolar disorder—both highly recurrent (HRUP) (> 4 MDEs) (n = 57) and low recurrent (LRUP) MDE (< 5 MDEs) (n = 32)—with patients having BD II MDE (n = 151) (2). Patients with HRUP did not differ significantly from those with BD II with respect to first MDE onset, but compared with LRUP patients, they had a significantly lower age of onset, more atypical features, and a family history of BD II. This suggests that HRUP could be midway between unipolar disorder and BD II, supporting Goodwin and Jamison’s view that recurrence can be as important as polarity in mood disorders (3).

A second study (4) compared persons with atypical features of unipolar disorder (n = 38), early-onset unipolar disorder (age < 21 years) (n = 39), and BD II MDE (n = 234). Compared with BD II patients, those with atypical features did not differ significantly in onset-age, in MDE recurrences, or in family history of BD II. However, compared with patients having nonatypical unipolar disorder, they had a significantly lower onset-age. Compared with BD II patients, those with early-onset unipolar disorder did not differ significantly in atypical features, in recurrences, or in family history of BD II. However, compared with patients having non–early-onset unipolar disorder, they had significantly more atypical features and recurrences. These findings suggest a link between atypical unipolar disorder and BD II, as well as a link between early-onset unipolar disorder and BD II, supporting Ghaemi and others’ BSD definition.

Ghaemi and others’ signs of bipolarity could also be useful in reducing the underdiagnosis of BD II (1). BD II underdiagnosis relates to many factors, including hypomania that patients do not view as a disorder (often, it has improved functioning). Other signs include difficulty in remembering positive events owing to depression-associated
negative cognitive bias (BD II patients usually present for MDE), clinician skills, use of structured vs semistructured (better) interviews, and lack of information from family members (5,6).

I have tested some of the Ghaemi and others’ bipolarity signs to find out whether, during MDE assessment, these signs could be useful to induce clinicians to carefully assess past hypomania, thus reducing BD II underdiagnosis and mis-treatment (1).

I describe the study methods in detail in previous reports (2,4,7–9). I interviewed a consecutive sample of 260 outpatients with BD II and 173 drug-free outpatients with unipolar disorder who presented for MDE treatment in a private clinic in Italy. These samples are more representative of mood disorders, which are usually treated in clinical practice vs tertiary care centres (10,11). I used the Structured Clinical Interview for DSM-IV (12). Systematic assessment of past hypomania was improved by more probing for overactivity and for information from family members; it resulted in increased BD II diagnoses (13,14). I assessed hypomania symptoms during MDE. The BD II group comprised 68.4% women, with a mean (SD) age of 41.7 (14.0) years. Of these patients, 81.1% presented with > 3 MDEs, with a mean (SD) MDE onset-age of 22.9 (10.8) years; 53% had atypical features; 59.2% showed depressive mixed state (DMX) (that is, MDE and > 2 concurrent hypomania symptoms, recently found to be very common in BD II [2,4,7]); and 54.1% a family history of BD I and II (assessed by structured interview) (15). Of the unipolar disorder group, 60.6% were women; the mean (SD) age was 47.0 (15.6) years; 58.9% had > 3 MDEs, with a mean (SD) onset-age of 32.0 (14.5) years; 25.4% had atypical features; 29.4% showed DMX; and 21.2% had a family history of BD. Sensitivity (SE) and specificity (SP) for predicting BD II were calculated by logistic regression for some signs of bipolarity (1). The results are as follows: > 3 MDEs (SE = 81.1%, SP = 41.0%), onset< 25 years (SE = 66.9%, SP = 64.1%), atypical features (SE = 53.0%, SP = 74.5%), DMX (SE = 59.2%, SP = 70.5%), and family history of BD (SE = 54.1%, SP = 78.7%). Family history of BD had the highest specificity (that is, few false positives). Family history, however, can be difficult to assess (3). Conversely, 2 cross-sectional bipolarity signs that are not memory dependent—atypical features and DMX—also had high specificity and were not difficult to assess during MDE assessment (7,8). In a busy clinical practice, these 2 cross-sectional markers of BD II can induce clinicians to carefully probe for past hypomania. Results not only support Ghaemi and others’ BSD but also suggest some clinical and family history markers to reduce BD II underdiagnosis.

References


Franco Benazzi, MD
Forlì, Italy

Re: Clinical and Family History Markers of Bipolar II Disorder

Dear Editor:

We thank Dr Benazzi for his letter. He reviews previous studies that support associations between what we call bipolar spectrum disorder (BSD) and early-onset, atypical features, and mixed mood symptoms. He also applies our proposed definition to its first empirical test and finds excellent sensitivity for recurrent depressive episodes (3 or more), together with good specificity for atypical depressive features and mixed mood symptoms. We appreciate Dr Benazzi’s careful empirical assessment. This is exactly the kind of empirical test that we hoped our heuristic definition of BSD would stimulate. We only hope that Dr Benazzi and other investigators will continue these studies, so that the criteria can be further refined empirically.

We wish to highlight 2 aspects of our proposal. On the one hand, we describe features of depressive symptoms, course, family history, and treatment response. We propose that these features outline a group of depression patients who have neither classic unipolar nor classic bipolar disorder (BD); that is, they never display spontaneous mania or hypomania. However, a unipolar diagnosis broad enough to encompass such patients may offer little in the way of predictive validity. These patients, in fact, have many more diagnostic features in common with BD than with unipolar depression. We therefore suggest the term BSD for this group, and we advocate empirical tests of
our definition. Conversely, as Dr Benazzi also emphasizes, our proposed definition can be seen as a way of assessing patients who may be at high risk for having BD or later developing the disorder, especially BD II. If patients have many of the bipolar spectrum depressive features we highlight, closer examination may reveal past episodes of hypomania (or sometimes even mania) that either have been denied or have escaped detection. Further, such patients may be at high risk for future spontaneous hypomanic or manic episodes and thus may warrant careful assessment for such symptoms longitudinally. Hence, our list of bipolar spectrum symptoms can also be seen as clues for bipolarity that, if present, warrant an even more extensive evaluation for hypomanic or manic symptoms in a patient who does not appear to have BD.

In any case, we wish to emphasize that these are testable hypotheses, and we welcome and request the type of empirical examination that Dr Benazzi has inaugurated.

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Effect of Olanzapine on the Liver Transaminases

Dear Editor:

The effect of olanzapine on liver transaminases is among the less frequently encountered side effects of this novel atypical antipsychotic drug. Initial clinical trials observed a transient, asymptomatic, non–dose-dependent elevation in the liver transaminases in 9.4% of olanzapine-treated patients (1). Although this suggests an increased risk for hepatitis, it has been argued that there has been no evidence of hepatitis in the patients (2). Some reports suggest that an even smaller percentage—1.9% in more than 2000 patients receiving olanzapine—had elevated enzyme levels, which gradually declined with continued treatment (3).

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP), however, has received 9 reports of olanzapine causing mainly mild increases in alanine aminotransferase (ALT).

We report 2 cases wherein olanzapine caused significant elevation of liver transaminases, up to 5 times the normal reference range.

The first case is a woman, age 37 years, who presented with auditory hallucinations and religious delusions. This was her first psychotic episode postpartum. On admission, her liver transaminases were minimally elevated (ALT = 95 U/L > asparate aminotransferase [AST] 50 U/L). The normal range is ALT = 7 U/L to 40 U/L and AST = 7 U/L to 40 U/L. She had been taking 5 mg daily of olanzapine prior to admission, and the enzyme levels prior to initiation of olanzapine were not known. The dosage was increased to 10 mg daily, and liver transaminases were closely monitored. The enzymes continued to increase rapidly to about 4 to 5 times the normal reference range (ALT 237 U/L max) over the next 10 days. The drug was discontinued, and the enzyme levels gradually normalized after 4 days.

In the second case, a woman aged 62 years, with a long history of schizophrenia, did not respond to risperidone and was switched to olanzapine. She had been on 5 mg daily of olanzapine, which her primary psychiatrist in the clinic gradually increased to 15 mg daily. After she had been on olanzapine for a month, we incidentally found a significant increase in her liver transaminases (ALT = 179 U/L and AST = 115 U/L), following her hospitalization for delirium secondary to pneumonia. Olanzapine was then discontinued. For the next 4 days, her ALT fluctuated between 137 U/L and 180 U/L before it normalized.

Both these patients did not have any clinical evidence of liver dysfunction. The remainder of the liver panel was normal, except for a decrease in albumin in the second case, which normalized after stopping olanzapine. All other causes of elevation of liver transaminases were ruled out.

The relevance of elevated transaminases remains controversial. Mild elevations have been reported with the use of olanzapine. However, relevance of marked increase in liver enzymes (> 3 to 4 times the normal reference range) remains to be elucidated.

It is unclear whether these patients can be rechallenged with this drug. Thus, further research is warranted to address the relevance of elevated enzymes.

References


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