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Detection and treatment of comorbid depression in people with epilepsy

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ABSTRACT

Background: Depression is one of the most common comorbidities in epilepsy patients. It contributes to lower quality of life, higher suicide and drug overdose risks. In spite of its importance for optimum management of people with epilepsy, major depression often goes underdiagnosed. One of the reasons may be the lack of an established clinical standard for depression screening. In regard to treatment, it is difficult to find a suitable antidepressant for patients who not only use antiepileptic drugs, but are also more prone to experience seizures as a side-effect than the general population. However, non-pharmacological treatment options for major depression can also be offered in such circumstances.

Aim: To select and analyse the newest data available on epilepsy with comorbid depression.

Method: The literature review was conducted using "PubMed'' database, selecting publications on the subject of epidemiology, quality of life, diagnostics and treatment of epilepsy comorbid with depression.

Conclusions: Epilepsy and depression have a bilateral relationship making it a substantial comorbidity to diagnose and to treat. Early screening can be conducted with sufficient accuracy using Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Patient Health Questionnaire (PHQ-9) or Emotional Thermometer (ET7). In epileptic patients major depression can be safely and effectively treated with SSRI's and SNRI's. Moreover, cognitive behavioural therapy (CBT) should also be considered as a mean to improve the quality of life, which is significantly reduced in more than a half of people with epilepsy.

Keywords: depression, epilepsy, major depressive disorder, screening tools, antidepressants.

Introduction

Epilepsy is one of the most common diseases affecting more than 70 million people worldwide (1). Predominately a chronic illness, it puts a heavy burden on healthcare systems, not to mention the uncertainty, mental and physical problems an individual has to deal with. Patients have to endure both the side-effects of treatment and impaired functioning. The effect this illness has on their daily lives includes difficulties at school, troubles finding work and enormous social stigma (2, 3). Correspondingly, patients suffering from epilepsy report significantly worse psychological health, greater cognitive impairment, difficulty participating in activities, reduced quality of health compared to adults without epilepsy diagnosis (4).

Major depressive disorder (MDD) is a debilitating mental illness affecting more than 264 million people worldwide (5). It causes functional impairment and can lead to suicide, the latter being the second leading cause of death in people aged from 15 to 29 worldwide (6). Psychiatric disorders are a common comorbidity in people suffering from epilepsy, ranging from anxiety to depression and bipolar disorder (7).

The link between depression and epilepsy

Major depression is observed to be one of the most frequent comorbidities of epilepsy, and its importance cannot be underestimated. People with epilepsy (PWE) tend to be diagnosed with MDD 3 to 10 times more often compared to the general population (7), making it a substantial issue. Regarding this problem, females are affected more than males (8) In PWE, psychiatric disorders, such as depression, may appear as a self-limiting disease resulting from seizure directly (periictal or postictal psychiatric disturbances), or occur independently in the context of epilepsy itself (interictal psychiatric disorders) (7). However, the relationship between depression and epilepsy is known to be bidirectional (9), meaning that people with depression have a greater risk to develop epilepsy as well (10). The number of seizures can be augmented by depression or vice versa and depressive symptoms can manifest before and after epilepsy diagnosis (11).

There are several theories about the risk factors of depression in epilepsy, but only a couple of them well-established. First is the psychosocial: unemployment, financial stresses, life uncertainty, poor seizure control, increasing burden of disease, stigmatisation and deteriorating psychological health. Second theory is based on neurobiology, such as similar substrates and findings in neuroimaging (10). Concerns about the medication, its perceived adverse effects and seizure-related worries seem to be some of the most important predictors of depression in PWE (12). Moreover, it is important to note that some medications that are used to treat epilepsy may have side effects which may add to development of depression and suicidal thoughts (9).

Major depression often goes underdiagnosed and undertreated in patients with epilepsy (13), sometimes it may even be underestimated (8). It greatly affects any treatment provided and has a major impact on the life quality

in PWE (12). Managing depression can improve seizure control and quality of life (3), therefore we would like to emphasize the importance of early diagnosis and treatment.

Diagnosing depression in people with epilepsy

Epilepsy and depression have been observed to have a bidirectional relationship, warranting the need to screen for depressive symptoms in PWE as early as possible (14, 15). While there are several validated screening tools, no clinical standard has been definitively established and their diagnostic accuracy is subject to debate (16). Most widely used tools are the following: The Neurological Disorders Depression Inventory for Epilepsy, Beck Depression Inventory, Hamilton Rating Scale for Depression, Hospital Anxiety and Depression Scale, Patient Health Questionnaire, and various Emotional Thermometers (16).

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a 6-item questionnaire, validated to screen for depression in PWE in over 13 languages, such as French, German, and Polish (17, 18, 19 ,20). As of early 2020, there is still a need for a translation and adaptation to Lithuanian language. NDDI-E has a median sensitivity (Se) of 81% and specificity (Sp) of 84%, positive predictive value (PPV) of 59%, and negative predictive value (NPV) of 96% (16, 23). It should be noted that although the original recommendation of the optimal cut-off score for the detection of major depressive disorder is > 15, more recent (2018) meta-analysis suggests lowering it to > 13, with estimated Se of 87% and Sp of 80% (17, 23). Overall, NDDI-E is simple to use and takes only a few minutes to complete, making it a relatively reliable and easily applicable assessment tool even in a busy clinical setting (21, 22).

Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory designed as a screening tool to measure the severity of depression (24, 25). The original version has been translated into more than a dozen languages, including Lithuanian (26, 27). For non-psychiatric patients, the mean correlation coefficient between the clinical ratings and the BDI is 0.60 (28, 29). Although the BDI cut point for general medical population is ≥ 13, in PWE it is recommended to use > 16 (Se, 94%; Sp, 90%; PPV, 79%; NPV, 98%). (16, 33) Studies on the concurrent validity with other self-rating scales report moderate to high correlation coefficients with mean coefficients ranging from 0.58 to 0.79 (29). Although sufficiently reliable, the BDI takes up to 10 minutes for the patient to complete and some more time to assess the result, making it a less convenient screening option when time is scarce (28). Another disadvantage of the BDI is that it is copyrighted; a fee must be paid for each copy used (26).

Hamilton Rating Scale for Depression (HAM-D) is a multiple item questionnaire that, in spite of its flaws, is still widely considered to be the golden standard for assessment of depression in various settings (22, 30). It has been translated to most European and a lot of non-European

languages, including Lithuanian (31, 32). When used to detect depression, performance of the HAM-D appears to be generally consistent even at different cut-off points – it has a mean Se of 76%, mean Sp of 91%, mean PPV of 77% and mean NPV of 92% (30). Although when it comes to screening patients with epilepsy specifically, the recommended cut point for the HAM-D is > 16 (Se, 95%; Sp, 76%; PPV, 59%; NPV, 98%) (16, 33). The HAM-D can be used as an adequately reliable screening tool in PWE, however, it takes around 20 minutes for the physician to complete the assessment, making its use problematic in ambulatory care (31). In addition to that, it is important to note that Hamilton himself stated that the HAM-D has been designed specifically to measure the severity of depression in patients already diagnosed with MDD, not as a diagnostic or screening tool (31, 34).

Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment scale comprising of seven questions for anxiety and seven questions for depression, tailored to measure anxiety and depression in general medical population (35). It is available in 115 languages, including Lithuanian (38). Optimal balance between sensitivity and specificity for HADS as a screening instrument is achieved at a cut-off score of > 8, with (means: Se, 77%; Sp, 85%; PPV, 58%; NPV, 95%) (16, 37, 41). However, for PWE the recommended cut point for the HADS can be lowered to 7 (means: Se, 81%; Sp, 86%; PPV, 49%; NPV, 96%) (16, 41). When compared to other commonly used questionnaires for depression, the mean correlation coefficients to HADS were between 0.60 and 0.80, which should be characterized as moderate to high correlation (37). Screening for depression with HADS takes up to 5 minutes, making it a quick and reliable tool, well-suited for a time-poor clinical setting. (35, 46, 37). The main downside is that, although freely available in the past, currently the scale is copyrighted, thus it must be purchased for administration (35, 46).

Patient Health Questionnaire (PHQ-9) is a 9-item self-administered questionnaire to screen for depression based on DSM-IV diagnostic criteria (38). There is also a short version (PHQ-2), which uses only the first two questions of PHQ-9: diminished interest or pleasure and depressed mood (39). It has been translated to over 50 languages, including Lithuanian (40). PHQ-9 has a pooled Se of 92% and Sp of 80% in various medical populations, the most optimal trade-off between sensitivity and specificity at a cut-off score of 11 (Se, 89%; Sp, 89%; PPV and NPV not provided; diagnostic odds ratio, 75.03) (38, 39 ,40). However, in PWE specifically, the best overall balance is noted at a cut-off score of 9 (Se, 83%; Sp, 82%; PPV, 42%; NPV, 97%), although a more recent systematic review suggests to stick with ≥ 10 (16, 43). PHQ-2 is not recommended to use in PWE due to inadequate sensitivity to detect cases, albeit it is still better than nothing (16, 39, 43, 46). Studies on the concurrent validity of both PHQ-2 and PHQ-9 demonstrate moderate to high correlation with other self-assessment measures for MDD (26, 33, 34).Taking only a few minutes to complete and available in public domain in numerous languages, PHQ-9 is convenient and

adequately reliable screening tool in PWE even for a busy clinical practice (16, 26, 33, 34).

Emotional Thermometer (ET) is a visual-analogue self-rating tool, composed of seven pictorial thermometers (each for one of the four predictor domains: distress, anxiety, depression, anger, and three outcome domains: duration of illness, burden, and need for help) (46, 47). The ET7 has been professionally translated into over 15 languages, albeit not yet to Lithuanian (46, 47). As it has been designed as a distress measuring tool among cancer patients, literature on ET7 as a screening tool for depression in general and/or medical populations is practically non-existent (46-52). A few studies have been specific to PWE and demonstrated that the optimal cut-off score for ET7 as a screening tool is ≥ 29 (Se, 85.4; Sp, 79.2; PPV, 48%; NPV, 96%) (16, 50). In 2012, due to it being optimal on its own, DepT has been launched as a stand-alone single-item tool for screening for depression with a cut-off score of ≥ 4 (Se, 80%; Sp, 79%), and it also seems to perform just as well in PWE (47, 48, 50, 51). When compared to other assessment measures, ET7 has also demonstrated moderate to high correlation (46-50). Depression screening with the ET7 takes only a couple of minutes, is sufficiently reliable and it being a visual-analogue tool makes ET7 the most applicable option for patients with low reading levels (16, 50).

An ideal tool to screen for depression in PWE should not only be of optimal sensitivity and specificity, but also convenient to use, brief, validated, easily accessible in various languages and cheap (17, 52). To conclude on the discussion above, we would recommend the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) as the clinician-conducted method of choice and the Patient Health Questionnaire (PHQ-9) for a self-administered assessment (16, 17, 43, 53). PHQ-9 can be considered slightly more specific than NDDI-E, but it requires more of the physician's time (16, 45). Owing to it being the only validated visual screening option, Emotional Thermometer (ET7) can be used to supplement either of the aforementioned tools or as a standalone measure (50, 53). In fact, Drinovac et al. (2015) recommends using enhanced depression screening in epilepsy tool (EDET) that contains both verbal and visual analog scales, which they created by combining NDDI-E and ET (Se, 89%; Sp, 88%; PPV, 61%; NPV, 97%) (54). However, further studies on EDET are needed.

The quality of life

The majority of studies that were performed on people suffering with epilepsy and depression conducted that these two comorbidities significantly decrease life quality of these patients. A study performed in 2019 by Greek scientists has shown that people with epilepsy were not only more susceptible to being diagnosed with depression, but also have a lower quality of life considering their physical health, psychological and social relationships. Being diagnosed with depression and adverse effects of antiepileptic drugs were the factors mainly associated with their low quality of life (55). Moreover, a study that compared cohorts of people, who were diagnosed with epilepsy and depression, and healthy

individuals found that people with these two illnesses are more likely to make a suicide attempt and have a drug overdose related with their suicidal ideation. The results between healthy people and the ones that have been diagnosed only with epilepsy differed only by a small amount. The population of people suffering from epilepsy had a significantly higher incidence rate with such psychiatric conditions as schizophrenia, insomnia, anxiety and alcohol related disorders (56). Concerning that 57,1% of epilepsy patients have a significant reduction in their life quality (57) it is a must to apply certain screening tools to identify it. It was shown that applying such scales as NDDI-E for major depressive disorder, GAD-7 for anxiety, and AEP for antiepileptic drug effects allows having a rapid and reliable screening of life quality in epilepsy patients (58). Therefore, an adequate treatment can be administered.

Pharmacological treatment

Choosing a safe antidepressant medication relies on having a therapeutic effect without provoking any seizures in epileptic patients. Since it was shown that tricyclic antidepressants can induce seizures even in patients without epilepsy (59) this would not be the first line choice in PWE. However, it has been tested that administering SSRI‘s or SNRI‘s in therapeutic doses does not induce seizures in epilepsy patients and may reduce seizure frequency for those who experience it more than 1 time a month. An improvement of psychiatric symptoms was experienced by 73% of participants, although a decrease in seizure frequency was not associated with it (60). Another study that was performed specifically with citalopram, mirtazapine and reboxetine also supports this idea (61). Even though antidepressants seem to be effective, studies have shown that such antiepileptic drugs as carbamazepine increase clearance of antidepressant medication and this often leads to the recurrence of depressive episodes. On the other hand, the clearance of antiepileptic drugs can be inhibited by some of the antidepressants (62). This suggests the idea that it would be ideal to have one medication to treat both epilepsy and depressive symptoms. A prospective multicentered study was performed in order to find if lacosamide would prove to be helpful. Testing scores in both depression and life quality have significantly improved in both 3 month and 6 month measuring periods. People who suffered from moderate depression seemed to benefit the most from this medication. Moreover, a significant decrease of the seizure frequency was observed and it was shown that the improvements on psychiatric symptoms were not associated with a better seizure control (57). Antipsychotic drugs are an area that could be investigated more since there are several case reports of olanzapine 2,5 mg/d being a valuable medication treating both seizures and depression in patients with difficult to treat epilepsy (63). However, larger studies are needed to establish its effectiveness.

Psychotherapy

The study that was performed on people with both refractory mesial temporal lobe epilepsy and comorbid psychogenic nonepileptic seizures proved that cognitive behavioural therapy based psychotherapeutic intervention can be an efficient

way to manage these problems. The duration of treatment was 8 weeks and several measurements took place before and after it. There were significant improvements in quality of life, depressive symptoms and seizure frequency compared to the control group (64). Also the Home Based Self-management and Cognitive Training Changes lives (HOBSCOTCH) program was shown to be effective at improving quality of life in epilepsy patients. It is composed of subjects such as psychoeducation, self-awareness training, compensatory strategies and applying those strategies in daily life. According to the study, the life quality significantly increased, but depression scores did not seem to be significantly different between the intervention and control groups (65). The reason to that might be that selected patients were not diagnosed with depression before applying the intervention. There is only one pilot study conducted that compares treatment with SSRI‘s and psychotherapy. People who were diagnosed both with major depressive disorder and temporal lobe epilepsy were compared after receiving a 12 week long treatment. Both symptoms of depression and quality of life improved after applying either one or another method but no significant differences were found (66). It suggests that more double blind controlled studies with a bigger sample size could be done in order to prove the efficacy of the psychotherapy.

Other treatments

Vagus nerve stimulation has proven to be an effective way of managing both depressive symptoms and seizure frequency in patients with difficult to treat epilepsy. It has been observed that more than 50% of patients who underwent this type of treatment experienced an improvement in their life quality, moreover their scores in depression measuring scales have improved and two thirds of patients experienced at least 50% of seizure frequency reduction (67). Another treatment that is established to be effective at improving depression and life quality of these patients is epileptic surgery. The Hispanic population was followed before and 1 year post surgery while a full neuropsychological evaluation was performed. The number of patients with moderate or severe levels of depression declined from 37,0% to 15,2%, the life quality was shown to be improved in moderate or large amounts (68). Moreover, since it has been demonstrated that electroconvulsive therapy can be used to control seizures in a refractory status epilepticus (69) and is an even more effective antidepressant treatment than pharmacological (60) it can be suggested that it is a valuable option for those who have already tried managing their illnesses with pharmacological and other kinds of therapies.

Conclusion

Depression is one of the most common psychiatric comorbidities in adults with epilepsy (7). Women are affected more than men (8). Epilepsy and depression have a bilateral connection meaning that those who are diagnosed with epilepsy are much more likely to be diagnosed with depression and otherwise (9). We would recommend the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) as the clinician-conducted method of choice and the Patient Health Questionnaire (PHQ-9) for a self-administered

assessment. (16, 17, 43, 54). PHQ-9 can be considered slightly more specific than NDDI-E, but it requires more of the physician's time (16, 45). Owing to it being the only validated visual screening option, Emotional Thermometer (ET7) can be used to supplement either of the aforementioned tools or as a standalone measure (50, 54). More than a half of epilepsy patients have a significant reduction in their quality of life (55, 56, 57) and the factors most associated with it are being diagnosed with depression and experiencing adverse effects from their antiepileptic medication (55). There are many treatment options that can be considered optimal and effective. SSRI's and SNRI's seem to help 73% of the patients with depressive symptoms while not putting them at an increased risk of a seizure (60, 61). Cognitive behavioural psychotherapy sessions seem to be helpful with providing a better life quality for these patients (64, 65). Moreover, there are many other treatment possibilities to consider if these do not help.

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