**ABSTRACT**

**Introduction:** Anxiety disorders represent one of the most frequently encountered comorbidities in patients with epilepsy, affecting quality of life and increasing, morbidity, mortality and healthcare costs. However, they are still underdiagnosed and undertreated.

**Areas covered:** This is a narrative review of the pharmacological treatment of anxiety disorders in adult patients with epilepsy discussing also major issues regarding pathophysiology and diagnosis.

**Expert opinion:** There is a total lack of studies about treatment of anxiety disorders in epilepsy and this is a serious gap in the literature. There is urgent need for treatment and outcome data in order to provide information to patients. Current evidence outside epilepsy focuses on SSRIs and SNRIs with strong evidence especially for the acute and long-term treatment of Generalised Anxiety Disorder and Social Anxiety Disorder. Although it is reasonable to adopt guidelines of treatment outside epilepsy, it is completely unknown whether anxiety disorders in people with epilepsy have the same response and remission rates observed outside epilepsy. Future research strategies for new drug treatments in epilepsy will probably take comorbidities into account. Pregabalin and buspirone represent an interesting starting point for the development of new compounds potentially indicated in both conditions.

**Key words: epilepsy, anxiety disorders, antiepileptic drugs, antidepressant drugs**

1. **INTRODUCTION**

Anxiety symptoms are common in the general population and in the primary and secondary care settings. These symptoms can be mild, transient and without associated impairment. In order to receive a diagnosis of anxiety disorder, patients have to experience a certain number of symptoms for a certain period of time and with associated personal distress and impairment in every day functioning [1]. Internationally adopted classificatory systems identify a number of anxiety disorders with the major ones being generalised anxiety disorder (GAD), panic disorder (PD) with and without agoraphobia, social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD). In addition to them, other clinical entities include specific phobias, separation anxiety disorder and illness anxiety disorder. In the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), DSM-5, OCD is not listed among anxiety disorders anymore, representing a separate category. However, in this paper, OCD will be mentioned among anxiety disorders, given the significant overlap in terms of pathophysiology and treatment.

Mood and anxiety disorders represent one of the most frequently encountered comorbidities among patients with epilepsy [2]. However, data on anxiety disorders are less systematic, as compared to depression, in terms of epidemiology, clinical phenomenology and treatment [3]. In terms of epidemiology, the few published studies suggest a uniformly increased prevalence of all anxiety disorders [3]. In the general population, 12-month prevalence of anxiety disorders ranges from 0.7% of OCD to 6.4% of specific phobias [4] while in epilepsy the 12-month prevalence is reported between 6% and 19.7% [5]. Two US National surveys show that people with self-reported epilepsy are two times more likely to report a diagnosis of anxiety disorder than those without [6,7]. These figures have been replicated by another cross-sectional, population-based study in unselected patients with an established diagnosis of epilepsy and using standardised clinical interviews for the diagnosis of anxiety disorders [8]. Although less established as compared to depression [9], a few preliminary studies are suggesting a bidirectional relationship between epilepsy and anxiety disorders. A US study in veterans older than 65 shows that a previous history of anxiety is significantly more common in those who developed epilepsy as compared to controls [10]. A population-based, case control study in Sweden show that patients hospitalised for anxiety disorders have a 2-time increased risk of developing unprovoked seizures [11]. A cohort study using data from the UK General Practice Research Database shows that the incidence for anxiety disorders is not only higher in people with epilepsy as compared to controls but it is already increased three years prior to the diagnosis of epilepsy [12].

Regarding the role of anxiety disorders on the prognosis of epilepsy, as classically shown for depression, anxiety disorders seem to be an important predictor of quality of life of patients with epilepsy [13,14]. In addition, a number of studies are now pointing out that anxiety disorders are associated with increased side effects of antiepileptic drugs (AEDs) [15], cognitive complaints [16], emergency department admissions [17] and outpatient appointments [18]. Still, anxiety disorders have been associated with increased suicidal risk [19] and poor response to antiepileptic drug (AED) treatment [20,21]. For all these reasons, the lack of systematic data and attention to this topic is surprising. This is narrative review of pharmacological treatments of anxiety disorders in adult patients with epilepsy discussing also major clinical problems in terms of pathophysiology and diagnosis.

1. **NEUROBIOLOGY OF ANXIETY IN EPILEPY**

 In general terms, anxiety is a set of preformed cognitive and behavioural patterns in response to threat or stress and, from an evolutionary perspective, represents a normal adaptive response [22]. The Pavlovian-fear conditioning and fear-potentiated startle response are well known animal models of anxiety and they have been extensively used to study the neurobiology of anxiety, identifying an extended neuroanatomical network which centres on the amygdala and a number of connected structures including the limbic system, the sensory thalami, the orbital and medial prefrontal cortex, the anterior insula, the hypothalamus, and multiple brainstem nuclei [23]. The amygdala is a key structure in the experience of fear and its autonomic and endocrine response (through the output to the hypothalamus). The output to the periaqueductal grey nuclei mediates avoidance behaviour while the hippocampi play a role in the re-experiencing of fear [24,25]. The spontaneous activation of these networks is the major neurobiological hypothesis for anxiety disorders and the reduction of such an excessive output from these neurons represents the main target of anti-anxiety treatments. In this regard, it is interesting to note that such a mechanism has a number of similarities with the excessive outburst typical of epileptic neurons and easily explain why some of the agents used in the treatment of epilepsy are also effective in anxiety and vice versa [26,27].

The neurobiology of anxiety disorders in epilepsy is still understudied. A number of hypotheses have been formulated ranging from psychological to neurobiological and familial (aggregation) theories. Psychological hypotheses focus mainly on the unpredictability of seizures and the potential for social embarrassment associated with them, leading to phobias and avoidance behaviour [27]. The few published neurobiological studies in epilepsy focused on the amygdala. A neuroimaging study in adults with drug-resistant epilepsy and comorbid anxiety disorders reports an enlarged right sided amygdala [28] while a study in children with epilepsy and anxiety disorders identifies a left amygdala enlargement [29]. Studies focusing on familial and genetic factors emphasise the role of parental psychiatric history as a number of family aggregation studies outside epilepsy have shown a close relationship between mood and anxiety disorders in parents and subsequent anxiety disorders in offspring [30,31]. Similar findings have been reported in epilepsy [32,33] but it is still unknown whether this represents a genuine genetic predisposition or it is mediated by social variables like stigma, parental attitudes towards the epilepsy and overprotection.

1. **THE ASSESSMENT OF ANXIETY IN EPILEPSY**

 A number of clinical instruments are used in the assessment of anxiety symptoms outside epilepsy and their development followed that of DSM (**Table 1**). As a consequence, it has never been relevant to identify masked or “atypical” symptoms belonging to psychodynamic theories but to identify specific symptom patterns that could be treated with psychotropic medications. In fact, the majority of these clinical instruments have been developed to assess treatment effects in controlled clinical trial. For all these reasons, the majority of clinical instruments evaluate state anxiety (a set of specific symptoms in response to stimuli) rather than trait anxiety (relatively stable anxiety proneness). State anxiety is obviously highly fluctuating in nature and may change over a very short period of time. In addition, it does not necessarily capture the individual distress and everyday impairment associated with an anxiety disorder per se like avoidance behaviour and social isolation. It is, therefore, evident that clinicians need to become familiar with the main features of major anxiety disorders and cannot entirely rely just on screening instruments.

Among the many clinical instruments, some have been validated in the epilepsy population, namely the Hospital Anxiety and Depression Scale (HADS) and the Generalised Anxiety Disorder-7 (GAD-7). Two studies investigate the psychometric properties of the Anxiety subscale of the HADS in epilepsy [34,35]. While one study shows quite good psychometric properties with a sensitivity of 81.3% and a specificity of 70% [35], the other study reports poor sensitivity, namely 61%, and inadequate area under the curve, suggesting unacceptable reliability [34]. The GAD-7 is a well-known screening instrument for anxiety in primary care. Two studies validate the use of GAD-7 in the epilepsy population and both of them show quite good psychometric properties with good sensitivity and specificity [36,37].

Inconsistencies among studies can be due to a number of reasons, including, as already mentioned, the fluctuating nature of anxiety symptoms themselves, but also the pleomorphic and atypical phenomenology of psychiatric symptoms in epilepsy [38]. For these reasons, a number of authors have tried to develop clinical instruments tailored on people with epilepsy. Among structured interviews, an adapted version of the Structured Clinical Interview for DSM Axis I (SCID-I), named SCID-E, has been suggested [39], and a specific epilepsy questionnaire to be used with the Mini Neuropsychiatric Interview (MINI), called the Epilepsy Addendum for Psychiatric Assessment, has been also developed [40]. However, the relative benefits of these various instruments, in the assessment of generic psychopathology in community-based studies, are the subject of considerable debate.

 In general terms, the phenomenology of psychiatric disorders in epilepsy has been a matter of debate for many years. Although it is established that patients with epilepsy can develop psychiatric disorders which are clinically identical to those of patients without epilepsy, several authors have pointed out that mood disorders in epilepsy can be characterised by atypical features that are poorly reflected by conventional classificatory systems such as DSM and ICD [38,40]. One of the reasons for such atypical features is the number of behavioural manifestations that may occur around the seizure itself. The practicality of classifying psychiatric symptoms according to their temporal relation to seizure occurrence (peri-ictal/para-ictal symptoms vs. interictal symptoms) is well established and it can be of great help in identifying concomitant contributors and in planning therapeutic interventions.

Pre-ictal anxiety is still controversial. It has been reported that up to 30% of patients refer a number of premonitory symptoms preceding their seizures including insomnia and anxiety [41], but pre-ictal psychiatric symptoms, in general, are still matter of debate and their neurobiology is still unclear.

 Ictal fear or ictal panic is very well-known. It has a strong localizing and lateralizing value [42], it is associated with the right mesial temporal lobe structures [43], and some authors suggest a possible association with a poor seizure outcome after epilepsy surgery [44]. In some selected cases, the differential diagnosis between ictal fear and panic attacks can be challenging but a thorough investigation plan including prolonged videoEEG monitoring and a detailed history taking should be able to distinguish between these two conditions quite easily. Recent evidence suggests that ictal fear has also a peculiar neurobiology as compared to anxiety disorders [45].

Post-ictal anxiety is reported by 45% patients and can last variably from a few hours to more than 24 hours [46] but in one third of cases it is reported by people with a pre-existing anxiety disorder and, in this specific subgroup, should be considered as a post-ictal worsening or the exacerbation of the underlying problem rather than a genuine post-ictal manifestation.

1. **THE PHARMACOLOGICAL TREATMENT OF ANXIETY DISORDERS**
	1. **Evidence outside epilepsy**

 It has to be acknowledged that the management of all anxiety disorders involve psychological interventions which represent the first line treatment for all conditions. In patients who are unwilling to engage in psychological treatments or showed no improvement, drug treatment should be offered and this will be discussed in this section. The pharmacological treatment of anxiety disorders is currently based on four drug classes, namely antidepressants, benzodiazepines, AEDs (i.e. pregabalin) and other drugs (i.e. antipsychotics and buspirone) (**Table 2**).

Guidelines of pharmacological treatment presented in this review are based on recommendations from the National Institute of Clinical Excellence [47–50] and the British Association for Psychopharmacology [4].

In general terms, it has to be taken into account that data from randomised controlled trials across a range of anxiety disorders have often shown a high placebo response [4,51], suggesting that assessment and monitoring can play a large part in the overall improvement. It is also established that pharmacological and psychological treatments can have addictive effects in some disorders and a combined approach is often recommended.

 Among antidepressants, all Selective Serotonin Reuptake Inhibitors (SSRIs) are widely considered first-line treatment for all anxiety disorders as they show to be effective in both short-term and long-term treatment and they are generally well-tolerated [4]. The Serotonin Noradrenalin Reuptake Inhibitors (SNRIs) duloxetine and venlafaxine have proven efficacy in the short-term and long-term treatment of GAD [51] while evidence on panic disorder is currently low [52]. Tricyclic antidepressants (TCA) are effective in some anxiety disorders, like OCD, and should be considered only in patients who did not respond or tolerate SSRIs or SNRIs, given the side effect burden and the potential for pharmacokinetic interactions [4]. TCAs should be avoided in patients at high suicidal risk due to their potential fatal toxicity in overdose [53]. Among other antidepressants, moclobemide, a Reversible Inhibitor of Monoamine Oxidase A (RIMA), has some evidence in SAD [54] and panic disorder [55]; agomelatine, acting on melatonin receptors, has shown some efficacy in the acute and long-term treatment of GAD [56] while the evidence on mirtazapine is inconsistent [4]. The multimodal agent Vortioxetine showed some evidence in severe GAD but additional data are needed [57] (**Table 3**).

 Benzodiazepines (BDZ) are very well-known anxiolytics and their efficacy has been shown in panic disorder, GAD and SAD [4,51]. However, BDZ are burdened by a number of limitations including troublesome sedation, cognitive problems, tolerance and dependence. It has been suggested that BDZ should be reserved to patients who failed at least three previous treatments (e.g. SSRIs, SNRIs and psychological treatments) but even in such a case they should be carefully used [4].

 A number of AEDs have shown some effect in anxiety disorders [26] but pregabalin is the only one currently licensed. Pregabalin has shown to be effective in the acute and long-term treatment of GAD [51] and SAD [26], and for the treatment of mild to moderate depressive symptoms in patients with GAD [58].

 Among other drugs, antipsychotics can be also prescribed in patients with anxiety disorders but available evidence supports the use of antipsychotics only for the augmentation of SSRIs in patients with OCD and the use of quetiapine for the acute and long-term treatment of GAD [4,51].

Buspirone is a 5HT1A receptor agonist and it is a well-known antianxiety drug with very strong evidence for the acute treatment of GAD [59]. It has also shown to be effective for the treatment of depression either as monotherapy [60] or for the augmentation of SSRIs in depression [61].

* 1. **Evidence in epilepsy**

 The lack of any evidence-based data for the treatment of anxiety disorders in epilepsy is quite striking. There are no published controlled trials and there is a single open study on the use of a homeopathic remedy [62] but no other studies. For this reason the Internal League Against Epilepsy has suggested a number of recommendations based on current guidelines adopted outside epilepsy [63,64]. Considering that pregabalin is an already licensed AED for the treatment of focal epilepsies, given the existing evidence in GAD and SAD, it seems reasonable to consider this compound first line treatment in patients with epilepsy and GAD or SAD. Clobazam is also a well-known agent for the treatment of both epilepsy and anxiety [65]. However, data on anxiety are not as robust as for PGB and, as already mentioned in the previous section, BDZ are burdened by a number of limitations and should be carefully used. Regarding other medications, buspirone is of particular interest. The US National Institute of Neurological Disorders and Stroke has sponsored a randomised, double-blind, placebo-controlled, cross-over Phase II study of buspirone for the adjunctive treatment of seizures in people with focal epilepsy (NCT01496612). Results are not currently available. The rational for the use of buspirone in epilepsy is based on data from animal models and human positron emission tomography (PET) imaging studies showing a role for 5HT1A receptors in the pathophysiology of epilepsy [66]. It is clearly evident that further studies on this compound would be of great interest.

 Even if it may be considered reasonable to adopt guidelines of treatment used outside epilepsy, it is still unknown whether people with epilepsy present with similar remission and response rates for the anxiety disorder and whether specific epilepsy syndromes may be associated with difference response rates. In addition, it is important to take into account individual needs of people with epilepsy, including interactions and risk of seizure relapse.

* 1. **Drug-interactions and seizure risk**

 It is established that first generation of AEDs like carbamazepine (CBZ), phenytoin (PHT) and barbiturates are powerful inducers of drug-metabolizing enzymes including the CYP and the UGT systems while valproate (VPA) is a broad spectrum enzyme inhibitor [67][68]. The CYP and UGT systems contribute to the metabolism of all antidepressants and, for this reason all first generation AEDs may have interactions with antidepressants. CBZ, PHT and barbiturates seem to reduce the plasma levels of SSRIs and SNRIs by at least 25% but whether this is clinically relevant depends on the individual patient [67][68]. Studies on VPA are limited but it seems that there are no clinically relevant pharmacokinetic interactions with SSRIs or SSRIs [67][68]. As far as other antidepressants, TCAs have a complex metabolism mediated by CYP and UGS systems and they represent complex drugs to be used in polytherapy especially with first generation AEDs. For this reason, clinical monitoring and dose adjustment according to clinical response are always recommended.

Compared to first-generation compounds, second and third generation AEDs have a better pharmacokinetic profile with a low risk for interactions. Oxcarbazepine and topiramate are the only ones which may have weak inducing properties at high doses but systematic studies on the clinical relevance of such an effect are lacking.

 Neurologists are often concerned by the potential risk of seizures with antidepressants. However, this was based on an *a priori* assumption rather than on clinical evidence [67]. The issue of drug-related seizures is quite complex and it does not involve only psychotropic medications as it has been described with a number of other drugs [69]. In general terms, multiple factors have to be taken into account and studies in animal models suggest that serotonin potentiation may even be anticonvulsant [70]. Among all antidepressants, a clear association with seizures has been established only for maprotiline, high doses of clomipramine and amitriptyline (>200mg), high doses of bupropion in the immediate release formulation (>450 mg) [67]. For all other antidepressants, there is no clear evidence of an increased risk of seizures. A systematic review of data from placebo-controlled trials with psychotropic drugs, submitted to the United States Federal Drug Administration (FDA), shows that that the frequency of seizures is for SSRIs is even lower than placebo [71]. In addition, if we take into account that patients with depression or anxiety disorders have an increased risk of seizures, as described at the beginning of this paper, the reported prevalence of seizures during treatment with SSRIs is even lower than the expected one, suggesting SSRIs reduce the risk of seizures [67]. It is anyway important to bear in mind that current knowledge on seizure prevalence during antidepressant drug treatment is based on psychiatric populations and it is still unknown whether these data can be transferred to patients with epilepsy and whether some epileptic syndromes are more at risk than others.

* 1. **The pharmacological treatment of anxiety in special populations**

 Data on the treatment of anxiety disorders in special population is limited even outside epilepsy. Regarding children, the use of antidepressants is still controversial. Data from controlled trials clearly indicate that SSRIs are effective in children and adolescents with GAD, SAD and separation anxiety [72] but the relative efficacy of pharmacological against psychological treatment is not established as well as the long term effect. Clinicians need also to keep in mind that there is evidence of an increased risk of suicide-related outcomes in children and adolescents treated with antidepressant medications, especially SSRIs [73]. In epilepsy the issue is even more complex as anxiety disorders are often associated with other problems such as attention deficit hyperactivity disorder (ADHD) or intellectual disabilities [74]. For all these reasons, further studies in epilepsy are urgently needed.

 Data on the treatment of anxiety disorders in patients over 65 is also limited even outside epilepsy. Data from epidemiological studies seem to suggest that anxiety disorders are less common in elderly patients as compared to young adults [75]. However, the increased incident rates of epilepsy among elderly patients is very well known and for this reason the possibility of such a comorbidity is increased [76]. In general terms, international guidelines suggest special attention to cardiac side effects of antidepressants and careful attention to drug-interactions [4]. For this reason, TCAs should be avoided and, in the case of SSRIs, the possibility of hyponatraemia or QT prolongation should be always considered, although a large pharmacoepidemiological study show no evidence of increased risk for arrhythmias or increased mortality with citalopram [77].

 Finally, the use of antidepressants during pregnancy is an important element to consider especially because women with epilepsy are already exposed to the risks connected to the AED treatment. Anxiety disorders are not uncommon during pregnancy and in the post-partum period. A systematic review suggests that antidepressants are associated with an increased risk of spontaneous abortions, preterm delivery, stillbirths, respiratory distress, endocrine and metabolic problems [78]. The overall balance between pharmacological and psychological treatments should be carefully considered in individual cases.

1. **CONCLUSIONS**

 Anxiety disorders are common in epilepsy but are still underdiagnosed and undertreated. However, anxiety disorders can significantly affect quality of life of people with epilepsy and are associated with increased mortality and morbidity. Current guidelines of treatment outside epilepsy focus on SSRIs and SNRIs with strong evidence especially for the acute and long-term treatment of GAD and SAD. TCAs should be considered only in patients who failed at least three different treatment options and, in the case of epilepsy, should be managed in tertiary centres.

1. **EXPERT OPINION (500-1000)**

 Despite the high prevalence in the general population, and the preliminary findings suggesting even high rates in epilepsy, anxiety disorders are still under-investigated. As a consequence, they are substantially under-recognised and under-treated. This may be due to a number of reasons including the general attitude of neurologists in considering anxiety in epilepsy as a natural consequence of having unpredictable seizures or the social embarrassment associated with them, the lack of training of neurologists and the lack of time in very busy clinics. However, anxiety disorders may be under-recognised even by specialists as anxiety disorders have high comorbidity rates with depression which may ultimately mask anxiety symptoms. It is, thus, evident that systematic studies are needed in order to clarify the epidemiology and clinical features of anxiety disorders in epilepsy.

The aim of future research should be to increase awareness of clinicians on anxiety disorders in people with epilepsy and to develop clinical pathways for screening and management. Among available clinical instruments, the GAD-7 has already shown very good psychometric properties in epilepsy, it is already very well-known in the primary care setting and it is user-friendly and time-effective. For all these reasons, the GAD-7 represents a valuable screening instrument in the epilepsy population. However, the GAD-7 focuses on GAD symptoms and the validity of this instrument in other conditions such as PD or SAD is not optimal even outside epilepsy. It is, therefore, evident that neurologists need to become familiar anyway with the basics of all major anxiety disorders in order to be able to identify red flags.

In terms of treatment, there is a total lack of studies in epilepsy, even open label studies and case series, and this is a serious gap in the literature. There is urgent need for treatment and outcome data in order to provide meaningful information to patients and their relatives. Although it is reasonable to adopt guidelines of treatment outside epilepsy, it is completely unknown whether anxiety disorders in people with epilepsy have the same response and remission rates observed outside epilepsy.

Finally, future research strategies for new drug treatments in epilepsy will probably take comorbidities into account. Pregabalin and buspirone represent an interesting starting point for the development of new compounds able to address multiple clinical problems at the same time. New research on the relationship between the neurobiology of epilepsy and that of anxiety disorders will be able to drive pharmacology research on new unexplored mechanisms of action for the development of new treatments.

1. **ARTICLE HIGHLIGHTS**
* Despite being highly frequent, anxiety disorders are still under-investigated and, as a consequence, under-diagnosed and under-treated in adults with epilepsy.
* SSRIs represent first line treatment for the pharmacological management of all anxiety disorders outside epilepsy
* There is no supporting evidence that SSRIs are associated with an increased risk of seizures
* Data on response and remission rates of anxiety disorders in epilepsy are urgently needed
* Pregabalin is the only antiepileptic drug currently licensed for the treatment of anxiety and epilepsy but there are no data about the effect on comorbid anxiety disorders in epilepsy
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**Table 1. Clinical instruments commonly used for the assessment of anxiety symptoms and disorders.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Rating Scale** | **Exploring area** | **Evaluation** | **n° items** |
| **Agoraphobia Rating Scale - ARS** | Agoraphobia | Interview | 12 |
| **Agoraphobic Cognitions Questionnaire – ACQ** | Agoraphobia | Self | 15 |
| **Anxiety Sensitivity Index - ASI** | Panic attack | Self | 16 |
| **Anxiety Status Inventory – ASI** | Anxiety-state | interview | 20 |
| **Audience Anxiousness Scale - AAS** | Social phobia | Self | 12 |
| **Beck Anxiety Inventory – BAI** | Anxiety-state | Self | 21 |
| **Body Sensations Questionnaire – BSQ** | Agoraphobia | Self | 18 |
| **Brief Social Phobia Scale - BSPS** | Social phobia | Interview | 11 |
| **Clinical Anxiety Scale – CAS** | Anxiety-state | interview | 6 (+1) |
| **Clinical Anxiety Scale – CAS** | Anxiety-state | Self | 25 |
| **Cognitive-Somatic Anxiety****Questionnaire – CSAQ** | Anxiety-trait | Self | 14 |
| **Covi Anxiety Rating Scale – CARS** | Anxiety-state | Self | 3 |
| **Fear of Negative Evaluation Scale – FNE** | Social phobia | Self | 30 |
| **Fear Questionnaire – FQ** | Simple phobia | Self | 24 |
| **Fear Survey Schedule-II - FSS-II** | Simple phobia | Self | 51 |
| **Fear Survey Schedule-II - FSS-II** | Simple phobia | Self | 51 |
| **Generalized Anxiety Disorder – 7 GAD-7** | Generalized anxiety disorder | Self | 7 |
| **Hamilton Rating Scale for Anxiety - HRSA or HAM-A** | Anxiety-state | interview | 14 |
| **Interaction Anxiousness Scale – IAS** | Social phobia | Self | 15 |
| **Liebowitz Social Phobia Scale – LSPS** | Social phobia | Interview | 24 |
| **Manifest Anxiety Scale – MAS** | Anxiety-trait | Self | 50/20 |
| **Marks-Sheehan Phobia Scale – MSPS** | Simple phobia | Self | 16 |
| **Mobility Inventory for Agoraphobia – MIA** | Agoraphobia | Self | 27 |
| **Panic Attack and Anticipatory Anxiety Scale – PAAAS** | Panic attack | Interview | 18 |
| **Panic Attack Cognitions Questionnaire – PACQ** | Panic attack | Self | 23 |
| **Schalling Anxiety Rating Scale - SARS** | Anxiety-state | interview | 10 |
| **Self-Rating Anxiety Scale – SAS** | Anxiety-state | Self | 20 |
| **Sheehan Clinician Rated****Anxiety Scale – SCRAS** | Anxiety-state | interview | 35 |
| **Sheehan Patient Rated****Anxiety Scale – SPRAS** | Anxiety-state | Self | 35 + 11 |
| **Social Avoidance and Distress Scale - SAD** | Social phobia | Self | 28 |
| **Social Avoidance and Distress Scale - SAD** | Social phobia | Self | 28 |
| **Social Interaction Self-Statement Test – SISST** | Social phobia | Self | 30 |
| **Somatic, Cognitive, Behavioral****Anxiety Inventory - SCBAI** | Anxiety-state | Self | 36 |
| **STAI (Form Y) S-Anxiety Scale** | Anxiety-state | Self | 20 |
| **STAI (Form Y) T-Anxiety Scale** | Anxiety-trait | Self | 20 |
| **Wang Anxiety Scale - WAS** | Anxiety-state | interview | 12 |
| **Yale-Brown Obsessive Compulsive Scale (Y-BOCS)** | Obsessive Compulsive Disorder | Checklist/Interview | 19 |

**Table 2. Drug classes used in the treatment of anxiety disorders.**

|  |  |
| --- | --- |
| **Benzodiazepines** | ClonazepamBromazepamLorazepamAlprazolamTemazepam |
| **Antidepressants** | **Selective Serotonin Reuptake Inhibitors (SSRIs)**Citalopram Sertraline Fluoxetine FluvoxamineParoxetineEscitalopram**Selective Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)**VenlafaxineDuloxetine**Tricyclic Antidepressants (TCAs)**ImipramineClomipramine**Other antidepressants**Moclobemide PhenelzineAgomelatineMirtazapineTrazodoneVortioxetine |
| **Antiepileptic drugs** | PregabalinGabapentinValproate |
| **Other drugs** | **Antipsychotics**QuetiapineOlanzapine**Azapirones**Buspirone**Beta-blockers**Propranolol |

**Table 3. Guidelines for pharmacological treatment of anxiety disorders outside epilepsy.**

|  |  |  |
| --- | --- | --- |
|  | **NICE [46-49]** | **BAP [4]** |
| **Generalized Anxiety Disorder** | 1st: Sertraline2nd: Another SSRI3rd: SNRI (Venlafaxine)4th: Pregabalin | 1st: SSRIs (citalopram, escitalopram, paroxetine, sertraline)2nd: SNRIs or Pregabalin |
| **Panic attack disorder** | 1st: SSRIs2nd: TCA (imipramine or clomipramine)3rd: Other antidepressant class | 1st: all SSRIs2nd: TCAs (clomipramine, desipramine, imipramine, lofepramine)3rd: Other antidepressants (venlafaxine, reboxetine)4th: Benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam),5th: Anticonvulsants (gabapentin, sodium valproate) |
| **Social anxiety disorder** | 1st: SSRIs (Escitalopram or sertraline)2nd: Other SSRIs (fluvoxamine or paroxetine) or SNRIs (venlafaxine)3rd: MAO (phenelzine or moclobemide) | 1st: most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)2nd: venlafaxine3rd: Other antidepressants (phenelzine, moclobemide, some benzodiazepines)4th: Benzodiazepines (bromazepam, clonazepam) or antiepileptic drugs (gabapentin, pregabalin) or antipsychotics (olanzapine) |
| **Post-traumatic stress disorder** | 1st: Paroxetine or Mirtazapine2nd: Amitriptyline or Phenelzine3rd: Another antidepressant class or olanzapine | 1st: SSRIs (Paroxetine, sertraline)2nd: SNRIs (Venlafaxine) |
| **Obsessive compulsive disorder** | 1st: all SSRIs2nd: Other SSRI or clomipramine3rd: Citalopram + Clomipramine or SSRI + antipsychotic or SSRI + buspirone | 1st: SSRIs2nd: Clomipramine3rd: SSRIs + clomipramine |

NICE: National Institute of Clinical Excellence; BAP: British Association of Psychopharmacology