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COMMENTARY

Shifting from prevention of the next episode to optimizing inter-episodic functioning *Commentary on "The neuroprogression hypothesis in bipolar disorders: Time for apologies?"*

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The question in science is: at what point is there enough evidence to shift paradigm? Strejilevich and colleagues argue in their editorial that the time is here for bipolar disorder (BD).[1] The authors argue that we have not been able to prove neuroprogression in BD and that holding on to it will harm patients. A (hyper)focus on prevention of new episodes in BD may lead to overprescribing medication that increases the risk for cardiovascular diseases, and both medication and cardiovascular diseases have been associated with cognitive impairment in BD.[2,3] This hyperfocus may also refrain clinicians and researchers from looking beyond a relatively narrow cause–effect treatment of BD that merely focuses on prevention of mood symptom recurrence. In our opinion, BD warrants a more differentiated, personalized approach, which also takes into account psychosocial and cognitive functioning. Thus, we should indeed shift focus: from prevention of the next episode to optimizing inter-episodic functioning by integrating psychiatric and physical care for individuals with BD.

The neuroprogression hypothesis has been appealing to many. On the one hand, clinicians are encouraged by the neuroprogression hypothesis to prevent new episodes, as according to this theory, each mood episode could be neurotoxic. Furthermore, neuroprogression provides focus for patients and their relatives: "The reality of the current episode cannot be changed, but we can aim to prevent the next." It provides a clear goal and treatment direction for clinicians: reduction of (future) mood symptoms and clinical recovery. On the other hand, researchers are fond of the theory because it fuels the search for a neurobiological origin of BD. To date, the pathophysiological underpinnings of BD have not been pinpointed despite global efforts in numerous genetic and imaging studies and that is frustrating. As researchers, we have postulated a hypothesis and then tried to prove it, or preferably disprove it, and that is what we do. However, the persistent belief in the neuroprogression hypothesis could also be the result of an epiphenomenon, namely the observation that patients with the worst course of BD have the highest risk of poor physical health and use of multiple psychotropic drugs in high doses, both of which can ultimately lead to cognitive impairment. Time to take a step back?

As clinicians in the field of old age bipolar disorder (OABD, aged 50 years and over), we have observed few indications of neuroprogression. It is true that some patients develop dementia, but overall the cognitive course of OABD patients mimics the natural course of healthy controls.[4,5] Similarly, we have perceived little evidence for *somatoprogression* (i.e., the accumulation of somatic comorbidities with every mood episode), in our clinical practice with OABD patients. Cross-sectional data from our clinic showed an even lower chronic physical burden in OABD compared to the general population.[6] In this study, the observed faster accumulation of chronic physical diseases in OABD that could be explained by differences in psychosocial, lifestyle, and health behavior factors.[6] What we do encounter in our daily practice is that our patients with OABD suffer from poor psychosocial functioning, polypharmacy, and poor physical health, all of which reduce their quality of life. Our clinical and

research findings in OABD urgently call for the use of integrated care in BD. In case of strong collaboration between psychotherapists, medical specialists, family physicians, pharmacists, and social workers, clinical outcome of patients could improve tremendously. Next, we should try to overcome barriers for psychosocial interventions and develop accessible evidence-based psychotherapeutic interventions that focus on improvement of daily functioning and quality of life instead of prevention of recurrence. Moreover, prevention of cardiovascular diseases and interventions to improve lifestyle should be offered to patients with BD of all ages. Such a clinical focus on "daily functioning" is perhaps less appealing than the search for a neurobiological origin of BD, but nevertheless our aim as clinicians and researchers is, and should ultimately be, to improve quality of life of those struggling with BD. If we don't, we should indeed apologize for not making that our focus in BD for the next decade(s).

CONFLICT OF INTEREST STATEMENT

None of the authors report a conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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