Psychological Medicine

cambridge.org/psm

Commentary

Cite this article: Samamé C (2024). What do psychiatrists do with hypotheses proven false? The case of neuroprogression in bipolar disorders. *Psychological Medicine* **54**, 41–42. https://doi.org/10.1017/S0033291723003318

Received: 16 September 2023
Revised: 9 October 2023
Accepted: 13 October 2023
First published online: 10 November 2023

Corresponding author:
Cecilia Samamé;
Email: ceciliasamame@gmail.com

What do psychiatrists do with hypotheses proven false? The case of neuroprogression in bipolar disorders

Cecilia Samamé

Universidad Católica del Uruguay, Montevideo, Uruguay

In the last 15 years, we have witnessed the development and rapid expansion of an alluring hypothesis aimed at describing the course of bipolar disorders (BDs). This hypothesis, known as *neuroprogression*, assumes that a pathological reorganization of the nervous system occurs together with progressive clinical and neurocognitive deterioration (Berk et al., 2011; Carvalho, Firth, & Vieta, 2020). In turn, this notion is the conceptual basis of staging models, which are partially adopted by the main clinical guidelines (Yatham et al., 2018) to describe the evolution of the disorder:

> The course of BD is heterogeneous but, on average, the risk of recurrence increases with the number of previous episodes. (…) The progressive course of illness in patients with multiple episodes is called clinical progression and the biological basis of clinical progression is defined as neuroprogression.
> The concepts of clinical progression and neuroprogression have provided the basis for the development of staging systems in BD. (…) Overall, the model of staging has helped clinicians to appreciate the importance of early identification and treatment as well as illness trajectories in BD.

The concept of clinical staging, long used in other fields of medicine, postulates that there is a stepwise progression through a series of identifiable 'stages', which have specific features and treatment targets (Berk et al., 2011). This notion was received with great hope and enthusiasm, as it was thought to bring significant advance to psychiatric practice by making more precise interventions possible.

Neuroprogression first appeared in the field of psychiatry as a falsifiable hypothesis; that is, as a statement capable of being tested and proven wrong as any other scientific hypothesis. However, while the data against neuroprogression have increased in amount and robustness over the last few years, the main promoters of this notion have managed to reinterpret the evidence in a very particular manner (Carvalho et al., 2020; Montejo et al., 2022; Solé, Martínez-Aran, Vieta, & Torrent, 2021) so as to 'save' the hypothesis, thus sacrificing scientificity.

Evidence for neuroprogression?

The main evidence considered to be supportive of neuroprogression in BDs derives from cross-sectional studies reporting a negative correlation between the number of previous episodes, especially manic ones, and neuropsychological performance. This finding has led to the assumption that the experience of multiple episodes causes progressive cognitive decline (Martino et al., 2013; Strejilevich, Samamé, & Martino, 2015). Interestingly, however, research findings have provided a different explanation to this correlation, suggesting that cognitive impairment might be a severity marker associated with an increased risk of recurrences and a poorer clinical course rather than being the consequence of cumulative effects of multiple mood episodes (Martino et al., 2013; Strejilevich et al., 2015).

Cognitive outcomes among late-life BD patients, with decades of illness duration in most cases, may also indirectly inform about the long-term neuropsychological trajectory of BD. If cognition worsens throughout the course of the illness, as the neuroprogression hypothesis assumes, we should expect elderly patients to display a more severe magnitude of impairment. In a recent study by the International Society for Bipolar Disorders (ISBD) Older Adults Task Force, Montejo et al. (2022) explored the neurocognitive outcomes of late-life patients by means of meta-analytic procedures. In line with another meta-analysis published 10 years earlier (Samamé, Martino, & Strejilevich, 2013), they found cognitive deficits of a magnitude that was similar to that observed in young and middle-aged patients. Interestingly, however, the promoters of the neuroprogression hypothesis failed to note the findings against progressive cognitive decline derived from their own work. Rather, they stated that the results of their meta-analysis were biased toward less severe presentations of BD, as patients considered to have 'progressed' (those developing major neurocognitive disorder) were excluded from patient samples at the primary study level. That is, the authors assume that dementia in BD

patients is the result of illness progression in the absence of any data supporting this statement. It is evident that dementia occurs in individuals without any previous neuropsychiatric disorders as well and, in primary neuropsychological studies of BD patients, participants meeting criteria for major neurocognitive disorder were also excluded from control samples. Further, the assumption of 'healthier presentations' of the disorder being included in neuropsychological studies may also seem counterintuitive as the main investigations on the topic were developed in tertiary, highly specialized care centers, where illness is not expected to be less severe.

Of note, however, the main evidence capable of shedding light on the long-term course of cognition in BDs derives from longitudinal research. A recent meta-analysis based on controlled studies of long-term (>5 years) cognitive outcomes found that the course of neuropsychological functioning over a mean follow-up period of 9.8 years was similar to that observed in healthy controls (Samamé, Cattaneo, Richaud, Strejilevich, & Aprahamian, 2022). Similarly, in a recently released controlled study with a follow-up period of 10 years, no evidence of decline was found among BD patients when compared to healthy controls (Flaaten et al., 2023). Although it may be argued that these follow-up periods were too short, the fact remains that the best available evidence from longitudinal research does not support the deteriorating course of cognition assumed by neuroprogression.

All this said, while we still lack a clear understanding of the long-term evolution of BD, robust evidence supporting worsening of cognition over time or as the result of the cumulative effect of mood episodes is virtually non-existent so far.

Implications for clinical practice and research

According to the promoters of the neuroprogression hypothesis (Carvalho et al., 2020; Montejo et al., 2022; Solé et al., 2021), 'resistant' BD presentations correspond to late stages of the disorder and require more aggressive treatments, including a more intensive exposure to pharmacotherapy, neuromodulation techniques, and even specific psychosocial interventions. Among the latter, they have placed great emphasis on a specific psychosocial approach known as cognitive/functional remediation that, according to their proposal, may arrest the effects of neuroprogression (Montejo et al., 2022; Solé et al., 2021). Once again, there is no evidence supporting the use of this intervention in people with BD (Samamé, Durante, Cattaneo, Aprahamian, & Strejilevich, 2023). Indeed, findings from a recent meta-analysis of randomized controlled trials showed that cognitive/functional remediation did not exert any improvement of functional outcomes among BD patients. Interestingly, negative findings were also found when considering studies of cognitively impaired patients only (Samamé et al., 2023). The available evidence rather than supporting 'precision psychiatry' makes us think that dealing with uncertainty would lead us to make more precise clinical decisions.

To conclude, the long-held assumption of neuroprogression in BDs as a self-evident truth discourages exploration of variables that are different from the illness itself that could cause deterioration and prevents redirecting research to more fruitful avenues. The progress of a scientific discipline such as psychiatry is not possible if we are not willing to reject hypotheses that have not proven consistent with the empirical data available.

The case of the neuroprogression hypothesis in BD briefly presented here illustrates how a belief-persistence attitude is seriously hindering progress toward a more complete understanding of a high-prevalence psychiatric disorder associated with a significant burden for patients, their families, and the health system.

References

Berk, M., Kapczinski, F., Andreazza, A. C., Dean, O. M., Giorlando, F., Maes, M., … Malhi, G. S. (2011). Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. *Neuroscience and Biobehavioral Reviews*, *35*(3), 804–817. doi:10.1016/j.neubiorev.2010.10.001

Carvalho, A. F., Firth, J., & Vieta, E. (2020). Bipolar disorder. *The New England Journal of Medicine*, *383*(1), 58–66. doi:10.1056/NEJMra1906193

Flaaten, C. B., Melle, I., Bjella, T., Engen, M. J., Åsbø, G., Wold, K. F., & … Ueland, T. (2023). Long-term course of cognitive functioning in bipolar disorder: A ten-year follow-up study. *Bipolar Disorders*, 10.1111/bdi.13364. Advance online publication. doi:10.1111/bdi.13364

Martino, D. J., Strejilevich, S. A., Marengo, E., Igoa, A., Fassi, G., Teitelbaum, J., & Caravotta, P. (2013). Relationship between neurocognitive functioning and episode recurrences in bipolar disorder. *Journal of Affective Disorders*, *147*(1–3), 345–351. doi:10.1016/j.jad.2012.11.037

Montejo, L., Torrent, C., Jiménez, E., Martínez-Arán, A., Blumberg, H. P., Burdick, K. E., … International Society for Bipolar Disorders (ISBD) Older Adults with Bipolar Disorder (OABD) Task Force (2022). Cognition in older adults with bipolar disorder: An ISBD task force systematic review and meta-analysis based on a comprehensive neuropsychological assessment. *Bipolar Disorders*, *24*(2), 115–136. doi:10.1111/bdi.13175

Samamé, C., Cattaneo, B. L., Richaud, M. C., Strejilevich, S., & Aprahamian, I. (2022). The long-term course of cognition in bipolar disorder: A systematic review and meta-analysis of patient-control differences in test-score changes. *Psychological Medicine*, *52*(2), 217–228. doi:10.1017/S0033291721004517

Samamé, C., Durante, P., Cattaneo, B., Aprahamian, I., & Strejilevich, S. (2023). Efficacy of cognitive remediation in bipolar disorder: Systematic review and meta-analysis of randomized controlled trials. *Psychological Medicine*, *53*(12), 5361–5373. doi:10.1017/S0033291723001897

Samamé, C., Martino, D. J., & Strejilevich, S. A. (2013). A quantitative review of neurocognition in euthymic late-life bipolar disorder. *Bipolar Disorders*, *15*(6), 633–644. doi:10.1111/bdi.12077

Solé, B., Martínez-Aran, A., Vieta, E., & Torrent, C. (2021). Commentary on 'The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary'. *Bipolar Disorders*, *23*(5), 513–514. doi:10.1111/bdi.13073

Strejilevich, S. A., Samamé, C., & Martino, D. J. (2015). The trajectory of neuropsychological dysfunctions in bipolar disorders: A critical examination of a hypothesis. *Journal of Affective Disorders*, *175*, 396–402. doi:10.1016/j.jad.2015.01.018

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*(2), 97–170. doi:10.1111/bdi.12609

https://doi.org/10.1017/S0033291723003318 Published online by Cambridge University Press