Review Article

Depression and neurological disorders

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ABSTRACT

الاكتئاب هو أكثر الاضطرابات النفسية انتشاراً في مرضى الاضطرابات العصبية مثل الصرع، التصلب اللويحي، الجلطة الدماغية والشلل الرعاش. عادة ما يكون الاكتئاب مصحوباً بنقص في جودة الحياة، التدني الوظيفي وزيادة الوفاة. تشخيص الاكتئاب المصاحب للاضطرابات العصبية يعتبر صعباً نظراً لوجود أعراض متشابهة في الاضطرابين مثل اضطرابات النوم، الشهية، الإرهاق،عدم التركيز والتبلد. إن سبب الاكتئاب المصاحب للاضطرابات العصبية غير معروف ولكن تفاعل العوامل البيولوجية، النفسية، الاجتماعية، والباثولوجية العصبية قد يكون مسئولاً عنه. قليل من الدراسات المحكمة قد تم إنجازها لبيان كفاءة التدخل العلاج النفسي والدوائي في تحسين الاكتئاب، جودة الحياة واستمرار الحياة. كما تعتبر الدراسات التي عنيت بمكافحة الاكتئاب في مرضي الاضطرابات العصبية واعدة.

Depression is the most common psychiatric disorder in neurological disorders such as epilepsy, multiple sclerosis, stroke, and Parkinson's disease. It is associated with reduction of quality of life, functional impairment, and higher mortality. The diagnosis of depression in neurological disorders is difficult because of the overlapping symptoms. Neurological disorders are usually associated with sleep and appetite disturbances, fatigue, apathy, and lack of concentration, which is similar to those of depression. The etiology of depression with neurological disorders is unknown, but the interaction between biological, psychosocial, and neuropathological factors could be responsible for it. Few controlled trials have been carried out to investigate the efficacy of psychotherapeutic and pharmacological interventions in this population, and it seems that they are effective in improving depression, quality of life, and survival. Studies pertaining to prevention of depression in neurological disorders are promising.

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The prevalence of major depression in the general population ranges from 2.6-5.5% in men, and from 6-11.8% in women.[1] Depression will be the second leading cause of disability worldwide, preceded only by ischemic heart disease in 2020.[2] The total cost of depressive disorders in the United States is generally estimated at $44 billion.[3] To diagnose depression, according to DSM-IV[4] criteria, the patients should have either depressed mood or lack of interest in addition to 4 out of the following 8 criteria: significant weight loss or gain; insomnia or hypersomnia; psychomotor retardation or agitation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate or indecisiveness; recurrent thoughts of death, recurrent suicidal ideation, suicidal attempt, or specific plan for suicide. These symptoms should be present most of the day, nearly every day for 2 weeks together with educational, occupational, or social impairment. These symptoms should not be due to a general medical condition, or substance abuse. The diagnostic criteria for dysthymic disorder (mild chronic depression) includes depressed mood for 2 years and 2 of the following symptoms: poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem, poor concentration; and hopelessness. The etiology of depression is multifactorial including genetic factors, monoamine neurotransmitter dysfunction, and psychosocial factors (biopsychosocial model). Depression is usually treated with psychotherapy or antidepressants or both. Psychotherapy includes cognitive behavioral psychotherapy (changing negative thoughts can change negative emotions) and interpersonal psychotherapy (improvement of interpersonal problems can improve depression). Antidepressants include tricyclic antidepressants (TCA) (amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, maprotiline), serotonin specific reuptake inhibitors (SSRIs), (citalopram, escitalopram, sertraline, fluoxetine, fluvoxamine, paroxetine), serotonin norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine), and others (mirtazapine, nefazodone, reboxetine). Electroconvulsive therapy (ECT) can be used in treatment-resistant depression, psychotic depression,

or depression associated with suicide. Vagal nerve stimulation (VNS) was approved by the US Food and Drug Administration (FDA) for treatment-resistant depression. Depression is common to occur in patients with neurological disorders such as epilepsy, multiple sclerosis (MS), stroke, and Parkinson's disease (PD). It is associated with reduced quality of life and higher suicidal rate. It is also underdiagnosed and undertreated. Neurological disorders are associated with fatigue, apathy, low concentration, and sleep disturbances, which makes the diagnosis of co-existing depression challenging. The etiology of depression associated with neurological disorders is multifactorial. Few controlled trials have investigated the efficacy of psychological and pharmacological interventions in treating depression in patients with neurological disorders. Most of the treatment guidelines or algorithms depend on clinical experience, consensus, or open studies. This article will review all studies, which investigate the epidemiology, etiology, diagnosis, impact, prevention, and treatment of depression associated with epilepsy, MS, stroke, and PD.

Depression and epilepsy. Depressive symptoms might occur a few hours or days before the onset of seizure (pre-ictal), during seizure (ictal) or after seizure (post-ictal). Depression commonly occurs in between seizures (inter-ictal), and this is our focus in this review. The relationship between epilepsy and depression is controversial. Both agonistic and antagonistic relationships have been proposed, and it is likely that both types of relationships do exist in different individuals and possibly in the same individual at different times.[5] Both disorders are characterized by dysfunctional episodes separated by intervals of normality and common pathogenic mechanisms are suspected.

Epidemiology. The prevalence of inter-ictal depression ranges from 20-55% in patients with recurrent seizures, and from 3-9% in patients with controlled epilepsy.[6] While a 12-month incidence of depression is around 7%, and the lifetime incidence is around 16%.[7] This variation is due to using different diagnostic criteria or different rating scales in diagnosing depression and recruiting epileptic patients with different seizure types, variable frequency and severity, and with different antiepileptic medications.

Pathogenic mechanisms. The etiology of depression in epilepsy has not been determined. The higher comorbidity of these 2 disorders may result from common pathogenic mechanisms in the 2 disorders. The biopsychosocial model can be applied for depression in epilepsy patients. The etiology is multifactorial and includes biological factors (genetic factors and neurotransmitter dysfunctions), psychosocial factors, seizure-related factors, and iatrogenic factors. These factors may operate individually or synergistically.

Biological factors. Decreased serotonergic and noradrenergic functions are responsible for depression. At the same time they facilitate the kindling process of seizure foci, exacerbate seizure severity, and intensify seizure predisposition in some animal models of epilepsy.[8] Also, genetic factors could play a role in comorbidity of depression and epilepsy because more than 50% of epileptic patients with depression have been reported to have a family history of psychiatric illness especially affective disorders.[9]

Psychosocial factors. Among the psychosocial factors, lack of acceptance and adjustment to epilepsy; stigma of epilepsy; discrimination; lack of control in their life caused by random occurrence of seizures; lack of social support and the need to make significant adjustments in life style, such as giving driving privileges and changing jobs have been of particular interest.[10,11]

Seizure factors. Seizure factors include age of onset, seizure type, frequency and severity of seizures, status epilepticus, and laterality of the temporal lobe spike focus.[12,13] Depression has been identified more frequently in patients with seizures of temporal and frontal lobe origin (seizures involving the limbic circuit), with prevalence ranging from 19-65%, which is higher than those of the patients with generalized seizure disorders.[14]

Iatrogenic factors. Depression could be related to antiepileptic medications such as: phenobarbital, primidone, tiagabine, vigabatrin, felbamate, and topiramate. Depression could occur after epilepsy surgery, especially anterotemporal lobectomy.[15] Lastly, the phenomenon of "forced normalization", which consists of the appearance of psychiatric disorders including depression associated with the cessation of epileptic seizures, could play a role.[16]

Diagnosis. Depression in epilepsy patients does not necessarily follow the diagnostic criteria of DSM-IV or ICD-10. A strong consensus is emerging among experts that "unique" syndromes of depression exist.[17] It is commonly present as a chronic mild depression "dysthymic like disorder of epilepsy"[18] or "interictal dysphoric disorder."[14] Depression in epilepsy is frequently identified clinically by structural or semi structural interview, but on some occasions the use of depression rating scales such as Beck Depression Inventory (BDI) is helpful. The BDI, which includes 21 self-report items, is a reliable diagnostic instrument for depression in epileptic patients.[19]

Impact. Quality of life. Depression affects the quality of life and mood is the strongest predictor of poor quality of life in epileptic patients even after controlling for seizure severity, seizure frequency, and other psychosocial factors[20,21] in all types of seizures.[22]

Suicide. The collective data yield an average suicide rate of approximately 12% among people with epilepsy, compared with 1.1-1.2% in the general population.[23] The lifetime prevalence of suicide and suicidal attempts is between 5-14.3% in people with epilepsy, and this rate has been reported to be 6 to 25 times higher in people with temporal lobe epilepsy than in the general population.[24] Suicide has one of the highest standardized mortality rates of all causes of death in persons with epilepsy.[25] The risk factors for suicide among epileptic patients include psychiatric comorbidity especially depression, family issues, physical health, personality, life stress, previous suicidal behavior, access to firearms,[23] and suppression of seizures in longstanding epilepsy.[26] According to the FDA alert issued December 16, 2008, antiepileptic drugs might increase the risk of suicide and patients being treated with antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Depending on a review of 199 trials of all antiepileptic medications, the FDA found that patients on antiepileptics were 2 times more likely to develop suicidal ideas and behaviors than those who received placebo (0.43 versus 0.24), which means one additional case of suicide out of 500 patients who were treated with antiepileptics instead of placebo.[27]

Treatment. Depression could occur after initiation of an antiepileptic drug with negative psychotropic properties or discontinuation of antiepileptic drug with mood stabilizing properties. In such cases, discontinuation or reintroduction of antiepileptic drug may be sufficient to achieve remission. Lamotrigine was found to be useful in treating epilepsy patients with comorbid depression.[28,29] Depression can be treated with psychotherapy or antidepressants or both.

Psychotherapy. A recent meta-analysis of psychological therapies in epilepsy found that no reliable evidence to support the use of relaxation therapy, cognitive behavioral therapy, EEG feedback, and educational interventions due to methodological deficiencies, and a limited number of patients studied.[30]

Pharmacotherapy. There has only been one double-blind, placebo-controlled study published to date that compared the efficacy of mianserin, amitriptyline (TCA) (75 mg/d), and placebo in depression of patients with epilepsy, and failed to demonstrate a significant benefit of antidepressants over placebo.[31] In a follow-up study, 26 non responders were openly treated with 150 mg/day of amitriptyline for 6 weeks, 17 patients had a remission of depression. Open and uncontrolled studies found that citalopram, sertraline, venlafaxine, mirtazapine, and reboxetine were effective and safe in treating depression in epileptic patients.[18,25,32,33] Non responders to TCAs could be treated by a combination of TCAs and SSRIs.[34,35] Bupropion, maprotiline, and clomipramine are the antidepressants with the strongest proconvulsant properties and should be avoided in epileptic patients.[36]

Drug-drug interactions. Antiepileptics with enzyme-inducing properties (phenytoin, carbamazepine, phenobarbital, primidone) accelerate the metabolism of most antidepressants in the liver and consequently adjustment of the dose is important.[37] There is evidence that phenobarbital and phenytoin may cause a 25% decrease in plasma concentration of paroxetine.[38] Whereas valproic acid may increase paroxetine plasma concentration. However, these pharmacokinetic alterations were not associated with any observable clinical effects.[39] On the other hand, SSRIs may alter antiepileptic drugs metabolism by inhibiting P450 isoenzymes (CYP1A2, CYP2D6, CYP3A4, CYP2C19).[40] This effect is greatest for fluvoxamine, fluoxetine, and nefazodone and least for sertraline, paroxetine, venlafaxine, and citalopram.[39] To summarize, SSRIs especially those with the least drug-drug interactions such as sertraline and citalopram, should be the first line treatment for depression in epileptic patients because they have the same efficacy as TCAs, better side effect profile, and no worsening of seizures. If the patients do not respond to 2 SSRIs trials for 8 weeks each, then an SNRI or TCA can be used.

Depression in epileptic children and adolescents. The prevalence of depression is estimated to be 1-3% in healthy children. and 4-8% in healthy adolescents.[41] On the other hand, the prevalence of depression in epileptic children and adolescents ranges from 26%[42] to 33%.[43] The prevalence of suicidal ideation was 20% in children (aged 5-16) with complex partial seizures and absence.[44] This was significantly higher than both the control group rate (9%) and estimates from the general population (5.2%).[45] A recent study in children and adolescents with epilepsy and depression showed promise for the use of SSRIs in this population, finding that sertraline and fluoxetine were effective and tolerable.[46]

Depression and multiple sclerosis. Depression commonly occurs in MS patients, and it is associated with reduced quality of life. Overlapping symptoms of depression and MS could make the diagnosis of depression difficult. The etiology of depression in MS is unknown, but it could be related to autoimmune mechanisms, site of MS lesion, or MS drugs. Psychotherapy is effective in treating MS patients with depression.

Epidemiology. Estimates of lifetime prevalence of depression in patients with MS range from 19-54%, depending on the diagnostic criteria used and the population sampled.[47-49] A survey of 739 patients

revealed 41.8% with significant depression and 29.1% with moderate to severe depression.[47] The prevalence of depression in MS is higher than in patients with other neurological disorders.[50] Risk factors for depression in MS patients include female gender, young age (<35 years), family history of depression, and a high level of stress.[49] However, a recent longitudinal study found no association between gender and depression in MS and functional impairment is the variable associated with depression over 7 years. While young age, long duration of MS, and progressive MS were associated with depression during the first year only.[51]

Pathogenic mechanisms. Although little is understood with respect to the pathogenic mechanisms of depression in MS, proinflammatory cytokines might play a role.[52] Depression treatment decreases production of cytokines, which potentially could alter the progression of MS.[53] A number of drugs such as steroids, anti-spasticity drugs, and interferon used to treat MS or its symptoms have been implicated as risk factors for depression.[54] However, the most recent prospective studies indicate no relation between interferon beta-1a or 1b and depression.[54] There is a continuous debate on MS lesion site and depression. However, imaging studies showed an association between depression and greater neuropathology in the left anterior temporal/parietal regions.[55]

Diagnosis. Vegetative or somatic symptoms like fatigue, insomnia, and lack of appetite do not tend to be good diagnostic discriminators for depression in MS as in other neurological disorders. Findings like guilt, worthlessness, withdrawal, and apathy are not reported frequently in MS depression as in primary depression.[56] Using rating scales with many somatic symptoms reveals elevated rates of depression in MS. Diagnosis of depression in MS should depend on structural or semi-structural interview using DSM or ICD criteria. In a recent longitudinal study, depressive symptoms fluctuated over time without an increase or decrease in severity.[51]

Impact and suicide. Comorbid depression in MS increases risk for suicide[57] and reduces quality of life.[58] Suicidal ideation may be seen in up to 22% of MS patients.[56] The rate of completed suicide in patients with MS has been reported to be 7.5 times what would be expected in the general population.[59] The MS patients in middle age (40-49 years) and during the first 5 years after the diagnosis of MS are more likely to commit suicide.[60] Comorbid anxiety with depression increases the incidence of suicidality in MS,[61] as well as in idiopathic depression.[62] With respect to physical and cognitive impairment, studies are controversial.

Treatment. Less than 50% of MS patients with depression were receiving antidepressants.[63] Treatment of depression in MS includes psychotherapy and antidepressants. Cognitive behavioral therapy (CBT) and supportive psychotherapy (emotion-focused and group) are effective in treatment of depression in MS patients.[64-67] Psychotherapy is associated with improvement of quality of life and reduction of disability and fatigue.[62] This effect is independent of depression improvement for CBT.[64] A meta-analysis of treatment of MS depression found no difference between psychotherapy and pharmacotherapy.[68] The only controlled study with SSRIs found no difference between paroxetine and placebo.[69] While open trials with sertraline (SSRI) alone or in comparison with psychotherapy have been carried out with positive results.[66,70] In a double-blind, placebo-controlled study, the TCA desipramine was superior to placebo although more than half of the patients did not reach to the specified dose because of the adverse events.[71]

Depression and stroke. Depression is the most common psychiatric disorder in stroke patients. Communication difficulties and somatic symptoms could make the recognition of depression not an easy task. There is a debate about the relation between depression and lesion side and site in stroke patients. Depression in stroke patients is associated with increased mortality and both depression, and mortality could be improved by using antidepressants.

Epidemiology. Around one-third of stroke patients had depression, and 20-25% had major depression.[72] Estimates of poststroke depression (PSD) prevalence range from 20-72%, depending on the diagnostic criteria used, patient population studied, and settings.[73,74] Incidence rates of major and minor depression in acute and rehabilitation hospitals are 19.3% and 18.5%, in community settings, the rates are 14.1 and 9.1%.[73] The prevalence of PSD peaks 3 to 6 months after stroke.[75] The risk factors for PSD include young age, female gender, functional and cognitive impairment, past history of depression, and a lack of social support.[76]

Pathogenic mechanisms. The etiology of PSD is thought to be multifactorial, involving psychosocial and biological mechanisms.[77] The PSD could be due to multiple losses (physical function, employment, change in marital or social status) or lesions of brain areas controlling mood.[55] There has been a debate on the relation between lesion location and PSD. Data from the 1980s first suggested that there were a relation between proximity of the lesion to the frontal pole and PSD. This appeared to have been contradicted by a meta-analysis that found 2 reports that supported, and 7 reports that failed to support the lesion-location hypothesis of depression risk.[78] This analysis was further criticized by others on the grounds that the hypothesis was not specific enough, and that some relevant studies

were excluded. When the data were looked at separately for each hemisphere, there was a clear relation between proximity of the lesion to the left frontal pole and depression, especially in the first few months after stroke.[79] In a review of the PSD studies, Cummings and Mega[80] found that early (within 2 months) PSD is associated with left hemisphere lesions while late (more than one year) PSD is associated with right hemisphere lesions. In a recent study, Koenigs et al[81] found that dorsal prefrontal cortex lesions are associated with high levels of depression while ventromedial prefrontal cortex lesions are associated with low levels of depression. Also, small subcortical lesions of the left hemisphere are associated with a higher frequency of depression than right-sided subcortical lesions.[82] A recent study found an association between serotonin transporter gene polymorphism (5-HTTLPR and Stin2 VNTR) and PSD.[83]

Diagnosis. Diagnosis of PSD is difficult due to communication problems and overlapping of symptoms of the 2 disorders. Depressed mood, lack of appetite, and crying are more sensitive than apathy, lack of insight, and feelings of guilt in the diagnosis of PSD.[84,85] The acute onset of major and minor depression after stroke lasted for 1- and 2-years.[86] In addition, 46% of the PSD patients remained depressed after 18 months.[87] Rating scales for depression can be used in stroke patients for screening or for measuring change over time. The best validated scales were the Hospital Anxiety and Depression Scale (HADS) and the General Health Questionnaire-12 (GHQ-12) for patients in the community or rehabilitation settings; Signs of Depression Scale on acute hospital wards; and Visual Analogue Mood Scale or Hospital Stroke Aphasic Depression Questionnaire (SADQ) for aphasic patients.[55]

Impact. Poststroke depression is associated with reduced quality of life in terms of recovery of cognitive impairment and recovery of activities of daily living (ADL). Poststroke depression is associated with cognitive impairment, especially with left hemisphere lesions.[88] Improvement of cognitive functions after treatment with antidepressants is controversial among studies,[89-91] and more studies are required for clarification of this issue. Poststroke depression is the most important predictor of poor recovery in ADL over a 2-year period,[92] which improved with antidepressant medication.[93] Poststroke depression is associated with higher mortality (50%) than nondepressed stroke patients over one year and antidepressant treatment increased the survival rate in comparison with placebo (61% versus 34%).[91]

Treatment. There are 9 controlled studies for antidepressants in the treatment of PSD: 2 positive studies for nortriptyline,[90,91] 2 positive for citalopram,[93-95] 2 positive, and 2 negative for fluoxetine,[91,96-98] and one negative for sertraline.[99] Depending on the findings of previous studies, we can conclude that SSRIs and TCAs are effective in the treatment of PSD. Antidepressants may reduce post stroke mortality. In a 9-year follow-up study, treatment with fluoxetine or nortriptyline for 12 weeks during the first 6 months after stroke significantly increased the survival of both depressed and nondepressed patients.[100]

Prevention. A recent meta-analysis[101] found that antidepressant treatment has promising results in preventing depression after stroke. In addition, there are 2 controlled studies with SSRIs (sertraline and escitalopram) and problem-solving therapy for prevention of PSD, and both were effective in preventing depression in comparison with placebo.[102,103]

Depression and Parkinson's disease. Depression is the most common psychiatric disorder in Parkinson's disease (PD) and it is underdiagnosed and undertreated in this population. Overlapping symptoms of the 2 disorders complicates the diagnosis of MS depression. Depression reduces quality of life in PD patients. Monoaminergic neurotransmitter dysfunction plays a role in the etiology of depression in PD. Dopamine agonists and antidepressants appear to be effective in treating depression in PD patients.

Epidemiology. Depression occurs with 40-50% of PD patients,[104] although prevalence rates ranging from 4-70% have been reported.[105] This variation is due to differences in sampling methods and case ascertainment with lower prevalence rates in community studies. According to the Global Parkinson's Diseases Survey (GPDS),[106] performed by the WHO, around 50% were in a state of depression, but only 2% of the patients, and 1% of the caregivers were aware of this. More than half of PD patients with depression, anxiety, and fatigue were not recognized by treating neurologists.[107] In a treatment survey, 26% of PD patients were using antidepressants, 51% on SSRIs, 41% on TCAs, and 8% on other antidepressants.[108]

Pathogenic mechanisms. The etiology of depression in PD is unclear. An integrated model including neuropathological, biochemical, and psychosocial factors has been proposed.[109,110]

Psychological factors. Depression could be a psychological reaction to PD disability at least in some cases, but not in all cases especially those who presented with depression before motor symptoms.[109]

Neuropathology and neurotransmitters. Parkinson's disease pathology affects the limbic system, which is the center for emotions and memory.[111] Alterations of neurotransmitter transporters (dopamine and norepinephrine) was found by PET studies to be associated with anxiety and depression in PD.[112,113] In

addition, post-mortem studies found morphological changes and severe neuronal loss in raphe nucleus (source of brain serotonin) and nucleus coeruleus (source of brain noradrenaline) in depressed PD patients.[113-115] Depression in PD seems to be caused by degeneration of monoaminergic neurotransmitter systems and fronto-cortical dysfunctions.[116]

Genetics. There is an association between serotonin transporter genetic variation, and mood disorder (anxiety and depression) in PD.[117,118] First-degree relatives of PD patients are more likely to have depression and anxiety disorders than are first-degree relatives of controls.[119]

Frontal lobe dysfunction. Decreased metabolic activity bilaterally in the inferior orbitofrontal cortex and caudate was found by PET in depressed compared with non-depressed, non-demented PD patients. The metabolism in the inferior-frontal cortex was inversely proportional to the degree of depression.[120,121] Positive treatment response to antidepressants was predicted by the metabolic state of the anterior cingulate.[122] The medial prefrontal cortex is a common area of dysfunction in depressed PD patients and those with primary depression.[123] The anterior cingulated bundles play an important role in depression in PD, and some aspects of depression in PD have pathological processes in common with de novo depression.[124]

Diagnosis. The profile of depressive symptoms observed in PD is not identical to that reported in patients with primary depression. Distinctive features of depression in PD include dysphoria, irritability, little guilt or feelings of failure, and a low suicidal rate despite a high frequency of suicidal ideation.[125,126] Overlapping symptoms of the 2 disorders complicates diagnosis of depression in PD. Psychomotor retardation, reduced mimics and apathy, sleep and appetite disturbances, lack of concentration occurs in both disorders. Diagnosis of depression in PD is based on feelings of hopelessness and emptiness; reduced reactivity to emotional stimuli; anhedonia (loss of pleasure); pervasive low mood with diurnal variation; early morning wakening; and pessimistic thoughts.[55,127] Using rating scales to assess depression severity is not reliable because of overlapping clinical symptoms.[127] Consequently, the diagnosis of depression should be made clinically using appropriate criteria.[55] The course of depression in PD patients is persistent, with 56% still depressed at one year.[128]

Impact. Depression is associated with reduction in quality of life, which is independent of motor deficits.[129,130] According to the GPDS, depression is the most significant predictor variable in health-related quality of life in PD.[131] Depression in PD is associated with rapid cognitive deterioration, which could be attenuated with treatment.[132]

Treatment. Although depression is prevalent in PD patients, only 10-26% of them received antidepressants in a review of 3 studies.[133] Dopamine agonists or antidepressants can treat depression in PD.

Dopamine agonist. Antidepressive effects of pramipexole have been confirmed in large populations of PD patients routinely using open study designs.[134,135] The affinity of pramipexole to cortico-frontal D2- and D3-receptors seems to play a role in its antidepressant effect.[128] Pramipexole improved depression in a double-blind trial in PD patients.[136] A comparison of pramipexole and sertraline in patients with PD without motor complications who were treated with levodopa showed that both interventions significantly improved depression with no significant difference in treatments.[137]

Antidepressants. TCAs. In a controlled 16-week crossover study, Nortriptyline, a TCA that inhibits reuptake of both serotonin and norepinephrine, was associated with significant improvement, but the study is limited by the small sample size.[138]

MAOIs. The MAO type B inhibitor selegiline was associated with significant improvement of parkinsonian and depressive symptoms after 3 months.[139] The MAO-A inhibitor has been used for depression in PD.[140] However, MAO-A inhibitors should not be co-prescribed with levodopa because of the potential risk of hypertension, or with SSRIs or TCAs because of the risk of causing a potentially serious serotonin syndrome, characterized by hyperpyrexia, tremor, myoclonus, autonomic dysfunction and mental changes.[141]

SSRIs. A 52-week study compared citalopram with placebo, and found no significant difference between the 2 groups.[142] A randomised study of the SSRI sertraline 50mg/day and the TCA amitriptyline 25 mg/day demonstrated that both treatments significantly improved depression. Sertraline, also significantly improved mobility, activities of daily living, emotions and stigma.[143] Three uncontrolled and open-label small studies found that SSRIs (paroxetine and sertraline) were effective in treating depression in PD, but 3% had worsening of the motor symptoms.[144-146] In contrast, the beneficial effects of fluoxetine on medication-induced dyskinesias and of citalopram on bradykinesia have been noted.[147,148] A treatment algorithm for PD depression includes optimization of L-dopa and addition of dopamine agonist (pramipexole) as a first step followed by addition of an antidepressant as a second step. The SSRI is the first line antidepressant because of better side effect profile and tolerability, while TCA is the last choice because of its side effects especially cognitive dysfunction and cardiac arrhythmia.[149]

In conclusion, depression commonly occurs in patients with neurological disorders and is not

simply reactive emotional response or a feature of these disorders, but a true comorbid condition that significantly affects the quality of life, increases the suicidal rate, and complicates treatment. Because of this impact, comprehensive treatment of people with neurologic disorders requires that their psychiatric manifestations be recognized and their treatment be incorporated into the overall management as early as possible. Treatment plans should be multidimensional and include education, psychotherapeutic interventions, and medications.

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