Clinical Factor 2011

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In 2011, Giovanni Fava [1] proposed that I select those papers published in psychiatric journals during the previous year that I would subjectively perceive as having a high ‘clinical factor’, i.e. the degree and extent to which a journal article provides information to the clinician that may improve his/her practice. The first selection of articles published in 2010 with a brief characterization of each of them followed in the fourth issue of last year’s volume of *Psychotherapy and Psychosomatics* [2].

As we announced this as a possible yearly tradition, I am presenting my subjective selection of this time 20 articles published in 2011 that I believe may provide some information to help the reader improve his/her clinical practice. As I noted before: ‘Many may find them useful, some will find them less useful or useless. I am certainly biased, as is anybody else. I also cannot review *all* psychiatric journals – I focused only on most of the major ones. If there is no article selected from a certain major psychiatric journal, it does not necessarily mean that I have not reviewed it or skimmed through that journal. It may mean that I did not find, in my opinion, anything clinically very interesting’ [2]. This year I expanded the number of journals I reviewed a bit. Thus the journals that may or may not provide an article for this selection include the following: *Acta Psychiatrica Scandinavica*, *American Journal of Psychiatry*, *Archives of General Psychiatry*, *British Journal of Psychiatry*, *Depression and Anxiety*, *European Psychiatry*, *General Hospital Psychia-*

try, *Journal of Affective Disorders*, *Journal of Clinical Psychiatry*, *Journal of Clinical Psychopharmacology*, *Journal of Nervous and Mental Disease*, *Journal of Sex and Marital Therapy*, *Psychological Medicine*, *Psychosomatics* and *Psychotherapy and Psychosomatics*. As I noted before [2], I view myself first and foremost as a clinician (though academically oriented) and I am, as most clinicians are, looking for a way to help patients, and thus looking for new, or innovative, or newly validated treatments. That is part of my clinician’s bias and that impacts my selection – the majority of the selected articles are on treatment issues. I had originally selected more articles and it has been difficult to narrow it down to the final 20. I am sure I missed some interesting ones, but as noted, this is a subjective selection.

Last but not least, as was the case last time [2] and will be next time, this selection is not a competition, there are no winners. The articles [3–22] are presented in groups according to similarity of their topic, not in any order of importance, preference or significance.

General Issues with Clinical Relevance

In his evaluation of 461 data sets in 41 meta-analyses of brain volume abnormalities in diverse brain structures in patients with various mental health conditions, Ioannidis [3] found that, in the literature, ‘... the number of

positive results is way too large to be true. Even if the effect sizes observed in the meta-analyses are accurate, the number of positive results ($n = 142$) is almost double than what would have been expected based on power calculations for the included samples.' The author suggested that the excess significance may be due either to unpublished negative results, or due to negative results having been turned into positive results through selective exploratory analyses. As Ioannidis [3] concluded, the literature on brain volume differences is probably a subject of considerable bias. It does not mean that none of the published observations in the literature are true. Nevertheless, these results raise serious questions about the usefulness of most of the available brain volume data and definitely about their clinical usefulness. (No funding for this study was reported.)

Predicting the future development of mental health complication after injury is an important issue. Richmond et al. [4] developed a short predictive screener that they used in a study of emergency department patients with various non-CNS injuries investigating the future development of depression or posttraumatic stress disorder (PTSD) in these patients. Patients were assessed within a week after injury and followed with in-person interviews after 3 and 6 months. Of 192 initially screened patients, 165 were assessed at the 6-month follow-up. Twenty-six were diagnosed with depression, 4 with PTSD and 1 with both. The authors then derived an 8-item predictive screener which had excellent sensitivity and moderate specificity for both clinically significant symptoms and for the diagnoses of depression and PTSD. However, the true predictive validity of this simple screener needs to be tested in a prospective study. The predictive screeners could help clinicians focus on patients vulnerable to the possible development of depression and/or PTSD. (This study was supported by an NIMH grant.)

Personality Disorders

Most practicing clinicians would be hesitant to conduct psychotherapy of patients with cluster A personality disorders (paranoid, schizoid and schizotypal), as they probably think that these personality disorders may not be amenable to psychotherapy. However, as Bartak et al. [5] in their study of patients with cluster A personality disorders in various psychotherapy settings demonstrated, psychotherapy can provide help to these patients (or, at least, as the authors state, it is not contraindicated). Patients treated in the outpatient setting did not do as well

as those treated in day hospital or inpatient settings, but direct comparison of these settings was not deemed possible. The strengths of this study include an 18-month follow-up and a fairly good number of patients for this kind of study. The main weakness was the fact that the majority of these patients suffered from paranoid personality disorder, making the results possibly generalizable to this diagnosis only. The medication status of the subjects in this study is not mentioned. More intensive forms and settings of psychotherapy may be useful in the management of cluster A personality disorders. (The authors reported no financial or other conflict of interest. It is not clear whether this study was funded by any agency.)

Gunderson et al. [6] compared the course of borderline personality disorder's (BPD) psychopathology and social function with those of other personality disorders (in this study, avoidant personality disorder and obsessive-compulsive personality disorder) and with major depressive disorder with no personality disorder over 10 years (this is a part of the Collaborative Longitudinal Personality Disorders Study of 19 centers in the United States). They found that the 10-year course of BPD was characterized by high rates of remission, low rates of relapse (actually lower than in major depression and other personality disorders), and by severe and persistent impairment in social functioning. The remission was slower than for major depression and minimally slower than for the other two personality disorders, and BPD patients remained more socially dysfunctional than patients in the other two groups. The authors felt that the pattern of remissions more enduring and by functional impairment more severe than many other psychiatric disorders highlights the potential therapeutic rewards of treating patients with BPD, though therapies helping to improve their social functioning need to be developed. The information about the relapse and remission rates of BPD could also be quite useful for patients and their families to gain some perspective on the course of this illness. (This study was funded by various grants from the National Institute of Mental Health.)

As Breslau et al. [7] indicate, 'international migration across societies presents a valuable opportunity for biobehavioral research to advance understanding of the interplay between environments and gene expression in the etiology of conduct disorder and other complex psychiatric disorders'. In their study of three generations of people of Mexican origin with increasing level of exposure to American culture (families of origins of migrants residing in Mexico; children of Mexican migrants raised in the USA, and Mexican-American children of US-born par-

ents), they found that the prevalence of conduct disorder (possible 'precursor' of antisocial personality disorder) increased dramatically across generations (from an OR of 0.54, 95% CI 0.19–1.51 in the general population in Mexico, to an OR of 4.12, 95% CI 1.47–11.52 in children of Mexican-born immigrants raised in the USA, to an OR of 7.64, 95% CI 3.20–18.27 in Mexican-American children of US-born parents). The association with migration was markedly weaker for aggressive than for nonaggressive symptoms. Though this study had several limitations (retrospective nature, reliance on contemporaneous samples of generational groups rather than samples drawn from actual multigenerational families), the results suggest significant environmental influence on conduct disorder. This could be considered in the evaluation and management planning of children of migrants. (This study was funded by the National Institute of Mental Health; National Institutes of Health, and the University of California Migration and Health Research Center.)

First-Episode/Early-Onset Psychosis

Gaebel et al. [8] studied what should be done, in terms of relapse prevention, after the recommended 1-year antipsychotic maintenance treatment of patients with the first episode of schizophrenia – whether to continue maintenance treatment, or stepwise discontinue medication and use targeted intermittent treatment. In their 12-month study, they found that the rates of relapse (19 vs. 0%) and deterioration (up to 57 vs. 4%) were significantly lower in the continuing maintenance therapy. The intermittent targeted therapy patients received lesser amount of antipsychotic medication and showed fewer side effects. The study sample was relatively small and the study suffered from several other limitations. Nevertheless, the results suggest that continuing maintenance treatment beyond 1 year after the first episode of schizophrenia could be a more effective treatment strategy. (This study was funded by the German Federal Ministry for Education and Research; haloperidol and risperidone were provided by Janssen-Cilag, and lorazepam by Wyeth-Pharma.)

In an interesting Scandinavian study, Larsen et al. [9] demonstrated the efficacy of a comprehensive early detection program of psychosis with public information campaigns and a low-threshold psychosis detection team in a 5-year follow-up of 192 patients with first-episode nonaffective psychosis. They compared two areas – one using this program and one without it. Patients in the

early detection program showed better scores on the Positive and Negative Syndrome Scale (negative, depressive and cognitive factors) and on the Global Assessment of Functioning (social functioning). These patients also had more contacts with friends. The findings could not be explained by any confounding variables. These results underscore the importance of early detection of psychosis for future treatment outcome. The results of this study together with the results of the study by Gaebel et al. [8] suggest that early detection combined with early continuous intervention should be the guiding principle in the management of the first episode of nonaffective psychosis. (This study was supported by the Norwegian National Research Council, the Norwegian Department of Health and Social Affairs, the National Council for Mental Health/Health and Rehabilitation Rogeland County and Oslo County, the Theodore and Vada Stanley Foundation, the Regional Health Research Foundation for Eastern Region, Denmark; Roskilde County, Denmark; NARSAD; NIMH, and Lundbeck, Lilli and Janssen-Cilag.)

Suicide Prevention with Medications

Leon et al. [10] conducted a longitudinal, observational study of patients with mood disorder with prospective assessment up to 27 years at 5 academic centers in the United States (the 757 patients were originally recruited for the Collaborative Depression Study between 1978 and 1981). Over the years, patients with more severe mood symptoms were more likely to receive antidepressants. Antidepressants significantly reduced the risk of suicide and suicide attempts by 20% (risk of suicide was only reduced, not eliminated). (This study was supported by several National Institute of Mental Health grants.)

As Oquendo et al. [11] note, bipolar disorder is associated with a high risk of suicide. While lithium has been known to decrease this risk significantly, not much has been known about the possible role of other mood stabilizers in decreasing the risk of suicide in bipolar disorder. Thus Oquendo and colleagues conducted a 2.5-year, double-blind, randomized, parallel-group study to determine whether lithium was superior to valproate in preventing the occurrence of suicidal events in bipolar patients with a major depressive or mixed episode who had a past suicide attempt. Contrary to their hypothesis, their trial revealed no difference in time to suicide attempt or suicide event between the patients treated with lithium

and those treated with valproate. There were no suicide deaths during the study. A total of 18 suicide attempts were made by 14 patients, 6 from the lithium group and 8 from the valproate group (both groups had 49 patients). As the authors point out, the lack of difference may be due to the modest sample size. Nevertheless, these results suggest that valproate may have a similar beneficial effect on suicidal behavior as lithium does. (This study was supported by the NIMH and by the Nina Rahn Fund. Medications were provided by Abbot Pharmaceuticals, Eli Lilly and Organon – these companies had no input into this study and article.)

General Pharmacotherapy/Psychotherapy Issues

In an interesting study in the primary care setting, Mergl et al. [12] studied whether better clinical outcome in depressed patients is associated with patients receiving their preferred treatment. Patients who received their preferred treatment, whether sertraline or group cognitive-behavioral therapy (CBT), responded significantly better than those who did not receive their preferred therapy (8-point difference on the Hamilton Rating Scale for Depression for CBT and 2.9-point difference for antidepressants). These findings suggest that treatment preference is a relevant factor influencing treatment outcome in depressed patients. Thus, patient treatment preference should be incorporated in the clinical decision about treatment strategies. (This study was supported by the German Ministry for Education and Research.)

In a complicated study comparing SSRI (escitalopram) pharmacotherapy and interpersonal therapy during 4 months of acute management of unipolar depression, Rucci et al. [13] found that time to suicidal ideation was significantly longer in patients allocated to SSRI compared to those allocated to interpersonal therapy, even after controlling for comorbid anxiety disorders and use of benzodiazepines. SSRI treatment was associated with a lower risk of treatment-emergent suicidal ideation than interpersonal therapy. Both treatments were considered safe, though. Clinically, it is important to realize that treatment-emergent suicidal ideation can occur during any treatment modality and that careful and frequent monitoring of suicidality, especially in patients with past suicide attempts, is required during any acute treatment. (This study was supported by the NIMH, Forrest Research Institute and Fondazione IDEA.)

Antidepressants Reevaluated

Potential use of antidepressants for the prevention of depression associated with interferon treatment of hepatitis C has been a controversial issue. Diez-Quevedo et al. [14] in their randomized, multicenter, double-blind, placebo-controlled study of escitalopram in the prophylaxis of interferon-induced depression during the first 12 weeks of treatment of 133 patients with chronic hepatitis C did not find any statistical difference between escitalopram and placebo (the rates of major depression were 3.2% with placebo and 7.6% with escitalopram). The results of this study suggest that the practice of prophylaxis of interferon-induced depression with antidepressants is not warranted. Targeted treatment of depression in these patients probably makes more sense. (This study was funded by Roche Prarma S.A., Madrid, Spain, and placebo pills were provided by Lundbeck A/S.)

Iovieno et al. [15] conducted a post hoc analysis of data from a clinical trial of fluoxetine in 203 patients with major depressive disorder. Patients were openly treated with fluoxetine for 12 weeks and those who responded were randomly assigned to continuation with fluoxetine or placebo for 52 weeks or till relapse. The main focus of this study was the assessment of the type and frequency of residual symptoms and their relationship to subsequent relapses of depression after remission of major depression with fluoxetine. More than 90% of patients who remitted with fluoxetine treatment had at least one residual symptom of depression (most frequently insomnia in about 60% of patients). These residual symptoms appeared to be a continuation of baseline symptoms rather than treatment-emergent symptoms or side effects. Importantly, the presence of residual symptoms was not significantly associated with an increased risk of relapse. (No direct funding for this study was reported.)

Hypochondriasis is usually considered to be a chronic difficult-to-treat condition with a low rate of remission. Schweitzer et al. [16] conducted a follow-up study of patients treated originally for hypochondriasis in two studies, one with fluoxetine and one with fluvoxamine. The average length of follow-up was 8.6 ± 4.5 years (4–16 years). They obtained data on 79% of patients. Forty percent continued to meet the full DSM-IV criteria for hypochondriasis at follow-up. Persistence of hypochondriasis was predicted by longer duration of prior hypochondriasis, history of childhood physical punishment and lower usage of SSRIs during the interval period. Actually, SSRI use during the follow-up interval was one of the most significant predictors of positive outcome. In spite of this

study's limitations (e.g. recall of SSRI use may be flawed), the results suggest that hypochondriasis may be treatable in some cases and that SSRIs may be helpful in this indication and may provide good long-term outcome. (This study was supported in part and indirectly by the Doris Duke Charitable Foundation and by the NIMH.)

CBT Expanding

Schneider et al. [17] developed a disorder-specific CBT program for separation anxiety disorder to be used in children with this disorder and their families. They tested this program in a randomized trial of 43 children assigned either to this 16-session program (including parent training and classical CBT components), or to a 12-week waiting list group. Intention-to-treat analyses indicated that 76.2% of children allocated to the treatment group no longer fulfilled DSM-IV criteria for separation anxiety disorder, compared to 13.6% in the waiting list group subjects. Parents also reported significant improvement. This is one of the first studies indicating the usefulness of specific CBT in children. It would be interesting to see what happens in a long follow-up with regard to the development of anxiety disorders in adulthood (as separation anxiety disorder may indicate an increased risk for development of some anxiety disorders later on). (This study was supported by Swiss National Science Foundation.)

Treatment of comorbid substance abuse and mental illness is quite difficult to conduct and evaluate. Watkins et al. [18] conducted a nonrandomized controlled trial to assess the efficacy of group CBT (16 two-hour group sessions) in patients with substance abuse and persistent depressive symptoms. They assigned 159 patients to usual care, and 140 patients to usual care plus group CBT. Patients receiving group CBT reported significantly fewer depressive symptoms and improved mental health functioning at 3 and 6 months of follow-up and fewer drinking days and fewer days of problem substance use at 6-month follow-up. As the authors point out, the results of their study support a new model of integrated care. (This study was supported by the National Institute on Alcohol Abuse and Alcoholism.)

Depression and Heart

Two studies addressed the complex relationship between depression and heart disease. Stafford and Berk [19] followed 193 patients (157 of them receiving statins)

hospitalized for myocardial infarction, angioplasty or coronary bypass graft surgery for 9 months to assess possible development of depression. Interestingly, statins at discharge had a protective effect on depression at 3 months after discharge and at 9 months after discharge, reducing the likelihood of depression by 69 and 79%, respectively. The authors felt that this finding supported the role of oxidative and inflammatory processes in depression, as the effect of statins on these processes is well known. (There was no funding for this study.)

In a prospective cohort study of 195 patients with coronary artery disease entering 1-year outpatient cardiac rehabilitation, Swardfager et al. [20] found that the rates of noncompletion of rehabilitation and of nonadherence (less than 70% attendance at scheduled cardiac rehabilitation visits) were 44.2 and 53% for those with major depressive disorder and 28.9 and 34.9% for those without major depression. The noncompletion of cardiac rehabilitation and nonadherence with it due to major depression may be another contributing factor to the increased morbidity and recurrence of coronary artery disease in patients with elevated depressive symptoms. (This study was supported by The Drummond Foundation, Montreal; The Physicians' Services Incorporated Foundation, Toronto, and the Heart and Stroke Foundation, Toronto.)

Internet-Based Therapies

Internet-based 'therapies' and interventions have been mushrooming lately. Grover et al. [21] examined the efficacy of a novel web-based systemic CBT intervention for carers (parents, partners) of patients with anorexia nervosa, designated to reduce carers' distress and teach skills in how to offer effective support. They compared the web-based intervention with limited clinician supportive guidance (by e-mail or phone) and with ad hoc usual support from the UK patient and carer organization, *Beat*. The online CBT program significantly reduced carers' anxiety and depression at post-treatment ('intervention' lasted 4 months) and this was maintained at follow-up of 6 months. The study design unfortunately did not allow separating the effects of online intervention from those of clinician guidance. Nevertheless, as the authors suggest the Internet-based package of carer support could be easily integrated into clinical care and could be offered as an adjunct treatment/help in anorexia nervosa. (This study was supported by South London and Maudsley Research and Development Fund; the Biomedical Re-

search Centre for Mental Health, South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London, and by a National Institute of Health Research Programme and by the Marie Curie Research Training Network.)

In another study of Internet-based intervention, Hollandare et al. [22] examined the possible role of Internet-based CBT in relapse prevention in patients with partially remitted major depression. All patients were previously treated with psychotherapy and/or antidepressants. Internet-based CBT significantly reduced the proportion of relapsed patients in the 6-month follow-up (CBT group: 10.5%; control group: 37.8%). The CBT group had also a larger reduction of depressive symptomatology. The groups were relatively small, 36 patients in the CBT and 35 patients in the control group were available for the 6-month follow-up evaluation. Nevertheless, the results of this study suggest that Internet-based CBT may be useful in the comprehensive management of post-treatment follow-up of major depression. (This study was partly

funded by the Swedish Psychiatry Foundation, the Capio Research Foundation and the National Association for Social and Mental Health.)

Last but not least, a word of caution. I selected two studies [21, 22] using various Internet-based interventions and I also suggested that Internet-based interventions have been mushrooming. However, as Kiluk et al. [23] in their review evaluating the current state of the science of research on the efficacy of computer-based therapies warn us, the field has not yet reached the level of methodological quality equivalent to those required for behavioral therapy or pharmacotherapy studies. (This review was supported in part by the National Institute on Drug Abuse and by VINS 1 Mental Illness Research, Education, and Clinical Center.)

Disclosure Statement

The author declares no conflict of interest.

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