Clinical and Therapeutic Challenges When Psychiatric Disorders Occur in Neurological Diseases: A Narrative Review

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Abstract: Background: Over the course of the 20th century, neurology and psychiatry diverged and became two separate disciplines. Subsequently, the continuous progress of neurosciences confused their boundaries. However, with ‘the splitting’ and ‘the lumping’ approaches, relevant difficulties remain in targeting clinical and therapeutic goals, when psychiatric signs and symptoms co-occur with neurological diseases.

Objective: The study summarize current evidence on psychiatric signs and symptoms comorbid with neurological diseases, with the aim to provide information on diagnostic problems and available therapeutic options.

Methods: Finding from searches of publications on ‘PsycInfo’, ‘Medline’, and ‘Science Direct’, from January 1993 to December 2018 (25 years) is summarized in a narrative manner on six main neurological areas: congenital neurological illnesses (n=16), dementias (n=15), basal ganglia diseases (n=30), epilepsy (n=22), strokes/focal brain injuries (n=29), and neurological neoplastic/paraneoplastic diseases (n=15).

Results: Clinical phenotypes of psychiatric syndromes are frequently described in neurological studies. Little evidence is provided on the most adequate therapeutic approaches.

Conclusion: Psychiatric syndromes in comorbidity with neurological diseases are heterogeneous and severe; evidence-based treatments are scarce. Despite a model supporting an equal approach between psychiatric and neurological syndromes, psychiatric syndromes in neurological diseases have been described, to a relevant degree, as less important, leading to a hierarchical primate of the neurological manifestations, and thus, in our opinion, limiting the systematic studies on psychopharmacological treatments in this area.

Keywords: Neuropsychiatry, psychiatric disorders, neurological diseases, comorbidity, psychopharmacological, neurosciences.

1. INTRODUCTION

Wilhelm Griesinger, the founder of Archives of Neurology and Psychiatry, in his theoretical point of view on psychiatric disorders as ‘brain disorders’, described neuropsychiatry as a unique discipline, promoting a ‘lumping’ theoretical approach. Over the course of the 20th century, with the rise of psychoanalysis, neurology and psychiatry diverged in two separate disciplines, thus enhancing a ‘splitting’ point-of-view [1]. The progress of neurosciences mixed again the boundaries between the two realms. Growing research suggests that clinical phenotypes of psychiatric disorders might be the expression of underlying neurobiological patterns. Crossley et al. [2], from the perspective of neuroimaging, describe neurological and psychiatric disorders as the expression of two separate neuro-physiological systems: basal ganglia, insula, sensori-motor and temporal cortex for the pathogenesis of neurological disorders; cingulate, medial frontal, superior frontal and occipital cortex subsiding psychiatric disorders.

From a genetic point of view, ‘The Cross Disorder Group of the Psychiatric Genomics Consortium’ (PGC) postulates that specific single-nucleotide polymorphisms (SNPs) are associated with five psychiatric disorders spectra: autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), bipolar spectrum disorders (BP), major depressive disorders (EDM), and schizophrenia spectrum disorders [3]. According to this model, variations in calcium-channel activity genes may have a pleiotropic effect on the expression of a number of psychiatric signs and symptoms.
Results from this study confirmed that voltage-gated calcium signaling, and, more broadly, calcium-channel activity, could be an important biological process in psychiatric disorders. Moreover, genome-wide studies identified rare copy-number variants that confer the risk for the five psychiatric disorders spectra examined.

This finding is relevant to the goal of moving beyond descriptive syndromes in psychiatry and towards a nosology informed by the disease cause.

Taken as a whole, questions on the clinical usefulness of a unitary approach in describing the area of overlap between psychiatric and neurological diseases are still unresolved, leading to theoretical (see the raise of ‘new disciplines’ such as the ‘Behavioral Neurology & Neuropsychiatry’) and practical problems, mainly due to the limited evidence regarding treatments’ options [4].

The aim of this narrative review is twofold: a) to summarize current evidence on psychiatric syndromes when co-occurring with neurological diseases, following a descriptive a-theoretical approach; b) to provide information on the available psychopharmacological options. We hypothesize that despite the rationale supporting an equal approach between psychiatric and neurological syndromes, the detection of psychiatric syndromes in neurological diseases has been carried out, to highlight their disadvantages, presuming a primate of the neurological syndromes, thus limiting the evidence on treatments options from a psychiatric point-of-view.

2. METHODS

2.1. Sources and Selection Criteria

We identified papers for this narrative review through searches of publications on the following databases: ‘PsycInfo’, ‘Medline’, and ‘Science Direct’, from January 1993 to December 2018 (25 years). We performed research on six (n=6) different areas, identified with the following search terms: [Autism Spectrum] and [ADHD] and [congenital neurological illnesses] (n=20); [Behavioral Symptoms] AND/OR [Psychological Symptoms] AND [Dementia] AND/OR [BPSD] (n=24); [Psychiatric symptoms] AND [basal ganglia diseases] (n=49); [Psychiatric symptoms] AND [Epilepsy] (n=35); [Post-stroke depression] AND/OR (PSD) AND [focal brain injuries] (n=49); [Psychiatric symptoms] AND [neoplastic diseases] AND/OR [para-neoplastic diseases] (n=18), for a total of one-hundred and ninety-five papers (n=195). We reviewed only articles published in English, and we excluded those published in non-peer reviewed journals. Moreover, the final list was based on the highest relevance to the topics covered in the narrative review. The two authors independently screened the resulting papers for their methodology and appropriateness for inclusion, and selected a total of one hundred and twenty-seven papers (n=127/195; 65.1%), sub-divided for disease as follows: 16/20 on congenital neurological illnesses (80%), 15/25 on dementias (60%), 30/49 on basal ganglia diseases (61.2%), 22/36 on epilepsy (61.1%), 29/50 on post-stroke depression and focal brain injuries (58%), 15/18 on neoplastic/paraneoplastic diseases (83.3%).

3. RESULTS

Due to the lack of homogeneity among the available studies, this review is presented as a narrative synthesis.

3.1. Autism Spectrum and ADHD Symptoms in Congenital Neurological Illnesses

Genetic neurological illnesses are often associated with Autism Spectrum Disorders (ASD) and Attention Deficit with Hyperactivity Disorders (ADHD) symptoms [5]. ASD core features (deficits of social communication and interaction, restricted and repetitive behaviors, interests, and activities) can be found also in other neurological congenital illnesses, such as Rett Syndrome (RS). ASD and ADHD signs and symptoms might be part of the clinical presentations of Fragile X Syndrome, Klinefelter Syndrome, Tuberosus Sclerosis and Neurofibromatosis type 1 [5]. It has been suggested the screening for the Fragile X for males with ASD symptoms, and the screening for the Rett mutation for females [5].

Rett Syndrome (RS) is a neurological disorder predominantly affecting females and occurring in 1/15,000-22,800 live female births [6]. It is caused by mutations on the X-linked MECP2 gene [7]. In its classic forms, development is relatively normal for the first 6-18 months. Then a regression appears, with a reduction in head circumference growth and a severe loss of language skills, ability to walk, and other learned motor activities. Patients regress in all phases of psychomotor functions to a state of severe intellectual disability. Moreover, 60-90% of them develop epilepsy starting at the age of three [5]. The presence of autism spectrum behaviors, mainly consisting of incessant hand wringing and hand washing, hair pulling, clapping, or flapping, ranges from 25% to 40% and up to 97% in subjects with the preserved speech variant of RS [8].

Fragile X syndrome is the most common cause of inherited intellectual disability (10% of all cases), occurring in 1/3600 male and 1/8000 female [9]. The genetic mutation consists of an excess of CGG trinucleotide repeats on the FMR1 (Fragile X Mental Retardation-1) gene at location Xq27-3 [10]. Compared to the normal complement of 5 to 44 CGG repeats, the full fragile X mutation typically has 200 or more CGG repeats. A subject with only 55 to 200 repeats has the pre-mutation, which leads to no major intellectual impairment or physical stigmata. Even the pre-mutation, may induce behavioral problems and psychiatric syndromes such as depression, ADHD and ASD [5]. Prevalence rate of ASD in Fragile X Syndrome is varying from 21% to 50% in males, and from 1% to 3% in females [10]. ADHD is also common: from 54 to 59% of Fragile X patients meet the diagnostic behavioral criteria for ADHD, especially the inattentive-type [11].

Klinefelter Syndrome (47, XXY) is the most common form of sex chromosome aneuploidy, (1/650 males). More than 10% of identified cases are diagnosed in the prenatal period by amniocentesis [12]. Several cases remain undiagnosed; others are diagnosed only in the following years, when hypogonadism, gynecomastia, infertility and learning disabilities become evident. Language difficulties are present in 70-80% of cases [5, 12]. Psychiatric features are also
common, with an inaccurate perception of social-emotional cues, marked difficulties to describe their own emotions, impaired communication capability. The 27% of Klinefelter’s patients meet criteria for ASD, and 63% have ADHD symptoms [13]. Despite such frequent comorbidities, evidence on treatment choices is limited to methylphenidate that improves ADHD symptoms in these patients, increasing serum levels of dehydroepiandrosterone (DHEA) and its main metabolite, dehydroepiandrosterone sulfate (DHEAS) [14].

Tuberous Sclerosis occurs in 1/6000 live birth, and is caused by a mutation in the TSC1 (9q34) or TSC2 genes (16p13) [10]. Mutations result in a deregulated cell growth in a number of tissues (skin, kidneys, heart and brain, with subependimal tubers) [15]. The clinical presentation is inhomogeneous from superficial skin lesions and mild seizures to profound intellectual disability. As the tubers grow, children may display a cognitive decline, with comorbid ADHD/ASD symptoms [5]. ASD in tuberous sclerosis ranges from 24% to 60% [10]; ADHD prevalence ranges from 30% to 60%, with hyperactivity behaviors more frequent in children experiencing at least one seizure [16]. As far as we know, no information on specific psychopharmacological treatment strategies for these patients is available.

Neurofibromatosis type 1 is an autosomal dominant genetic condition with a prevalence of 1 in 2,000-3,000 live births [17]. The main clinical manifestations include café-au-lait macules, skin fold freckling, and neuro-fibromas. The most common complications are cognitive (decrease of about 5 to 10 IQ points) with a relevant comorbidity for ADHD and ASD [5]. Approximately 38% of affected children have ADHD, prevalently of inattentive-type [18]. 29% of children with neurofibromatosis 1 have ASD symptoms, such as social-communication impairments without repetitive behaviors, eye contact failure, or language deficits [5, 17].

Taken as a whole, the psychopharmacological treatments for ADHD and ASD symptoms when occurring in the context of neuro-genetic illnesses seem to be the same as recommended for the idiopathic disorders. Evidence is limited to risperidone and aripiprazole for irritability in ASD, methylphenidate and atomoxetine for ADHD [19]. Glutamatergic agents and intranasal oxytocin are promising treatments for ASD core social symptoms, albeit with mixed results [20].

### 3.2. Behavioral and Psychological Symptoms of Dementias (BPSD)

Dementia is a neuro-cognitive disease involving memory and symbolic functions (language, praxis, gnosis). Neuropsychiatric symptoms, the so-called ‘behavioral and psychological symptoms of dementia’ (BPSD) spread across all clinical variables and stages of dementia and are diagnosed in 97% of cases [21, 22]. BPSD includes depression and apathy, delusions and hallucinations, agitation and aggression, sexual disinhibition, and severe sleep disorders [23].

Alzheimer’s disease is the most common form of dementia, accounting for 60-80% of cases [24]. The two hallmarks required for the diagnosis are the extracellular plaque deposits of the β-amyloid peptide (Aβ) and the flame-shaped neurofibrillary tangles of the microtubule binding protein tau [25]. Neurofibrillary tangles initially involve medial temporal lobe and then extend to parietal and frontal lobe association areas, as the disease progresses. Aβ deposition begins in parietal, temporal and frontal association areas. Patients typically present prominent episodic memory impairment, with secondary deficits in word-finding skills, spatial cognition and executive functions [26]. BPSD are, in early stages, mainly represented by depressive symptoms such as apathy, anhedonia and dysphoria, raising problems in differential diagnosis [27]. Psychotic symptoms like delusions tend to be common in the middle stages, mainly with themes of theft [26]. Anxiety disorders are also common and disabling [27].

Vascular dementia accounts for 10-20% of the overall cases [25, 28]. Patients usually have comorbid conditions such as diabetes, hypertension and hyperlipidemia [28]. Vascular dementia can present as an abrupt deterioration in cognitive function or in a fluctuating stepwise manner. Patients might have focal neurological symptoms, such as hemiparesis, visual field deficits and hemi-sensory deficits [28]. As the capacity for judgment and a degree of insight are sometimes maintained for a long time in these forms of dementia, BPSD consists of a reaction to the awareness of deficits by severe anxiety and depression, marked apathy and emotional instability [27]. Apathy, aberrant motor behaviors, and hallucinations are more frequently associated with small-vessel impairment; euphoria and agitation with aggressive behaviors are more relevant among patients with large- vessel damages [29].

Dementia with Lewy bodies is accounting for the 10% of cases [25]. The neuro-pathological characteristics of the disease are the Lewy bodies, insoluble α-synuclein seen on microscopic examination in cortical and sub-cortical areas [28]. Clinical features are memory loss, fluctuating levels of alertness, deficits in attention and concentration, reduced fluency, difficulty performing visuo-spatial tasks and Parkinsonism. BPSD mainly involves psychotic features, with complex, vivid and rapidly moving visual hallucinations associated persecutory delusions. Depression with apathy and/or agitation is also present in 50% of patients [27]. These symptoms tend to fluctuate in severity and are often present during the night. Considering that dementia with Lewy bodies is sensitive to typical and atypical neuroleptics, with paradoxical reactions, psychotic features and agitation are challenging, and the adoption of alternative drugs, such as mood stabilizers or antiepileptic drugs can be useful [25].

Fronto-temporal dementia or fronto-temporal lobar degeneration is a neurodegenerative disorder with changes in behaviors, rather than in cognitive functions [30]. Clinical presentations encompass early changes in language function, as observed in semantic dementia and in primary progressive non-fluent aphasia [31]. BPSD are clinically dominant in the most common variant, known as ‘behavioral variant of fronto-temporal dementia’, characterized by apathy, lack of empathy, disinhibition, euphoria and aberrant motor behaviors [32]. Delusions and hallucinations are less frequent [27]. Ritualized and stereotypic behaviors (caused by the lack of mental flexibility and the marked difficulty in planning), hyper-orality, and loss of social awareness are also frequent.
When present, depression is characterized by irritability and agitation [25, 26].

Unfortunately, there are no FDA-approved medications for the treatment of BPSD in patients with the above-mentioned forms of dementia [21]. Citalopram has been considered as an option for depressive and anxiety symptoms. Vortioxetine seems to be a promising choice for its pro-cognitive effects [33]. There is still the FDA warning on the use of both typical and atypical antipsychotics to control agitation and aggression due to the increased risk of stroke and related mortality in this special population. In Europe, risperidone is licensed for up to 6 weeks treatment of persistent aggression in subjects with moderate-to-severe Alzheimer’s dementia [30]. Pimavanserin, a selective 5-HT2A inverse agonist/antagonist, has been also proposed for dementia-related psychosis, but no systematic studies are available [34].

Recently, a ‘tailored’ approach to the assessment and management of behavioral and psychological symptoms of dementia (BPSD) has been proposed, namely the DICE model [35]. DICE includes the following four steps: step 1 (describe) is focused on the accurate characterization of the context in which symptoms occur through a discussion with the caregiver and the patient (when possible); step 2 (investigate) based on the identification of underlying and modifiable causes for BPSD, including the caregivers’ historical relationships with the patient, their communication styles, and their reciprocal expectations; step 3 (create); exploring the possible treatment plans and the integration of medical, non-pharmacological (namely behavioral and environmental modifications) and pharmacological options; step 4 (evaluate); assessing whether the recommended strategies were attempted and implemented effectively, the target symptoms improved, the caregiver distress reduced and the side effects or consequences managed. Even if promising, a full evidence base for this approach is still lacking, mainly because tailoring the treatments of BPSD in the proposed way is challenging in the usual care settings [35].

### 3.3. Psychiatric Syndromes in Basal Ganglia Diseases (BGD)

Basal ganglia diseases (BGD, such as Parkinson’s disease, Huntington’s chorea, Tourette syndrome, Wilson’s disease and Fahr’s disease) manifest with a number of psychiatric symptoms as part of the clinical picture. Thus, basal ganglia have not only a leading role in the control of motor functions, but also have a key role in the integration of emotions with cognitive and motor functions [36].

Parkinson’s disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra, and in the locus coeruleus, nucleus basalis, raphe and ventral tegmental area. Prevalence ranges from 100 to 200/100,000, and the core clinical manifestations are tremor, rigidity, bradykinesia, and postural instability [37]. Deficits in cognitive functions (speed of mental processing, executive function, visuospatial function, memory) are present in about 19% of patients, leading to dementia in about 40% of patients [38]. Psychiatric symptoms occur in 70% of cases [39]. Depression is the most frequent diagnosis (40%) and may predate motor symptoms of PD [40]. Depressive features are characterized by dysphoria, pessimism, irritability, sadness, and suicidal ideation, less often by apathy, guilt and self-blame/reproach [40]. Unfortunately, the pharmacological treatments for PD complicate the course of comorbid psychiatric syndromes. Depression tends to run unmodified by dopaminergic drugs [37]. Conversely, levodopa and dopamine agonists may trigger pathological gambling, euphoria (10%), hypomania, increased libido/hyper-sexuality, and severe sleep disturbances [37, 39]. Generalized Anxiety Disorder (GAD), Panic Disorder, and phobic features (40%) are also common, especially in younger patients [41]. Psychotic symptoms occur in 40% of cases, again related to dopaminergic drugs [42]. Psychoses unrelated to treatments are sparse and associated with the onset of dementia. Visual hallucinations are the most prevalent drug-induced psychotic symptoms, occurring in 20% of cases, commonly nocturnal (often associated with sleep disturbances) and involving formed objects or animals [37]. Some patients describe vivid and non-threatening visual hallucinations, in clear consciousness with preservation of insight. The prevalence of delusions of jealousy ranges from 3% to 30%, usually related with higher doses and longer time of dopamine-agonist treatment [43]. Evidence on treatment of depression and anxiety in Parkinson’s disease is limited to SSRIs, although they may sometimes worse motor symptoms [44]. Vortioxetine is again promising for pro-cognitive effect, but no systematic data are available. For psychotic symptoms, clozapine and pimavanserin are the first-line choices [45]. Deep Brain Stimulation (DBS) has been proposed not only for the treatment of motor symptoms of PD but also for the treatment of resistant forms of depression [46]. There is a preliminary evidence of the efficacy and safety of DBS for treatment-resistant depression in the subgenual anterior cingulate cortex, the ventral capsule/ventral striatum, the nucleus accumbens, the lateral habenula, the inferior thalamic peduncle, the medial forebrain bundle, and the bed nucleus of the stria terminalis [46].

Huntington’s chorea is an autosomal dominant neurodegenerative disorder caused by an expanded CAG trinucleotides repeat in the gene encoding the Huntington protein on chromosome 4 [47]. This mutation leads to striatum degeneration, mainly in caudate nucleus, with selective loss of GABAergic neurons, and degeneration of the deep layers of the frontal cortex [37]. The disease prevalence ranges from 10.6 to 13.7 individuals per 100000; its onset is typically between 35 and 50 years of age [48]. The trinucleotide repeat lengths are different: they are not pathological if ranging from 10 to 35; they cause a disease at reduced penetrance, when ranging from 36 to 39; when expanded to 40 or more repeats, there is the full-blown disease [49]. The repeat lengths are inversely correlated with the age at onset and, if inherited from the paternal line, they are more likely to expand and produce clinical features earlier in the following generations (genetic anticipation) [50]. The main clinical features of Huntington’s disease are movement disorder (chorea, athetosis, dystonia, motor restlessness, tremor, myoclonus), and cognitive impairment with psychiatric signs and symptoms. Cognitive impairment is early in the disease, with slow cognitive speed and impairment of verbal fluency. Memory disturbance is also common, and more frequently
related to retrieval problems than to actual encoding. Later on, executive dysfunction occurs and the cognitive impairment gradually worsens to dementia [37]. Psychiatric symptoms might be the earliest manifestations, as related to initial damages in more ventral striatal regions receiving input from areas of the prefrontal cortex involved in behavioral processes [51]. Depressive symptoms may predate movement disorders and are present in 40% of cases. Of these, 20% might show mood congruent psychotic features [52]. Apathy, when present, tends to worse over time. Irritability and aggressiveness are also common, occurring in 1/3 of patients [37]. Manic/hypomanic episodes are diagnosed in 10% of cases [53]. The prevalence of psychosis is around 4%-12%, and related to early-onset, with poorly defined delusions, delusional states, or schizophrenia-like psychoses [53]. Obsessive-compulsive symptoms are diagnosed in 10%-52% of cases [54]. Patients become obsessively preoccupied about cleanliness or have obsessional rituals in daily life. These symptoms are explained by caudate and related networks alterations [54]. Again, SSRIs are the first option for depression and anxiety symptoms. Valproic acid has been proposed for irritability, aggressiveness and manic symptoms [55]; risperidone and olanzapine for psychotic symptoms [56].

Tourette’s syndrome is a movement disorder with childhood onset, characterized by multiple fluctuating motor and phonic tics lasting for more than 1 year. Its prevalence is estimated about 0.85-1% [57]. The etiology is related to an alteration of basal ganglia functions within the cortico-striatal-thalamo-cortical circuitry, with the involvement of the dopaminergic nigrostriatal pathway, as suggested by the response to dopamine-antagonist, such as haloperidol, pimozide or risperidone [58]. Movement disorders are frequently accompanied by a wide range of psychiatric comorbidities: OCD occurs in about 11-80% of cases, ADHD ranges from 21 to 90%, and depression (or depressive symptoms) in 13%-76% of patients [59]. Many patients report that the psychiatric symptoms are subjectively more debilitating than the motor tics [58]. SSRIs are the first-line treatment for OCD and depressive symptoms, with clomipramine as the second choice [58]. Clonidine, a centrally acting alpha-2 adrenergic agonist, is an option for ADHD and also for tics in mild Tourette syndrome presentations [59, 60].

Wilson’s disease or hepato-lobar degeneration, is an autosomal recessive disorder of copper metabolism caused by a genetic mutation (ATP7B) located in chromosome 13 [61]. The mutation prevents caeruloplasmin from binding copper, and its excretion by the liver is impaired. The excess of copper accumulates first in the liver and then in the brain (mainly the lenticular nuclei: pallidus and putamen) and in corneal tissues (the pathognomonic Kayser-Fleischer rings) [62]. Prevalence is 1/40000 and the onset is between 5 and 35 years [37]. The main neurological manifestations are on the motor side (rigidity, dystonia, chorea, athetosis, dystartria, and tremor); cognitive impairment occurs in 25% of cases [63]. Psychiatric symptoms at the onset of the disease are present in 30-40% of cases (mainly psychotic symptoms, such as delusions, or disorganized thinking). During the overall course of the disease, major depressive episodes (4-47%) and bipolar disorders (18-39%) with incongruous behaviors and irritability are the most frequent diagnoses [63]. OCD is rare. Neurological and psychiatric manifestations can improve with copper chelating or depleting agents, while neuroleptics should be avoided, when possible [37].

Fahr’s disease is an idiopathic calcification of the basal ganglia, due to a progressive calcium deposition. The commonest neurological features are Parkinsonism, chorea, dystonia, tremor, gait disturbance, dysarthria, seizures, and myoclonus [64]. Fahr’s disease must be differentiated from Fahr’s syndrome secondary to specific causes of calcium deposition in the basal ganglia (hypoparathyroidism). The prevalence is not known. Onset between the 40 and 60 years is associated with dementia and choreo-athetosis; onset between 20 and 40 years is associated with a more extensive calcification and more severe psychiatric features, such as schizophreniform psychoses and catatonia in 50% of cases. Depression is also very common. No specific treatments are available in the literature [64].

In conclusion, available data on antidepressants demonstrate their limited effectiveness in BGD. However, they might improve anxiety, irritability, mood lability, and depressive symptoms that often complicate the course of BGD. Findings on antipsychotics are controversial, except perhaps for clozapine in PD, mainly because the risk-benefit ratio between side effects and clinical response is limited. Alternative treatments, such as DBS are currently available for a small number of patients.

3.4 Psychiatric Disorders in Epilepsy

Epilepsy is a heterogeneous and chronic condition, currently classified using a disease approach according to seizure type, including both focal and generalized epilepsies [65]. Prevalence ranges from 0.4 % to 1% and 1/3 of epilepsies are diagnosed as idiopathic genetic generalized [66]. Localization-related or focal epilepsy, especially of temporal lobe, is the most frequent type [66]. Epilepsy is commonly associated with psychiatric disorders. Nearly 50% of patients with epilepsy fulfill the criteria for one or more comorbid psychiatric syndromes [66-68]. Psychiatric disorders are classified according to whether they are a direct expression of seizures (ictal), or features of a post-ictal state, or occurring in the inter-ictal period [65].

Depression has a prevalence of 30% in epileptic patients [69-71]. Alterations in neurotransmitters, such as dopamine, serotonin and norepinephrine are common as well as limbic system’s structural changes and frontal lobe hypometabolism [65]. Depression can be ictal, pre-ictal, post-ictal, or inter-ictal. Some epileptic patients may experience decline in mood for 1 to 3 days before a seizure as a pre-ictal prodromal. Ictal depression refers to the mood alteration that results directly from a simple partial seizure and is common in patients with temporal lobe epilepsy. Symptoms’ severity ranges from mild feelings of sadness to profound helplessness and despair, feelings of guilt, and suicidal ideation that last for a short period of time [72]. Post-ictal depression is uncommon, sometimes as exacerbation of an inter-ictal depression following a seizure, and usually lasting from 6 to 48 hours after. Symptoms include anhedonia, irritability, poor tolerance to frustration, feelings of hopelessness and helplessness, suicidal ideation, feelings of guilt, self-deprecation,
and crying bouts [72, 73]. Inter-ictal depression is the most common type of depression in epileptic patients [69]. Symptoms are usually chronic but milder than in classic major depression and more consistent with a diagnosis of dysthymia or inter-ictal dysphoric disorder (IDD). IDD is a specific type of mood disorder of epileptic patients, with variable or labile dysphoric mood, irritability, insomnia, pain, anergy and intermittent euphoria [65, 73]. Manic episodes in epileptic patients are less frequent than depressive episodes, more likely to present with irritability and over-activity than in ‘pure’ bipolar disorders [70].

Obviously, antiepileptic agents are the first-line treatments for mood disorders in epilepsy, considering the number of studies on their efficacy and effectiveness on both epilepsy and mood disorders. It is well known that valproate and carbamazepine have anti-manic properties and should be considered as the main choice for patients with comorbid mixed episodes and that lamotrigine has an antidepressant action [65]. Other antiepileptic drugs (such as, pregabalin, gabapentin) are also available. Evidence of levetiracetam is limited with case reports on the risk of manic episodes drug-induced [74].

The prevalence of psychosis in epilepsy is 6% [75]. Again, the psychoses of epilepsy are classified according to their temporal relationship to ictal events (ictal, post-ictal and inter-ictal psychoses). In ictal psychoses, psychotic symptoms are part of the seizure, with a sudden onset and brief duration. Ictal psychosis may occur in the context of a non-convulsive epileptic status, with bizarre behaviors and thoughts’ incoherence, with or without loss of awareness. Delusions and hallucinations are uncommon [76]. In post-ictal psychoses, symptoms began 24 hours after a new-onset cluster of seizures. There is a lucid period of between a few hours and a few days, followed by insomnia and agitation and finally ultimately leading to a psychotic episode. Psychotic symptoms are essentially positive, with prominent persecutory delusions [77]. Symptoms generally last a few days, although they are sometimes more protracted, lasting weeks to months [76]. Commonly, post-ictal psychoses occur in patients with temporal lobe epilepsy [75]. Inter-ictal psychoses may manifest both as brief and chronic forms. Some cases of brief inter-ictal psychoses are caused by Landolt’s ‘forced normalization’, namely by the development of a psychosis due to the limbic system disinhibition, when there is a normalization of the EEG [78]. The chronic forms of inter-ictal psychoses may last days to months, mimicking a schizophrenia onset. These forms manifest predominantly with positive psychotic symptoms (delusions and hallucinations), less likely to be third person auditory [76]. Although all antipsychotics may increase seizure incidence, haloperidol and risperidone are considered generally safe, especially in combination with antiepileptic drugs [65]. Patients with epilepsy may report an intense sense of fear as part of the epileptic aura in up to 15% of cases; inter-ictal anxiety and panic symptoms are described by 66% of patients, most frequently in partial seizures related to limbic foci. Again, mood stabilizers (namely valproate) and SSRIs are considered the first-line treatments [67].

ADHD has a prevalence of 23% in children with epilepsy [79]. Patients with ADHD are 2.5 times more likely to develop epilepsy than controls, although the risk is limited to children with the inattentive subtype of ADHD [80]. Moreover, non-epileptic children who have ADHD have a higher rate of abnormalities on EEG than controls (increased theta and decreased alpha waves) [81]. Seizures’ early onset is associated with a greater impairment of attention, and with a poor control of epilepsy, especially during sleep [82]. Alterations in the noradrenergic system are a common underlying pathway in epilepsy and ADHD [80]. Methylphenidate is considered a safe therapeutic choice for children with ADHD who have also epilepsy, and seems to reduce EEG abnormalities [83].

A pooled prevalence of 6.3% for ASD was found in individuals with epilepsy [82, 84]. Epilepsy is common in people with autism with reported rates of approximately 20% [85]. Some epileptic syndromes, such as Landau-Kleffner syndrome, may include peculiar communication styles or atypical social pragmatic language, similar to autism spectrum signs and symptoms [86]. Epileptiform abnormalities are described in autism, in the absence of clinically evident seizures [87]. The presence of a neuronal hyper-excitability associated to a deficit in γ-aminobutyric acid (GABA) interneurons in both ASD and epilepsy could reflect an underlying pathophysiological pathway, common to both conditions [86].

Treatment with antiepileptic drugs in ASD is mainly based on valproate, efficacious also in the treatment of irritability and repetitive behavioral patterns [20]. No systematic data are available.

3.5. Post-stroke Depression (PSD) and other Psychiatric Syndromes in Focal Brain Injuries

Stroke is a sudden loss of blood supply to the brain, leading to permanent tissue damage caused by thrombotic, embolic, or hemorrhagic events. More than 85% of strokes are ischemic; 15% are hemorrhagic [88]. Current epidemiological data indicate that stroke is the third leading cause of death, with 16.9 million people suffering a stroke each year, and a global incidence of 258/100,000/year [88].

Psychiatric syndromes comorbid with strokes lead to significant psychological distress, functional impairment, poor rehabilitation outcome, and mortality increase. The most common psychiatric symptoms after stroke are depression, apathy, anxiety disorders, mania, psychotic symptoms and pathological laughing and crying, the so-called ‘involuntary emotion expression disorder’ (IEDD) [89].

Post-stroke depression (PSD) is different from demoralization related to stroke, considering its severity and long-lasting course [65]. Between 29% and 33% of patients may suffer for depression up to 1 year after stroke [90]. An association between left basal ganglia or left frontal (mainly in proximity with frontal pole) lesions and PSD, at least 2 months following stroke, has been suggested [91]. Correlation between the proximity of the lesion to the frontal pole and the severity of depressive symptoms may be due to anterior lesions interrupting ascending noradrenergic and serotonergic fibers closer to their origin from the brainstem, and causing greater depletion of neurotransmitters than more posterior lesions [91, 92]. This correlation is supported by
the finding of the focal brain stimulation with repetitive trans-cranial magnetic stimulation (TMS) as effective only when administered to the left dorso-lateral prefrontal cortex in patients with vascular depression [88]. From a phenomenological point of view, catastrophic reactions, hyper-emotionalism, and diurnal mood variation are the most common features in PSD [92]. SSRIs, especially fluoxetine, are the first-line treatment choice for patients with PSD and may exert a neurotrophic effect [93, 94].

Apathy, characterized by motivation loss, decreased spontaneous activity and emotional indifference, is a common PSD feature. It is also often present as a syndrome itself, without other depressive symptoms, in about 21% of cases [95]. Apathy is related to the damage of the genu and splenium of the corpus callosum, the left anterior corona radiata and the white matter of the right inferior frontal lobe [96]. Dopaminergic agents, including dopaminergic antidepressants (i.e. bupropion), are the first-line pharmacological treatment for apathy, while SSRIs are less effective [97].

GAD has a prevalence of 24% after stroke, and it is commonly associated with PSD [98]. Depression and anxiety are comorbid with left-cortical lesions, whereas anxiety alone is more frequent in right-hemisphere lesions [99]. Comorbidity between PSD and GAD may trigger depressive episodes characterized by a longer duration than observed in PSD alone, and a more severe impairment in physical and social functioning [100]. SSRIs (i.e. citalopram) are preferable to BDZs to treat post-stroke anxiety symptoms [92].

Post-stroke mania is less common than depression, with an estimated prevalence of 2% [101]. Lesions of the right frontal lobe (mainly ventral prefrontal and medial frontal) and basal ganglia are associated to manic episodes in post-stroke [102]. Lithium is the most widely administered treatment for secondary mania, even if evidence is limited [92].

Psychotic symptoms (delusions or hallucinations with poor insight) occur in 4.8% of patients with post-acute stroke and are associated with the right hemisphere (frontal, temporal and parietal), or with the right caudate nucleus lesions [103]. No studies evaluated treatments for post-stroke psychoses. Haloperidol and risperidone are the most frequently prescribed drugs, followed by quetiapine, olanzapine [101] and anticonvulsants, as add-on for treatment-resistant patients [99].

The ‘involuntary emotion expression disorder’ (IEED), also considered a pseudo-bulbar affect, is a disorder of emotional expressions described in 10-20% of cases after stroke [65]. Patients tend to emotional displays, such as laughing or crying without appropriate stimulation, in the absence of congruent mood changes. These episodes are irresistible, slow to resolve, severe and disabling [65]. Its pathogenesis is related to a disconnection in the cerebro-ponto-cerebellar pathways [104]. IEED after stroke can persist for many months. SSRIs can lead to a partial improvement of symptoms, as well as dextromethorphan, a sigma receptor agonist, combined with quinidine to reduce dextromethorphan metabolism [65].

Traumatic Brain Injury (TBI) occurs when a blow or jolt to the head or a penetrating injury results in damage to the brain. Ten million people/year are affected by TBI [105]. Psychiatric sequelae of TBI are common, together with physical and cognitive deficits (such as fatigue, dizziness, headaches and memory deficits) [64]. Major depression is the most common psychiatric disorder after TBI (25%-50%) within the first year following injury [106]. The depressive phenotype is typical. Pre-trauma social functioning and left dorso-lateral frontal and/or left basal ganglia lesions are the main risk factors for a post-TBI MDE [65]. Again, SSRIs are considered the first-choice treatments [106].

As in stroke, in TBI, apathy not always occurs in the context of a depressive episode and may represent a distinct condition. Differently from stroke-related apathy, in TBI, apathy is resistant to treatment with dopamine-agonists. The development of apathy after TBI is related to the damage of the mesial frontal lobe and sub-cortical structures [65].

Manic symptoms affect approximately 9% of patients with TBI, usually associated with lesions of the ventral prefrontal and baso-temporal cortex [102]. Mania is characterized by irritability, agitation, impulsivity, violence, and persecutory delusions or auditory hallucinations, only partially controlled by valproate [107].

Post-TBI psychoses occur in less than 1% to 15% of cases, especially when brain injury involves frontal and temporal lobes [106]. EEG abnormalities, mainly in temporal lobe, are present in more than 50% of patients [108], and anticonvulsants are administered with this rationale, when a left-temporal injury is present [106].

Anxiety disorders, common in TBI patients, include post-traumatic stress disorder (PTSD) (27%), OCD (11%), and GAD (15%) [105]. Panic disorder (PD) is less frequent. GAD is associated with post-TBI right hemispheric cortical lesions [64]. PTSD following TBI is mainly characterized by an absence of re-experiencing [109]. However, circuits bypassing cortical structures could form traumatic implicit (unconscious) memories [110]. Patients with anxiety disorders and TBI are treated in the same way as anxious patients without TBI [105].

Multiple Sclerosis (MS) is a chronic disease of the central nervous system characterized by loss of motor and sensory functions that results from an immune-mediated inflammation, a demyelization and a subsequent axonal damage. The prevalence of the disease varies from 15/100,000, to 250/100,000 [111]. Psychiatric disorders, including affective, psychotic and anxiety disorders, are described in 60% of patients with MS [112].

The lifetime prevalence of MDEs in MS is approximately 50% [113]. Phenomenology of the MS depressive syndromes overlaps with that of primary depression. However, irritability, discouragement, and sense of frustration are more likely to accompany the depressed mood than feelings of guilt and poor self-esteem [114]. Lesions in the left medial inferior prefrontal region together with atrophy affecting the dominant anterior temporal lobe are more frequently associated with MDEs [114]. Helplessness, uncertainty and perceptions of disability are equally important in explaining comorbid depression in MS patients [115]. The first-line pharmacological choices for MDEs are SSRIs (fluoxetine), given their relatively good tolerability and effectiveness, with another putative benefit related to reduction of axonal degradation.
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via induction of glycogenolysis in astrocytes [116]. Mirtazapine, due to its low propensity for sexual dysfunction and inhibition of cerebral pro-inflammatory cytokine production, is considered an alternative to SSRIs [112].

Bipolar spectrum disorders occur in 4.7% of patients with MS [102] and euphoria is present in up to 25% of patients, sometimes secondary to steroid treatments [113]. A neuropathological correlation has been suggested with the frontal lobe white matter lesions [102]. Lithium, in add-on to mood-stabilizing effect, might have a disease-modifying action in patients with manic episodes and MS, although it can lead to incontinence when a bladder dysfunction is present [112, 113].

Psychotic symptoms are described in 23% of cases, associated to temporal lesions [114]. Treatment of psychosis is similar in individuals with MS to those without comorbid MS.

The lifetime prevalence of anxiety disorders is 36%, with GAD (19%), panic disorder (PD) (10%), OCD (9%) and social anxiety disorder (SP) (8%) as the most common diagnoses [112]. As in major depression, SSRIs should be considered the first line treatment, even if the evidence is scarce [116].

IEED occurs in 10% of MS patients, with clinical features similar to the same syndrome in strokes [65].

3.6. Psychiatric Symptoms in Neurological Neoplastic and Para-neoplastic Diseases

Brain tumors have an annual incidence of 9 per 100,000 for the primary forms, and 8.3 per 100,000 for the metastatic ones [117]. The most frequent brain tumors are gliomas accounting for 40%-55%. Brain-metastasing tumors account for 15%-25% of all cases [117, 118]. More than 50% of patients with brain tumors experience psychiatric symptoms [119]. Depression occurs in 44% of cases, and it is associated both with functional impairment and reduced survival rates [120, 121]. Depression is more often associated to frontal lobe tumors (especially left frontal) [119]. Apathy is common in frontal lobe and para-limbic lesions, not only as part of a depressive episode [122, 123]. Manic symptoms, such as euphoria, disinhibition, hyper sexuality, and aggressive behaviors, are associated to right frontal, temporal, or sub-cortical limbic lesions in 80% of cases [102, 117]. Psychotic symptoms, often with delusions and visual hallucinations, are diagnosed in 22% of patients [124] and are more commonly associated with pituitary and temporal lobe lesions [121].

Surgery may completely resolve the psychiatric symptoms. Psychopharmacological management of psychiatric symptoms follows the general therapeutic principles of tumor-free patients. However, we should consider, in treatment choices that patients with brain tumors have an increased susceptibility to delirium, seizures, medication side effects, and drug-drug interactions [117].

Anti-NMDA receptor (NMDAR) encephalitis has been increasingly identified as an important cause of autoimmune and para-neoplastic syndrome, recognized for the first time in 2007 by Dalmau and Bataller [125]. The true rate of anti-NMDA receptor encephalitis in the general population and in individuals with psychoses is not yet defined. The pathogenesis is linked to anti-NMDA receptor antibodies binding to the glycine subunit of the NMDA receptors (GluN1), and leading to receptor internalization. The subsequent neuronal dysfunction results in symptoms through disruption to fronto-striatal connections and other neuronal networks [126]. Approximately 80% of patients are females, and about 50% of cases are associated with neoplastic lesions, such as ovarian teratoma [127]. The syndrome evolves in several stages, with approximately 70% of patients presenting with a prodromal phase of fever, headache, malaise, upper respiratory tract symptoms, nausea, vomiting and diarrhea [128].

The next phase (typically within two weeks) is characterized by insomnia, speech disturbances, delusions, paranoia, hallucinations, apathy, depression, agitation/aggression and catatonia. Neurological symptoms such as seizures, abnormal movements, autonomic instability and memory deficits may also develop during the course of the disease [128, 129]. The most common psychiatric symptoms are agitation/aggression and speech disturbances, with psychosis occurring in less than half of cases and catatonia, especially when fluctuating, as the key diagnostic feature [126]. Confirmation of the clinical diagnosis of anti-NMDA requires a positive serum or CSF sample screening for antibodies to the NMDA receptor subunit (GluN1), which also should lead to a search for a possible underlying tumor, such as teratoma [130]. Treatment is focused on tumor resection, and first-line immunotherapy (corticosteroids, plasma exchange, and intravenous immunoglobulin). The second-line choice for non-responders includes immunotherapy (rituximab or cyclophosphamide or combined). More than 75% of patients may recover completely or may have mild sequelae, while a persistent severe disability through death is described in 25% of patients [128].

There is a paucity of literature on the management of psychiatric symptoms in these patients. Catatonic symptoms are treated with lorazepam [131], while clozapine and olanzapine are the first-line treatment options for enduring psychotic symptoms, preventing NMDA receptor antagonist toxicity [128].

4. DISCUSSION

Limited studies have addressed the problematic issue of the psychopharmacological management of patients with comorbid psychiatric syndromes in neurological diseases, and only a few have offered valid treatment options.

The findings of our review identified several shortcomings, including treatment-specific biases arising from small sample sizes, research conducted in neurological instead of psychiatric settings, and clinical rather than statistical interpretation of results, mainly due to the limited number of observed cases. These limitations derive from the difficulties in conducting systematic researches with inhomogeneous and complicated patients, and from the absence of the organization of long-term follow-ups.

Taken as a whole, treatment responses are unsatisfactory in a number of comorbid psychiatric disorders, mainly because neurological syndromes are often characterized by a clinical course resistant to every type of available treatments, thus leading to a treatment resistance of the co-occurring psychiatric signs and symptoms.
The clinical evidence of a non-response to treatment for a number of neurological conditions (see dementias, PD, or congenital neurological illnesses) lead to, in our opinion, the idea that psychiatric comorbidities become relevant only when complicating the behavioral management or when exacerbating the clinical course of the neurological diseases. Despite a theoretical model supporting an equal approach between psychiatric and neurological syndromes, psychiatric syndromes in neurological diseases have been described as less important, leading to a primate of the neurological manifestations, and thus limiting the interest for systematic studies on psychopharmacological treatments in this area. The influence of such over-valued ideas might help to explain why psychiatric syndromes in neurological diseases have remained with no systematic studies in many areas.

We believe that, above all the disappointing findings of treatment, there is a need for a better understanding of psychopathological features when comorbid with neurological diseases, raising again questions on the utility of a combined systematic approach.

CONCLUSION
Neuropsychiatry is reappearing as a renewed specialty that deals with disorders at the intersection between neurology and psychiatry. It constitutes a clinical area of conceptual overlap and re-unification of both disciplines, once considered inseparable. Psychiatric disorders in the context of neurological diseases are complex and incompletely understood. Moreover, finding on available treatments is scarce, and only recently there is a need for different approaches, based on non-pharmacological treatments, as for the behavioral and psychological symptoms of dementia. Unfortunately, non-pharmacological strategies (behavioral, environmental or caregiver supportive interventions) are, at present, not frequently translated into routine standard care, thus remaining largely unapplied to a management in which drugs are preferred over non-pharmacological strategies.

However, even with all these limitations, we believe that advances in neuroscience research are beginning to elucidate the biological underpinnings of many of these conditions. We speculate that the new findings in all these fields might have the potential to improve the diagnostic approach, to optimize treatment selection, and to facilitate the development of new and evidence-based interventions in neuropsychiatric practice.

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