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Cognitive Dysfunction In Bipolar Disorder: Possibilities And Limits Of Antipsychotic Chemotherapy

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Abstract:
Bipolar disorder (BD) evolves in episodes, with profound cognitive impairment during acute episodes of mania or depression. More recently, it has emerged that euthymic periods are also associated with persistent cognitive dysfunction. These cognitive alterations are largely responsible for disability in patients suffering from (BD). However, this cognitive impairment appears to be both specific and heterogeneous. Not all cognitive functions are affected. Moreover, not all patients present the same disorders, and for the same patient, the cognitive assessment may vary according to the time at which it is carried out. According to the literature, several external factors are associated with cognitive disturbances, notably antipsychotic drugs, which are currently widely prescribed for BD, including long-term use to prevent relapses. It is therefore important to know whether antipsychotics prescribed to bipolar patients worsen or improve their cognitive functioning. The aim of this article is to provide an update on the cognitive state of patients suffering from bipolar disorder, to enable physicians to better understand the origins of the handicap generated by the disease, and the role played by antipsychotics in inducing or aggravating these cognitive distortions.
Key Word*: bipolar disorder, cognitive impairment, antipsychotics.*

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I. General Introduction

Neurocognitive disorders are described in the literature as central to bipolar disorder (BD), particularly in the euthymic phase. These cognitive impairments are largely responsible for the disability associated with this mood disorder [1-2]. Indeed, Bipolar Disorder evolves in episodes, with significant cognitive impairment during acute manic or depressive episodes. More recently, it has emerged that euthymic periods are also associated with persistent cognitive dysfunction [3]. Indeed, the level of cognitive performance in patients suffering from bipolar disorder is unfortunately worrying: it is estimated that 30-50% of bipolar patients in remission remain unable to reach a premorbid level of psychosocial functioning, due to cognitive impairment [4]. However, this cognitive impairment appears to be both specific and heterogeneous. Not all cognitive functions are affected. Moreover, not all patients present the same disorders, and for the same patient, the cognitive assessment may vary according to the time at which it is carried out. According to the results of certain research studies, BDI is associated with cognitive disturbances that worsen as the disease progresses, probably as a result of both neurodevelopmental and neurodegenerative processes, in the areas of attention, verbal memory and executive functions [5-6]. As well as a number of external factors that come into play, such as the predominant polarity of the disorder, psychiatric and somatic comorbidities, and medication. Indeed, the effect of pharmacological treatments, notably antipsychotics, can be a confounding factor. First- and second-generation antipsychotics are increasingly used in bipolar disorder, but are associated with undesirable cognitive effects [7]. The cognitive effects of antipsychotics in mood BD, for which they are increasingly prescribed, including on a long-term basis to prevent relapses, remain poorly understood. It is therefore important to know whether the drugs prescribed to bipolar patients worsen or improve their cognitive functioning. The aim of this article is to provide an update on the cognitive state of patients suffering from bipolar disorder, to enable physicians to better understand the origins of the handicap generated by the disease, and the role played by antipsychotics in inducing or aggravating these cognitive distortions.

II. Preliminary Notions

Definition Of Cognition

Cognitive functions are the mental activities by which we elaborate a representation of our world and ourselves. They enable us to adapt to the situations we face.

Beck defines cognitions as "specific thoughts, of any mental activity with verbal or pictorial content. They include not only ideas and judgments, but also self-criticisms and desires (such as the desire for suicide). He

identifies two types of automatic thought. One corresponds to an immediate reaction to external events, the other to ruminations, independent of external stimuli.

These cognitions can be affected in their content by reasoning that can become erroneous, known as an erroneous or dysfunctional "cognitive process".

Methods for identifying and assessing cognitive functions

Neurocognitive hetero-assessment

There is a wide range of psychometric tests available for both global and specific assessment of cognitive functions. One or more functions are assessed per test. No test is specific to bipolar disorder. For example, the Brief Assessment of Cognition in Schizophrenia (BACS) is one of the most comprehensive batteries, assessing six cognitive domains, and despite its name, is applicable to both schizophrenia and bipolar disorder. Among the most common tests :

- The Wisconsin Card Sorting Test (WCST) assesses mental flexibility and inhibition via a card game;
- The Weschler Adult Intelligence Scale (WAIS) uses a series of codes and symbols to assess information processing speed;
- Trail Making Test, flexibility;
- Stroop test, inhibition;
- CPT: Continous Performance Test
- The figure of Rey, memory, etc.

Brain Imaging

Structural and functional neuroimaging is an essential neurocognitive assessment tool, thanks to the links that can be made between brain structures and functions. *Hafeman and al* examined the neurofunctional impact of medication in bipolar disorder through 74 structural magnetic resonance imaging (sMRI) studies, 46 functional MRI (fMRI) studies and 15 diffusion tensor imaging (DTI) studies [8]. Within functional imaging, the authors were particularly interested in the Blood Oxygen Level Dependent signal (BOLD signal), which enabled Hafeman and his team to report data on the neurofunctional activity of treated bipolar patients.

Neurotransmitters and cognition

The involvement of several systems in the onset of cognitive dysfunction in TB, in this case [9].

1. The noradrenergic system acts on wakefulness, stress, learning and working memory;
2. Deficiency of the serotonin system leads to behavioral disinhibition and impulsivity;
3. The cholinergic system increases wakefulness and acts on memory;
4. Dopaminergic system: acts on working memory, planning and organization of behavioral sequences. On procedural memory (memorization of behavioral sequences).

These cognitive functions are dependent on dopaminergic action in the prefrontal cortex [10]. Pharmacological studies therefore focus on neuromediators and antipsychotics that act on these regions of the cerebral cortex.

The effects of 1re and 2me generation antipsychotics on cognition:

1st generation antipsychotics:

Certain effects of 1ère generation antipsychotics are invoked:

On the one hand, many authors have put the hypothesis of a deleterious effect of D2 dopaminergic blockade in the prefrontal cortex on cognitive functions forward;

On the other hand, the sedative effect of blocking histamine H1 receptors is correlated with cognitive dysfunction, and it has been shown that blocking histamine H1 receptors impairs learning ability and memory performance. They have no recognized action on explicit memory, except at high doses. They do however; impair implicit or cognitive procedural memory. However, it is difficult to distinguish the exact proportion of deficits linked to the disease from those linked to neuroleptics.

2nd generation antipsychotics:

Atypical" neuroleptics are known to be of interest in the sense that their clinical efficacy is at least comparable to that of typical neuroleptics, with fewer side effects. What's more, current clinical experience suggests an improvement in cognitive function in treated patients. From a neurobiological point of view, this improvement is linked to an antagonistic effect on the 5-HT2A receptor. Atypical antipsychotics appear to be superior in the areas of attentional function, executive function and procedural memory, particularly when the tasks are complex and involve the most integrated cognitive functions.

III. Cognitive Functions In Bipolar Disorder

Cognitive disorders play a key role in bipolar disorder. They are an integral part of the diagnostic criteria, and have a major impact on functioning and compliance with treatment. They may therefore be associated with symptomatology and constitute a state marker, but they may also persist in the absence of symptoms and represent a treatment marker. Indeed, in recent years, we have seen a particular interest in the search for trait markers of disease linked to genetic vulnerability, or endo-phenotypes, with the aim of identifying at-risk subjects at an early stage and proposing specific management. This mainly concerns impairment of executive functions, notably inhibition, mental flexibility and planning, but also verbal memory [11-12].

These cognitive deficits are more pronounced in the acute phases of bipolar disorder. Numerous clinical arguments (psychomotor slowing or hyperactivity, distractibility, impulse control disorders, behavioral disinhibition, limited awareness of disorders) testify to the existence of underlying cognitive deficits. In both depressive and manic phases, various aspects of executive function, verbal memory, selective and sustained attention, categorical and verbal fluency, visuo-motor and spatial skills and, depending on the study, overall intellectual functioning, are impaired compared with healthy subjects [9].

Cognitive profiles:

Cognitive profiles depend on the subject's thymic state, and the meanings of cognitive distortions that may occur during the depressive and manic phases are as follows (Tab.1):

Table 1: Cognitive profile of thymic episodes

Manic episode	Depressive episode
• Distractibility • Flight of ideas and one-upmanship • Sense of power • Impaired judgment • Feels like thoughts are racing by • Greater communicability • Constant desire to talk • Increased goal-oriented activity • Involvement in potentially harmful activities	• Decreased ability to think • Difficulty concentrating • Decision-making difficulties • Psychological slowdown • Memory disorders • Impaired judgment

Neuropsychological deficits:

Studies comparing the cognitive functioning of patients with type 1 and type 2 bipolar disorder show that type 1 verbal memory is more impaired than type 2 [9]. Mental flexibility and verbal working memory are more impaired in cases of comorbid hyperthymic temperament, particularly in bipolar type 1 subjects [13].

Irritable temperament and cyclothymia are both associated with better performance in processing speed, working memory, reasoning and problem solving. Other studies have specifically compared cognitive impairment between type I and type II bipolar patients (Tab. 2) [14].

Table 2: Distribution of cognitive dysfunctions by type of bipolar disorder

BD type 1	BD type 2	BD with psychotic features
- Cognitive impairment in 24% of cases; - Impaired verbal memory with impaired recall, recognition and learning; - The CVLT: disrupted - Sustained, directed attention and executive functions affected (similar to schizophrenia)	- Less frequent, it affects 7 to 13% of bipolar patients; - Attention would be normal; - Executive functions are less affected; - Impaired verbal memory, verbal fluency and interference control; - CVLT: disturbed (similar to recurrent or unipolar depression)	The tests reveal a : - More severe cognitive impairment during episodes; - Impaired verbal declarative memory - Impaired inhibition - Impaired spatial working memory - Impaired mental flexibility

CVLT: California Verbal Learning Test

With regard to the inter-critical or euthymic period, cognitive deficits during the inter-critical period appear to be the result of multiple factors, both developmental and neurotoxic, and remain influenced by certain markers of bipolar disorder. A multifactorial model has been proposed by *Gildengers and al* (2010) to account for the cognitive disturbances observed during the course of this disorder [15] . These would be the result of the initial etiopathogenic process and neurodevelopmental abnormalities. They are also the result of the disease's evolutionary course.

Overall, cognitive dysfunctions particularly affect processing speed, episodic memory, sustained attention and executive functions, as well as social cognition. In terms of severity of impairment, cognitive dysfunction is more severe in bipolar patients with a history of psychotic symptoms and other factors influencing

cognitive functioning (see chapter below). The persistence of these disorders has an effect on the course of the illness and on social, educational and occupational disability [3].

Factors influencing cognitive functioning
Several factors can be identified as influencing cognitive functioning.

Number of episodes and duration of illness:
Firstly, according to the neurotoxic and neuropsychological deficits hypotheses, the repetition of thymic episodes leads to cerebral degeneration, resulting in the onset or worsening of cognitive disorders and the duration of the disease [10, 16]. The number of hospitalizations and duration of disease progression are negatively associated with the presence of cognitive deficits [1,3].

Psychotic features :
The clinical characteristics of thymic episodes, in particular the existence of psychotic features; cognitive disorders are thus more severe in melancholic depressions than in non-psychotic depressions. *Albus M and al* [17] suggest that the psychotic process is involved in cognitive disturbances.

Substance abuse:
They are the cause of significant deficits in cognitive tests, particularly those involving memory and executive functions. The prevalence of these comorbidities in bipolar disorder (42%), particularly alcohol abuse (33%). According to *Van Gorp and al* [18], length of illness predicts greater cognitive impairment in bipolar patients with alcohol dependence than in those without.

Functional brain abnormalities :
The importance of cognitive deficits during acute episodes has led to the suggestion that these deficits are secondary to functional brain abnormalities characterizing these episodes. Several functional imaging studies during depressive states have described hypo-activation of the dorsolateral, sub-genual, anterior cingulate and medial prefrontal cortex. However, Blumberg et al [19] showed that activation of the dorsolateral and anterior cingulate cortexes decreased, while that of the ventral prefrontal cortex increased. The opposite phenomenon could be observed in mania. These changes in cerebral metabolism could reflect the changes in local synaptic activity and neurotransmission involved in the cognitive deficits present during acute episodes. Neuroanatomic ally, bipolar patients show significantly greater atrophy of the hippocampus and fusiform gyrus, which correlates with the number of thymic episodes and the severity of cognitive impairment. A recent study also found a significant association between reduced frontal and temporal cortical thickness, and age of onset, intensity of depressive episodes, as well as impaired executive function and processing speed [20].

Comorbidities:
Bipolar patients frequently suffer from psychiatric or somatic comorbidities. The presence of alcohol addiction increases cognitive impairment in most areas (impaired executive function, attention, visuo-motor coordination, inhibition, learning and memory) [21].

The presence of anxiety-related comorbidities also impacts all cognitive functions, with more severe impairments in immediate memory, visual memory, working memory and processing speed in bipolar disorder type 2. The presence of Attention Deficit and Hyperactivity Disorder (ADHD) is said to have a deleterious impact on verbal memory, attention and executive functions. At somatic level, cerebrovascular co-morbidities may favour the emergence or aggravation of cognitive disorders [22].

The effects of drug treatments :
According to the Food and Drug Administration, no drug treatment can improve cognitive function. On the contrary, it cannot be ruled out that they may have a negative effect. Lithium, Valproate, Lamotrigine and Carbamazepine have been extensively studied [23].

Few studies have been carried out on atypical antipsychotics. Antipsychotics do not appear to markedly impair patients' cognitive performance, except at very high doses and in particularly fragile populations (age). It is now recognized that atypical (second-generation) antipsychotics have a better neurocognitive profile than typical (first-generation) antipsychotics [3]. Thus, pharmacotherapy should be chosen to have the lowest neurocognitive adverse effects, or according to the patient's cognitive profile [3, 24].

The question remains as to whether these dysfunctions persist or disappear during phases of remission (euthymic phase). The authors hypothesize that deficits persist in sustained attention and verbal episodic memory, and to a lesser extent in executive functions and non-verbal episodic memory. Performance on the Continuous

Performance Test (CPT) was significantly impaired. Without, however, reaching the intensity revealed in schizophrenic subjects in remission.

However, even the performance profiles of subjects in remission are variable, with studies showing that in half the cases of executive function tests, performance deficits are identical to the profile of schizophrenic patients in remission. These distinct executive profiles in euthymic patients can also be understood as the consequence of other influencing factors, mentioned above.

Functional consequences of cognitive disorders :

Several studies confirm the association between cognitive impairment and functional disability in bipolar patients

- Impairment of planning and problem-solving skills is more marked in the presence of difficulties in social functioning. A 15-year prospective study highlights the important role of a deficit in information processing speed [26].
- A negative association is also highlighted between patient functioning and impaired verbal fluency and attention, irrespective of the presence of residual thymic symptomatology. According to *Bonnin and al* (2010) [27], the predictors of psychosocial functioning are the presence of residual depressive symptomatology and a verbal memory deficit.1 Despite the heterogeneity of the results, the presence of cognitive deficits in the inter-critical state appears to be a robust marker of psychosocial functioning.
- Recently, a meta-analysis demonstrated that all cognitive functions were significantly related to functioning, with a maximum effect size of 0.34 for global intellectual capacity, and 0.29 for working memory [26].

These results underline the important role of working memory in the functioning of bipolar patients. Its verbal component is particularly involved, predicting long-term functioning (Tab. 3). Indeed, initial impairment of verbal memory is correlated with final functional handicap. It would also act as a mediator between residual depressive symptomatology and functional impairment [27]. Specific retraining of working memory could therefore prove particularly useful in improving patient functioning. A number of programs targeting this cognitive function have been shown to be effective in improving the functioning of patients with traumatic brain injury or attention deficit hyperactivity disorder, disorders in which working memory is also impaired [28-29].

Finally, the functional handicap to which the patient suffering from bipolar disorder is forced may be the source of significant psychosocial stress factors, favoring the onset or worsening of a suicidal crisis. Improving the patient's functioning would probably lead to greater thymic stability, and reduce the risk of suicidal behaviour.

Table 3: Distribution of deficits in selective attention, learning and memory, executive and decision-making functions in thymic and euthymic episodes

	Manic / Depressive	Euthymic
Selective attention	Alteration	No alteration
Learning and memory : ***Verbal** *** Non-verbal**	 Alteration Little or no alteration	 Alteration Alteration
Executive functions	Alteration	No alteration
Emotional decision-making	Alteration	No alteration

IV. Possibilities And Limits Of Antipsychotics In Cognitive Dysfunction In Bipolar Disorder

Drug treatments, in particular antipsychotics, may also have an impact on the neurocognitive disturbances associated with the disease. Indeed, bipolar disorder patients treated with first- or second-generation antipsychotics tend to have poorer cognitive performance than bipolar disorder patients treated with other families of mood regulators [3, 28]. In a study of bipolar disorder patients treated associated with antipsychotics, thymoregulators, antidepressants and benzodiazepines, patients receiving antipsychotic treatment performed significantly worse on semantic fluency, verbal learning, recognition memory and some executive functions than patients not receiving antipsychotic treatment and control subjects, even after adjustment for other clinical factors [27]. Little work has been done on atypical antipsychotics. Nevertheless, they are associated with a more marked deficit in verbal fluency and verbal memory, Quetiapine appearing less deleterious than Olanzapine or Risperidone at equivalent doses [24].

Demonstrating cognitive dysfunction related to antipsychotic use in bipolar patients, and determining the extent to which this is due to the disease and the treatment, is very difficult. A limited number of studies, compared with depression and schizophrenia, have explored the effects of antipsychotics on cognition, and have put forward certain hypotheses regarding their beneficial action on bipolar pathology, but also the cognitive distortions induced by the product [27].

Possibilities

1st generation antipsychotics

- They have a long-term beneficial effect on selective and sustained attention;

- They are also beneficial for verbal memory.
- They have no effect on basic perceptual skills, working memory and executive functions;
- They are an improvement in psychosocial functioning.

2nd generation antipsychotics

- They are a general improvement on cognitive functioning, especially in the area of learning and process speed.
- They improve attention and alertness;
- They have an effect on the retention of better cognitive flexibility and occupational adaptation capacities;
- They have an effect on adherence to treatment, as well as on social skills and understanding of the disease;
- They improve social functioning and quality of life.

Limitations

1st generation antipsychotics

- They have an accentuating effect on cognitive disorders;
- They cause sluggish ideation and impair attention and vigilance;
- They can lead to depression and anhedonia;
- They do not improve working memory;
- They impair mental flexibility or shifting capacity;
- They weaken visual-spatial skills and verbal and non-verbal learning abilities;
- Persistence of cognitive impairment in euthymic phases.
- High doses of conventional neuroleptics, particularly in the acute phase or TB with psychotic symptoms, and the duration of long-term administration impair cognitive abilities, especially executive functions:

✓ Flexible organization and planning skills,
✓ Working memory and inhibition control.

- They also disrupt the process of metacognition (or meta-memory), i.e. altering patients' ability to judge their own solving performance.
- Treatments associated with classic neuroleptics, in particular :

✓ The co-prescription of antipsychotic correctors or the use of neuroleptic molecules with intrinsic anti-cholinergic activity can aggravate these deficits, since acetylcholine is known to mediate memory circuits in the brain. They interfere with learning and memorization, and impair attention and memory. Anticholinergics should no longer be used [26].
✓ Combination of neuroleptics with addictive comorbidities (alcohol, cannabis, etc.) accentuates cognitive dysfunction
✓ The influence of tobacco and coffee in combination with neuroleptics on cognitive abilities.

- Low-functioning bipolar patients on conventional neuroleptics may have limited insight, leading to poor compliance, higher risk of relapse and increased hospitalization;
- And last but not least, neuroleptics may abrade emotional feelings, which are closely linked to cognitive functions.

2nd generation antipsychotics

The results of several studies in the literature are heterogeneous, and it seems difficult to classify second-generation antipsychotic molecules according to their neurocognitive profile. There does not appear to be a trend towards greater improvement in cognitive performance when bipolar disorder is treated with antipsychotics than when it is not: depending on the study, there is either more marked impairment, less marked impairment, or equivalent impairment of cognitive functions with or without antipsychotic treatment [26].

Clozapine, risperidone, olanzapine, quetiapine and aripiprazole were all found to have very few adverse effects on cognitive functioning, although aripiprazole and, to a lesser extent, olanzapine may cause disinhibition [27]. In one study, risperidone was associated with better cognitive performance and functional indices than first-generation antipsychotics [30].

In a recent cross-sectional study [24] of 84 euthymic patients, the cognitive performance of patients receiving olanzapine (n=26), risperidone (n=30) or quetiapine (n=12) was compared with that of patients receiving no antipsychotic treatment (n=16) and matched healthy subjects (n=35). The wide-ranging test battery covered attention, short- and long-term memory and executive functions. Overall, patients showed poorer cognitive performance than healthy subjects. Patients on quetiapine showed performances that did not differ significantly from those of subjects on risperidone or olanzapine.

However, these differences disappeared when the existence of a history of psychotic symptoms was taken into account. Indeed, these patients show more severe cognitive impairment than the average of bipolar disorder patients.

V. Conclusion

A lot of attention is being paid to cognition these days. This is partly due to the influence of cognition on general functioning, which is important for patient resocialization. Atypical antipsychotics, compared with 1ère generation antipsychotics, appear to have a positive influence on cognition, without being 100% convincing. This beneficial effect in terms of cognitive disorders would have an impact on compliance with treatment, as well as on adherence to care, social skills and the patient's understanding of the illness. Given the extent of cognitive impairment associated with bipolar illness, other treatment strategies need to be developed. Today, research is focusing on neuroprotective treatments. Non-drug treatments such as functional remediation programs, which have already demonstrated their effectiveness in schizophrenia, would be of interest.

Finally, it seems necessary to evaluate the efficacy of various types of cognitive remediation programs, with a particular focus on programs of limited duration and more specific to a given function. In view of the data described above, specific retraining of working memory could be of particular interest.

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