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Bipolar Disorders in Late Life: Early Days, Gradual Progress

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Introduction

Three papers in this issue of the American Journal of Geriatric Psychiatry journal focus on late-life bipolar disorders and aim to characterize their neuro-biologic underpinnings. These studies assessed euthymic older bipolar patients and aimed to identify traits that may help elucidate underlying pathophysiologies and etiologies. Existing literature regarding late life mania and bipolar disorders has emphasized a number of robust findings including the high prevalence of cognitive dysfunctions (Young et al) [1], frequent abnormalities on structural neuroimaging, and the association between these disorders and neurologic disorders - especially cerebrovascular disease (Shulman & Herrmann) [2]. The studies reported in this issue describe findings from the application of cognitive assessments, neuroimaging methods and medical evaluations to these patients.

Studying such dimensions in older bipolar patients can ultimately have direct clinical and public health importance in these aged patients, who carry significant morbidity, mortality and economic burden (Sajatovic and Blow) [3]. They also can have heuristic value through shedding light on the nature of bipolar disorders in younger patients, a much larger clinical cohort.

Contributions in This Issue

Tsai et al [4] investigated differences in cognitive function, medical burden and socio-demographic characteristics between elderly community-dwelling Taiwanese euthymic BD patients and age and –education matched normal individuals in a case-control study. All subjects had measurements of global cognitive function using the Clock-drawing test and Mini-Mental State Examination and an assessment of medical morbidity and health. Elderly bipolar patients were more likely than the comparison group to have diabetes mellitus, smoking habit, and unfavorable social functioning. Mini-mental-State scores were significantly lower in the patients than in the comparison group.

Two surprising findings emerged from this study. One was the association of BD with atopic diseases, implicating a possible immunologic contribution. The second was the lack of “circulatory morbidity” in the patient group; although they had increased vascular risk factors including diabetes and smoking they had lower blood pressure values and diagnosed hypertension relative to the comparison group. These findings therefore conflict somewhat with a strong association of stroke and cerebrovascular disease with late life BD, including a

previous report using a large Taiwanese health database [5]; the authors suggest some explanations, but their current findings await further investigation.

Given that previous studies reported that the severity of cognitive deficits in euthymic patients with BD increases with the duration of illness and postulated that progressive neuronal loss or shrinkage and white matter changes may be at the origin of this phenomenon, Delaloye et al [6] performed a case-control study of both cognitive and magnetic resonance imaging assessments in seventeen euthymic elderly bipolar patients and a healthy comparison group. BD patients performed significantly poorer in processing speed, working memory and episodic memory but not in selected executive tasks. Neuroimaging analyses did not reveal significant volumetric or white matter differences between the two groups. The cognitive deficits were considered to be comparable both in terms of affected functions and effect size to those previously reported in younger BD cohorts. This observation and the absence of structural differences between groups did not provide support for a progressively evolving neurotoxic effect in BD. However, the study did not include a group of younger bipolar patients. The authors also suggest that the potential neuroprotective role of mood stabilizers over time could minimize the differences between young and older bipolar patients.

The Delaloye et al study also produced findings that are different from published literature which associates both abnormalities on structural imaging and executive dysfunction with late life bipolar disorder. With respect to the lack of executive dysfunction, the Swiss group offer possible explanations including their exclusion criterion regarding substance abuse. Also, the lack of differences in structural measures between the BD patients and controls is consistent with the lack of executive dysfunction in the patients. Further, the inconsistent imaging findings in the literature invite additional rigorous studies in larger samples.

The study by Brooks et al [7] complements the other papers in evaluating delayed free verbal recall and resting cerebral glucose metabolism, in euthymic ambulatory BD patients and controls. All participants received resting positron emission tomography (PET) with fludeoxyglucose (FDG) and, within 10 days, delayed free verbal recall testing with the California Verbal Learning Test II (CVLT). BD patients had significantly poorer delayed free verbal recall. In BD patients, prefrontal hypometabolism (dorsolateral prefrontal cortex) and paralimbic hypermetabolism (hippocampus, parahippocampal gyrus, and superior temporal gyrus) were associated with recall deficits. Prefrontal and limbic metabolism were inversely related. The authors proposed that verbal memory deficits may be a clinical consequence of corticolimbic dysregulation even during euthymia, and that such dysregulation and related deficits could be trait characteristics in older BD patients, comparable to that in young BD patients. The impact of possible neuroprotective effects of mood stabilizers in the BD patients could again not be excluded.

Discussion

These papers highlight conceptual themes, methodological challenges, and opportunities and in studying BD in late life. Their findings are important additions to a gradually enlarging literature, but some are disparate and require careful re-examination.

BD in late life is a complex, clinically heterogeneous population, perhaps more so than in early life. This heterogeneity presumably reflects the combined influences of genetic vulnerabilities and the interplay of physical and psychosocial factors across the lifespan, including comorbid conditions, illness episodes, effects of treatments, and increased mortality.

Methodological challenges to progress include the multiple factors that must be considered in defining a patient sample. One example is the cut-off for index age, i.e. 'older adult' or 'late life'. In the Brooks et al study the mean age of the patients was 58.7 years, while in the Delaloye et al sample the mean age was 69 years, and that of Tsai et al had a mean age of 71 years. Lack of age of onset estimates can also limit interpretation of, and comparison of, study findings. Other important variables that need to be assessed include treatment exposures, as well as type I and II illness patterns and other indices of severity. An overarching problem is the limited size of samples that can be studied at single clinical centers.

Combining clinical features with behavioral measures and structural and functional neuroimaging characteristics can help to identify older BD subtypes that may carry different prognoses, require different use of existing treatments, or respond to novel treatments. Additional biological tools that can contribute to this effort include genetic and postmortem brain measures.

These studies reinforce the need for clinicians to assess cognition carefully in older BD patients, including memory. Although executive dysfunction was not found to be significant in the Delaloye et al study, the existing literature and the hypometabolism found by Brooks et al in the DLPFC suggest that clinicians would be wise to include executive testing in their assessments of older bipolars. The mixed results related to structural neuroimaging suggest we are still some way from identifying lesions and pathologies associated with BD in older adults. Since the body of evidence to date shows a strong association between stroke, cerebral hyperintensities and bipolarity, clinicians should be alert for vascular risk factors, which may be modifiable, and for evidence of recent cerebrovascular pathology including infarcts and small vessel disease (amyloid angiopathy).

The recent increase in interest in older BD patients is encouraging. Individually the studies illustrate that important work can be done, for example using functional neuroimaging, at single sites using modest samples. Each of these studies offers intriguing findings for further testing and contributes incrementally to our understanding of late life BD patients and their underlying pathobiologies. Additionally, to make substantive progress will require larger scale studies in order to address many clinically important questions with adequate power. Smith & Alexopoulos [8] have emphasized the value of integrating a variety of methodologies to understand the neurobiology of late-life psychiatric disorders. BD awaits as an ideal paradigm for such integration.

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