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**TRABALHO FINAL**
**MESTRADO INTEGRADO EM MEDICINA**

Clínica Universitária de Psiquiatria e Psicologia Médica

# Bipolar disorder and the risk of developing dementia:

## A literature review

Rita Vilar da Mota

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# Bipolar disorder and the risk of developing dementia:

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Rita Vilar da Mota

**Orientado por:**
Dr.ª Inês Chendo

**julho2017**

**Abstract**

In the last centuries, the concept of bipolar disorder has suffered multiple modifications at many levels, including the diagnosis and the recognition of the prognosis associated with it. Many authors, based on their clinical observations, have recently conducted studies in order to appraise the possible underlying neuroprogression of the bipolar disorder.

*Objectives*: The aim of this review is to evaluate the existence of a correlation between bipolar disorder and the risk of developing dementia. If this proposition is verified, the target will also be determining which subtype of dementia is more often found in these patients.

*Methods*: a literature review of key papers of all English language articles from a *PubMed* and *b-on* literature search (2007–2017) using the keywords "*bipolar disorder", "dementia", "frontotemporal*" and "*staging"*. In addition to all the articles identified as relevant, the search was augmented by manually reviewing bibliographies from identified reports and recent reviews. Articles were selected for review if their content was instructive to the current topic.

*Results*: There is strong evidence that history of bipolar disorder significantly increased the risk of dementia, specifically behavioral variant frontotemporal dementia. Biomarkers, such as Brain-Derived Neurotrophic Factor and oxidative stress markers, and neuroimaging findings support the hypothesis of an underlying neuroprogression associated with bipolar disorder.

*Conclusion*: A higher risk of dementia, specifically behavioral variant frontotemporal dementia, is patent in bipolar disorder patients. It is also evident that the likelihood of developing cognitive and functional impairment is elevated when there is inadequate treatment and, consequently, increased duration and number of the affective episodes per year. Future studies are necessary, in order to enhance these patients' outcome, by clarifying the underlying mechanisms of this neuroprogression and, also, by defining the best possible interventions that might avoid developing dementia.

*Keywords:* *bipolar disorder, frontotemporal, dementia, staging*

**Resumo**

Nos últimos séculos, o conceito de perturbação afetiva bipolar sofreu múltiplas modificações a diversos níveis, incluindo o diagnóstico e o reconhecimento do prognóstico associado. Vários autores, com base nas suas observações clínicas, realizaram, recentemente, estudos com o objetivo de avaliar a possível neuroprogressão subjacente a esta patologia.

Objetivos: Esta revisão da literatura tem como propósito apreciar a existência de uma correlação entre perturbação afetiva bipolar e o risco de desenvolvimento de demência. Se esta proposição for verificada, o objetivo será também determinar que tipo de demência é mais frequentemente encontrado nestes pacientes.

Métodos: Procedeu-se a uma revisão da literatura dos artigos em Língua Inglesa, resultantes de uma pesquisa nas plataformas *PubMed* e *b-on* (2007-2017), usando as palavras-chave "bipolar disorder", "dementia", "frontotemporal" e "staging". Para além de todos os artigos identificados como relevantes, a pesquisa foi aumentada com uma revisão manual das bibliografias dos mesmos.

Resultados: Há forte evidência que suporta a correlação entre o diagnóstico de perturbação afetiva bipolar e o posterior desenvolvimento de demência, especificamente a variante comportamental da demência frontotemporal. Biomarcadores e achados imagiológicos apoiam a hipótese de que há um possível mecanismo de neuroprogressão subjacente à perturbação afetiva bipolar.

Conclusão: Um risco aumentado de demência, particularmente a variante comportamental da demência frontotemporal, parece estar patente nos doentes com perturbação afetiva bipolar. Também é evidente que a probabilidade de desenvolvimento de défices cognitivos e funcionais é superior, quando existe tratamento inadequado e, consequentemente, maior número e duração dos episódios afetivos. Estudos futuros são necessários, de modo a melhorar o *outcome* destes doentes, através do esclarecimento dos mecanismos de neuroprogressão subjacentes e, ainda, pela definição de quais as possíveis intervenções mais adequadas, de modo a evitar o desenvolvimento de demência.

Palavras-chave: *perturbação afetiva bipolar, frontotemporal, demência, estadiamento*

***O Trabalho Final exprime a opinião do autor e não da FML***

**Resumo II**

Introdução

A perturbação afetiva bipolar (PAB) é reconhecida como uma doença crónica, caracterizada por episódios recorrentes de mania e/ou hipomania**,** alternando com episódios de depressão. Estas perturbações do humor são suficientemente severas para ter impacto no funcionamento social e ocupacional dos doentes. Em relação aos tipos I e II da perturbação afetiva bipolar, estudos apontam para uma prevalência de cerca de 2 a 3%.

No século XIX, Emil Kraepelin descreveu a patologia em questão como sendo um conjunto de quadros clínicos muito distintos. Referiu ainda que após um episódio afetivo, os sintomas poderiam regredir por completo. Porém, observou que alguns pacientes com maior frequência e maior gravidade dos episódios afetivos teriam menor probabilidade de retomar um estado de eutimia. Schott, após a revisão de diferentes estudos com casos de "mania crónica", descreve que esta poderia ser considerada uma "forma especial de demência".

Assim, apesar de inicialmente a PAB ser considerada uma doença cíclica, com recuperação total entre os episódios de humor, nas últimas décadas, este conceito tem vindo a ser abandonado. Passou a ser cada vez mais aceite que a existência de défices cognitivos, relacionados com os mecanismos neuroprogressivos subjacentes, fazem parte do fenótipo desta patologia.

Porém, ainda existe escassa informação acerca desta possível relação entre PAB e demência. É essencial aprofundar o conhecimento sobre a possível evolução desta perturbação do humor, de modo a poder desenvolver e aplicar um modelo de estadiamento adequado. Assim, será possível providenciar o melhor tratamento, individualizado, de acordo com o prognóstico específico de cada doente.

Objetivos

Esta revisão da literatura tem como objetivo clarificar se há realmente uma correlação entre a PAB e o risco de desenvolvimento de demência. Caso ela exista, o passo seguinte será determinar qual o tipo de demência mais frequentemente observável nestes doentes.

Metodologia

Foi feita uma revisão narrativa da literatura resultante de uma pesquisa nas bases de dados *b-on* e *PubMed*, com as palavras-chave "bipolar disorder", "dementia", "frontotemporal" e "staging". Foram definidos como critérios de inclusão artigos escritos em Língua Inglesa, publicados desde 2007 até 2017. Para aumentar e melhorar o conteúdo, artigos identificados como relevantes foram selecionados manualmente e, posteriormente, revistos.

Espectro da perturbação afetiva bipolar

Ao longo das últimas décadas, a conceptualização de perturbação afetiva bipolar tem vindo a sofrer alterações. A evidência cumulativa levou ao reconhecimento da existência de um continuum de manifestações de mania e de hipomania, com diferentes graus de severidade. Tendo sido inicialmente proposto por Kraepelin, o espectro da PAB só ganhou maior popularidade com a publicação de teorias semelhantes pelos autores Akiskal e Klerman, em 1977 e 1981, respetivamente. Foi gradualmente abandonada a tradicional dicotomia PAB tipo1 vs PAB tipo 2, tendo o reconhecimento de diversos outros subtipos de PAB levado a um aumento significativo da prevalência da doença.

No fim do século passado, Akiskal propôs a seguinte classificação: tipo I, com alternância entre mania e depressão; tipo II, quando há alternância entre depressão e hipomania; tipo II½, se houver depressão sobreposta a um temperamento ciclotímico; tipo III, no caso da depressão e hipomania induzida por fármacos; tipo III ½, com mania/hipomania provocada pelo abuso de substâncias e tipo IV, na depressão de início tardio, sobreposta a um temperamento hipertímico. É acrescentado mais tarde o tipo V, em relação aos pacientes com estados mistos unipolares recorrentes. Em 2005, Akiskal cria outro protótipo, o tipo VI, para incluir pacientes com episódios mistos, associados a labilidade emocional, com a instalação de declínio cognitivo. Surgiu assim a necessidade esclarecer a relação entre estes sintomas e os respetivos mecanismos fisiopatológicos subjacentes.

Estadiamento da perturbação afetiva bipolar

O estadiamento da PAB pode vir a ter um papel fundamental na definição mais precisa do tratamento mais adequado e na avaliação do prognóstico. Vários modelos de estadiamento de PAB têm vindo a ser desenvolvidos ao longo dos últimos anos.

Berk et al. criaram um modelo que diferencia os pacientes numa fase assintomática, com fatores de risco ativos, dos doentes refratários ao tratamento, sem remissão dos sintomas. Por outro lado, Kapczinsky et al. incluíram no seu modelo de estadiamento alterações de biomarcadores inflamatórios e de stress oxidativo bem como alterações neuroimagiológicas. Estes critérios basearam-se em estudos que revelaram que doentes bipolares mais velhos, comparativamente ao grupo de controlo, apresentavam mais sinais de atrofia e lesões cerebrais vasculares. Verificou-se ainda uma atrofia bilateral frontotemporal, mais acentuada na região frontal. Anos mais tarde, Duffy et al. desenvolveram um modelo de estadiamento que enfatiza a história psiquiátrica familiar, bem como os percursores na história de infância e a psicopatologia na adolescência, defendendo que estes podem predizer a evolução dos quadros clínicos. Não obstante, os modelos até à data propostos apresentam algumas limitações, tornando-se necessário desenvolver um modelo de estadiamento mais robusto.

Casos clínicos

Múltiplos estudos foram conduzidos com o fim de esclarecer a possível neuroprogressão da PAB. Recentemente, uma revisão sistemática e meta-análise, publicada por Diniz et al., demonstrou claramente que os doentes com perturbação afetiva bipolar têm risco aumentado de demência, não especificando, porém, o seu subtipo.

Por sua vez, Dols et al. publicaram uma série de casos clínicos de doentes com PAB em estádios avançados. Estes apresentavam défices cognitivos e comportamentais, cujo fenótipo correspondia ao habitualmente encontrado em doentes com a variante comportamental da demência frontotemporal. Contudo, a nível imagiológico, não se verificavam alterações ao longo do tempo, o que levou os autores a colocar em causa a natureza neuroprogressiva da PAB.

Para além disso, os autores Cerami e Cappa e Pose et al., corroborando a hipótese da associação causal entre PAB e demência frontotemporal, também defendem que esta relação é mais forte em casos com longa evolução da PAB, principalmente em doentes

com um diagnóstico feito em idades mais jovens, suportando a hipótese da sua natureza neuroprogressiva .

Demência frontotemporal

A demência frontotemporal (DFT) é clinicamente heterogénea. A nível imagiológico, carateriza-se pela atrofia dos lobos frontal e temporais. Estão descritos três fenótipos diferentes: a variante comportamental, a afasia progressiva não-fluente e a demência semântica.

Relativamente à variante comportamental, a deterioração do lobo frontal e da região anterior dos lobos temporais conduz a alterações do comportamento e da personalidade.

Perturbação afetiva bipolar nos idosos

O diagnóstico de PAB em idades mais avançadas está associado a um maior número e a uma maior duração de episódios afetivos. Para além disso, há evidência de que nestes doentes há um declínio cognitivo mais profundo, relativamente aos doentes com diagnósticos efetuados em idades mais precoces. Vários estudos demonstraram uma associação entre o número de episódios maniformes em idosos com PAB e demência.

Todavia, certos autores propõem que, em indivíduos com predisposição prévia, tal como determinados temperamentos, a demência poderá favorecer a manifestação de uma PAB latente.

Conclusões

Ao longo do tempo, o conceito de PAB, quer a nível de diagnóstico, quer a nível de evolução e prognóstico, sofreu grandes mudanças. Para além da adoção da visão da perturbação como um espectro, o declínio cognitivo e funcional foi reconhecido como parte do curso natural da patologia.

Ao longo dos anos, diversos autores desenvolveram estudos para avaliar a relação existente entre PAB e demência, tendo constatado que existe uma associação entre as duas patologias. Para além disso, verificou-se que quanto maior o número e a gravidade dos episódios afetivos, maior a probabilidade de evolução para demência.

Porém, os estudos desenvolvidos nesta área ainda não são suficientes e será necessário aprofundar a pesquisa, de modo a avaliar os potenciais mediadores desta associação e, também, para delinear as possíveis intervenções que poderão reduzir o risco de desenvolvimento de demência nestes doentes.

**Contents**



## Introduction

Bipolar disorder (BD) is recognized as a chronic mood disorder, characterized by alternating recurrent episodes of mania or hypomania and depression. (1) These mood disturbances are sufficiently severe to cause marked impairment in social or occupational functioning. It is a disorder associated with negative health outcomes, both medical and psychiatric conditions, such as cardiovascular disease (2–4) and increased risk of suicide. (5) A recent meta-analysis conducted by Clemente et al. has revealed this condition has lifetime prevalence rates ranging from 2% to 3%, for bipolar disorder type I and II.(6)

In the XIX century, Emil Kraepelin described for the first time the concept of a mental disease with great manifoldness of clinical pictures, including periodic and cyclic melancholia and mania (7,8). The author stated that, after a mood disorder episode, the

symptoms could totally disappear. Notwithstanding, he also has described that when patients presented episodes of manic-depressive illness very frequently and with great severity, they could have lower odds of full recovery and the symptoms could acquire chronicity (7,8). Over time, multiple cases of chronic mania had been described and the author Schott, in 1904, after reviewing this subject, considered it a “special form of dementia”, with extreme heritability associated, in most cases. (7) Since then, the idea that affective states could evolve into dementia was consensually accepted. (7)

Therefore, initially, BD was classically recognized as a cyclic disease, with full recovery between mood episodes. (8) However, especially in the last decades, the accumulated evidence has led to a different understanding of the pathology, recognizing more and more cognitive impairment as an integral part of the BD phenotype, which points to the existence of underlying neuroprogressive mechanisms. (9)

Howsoever, there is still limited and scattered information about this relationship between BD and dementia. It becomes essential to fully understand the natural history of this affective disorder, in order to develop and to apply an accurate staging model, which is fundamental to provide the best treatment, according to the corresponding prognosis.

**Objectives**

The aim of this review is to clarify, by performing a literature review, if there is truly a correlation between BD and the risk of developing dementia. If it is verified a relationship between these two entities, the goal will also be to determine which subtype of dementia is found in these patients.

**Materials and methods**

A narrative overview of the literature was made, synthesizing the findings of literature retrieved from search performed on the computerized databases *b*-on and *PubMed*, with the keywords "bipolar disorder”, “dementia”, “frontotemporal” and “staging”. The following inclusion criteria were applied during the search and screening process: original research published in peer-reviewed journals from 2007 to 2017 and articles published in English. To enhance the content, articles identified as relevant were selected manually and reviewed.

## The bipolar disorder spectrum

Over the last decades, authors, basing themselves on clinical observations, have been describing BD as a natural continuum of hypomanic and manic manifestations, which occur over a broad spectrum of severity, making more difficult the differentiation of all its subtypes. (10,11)

Kraepelin was the first to envisage this concept. One of his most important observations was that, in many patients, mania and depression were often intermixed in the same episode. (8,12) It had not always been accepted by the scientific community, but he started gaining support when in 1977, the cyclothymic–bipolar spectrum was proposed by Akiskal and in 1981 Klerman described the mania spectrum. (13,14) The loss of the binary traditional concept of BD to the bipolar spectrum has also increased, substantially, the prevalence of the disease, since patients that did not meet the criteria for BD type 1 or type 2 are now included. (15)

Contemplating this concept of bipolar disorder as a spectrum, a model has been proposed by Akiskal in the ending of the last century. (12) This model differentiates type I, with alternating periods of mania and depression; type $I^{1/2}$, when there is depression protracted with hypomania; type II, which consists in variations between depression and hypomania; type $II^{1/2}$ when cyclothymic depressions are found; type III, when there is depression plus antidepressant-associated hypomania; type III½, relatively to bipolarity masked – and unmasked – by stimulant abuse and, finally, type IV, with late-onset depression superimposed on hyperthymic temperament. (12) Later, it was created type V, to include patients with recurrent unipolar mixed states. (16) In 2005, Akiskal added a prototype, type VI, to include elderly patients with frequent mood lability, with a setting of a dementia-like process, due to their cognitive decline. (17) Bearing in mind this model, Ng and colleagues supported it when publishing a set of case series with patients that fit these criteria (11,16) Hence, this new subdivision creates the need to comprehend the real connection between these symptoms and respective causing mechanisms. (11,16,18)

## Staging bipolar disorder

BD staging models use clinical presentation and specific biomarkers to define at which point the disease has progressed, allowing a better guidance of the treatment, the prediction of outcomes and a more accurate prognosis. (19–21) As a lifelong disorder with neuroprogressive nature, it has been proposed that it is reasonable to apply a

staging model, since patients might have a background of specific and nonspecific risk factors, both genetic and environmental, and may also develop non-specific early symptoms and syndromes. (22–24) Although BD has a great variety of temporal evolution patterns, the longitudinal trajectory is often clear. (25)

Several models have been created, based on the evidence towards the disease evolution and the underlying physiopathological mechanisms, with the aim of delivering a individually tailored management of the disorder, in order to cease its neuroprogressive nature and change the natural course of the disease. (26,27)

Family history seems to play a major role in the risk of developing BD. (28) Notwithstanding, BD seems to evolve through a predictable sequence of clinical phases, but it is not mandatory for all-risk individuals to ever manifest all the different stages or reach end-stage illness. (26) The progression of the illness also appears to be linked to inadequate treatment and, consequently, to a higher number of spontaneous episodes. (29) In these cases, there is usually a greater rate of comorbidities, whether medical or psychiatric, with increased risk of suicide and higher number of hospitalizations. (30) Furthermore, BD can be considered to evolve through cumulative allostatic states. Thus, individuals are exposed to a repetitive impairing stimulus, resulting in the progression of the disease, through repeated affective episodes, which can also be designated by "allostatic load". (31) Researchers have presented mounting evidence that inflammation and oxidative stress are responsible for the worsening of the clinical course in BD, with cognitive deterioration and functional decline. (32) However, besides biomarkers as Brain-Derived Neurotrophic Factor (BDNF), some of the oxidative stress markers present higher levels in plasma or blood cells in individuals with BD. (33,34) Kapczinski and colleagues presented a study in which they demonstrate that, during acute BD episodes, oxidative damage can be as high as in patients with sepsis. (35)

The systematic review conducted by Muneer et al. thoroughly describes the staging models proposed for bipolar disorder, with more supporting evidence in literature. (26) Berk and colleagues created a comprehensive model that differentiates patients from the asymptomatic phase with active risk factors, until those refractory to treatment, with no remission of their symptoms. Nonetheless, the proposed stages are very heterogeneous and non-specific, which might lead to false positives. (25,26)

On the other hand, Kapczinsky and colleagues put more emphasis on biomarkers and on neuroimaging findings, correspondent to each stage. The proposed criteria are based on neuroimaging studies, in which it is described that older people with BD may show

more signs of atrophy and cerebral vascular lesions, when comparing to normal age-matched control subjects. (36,37) Using brain MRI, it has been shown that bilateral frontotemporal symmetric atrophy, more prominent in frontal areas, is often found. (38–40) Widespread gray matter loss was also documented, with bigger involvement of orbitofrontal cortex, when comparing to the dorsolateral prefrontal cortex. In addition, marked involvement of the fronto-insula, cerebellum and anterior cingulate gyrus has also been described. (39–41)

Kapczinsky and colleagues' model also proposes to discriminate patients with vague symptomatology or at higher risk of developing BD from those with cognitive and functional impairment, with loss of autonomy. (26,42)

Years later, Duffy et al.'s made a proposal, which puts emphasis on family history, early childhood precursors and adolescent psychopathology, that, when combined, potentially help predicting the disease progression. (43)

Hence, Muneer et al. consider that these models still have limitations and need refinement, since an early intervention increases the chances of preventing or delaying the progression of the condition, with simple and effective tools. (26,44)

**Case series studies**

Over the last decades, multiple researches have been conducted, in order to evaluate the possible neuroprogression, as part of the natural course of bipolar disorder. (45)

A systematic review and meta-analysis published by Diniz et al., after analysing 6 studies with a total of 194.055 subjects, it was demonstrated that the diagnosis of bipolar disorder profoundly increases the risk of dementia in older adults. (46) With this clear relationship between these pathologies, still, it was not evaluated which type of dementia is often found in bipolar disorder patients.

Dols et al. published a case series, in which patients with advanced or end-stage bipolar disorder were analysed. They described deficits in cognition and changes in behavior, which were symptoms not attributable to their base condition and were reported as a distinct loss of insight and empathy, with disinhibition and socially inappropriate behavior. This is a phenotype compatible with the one found in patients with frontotemporal dementia (FTD), specifically the behavioral variant (bvFTD). (9) Notwithstanding, these authors advise to not consider it a diagnosis of bvFTD, due to the absence of clear clinical and radiological progression over time. Thus, these patients

are not considered to have a neurodegenerative illness, being hypothesized a probable functional involvement of the frontal-subcortical networks. (9)

Furthermore, Cerami and Cappa have developed a case study with two patients, which presented bipolar disorder, prior to the FTD diagnosis. Such as described by other authors, it is supported the hypothesis that BD might be a long preclinical phase that precedes FTD. (47–49) It has also been established a relationship between early onset bvFTD, previous psychiatric history and tau-negative ubiquitin-positive inclusions consistent with a pathological diagnosis of ubiquitinopathy. (50)

On the one hand, BD and bvFTD have in common deficits in emotion recognition as early symptoms. (9,51,52) But on the other hand, at the examination of bvFTD patients, executive disturbances are the main finding, while executive impairment is only common in elderly patients with bipolar disorder. (9,18,53) There are also published cases of patients presenting manic symptoms as first manifestation of bvFTD. (54,55) Dols et al. refer a male predominance in their case study. (9)

Furthermore, other authors propose that psychiatric disorders might simulate bvFTD, particularly when bvFTD is diagnosed in the early stages of the disease, without neuroimaging anomalies, such as frontotemporal atrophy. (1)

**Frontotemporal dementia**

As it is evident on the clinical researches previously described, some bipolar disorder patients present symptoms that fit the criteria for the diagnosis of frontotemporal dementia, specifically the behavioural variant. (1,9,48,49) Frontotemporal dementia is characterized by atrophy of frontal and temporal lobes and represents the second most prevalent early onset dementia. (56) It has a wide clinical heterogeneity (57–59) allowing the distinction of three different phenotypes, according to the clinical variants: the most common, which corresponds to about half of all the clinical cases, (58,60) the behavioural variant (bvFTD), the progressive non-fluent aphasia and the semantic dementia, (40,61,62)

Specifically about bvFTD, it has been described as a progressive deterioration of the frontal and anterior temporal lobes, leading to alterations of the behaviour and of the personality. (1,40,50,63,64) In 2011, an international consortium made a revision of the diagnostic criteria for bvFTD, based on literature and collective experience. (57) These proposed guidelines showed better sensitivity and diagnostic accuracy, comparing to the previously established criteria published in 1998. (61) It facilitated the discrimination

from other dementias and psychiatric disorders. The authors have also described the 'phenocopy syndrome'. Patients with this disease had an indistinguishable behaviour from the ones with true bvFTD, when applying the previous criteria. However, it appears to be non-progressive, without functional decline or imaging changes, not being verified an active progression into frank dementia: functional abilities are preserved and imaging abnormalities are absent. (58,60,65–68) It has also been demonstrated attenuated cognitive impairment and less impact on patients' performance on activities of daily living (ADL) and it remains stable throughout the time. (1,69)

Studies have shown that some patients with bipolar disorder preceding FTD often carry in chromosome 9 open reading frame 72 a GGGGCC hexanucleotide repeat expansion, with 70 repeats (C9ORF72). (9,40,49,65,70–77) However, some authors reached the conclusion that expanded C9ORF72 repeat was not a relevant contribution to bipolar disorder, by being a very rare mutation whether in familial or sporadic BD (0-1%). (70,77)

**Bipolar disorder in the elderly**

The onset of bipolar disorder at older ages is connected to increased duration and number per year of the affective episodes. (1,78) Moreover, studies have shown that these patients demonstrated more evident and profound neurocognitive impairments than those diagnosed at an early age. (18) Neuroimaging findings show, on late-onset BD cases, subcortical hyperintensities, decreased cerebral blood flow, and silent cerebral infarctions. (79)

Nevertheless, even when patients are in a euthymic state, it is discernible persistent impairments at many levels, including verbal memory, executive functions (1,80,81) and social cognition. (63)

Hence, the differential diagnosis of frontotemporal dementia becomes more challenging, once patients seem to present chronic instead of episodic affective symptoms and, also, the presence of impaired executive functions.(1)

It also became evident that it is advantageous to distinguish older BD patients by age at onset, once the frequency of with family history of affective disorders is lower in late-onset patients, compared with the early onset cases. (1,18,82)

Research studies have described a correlation between the number of manic episodes in older people with BD and the prevalence of dementia. (83) Pose et al. have also hypothesized that dementia releases latent bipolarity in individuals with already

previous predispositions, including affective temperaments, or even that it is nothing more than the expression of atypical psychiatric disorders. (1)

## Conclusion

In sum, bipolar disorder was initially recognized as a cyclic disease, with full recovery between affective episodes. Nevertheless, in the last decades, evidence has led to a different vision of BD. Along with the assessment as a spectrum, with a great variety of clinical presentations and different levels of severity, cognitive and functional impairment became recognized as part of the bipolar disorder course.

Many authors verified a progression of the disease on their clinical practice. Therefore, multiple researches were conducted, which demonstrated that BD is a life-long condition acquiring a more and more predictable path. Regarding the later stages of bipolar disorder, very strong evidence shows that these patients have higher risk of developing dementia, specifically the behavioural frontotemporal subtype.

Moreover, the differential diagnosis of frontotemporal dementia is complex due to the similarities to other disorders, especially in patients with late-onset bipolar disorder, in which the chances of misdiagnosing are high.

## Acknowledgments

First of all, I would like to express my special thanks of gratitude to Dr. Inês Chendo, for suggesting this theme and, of course, for all the commitment and dedication.

I also would like to thank my parents, my sister and my grandmother for all the support, because without them, my dreams would never become a reality.

My friends and colleagues cannot be forgotten, because if it wasn't them, this academic (or, should I say, life) course would be much more difficult.

For last, but certainly not the least, thank you Diogo, for always being by my side, even hundreds of kilometers away. Thank you for everything.

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