Pharmacological Treatment of Generalised Anxiety Disorder: Current Practice and Future Directions

Title Page

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Abstract

Introduction: Generalised Anxiety Disorder (GAD) is a common psychiatric condition, characterised by the presence of general apprehensiveness and excessive worry. Current management consists of a range of pharmacological and psychological treatments. However, many patients do not respond to first line pharmacological treatments and novel anxiolytic drugs are being developed.

Areas covered: In this review, we first discuss the diagnostic criteria and epidemiology of GAD. The effective pharmacological treatments for GAD and their tolerability are addressed. Current consensus guidelines for treatment of GAD are discussed, and maintenance treatment, the management of treatment resistance, and specific management of older adults and children/adolescents are considered. Finally, novel anxiolytics under development are discussed, with a focus on those which have entered clinical trials.

Expert opinion: A range of effective treatments for GAD are available, particularly duloxetine, escitalopram, pregabalin, quetiapine, and venlafaxine. There is a limited evidence base to support the further pharmacological management of patients with GAD who have not responded to initial treatment. Although many novel anxiolytics have progressed to clinical trials, translation from animal models has been mostly unsuccessful. However, the potential of several compounds including certain psychedelics, ketamine, oxytocin, and agents modulating the orexin, endocannabinoid, and immune systems merits further study.

Article Highlights

* Generalised Anxiety Disorder (GAD) is a psychiatric condition, characterised by the presence of general apprehensiveness and excessive worry.
* A range of pharmacological treatments are available for GAD, with greatest evidence for the efficacy of quetiapine, duloxetine, pregabalin, venlafaxine and escitalopram.
* Although effective, benzodiazepines, paroxetine and quetiapine are associated with poorer tolerability in the treatment of GAD.
* Current consensus treatment guidelines recommend prescription of a selective serotonin reuptake inhibitor (SSRI) as a first line pharmacological approach, with serotonin-noradrenaline reuptake inhibitors (SNRIs) or pregabalin suggested if SSRIs are not tolerated or unsuitable.
* A range of novel anxiolytics are currently under development, including modulators of the serotonergic, GABAergic and glutamatergic neurotransmitters systems, several neuropeptide systems, and the immune system.
* Several failures of novel anxiolytics have occurred in recent clinical trials, including two α2/α3-GABAA receptor positive allosteric modulators (AZD7325 and PF-06372865), a NK1R antagonist, a CRF1 receptor antagonist and simvastatin.
* Early phase trials show promise for an anxiolytic effect of the psychedelic psilocybin, and further studies are merited to evaluate the full potential of several other agents including ketamine, oxytocin, and modulators of the orexin, endocannabinoid, and immune systems.

Keywords

* Generalised Anxiety Disorder
* GAD
* Novel anxiolytics
* Pharmacological Treatment
* Pharmacotherapy

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The authors are planning to initiate a study investigating the anxiolytic effect of an orexin receptor antagonist in healthy volunteers. In February 2023, an application for complete funding of this study and provision of an orexin receptor antagonist (daridorexant) was requested from Idorsia Pharmaceuticals Ltd, through their Investigator Sponsored Study (ISS) programme. At time of submission, no decision had been made.

DSB has acted as an advisor to Idorsia Pharmaceuticals Ltd (no honorarium sought or paid) and is a Medical Patron of Anxiety UK. He is current President of the British Association for Psychopharmacology and Editor-in-Chief of *Human Psychopharmacology*.

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1. Introduction

Generalised Anxiety Disorder (GAD) is a common psychiatric condition and is one of a small number of anxiety disorders recognised in modern classification systems. The concept of GAD developed from earlier concepts of “neurasthenia” and “anxiety neurosis” introduced in the late 19th and early 20th century [1]. GAD was first described and differentiated from panic disorder (PD) in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 [2]. GAD was first included as a distinct anxiety disorder in the 10th edition of the International Classification of Diseases (ICD-10) in 1994 [3]. The most recent versions of these classification systems (the 2013 DSM-5 [4] and the 2022 ICD-11 [5]) both retain the diagnosis of GAD.

Both classification systems describe a similar range of symptoms [4,5]. The DSM-5 emphasises the presence of excessive anxiety and worry, which is difficult to control. Additional associated symptoms include restlessness, muscle tension, difficulties in concentration, the subjective feeling of one’s mind going blank, irritability and sleep disturbance. The ICD-11 highlights the presence of general apprehensiveness (or “free-floating anxiety”) or excessive worry of negative events occurring in several different aspects of everyday life. Additional associated symptoms include restlessness, muscle tension, sympathetic autonomic overactivity, difficulties in concentration, irritability, and sleep disturbance. Both systems require symptoms to be present for more days than not for at least 6 months (DSM-5) or several months (ICD-11), and to result in some degree of functional impairment.

The prevalence of GAD has been assessed in a range of epidemiological studies, with a focus on the United States (US) and Europe. The US-wide National Comorbidity Study- Replication (NCS-R) conducted between 2001 and 2003 identified a 12-month prevalence of 2.9%, and a lifetime prevalence of 6.2% [6]. A systematic review of European epidemiological studies which included 12 studies in GAD, estimated the median 12-month prevalence at 1.7% (with a range from 0.2% to 4.3% in the included studies) [7]. A cross-sectional study conducted across 26 countries (including high, medium and low-income countries) in 2015/2016 identified a similar 12-month prevalence of 1.8% and a lifetime prevalence of 3.7% [8]. Substantial differences in prevalence were seen, with a 12-month prevalence of 2.3%, 1.6% and 0.9% in high, medium, and low-income countries respectively. The global prevalence of anxiety disorders has been estimated to have risen markedly during the SARS-CoV-2 pandemic with an estimated 76.2 million additional cases of anxiety disorders in 2020 [9]. However, the proportion of these accounted for specifically by GAD is unclear.

Cohort studies have identified a number of aetiological factors associated with the development of GAD, although these studies are predominantly based on US or Western European populations [10]. A parental history of GAD, depression or any psychiatric disorder, female gender, the personality dimension of ‘neuroticism’, stressful life events during childhood and reduced economic resources have all been identified as potential aetiological factors [10]. Compared to other psychiatric disorders the onset of GAD is relatively later in life, usual developing in early adulthood or middle age. A 2022 meta-analysis identified a median age of onset at 32 years, with a further 25% of cases having an onset beyond 42 years [11]. There is some evidence to suggest an earlier age of onset in high-income countries [8]. The longitudinal persistence of GAD is substantial and is associated with an earlier age of onset, lower education levels, low family income and a lack of employment outside the home [8].

Several studies have investigated the neurobiological basis of GAD, including the role of particular neurotransmitters, by measuring concentrations of their metabolic breakdown products. Relative to healthy controls, GAD is associated with increased serum levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylgycol; and a blunted response to clonidine treatment which is suggestive of increased α2-adrenocopter sensitivity [12,13]. Urinary concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid are positively correlated with somatic anxiety symptoms in patients with GAD [14]. Neuroimaging studies in GAD have identified structural and functional differences relative to healthy controls, although these are not noted consistently [15]. Common findings include increased amygdalar and decreased hippocampal grey matter volume, increased connectivity between the amygdala and prefrontal cortex, and increased amygdala activation in response to threatening stimuli [15].

The majority of patients with GAD have additional psychiatric comorbidities, most commonly major depressive disorder (MDD) in 52.6% of lifetime cases of GAD, specific phobia in 25.6%, social phobia in 26.1% and substance misuse disorder in 22.5% [8]. Across all physical and psychiatric illnesses, anxiety disorders are the 6th leading cause of disability globally (as measured in years lived with disability) [16]. A systematic review of the morbidity associated specifically with GAD, noted that in US and European studies, GAD was associated with reduced quality of life, role functioning, and increased number of disability days taken each year [17]. The associated disability seen in GAD was on a equivalent level to that seen in MDD [17]. Perhaps unsurprisingly, the addition of co-morbid MDD in patients with GAD is associated with a greater level of disability than that seen in isolated (i.e. non-comorbid) GAD [8,17].

2. Current pharmacological treatment options in generalised anxiety disorder

In this section, we discuss the current classes of medications with an evidence base for efficacy in the treatment of patients with GAD, based on individual randomised controlled trials (RCTs) and meta-analyses of such trials. In the subsequent section, we discuss the place of different medication classes based on current guidelines.

2.1 Overview of pharmacological treatment for GAD.

A recent 2019 systematic review and network meta-analysis identified RCTs in adult patients with GAD in an outpatient setting [18]. A total of 89 studies were identified, published between 1994 and 2017, with the primary outcomes of interest being change in Hamilton Anxiety Scale (HAM-A) score and tolerability (as measured by trial dropout rate). The authors identified trials with 22 different medications, including the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, paroxetine and sertraline, the serotonin-noradrenaline reuptake inhibitors (SNRIs) duloxetine and venlafaxine, the tricyclic antidepressants (TCA) imipramine, maprotiline, and opipramol, the serotonin-modulating antidepressant agomelatine, mirtazapine, vilazodone and vortioxetine, the noradrenaline-dopamine reuptake inhibitor (NDRI) bupropion, the azapirone buspirone, the gabapentinoid pregabalin, the antihistamine hydroxyzine, the anticonvulsant tiagabine, the second generation antipsychotic quetiapine, a number of benzodiazepines (alprazolam, bromazepam, diazepam and lorazepam) and the pyrazolopyrimidine ocinaplon.

Most medications were more effective than placebo, with only the three included TCAs, tiagabine, vilazodone and vortioxetine showing no overall difference in HAM-A scores. The largest differences in HAM-A score *vs.* placebo were noted for quetiapine (3.60 points), duloxetine (3.13 points), pregabalin (2.79 points), venlafaxine (2.69 points) and escitalopram (2.40 points). The HAM-A has a total score varying between a minimum of 0 and a maximum of 56 points [19]. There is no clear consensus in the literature on which HAM-A score difference should be considered the ‘minimum clinically important difference’ (MCID). Most medications had no worse tolerability to placebo, with notable exceptions being benzodiazepines, paroxetine, quetiapine, tiagabine and vilazodone. Of these, quetiapine was associated with the highest trial drop out (odds ratio: 1.44 of dropping out *vs.* placebo). The available data on tolerability for many agents was limited, and with wide confidence intervals, which impairs the ability to confidently determine their tolerance *vs.* placebo. However, this was not the case for duloxetine, escitalopram, pregabalin, venlafaxine and vortioxetine.

In summary, the available RCT evidence in adults with GAD provides good support for the particular efficacy and tolerability of duloxetine, escitalopram, pregabalin, and venlafaxine. Although quetiapine shows the greatest efficacy of all agents, it is also associated with the worst tolerability. Limitations noted in the review include the relatively short length of RCTs, with a median follow-up of only 8 weeks. In addition, the focus on trial drop-out rate as a proxy outcome for tolerability, does not consider the adverse effects which patients may experience without completely stopping treatment.

2.2 Selective serotonin reuptake inhibitors (SSRIs)

Evidence from RCTs supports the efficacy of citalopram, escitalopram, fluoxetine, paroxetine, and sertraline compared to placebo. Paroxetine and escitalopram have the greatest number of RCTs, with 17 and 13 trials respectively. SSRIs are widely prescribed in psychiatric practice as a first line pharmacological treatment for major depressive disorder (MDD), panic disorder, social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder [20,21]. SSRIs selectively inhibit the serotonin transporter (SERT), increasing extracellular concentrations of serotonin. They are relatively safe in overdose and lack the monitoring requirements often needed with other psychotropic medications [22]. Common adverse effects of SSRIs include gastrointestinal effects (nausea, vomiting and changes in bowel habit), sedation, sexual dysfunction and increased risk of bleeding [22]. Gastrointestinal effects likely stem from 5-HT3 stimulation and sexual dysfunction from post-synaptic 5-HT2A stimulation, while the increased bleeding risk results from impaired platelet-mediated haemostasis [23,24] Anxiety symptoms may increase during the first 2 weeks of treatment. Citalopram and escitalopram are also associated with a dose-dependent effect on QT prolongation [25]. Paroxetine has an additional anticholinergic action with associated adverse effects, which may account for the higher dropout rates from RCTs [18]. As with other antidepressant classes, SSRIs are associated with discontinuation/withdrawal symptoms when treatment is stopped, which are severe in a minority of patients [26]. The discontinuation/withdrawal syndrome is generally more prevalent and severe in antidepressants with a shorter half-life, such as paroxetine [26].

2.3 Serotonin-noradrenaline reuptake inhibitors (SNRIs)

Two SNRIs, venlafaxine and duloxetine, are also widely used in psychiatric practice. SNRIs inhibit both SERT and the noradrenaline transporter (NET), increasing extracellular concentrations of serotonin and noradrenaline. There is RCT evidence to support the relatively good efficacy of both agents, alongside generally good tolerability [18]. The adverse effect profile of both agents is broadly similar to SSRIs. Additional adverse effects seen are related to the increased noradrenergic stimulation: principally dry mouth, increased sweating, urinary retention, blurred vision, and constipation [22]. Both are also associated with dose-dependent increases in blood pressure (more so for venlafaxine) [22]. Venlafaxine has a relatively short half-life, and is associated with a more marked discontinuation/withdrawal syndrome [26].

2.4 Tricyclic and related antidepressants (TCAs)

Although TCAs have evidence for efficacy in MDD and in other anxiety disorders and OCD, there is relatively little evidence to support their use in GAD. TCAs act primarily through SERT and NET inhibition, increasing extracellular concentrations of serotonin and noradrenaline. However, different TCAs inhibit the two transporters to differing degrees. Many TCAs have additional antagonism at α1-adrenoceptors, 5-HT2A and 5-HT2C receptors, H1 receptors and muscarinic acetylcholine receptors. Small sample size RCTs of imipramine and maprotiline, and two RCTs of opipramol (a sigma receptor agonist) did not demonstrate efficacy [18]. Given the lack of efficacy, we do not consider the adverse effect profile of these agents further in this review.

2.5 Additional serotonin-modulating antidepressants

There is evidence to support the efficacy of agomelatine (2 RCTs) and mirtazapine (10 RCTs) in the treatment of GAD, although all RCTs with mirtazapine were conducted and published in China [18]. Agomelatine exerts agonist effects at melatonin 1 and 2 receptors and antagonism at 5-HT2C receptors [27]. It is relatively well tolerated but associated adverse effects include nausea, dizziness, sedation (likely secondary to melatonin agonism), gastrointestinal upset and, rarely, abnormal liver function tests and hepatotoxicity (necessitating regular liver function test monitoring throughout treatment) [27]. Mirtazapine exerts antagonist effects across multiple receptor types (including α2-adrenergic, 5-HT2, 5-HT3 and H1 receptors) [28]. The principal adverse effects of mirtazapine are weight gain and sedation (secondary to H1 receptor antagonism), although the latter appears to be less marked at higher treatment doses [28]. Similar support was not found for the newer serotonin-modulating antidepressants vilazodone and vortioxetine [18]. Both vilazodone and vortioxetine inhibit SERT with additional effects on serotonin receptors, with vilazodone demonstrating 5-HT1A partial agonism and vortioxetine demonstrating 5-HT1A full agonism, 5-HT1B partial agonism and 5-HT1D, 5-HT3 and 5-HT7 antagonism [29,30].

2.6 Noradrenaline-dopamine reuptake inhibitors (NDRI)

The only NDRI widely used in psychiatric practice is bupropion, either as an adjunct for smoking cessation or as an augmentation strategy for patients with treatment-resistant depression [20]. Bupropion inhibits both NET and the dopamine transporter (DAT), increasing extracellular concentrations of both neurotransmitters. Two small RCTs support the efficacy of bupropion in GAD [18]. Principal adverse effects include dry mouth, insomnia, increased anxiety, gastro-intestinal upset, sweating and hypertension and are thought primarily to result from increased noradrenergic stimulation. [31]. Higher doses are associated with a reduced seizure threshold (hence use in patients with epilepsy is contra-indicated) and appetite suppression [31].

2.7 Azapirones

Azapirones act as anxiolytics through 5-HT1A partial agonism. The azapirone buspirone is used relatively widely in psychiatric practice, with another azapirone tandospirone used in some Asian countries [32]. RCT evidence supports the efficacy of buspirone in the short-term treatment of GAD [18]. It has a short half-life, necessitating multiple daily dosing. Adverse effects noted in clinical trials include nausea, dizziness, headaches and rarely akathisia [33]. The basis of these adverse effects has not been widely studied.

2.8 Gabapentinoids

Gabapentinoids, such as gabapentin and pregabalin, are derivatives of gamma-aminobutyric acid (GABA) and demonstrate a high affinity for the α2δ subunit of voltage-gated calcium channels, disrupting their function. Gabapentinoids are widely used in clinical practice, due to their analgesic, anticonvulsant, and anxiolytic effects. Pregabalin shows high affinity for P/Q type voltage-gated calcium channels and appears to also increase extracellular GABA and decrease extracellular glutamate concentrations [34]. Several RCTs support the efficacy of pregabalin in the treatment of GAD and pregabalin is the only medication to be associated with reduced drop-out numbers in treatment *vs.* placebo arms (odd ratio 0.8) [18].

Pregabalin is generally well tolerated with common adverse effects including drowsiness, dizziness, vertigo, and weight gain, although the basis for these adverse effects is not well understood [35]. Abrupt withdrawal is associated with discontinuation effects, but this appears to be less prominent that with benzodiazepine use [35]. In recent years, gabapentinoids have been increasingly recognised to have addictive potential with the risk of misuse [36,37]. Systematic reviews of the use of pregabalin in the treatment of epilepsy identify that 5-8% of patients describe euphoria, with a greater prevalence at higher doses (≥450mg/day) [38]. Non-prescribed use of pregabalin is increasingly recognised, often through supra-therapeutic dosing or alternate administration routes [39]. In recognition of this pregabalin (and gabapentin) have been classified as controlled drugs in several countries, including the United Kingdom and the US. Risks for non-prescribed use of pregabalin include a history of substance use disorders, particularly opiate or poly-substance misuse [40]. A Swedish cohort study has associated non-prescribed use of gabapentinoids with increased risk of suicidal behaviour, unintentional overdoses, road traffic accidents and violent crime [41].

2.9 Antihistamines

The antihistamine hydroxyzine has demonstrated efficacy *vs.* placebo treatment in two RCTs for GAD, over either 4 or 12 weeks [42,43]. The predominant mechanism of action is H1 receptor inverse agonism, however hydroxyzine shows weak antagonism at the 5-HT2A receptor, not seen with other antihistamines [44]. The principal adverse effect noted in RCTs for GAD is daytime somnolence (due to H1 receptor blockade), however this appears to largely resolve by day 10 of treatment [43].

2.10 Anticonvulsants

The anticonvulsant tiagabine acts through selective inhibition of the GABA transporter (GAT-1), increasing extracellular GABA concentrations [45]. It has been investigated in 5 RCTs of GAD, but without evidence to support efficacy over placebo [18].

2.11 Antipsychotics

As highlighted above, the second-generation antipsychotic quetiapine demonstrated the highest efficacy in the treatment of GAD [18]. This is based on 4 RCTs using extended-release dosages of 50-300mg daily. It was, however, also associated with significant rates of drop out in treatment *vs.* placebo groups [18]. Quetiapine displays a broad range of receptor antagonism including H1, α1 and α2-adrenocepter, 5-HT2A and 5-HT2C receptors, alongside a comparably low affinity to the D2 dopamine receptor [46]. It is widely used in psychiatric practice, in the treatment of patients with schizophrenia, bipolar disorder or unipolar depression. Common adverse effects of quetiapine include sedation (secondary to H1 receptor blockade), dizziness (secondary to adrenergic blockade) and weight gain (secondary to H1 and 5-HT2C receptor blockade) [47]. Unlike most other antipsychotics it is rarely associated with extra-pyramidal side effects or hyperprolactinaemia [47]. No other antipsychotic has been considered as a monotherapy in RCTs for GAD, although other antipsychotics (most notably olanzapine) have been investigated as augmentation strategies (see section 3.2).

2.12 Benzodiazepines and non-benzodiazepines

Benzodiazepines are among the oldest anxiolytic agents which remain in widespread clinical practice, with the earliest agent, chlordiazepoxide, entering clinical practice in 1960 [48]. A wide range of agents are currently available, with differing pharmacokinetic properties. Other common indications are induction and maintenance of sleep, muscle relaxation and management of epileptic seizures [49]. Benzodiazepines achieve these varied effects through positive allosteric modulation of GABAA receptors, increasing the affinity of these receptors to endogenous GABA [48]. The rapid rise in the use of benzodiazepines in the Western world in the 1960s and early 1970s was followed by a marked fall in use, with the recognition of dependence and withdrawal associated with these agents [48].

RCTs of benzodiazepines in GAD demonstrate efficacy *vs.* placebo, however the dropout rates are higher in the benzodiazepine groups on average [18]. Benzodiazepines with a relatively long half-life are preferred in treatment of GAD, to prevent the need for multiple daily dosing. Common adverse effects of benzodiazepine treatment include cognitive effects (sedation, drowsiness, and mental slowing) and psychomotor impairment (including when driving), both related to increased GABAergic stimulation, and the development of tolerance and dependence [49]. Tolerance to benzodiazepines can occur for the anticonvulsant and sedative effects, however it is less clear to what this extent this occurs for the anxiolytic effects [49]. Dependence on benzodiazepines can also occur with an associated withdrawal syndrome, usually characterised by anxiety-related physical and psychological symptoms alongside perceptual disturbances [50]. Treatment of benzodiazepine dependence, usually entails the conversion of benzodiazepine polypharmacy to monotherapy and the gradual tapering of the total dose, combined with psychological support [51].

Non-benzodiazepine hypnotics (or “Z-drugs”) are GABAA receptor positive allosteric modulators that fall within one of several different chemical classes to benzodiazepines. Several have specific affinity to particular sub-units of the GABAA receptor. Non-benzodiazepines are widely used in psychiatric practice as hypnotics but have largely failed to enter clinical practice for the treatment of anxiety disorders. A single small RCT which assessed the pyrazolopyrimidine ocinaplon in GAD found greater efficacy than placebo, but due to adverse effects in phase 3 trials, its development was subsequently discontinued [52].

3. Current guidelines on the treatment of generalised anxiety disorder.

Current consensus guidelines summarise the current evidence and suggested treatment strategies for GAD. These include the World Federation of Societies of Biological Psychiatry (WFSBP) 2022 guidelines and the British Association for Psychopharmacology (BAP) 2014 guidelines [21,53]. Below we briefly summarise guidance related to initial treatment, treatment-resistance, the place of psychological therapies, the management of psychiatric co-morbidities, the specific management of pregnant and postpartum patients, older adults (>65 years) and children/adolescents, and maintenance treatment.

3.1 Initial pharmacological treatment

The WFSBP guidelines advise, if a pharmacological treatment is preferred, to offer a SSRI or SNRI as a first line treatment. Due to its abuse potential, pregabalin is suggested as a second line treatment. Benzodiazepines are only recommended as a first line treatment if SSRIs or SNRIs are not tolerated. The BAP guidelines advise SSRIs as a first line pharmacological treatment, with both SNRIs and pregabalin suggested as alternative first line options if SSRIs are judged to be unsuitable.

A recommended trial of at least 12 weeks is recommended for the first line treatment [21]. However, there is recognition that the lack of any signs of response within the first 4 weeks is predictive of treatment failure for many first line treatments [21]. There is no strong evidence that dose increases of SSRIs or SNRIs improve treatment response [54]. However, pregabalin is noted in RCTs to have greater efficacy at higher doses [55].

3.2 Treatment resistance to initial pharmacological treatment

Failure of response or remission to initial pharmacological treatment is common and has been estimated at 40-50% in anxiety disorders generally [56]. The concept of ‘treatment resistance’ is widely used in the discussion of other psychiatric illnesses, particularly schizophrenia and major depressive disorder, where definitions of treatment resistance are clearly defined [57]. Treatment resistance in anxiety disorders has been inconsistently defined in the research literature, and has usually referred to the failure of one first line pharmacological treatment [58]. A recent systematic review of definitions for treatment resistance in anxiety disorders proposed at least one failed first line pharmacological and psychological therapy, provided for an adequate duration (at least 8 weeks) [58].

The potential causes of treatment resistance in anxiety disorders may be divided into pseudo- or true- resistance [56]. Causes of ‘pseudo-resistance’ include the use of ineffective pharmacological agents, the use of effective agents at inadequate dosages or treatment durations and, most commonly, poor medication adherence [56]. ‘True resistance’ may result from substance use (such as alcohol or caffeine), sleep deprivation, an incorrect initial diagnosis of GAD and/or undiagnosed comorbid psychiatric conditions or, rarely, an underdiagnosed medical illness (such as hyperthyroidism) [56]. Initial treatment resistance should prompt a further assessment of the patient and consideration of the potential resolvable causes.

Suggested pharmacological options after failure to respond to initial treatment include the switching to a different SSRI or SNRI, pregabalin, agomelatine, vilazodone, buspirone, imipramine, hydroxyzine, quetiapine and trazodone [21,53]. Specific benzodiazepines (alprazolam, bromazepam, diazepam and lorazepam) are suggested after initial treatment failure, provided the patient does not have a history of substance use disorder [21,53]. Combination pharmacological treatment is also suggested with specific guidance to consider the addition of olanzapine to fluoxetine treatment, or the addition of pregabalin to a SSRI or SNRI; both recommendations based on individual RCTs [59,60].

3.3 The place of psychological therapies

Several forms of psychotherapy have been investigated in the treatment of GAD, including cognitive behavioural therapy (CBT) (individual, group, or internet), applied relaxation (AR), psychodynamic psychotherapy and mindfulness-based psychotherapy [61,62]. CBT has been most widely studied with evidence of efficacy over waitlist controls in GAD but not over psychological placebo [61,62]. Guidelines support the use of CBT as a first line treatment [21,53]. However, it should be considered that RCTs have rarely compared pharmacological and psychotherapeutic treatments in individual trials and a network meta-analysis (of pharmacological and psychotherapeutic treatments) found overall larger treatment effect sizes for pharmacological *vs.* psychotherapeutic treatments [61].

3.4 Management of psychiatric co-morbidities

As the majority of patients with GAD have psychiatric co-morbidities (particularly MDD, an additional anxiety disorder, or substance misuse disorder), concurrent management of these co-morbidities should ideally occur alongside treatment of GAD [21]. Specific treatment will depend on the nature and severity of the co-morbid condition and may include pharmacological treatment. Many effective pharmacological treatments in GAD such as SSRIs or SNRIs are effective in MDD and in other anxiety disorders and choosing a single effective pharmacological treatment for GAD and a psychiatric comorbidity is therefore a sensible strategy. In patients with a diagnosis or suspected diagnosis of bipolar affective disorder (BPAD), the risk of a pharmacological treatment inducing mania or hypomania should be considered. This is a particularly relevant issue, considering epidemiological studies have estimated the lifetime risk of an anxiety disorder in patients with BPAD is 60% [63]. Finally in patients with co-morbid substance misuse, the potential for interactions between substances and pharmacological agents (particularly sedating agents such as benzodiazepines) and the risk of diversion of agents such as pregabalin should be considered.

3.5 Treatment of GAD in pregnancy and the postpartum period

Although epidemiological studies of GAD during pregnancy and the postpartum period are limited, there is evidence to suggest an increased prevalence postpartum [64]. The decision to start or continue pharmacological treatment for GAD during this period should consider the risks of potential harm to the unborn child or breastfeeding infant balanced against the risk of untreated GAD. Full clinical guidelines are published elsewhere [65]. For the recommended first line pharmacological treatment (SSRIs), their use in pregnancy is associated with small reduction in gestational age at delivery and birthweight and an increased risk of postpartum haemorrhage [65]. There may be increased risks of cardiac defects and persistent pulmonary hypertension of the new-born (PPHN), particularly with paroxetine, although this association may result from confounding factors [65]. SSRI use is also associated with a short-lived neonatal syndrome characterised by irritability, jitteriness, vomiting and eating and sleeping difficulties [65]. SSRIs are present in breast milk, with lowest levels of exposure seen with sertraline and paroxetine [65]. Due to the greater risk of discontinuation symptoms with paroxetine, sertraline has been recommended as the SSRI of choice in breastfeeding patients [65]. Effective psychological therapies may be the preferred first line choice of treatment in these circumstances, to avoid these potential risks to the unborn child or breastfeeding infant.

3.6 Treatment of GAD in older adults

Epidemiological studies have estimated the prevalence of GAD in the community between 1.3% and 3.7% in older adults, broadly in line with general population estimates of prevalence [66]. Most trials of pharmacological therapy for GAD have excluded older adults, however individual RCTs have demonstrated the effectiveness of citalopram, pregabalin and quetiapine [67–69]. Despite this, current treatment guidelines recommend broadly similar use of pharmacological agents, while recognising the increased sensitivity to adverse effects in this patient group [21,53]. Of particular importance is the increased risk of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), increased sensitivity to extrapyramidal symptoms, increased risk of QTC prolongation and increased sensitivity to orthostatic hypotension (and resultant dizziness and falls). Several RCTs of CBT have been specifically conducted with older adults however, and support the efficacy of CBT over wait list control in meta-analysis of trial data [70].

3.7 Treatment of GAD in children/adolescents

As previously discussed, the average age of onset of GAD is relatively late for a psychiatric illness with a median age of 32 years [11]. In children between 5 and 16 years of age in the UK, 0.7% were noted to have GAD in a 2004 cross-sectional study [71]. The presence of comorbid anxiety disorders alongside GAD, appears particularly common in this patient group [72]. Psychological treatments are preferred. A limited number of RCTs supports the efficacy of SSRIs in this group, and current guidelines recommend use of SSRIs as a first line pharmacological treatment [21,53,73].

3.8 Maintenance treatment

Most RCTs conducted in children and adolescents with GAD, as with other psychiatric illnesses, are relatively short in duration (the median length of follow-up in the previous discussed meta-analysis was only 8 weeks [18]). The efficacy and need for long-term pharmacological treatment can be assessed with placebo-controlled relapse prevention trials. A 2017 systematic review and meta-analysis of risk of relapse after antidepressant discontinuation in anxiety disorders, identified 6 trials in GAD (for paroxetine, escitalopram, duloxetine, venlafaxine, agomelatine and vortioxetine) [74–80]. Two further relapse prevention trials have shown reduced relapse rate in patients continued on either pregabalin or quetiapine XR [81,82]. The duration of these trials was between 16 and 72 weeks. Current guidelines advise to continue pharmacological treatment after relapse for at least several (or 6) months [21,53].

4. Future developments in the pharmacological treatment of generalised anxiety disorder

The above survey of effective pharmacological treatments in GAD suggests the modulation of either the serotonin or the GABA neurotransmitter systems as the basis for most effective treatments. Anxiolytic forms of serotonergic modulation include serotonin transporter (SERT) inhibition, 5-HT1A receptor partial agonism or 5-HT2/5-HT3 receptor antagonism. Additional noradrenergic modulation via noradrenaline transporter (NET) inhibition or α-adrenoceptor antagonism appears to augment the efficacy of serotonergic agents but there is limited clinical evidence to suggest an anxiolytic effect of pure noradrenergic modulating agents. Anxiolytic forms of GABAergic modulation include increasing the affinity of GABAA receptors to GABA (benzodiazepines), or indirectly increasing GABA transmission, through disruption of voltage-gated calcium channels thereby reducing glutamatergic neurotransmission (pregabalin). The role of modulation of the melatonin (in agomelatine), histamine (in hydroxyzine) and dopamine (in quetiapine) neurotransmitter systems are less clear, as these medications all have additional serotonergic effects.

Beyond the neurotransmitters discussed above, several additional neurotransmitter systems have been implicated in the neurobiology of GAD and other anxiety disorders based on animal models of anxiety disorders, molecular genetic studies and preclinical studies in human volunteers [83]. These include the neurotransmitter glutamate and various neuropeptides including neuropeptide Y (NPY), tachykinins, corticotropin-releasing factor (CRF), oxytocin, orexin and endocannabinoids [83,84]. The influence of the immune system and pro-inflammatory mechanisms have also been implicated in the pathophysiology of anxiety disorders, including GAD [85]. Below we discuss recent and ongoing develops to develop novel anxiolytics based either on alternate serotonergic or GABAergic modulation, through modulation of glutamate or neuropeptides, and through modulation of the immune system.

4.1 Novel serotonergic agents

Several additional 5-HT1A partial agonists are currently under development for the treatment of anxiety disorders. The azapirone gepirone was demonstrated to improve symptoms in patients with co-morbid GAD and panic disorder with agoraphobia in an open study [86]. However, no RCTs have been conducted to assess its efficacy in any anxiety disorder. In patients with MDD and a high level of anxiety symptoms, augmentation of SSRI treatment with the azapirone tandospirone improved both depressive and anxiety symptoms [87]. A multicentre RCT conducted in China, compared 60mg *vs.* 30mg/day of tandospirone in patients with GAD over 6 weeks [88]. However, the lack of a placebo group in this study makes overall interpretation of the efficacy of tandospirone challenging. The higher tandospirone dosage was associated with a greater HAM-A decrease but no difference in overall response rate. An additional 5- HT1A partial agonist with 5-HT2 antagonist actions (FKW00GA) is under development with reported efficacy in phase 2 trials in GAD [89]. To date, the results of these trials have not been published.

In recent years, there has been a resurgence of interest in psychedelics, pharmacological compounds which alter consciousness in a variety of ways [90,91]. Psychedelics are naturally produced by plants, fungi and animals, and have been used by different cultures throughout human history [90]. The current consensus is that psychedelics act through agonism or partial agonism at 5-HT2A receptors. There is some evidence for the use of psilocybin in the treatment of depression [92], and limited evidence to support a potential anxiolytic effect of these agents. In a small cross-over RCT, patients with cancer and associated anxiety showed significant improvements in anxiety symptoms after a single dose of psilocybin (0.3mg/kg) [93]. Two other cross-over studies in patients with cancer found similar results with psilocybin [94,95]. A recent crossover phase 2 study of patients with any anxiety disorder (62% had GAD) with or without a life-threatening illness compared 2 sessions of lysergic acid diethylamide (LSD)-assisted psychotherapy toplacebo-assisted psychotherapy. [96] A significant difference in scores on the Spielberger State-Trait Anxiety Inventory–Global (STAI-G) score was noted immediately after the psychotherapy sessions and at 2, 8 and 16 weeks after the sessions [96]. These relatively small trials, although focussed on anxiety symptoms in the context of serious physical illnesses, should encourage the exploration of potential anxiolytic effects of psychedelics in standard clinical populations with GAD.

4.2 Novel GABAergic agents

The description of the GABAergic system and its receptors (GABAA and GABAB) stimulated the desire to develop non-sedating GABAergic anxiolytics, described as a “Holy Grail” of psychopharmacology [97,98]. The GABAA receptor structure is notably complex, as the receptor has a pentameric structure assembled from 19 possible subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3) [98]. Different GABAA receptor subtypes are expressed selectively throughout the mammalian brain and appear to have different functions [98]. The α subunit present in the GABAA receptor has been found to be of particular importance, with GABAA receptor subtypes containing α1 subunit mediating sedative effects of BZDs while those containing α2/3 subunits mediating anxiolytic effects [98].

Several α2/α3-GABAA receptor positive allosteric modulators (PAMs) have been developed and progressed into clinical studies in patients with anxiety disorders [98]. The promise of such agents was demonstrated in the development of TPA023, which demonstrated anxiolytic effects (without sedation) in animal studies and three phase 2a trials in GAD were initiated [99]. However, cataract formation was noted in high-dose, long-term animal studies and these three trials were discontinued, although *post-hoc* analysis of the available findings identified a greater decrease in HAM-A score *vs.* placebo [99]. An additional agent, AZD7325, also demonstrated an anxiolytic effect (without sedation in animals) and was investigated in two 4-week RCTs in GAD at a range of dosages *vs.* placebo [100,101]: however, no dosage of AZD7325, showed a different in HAM-A score *vs.* placebo. Finally, the agent PF-06372865 (CVL-865), which demonstrated anxiolytic and anticonvulsant effects in rodent studies, was evaluated in a RCT in patients with GAD, not responding to initial pharmacological treatment [102]. This study was terminated early (due to a change in portfolio prioritisation) with no difference was seen in HAM-A score after 4 weeks of treatment, however less than 25% of the proposed sample size was recruited [102].

4.3 Glutamatergic agents

The dissociative anaesthetic ketamine has entered psychiatric practice in recent years for the treatment of depression, administered intravenously (IV) or intranasally as esketamine [103]. Ketamine/esketamine is a strong antagonist at the glutamate *N*-methyl-D-aspartate (NMDA) receptor, with additional actions on monoamine, opioid and cholinergic neurotransmitter systems [103]. A large number of trials have demonstrated the short-term efficacy of ketamine in the treatment of depression [104]. A small open-label study using IV ketamine in patients with refractory GAD or social anxiety disorder (SAD) demonstrated anxiolytic effects after a single dose and after regular weekly dosing for 3 months [105,106]. No RCT for the use of ketamine in GAD has been conducted to date, although pooled analysis of 2 RCTs conducted for SAD supported the efficacy of ketamine *vs.* placebo [107].

Metabotropic glutamate receptors, particularly mGluR2 and mGluR3 have been identified as a potential anxiolytic target. Clinical studies have not yet shown promise. The agent LY544344 (a pro-drug for a selective mGluR2/3 agonist) was trialled in GAD but was discontinued at a very early stage, due to concerns about proconvulsive effects seen in animal studies [108]. An additional mGluR2 PAM JNJ-40411813, when trialled in patients with MDD and significant anxiety symptoms, did not show any effect on HAM-A score *vs.* placebo treatment [109].

4.4 Neuropeptides

Neuropeptide Y (NPY) is a 36 amino acid peptide expressed throughout the mammalian brain [110]. Four Y receptors have been identified in humans (Y1, Y2, Y4 and Y5). NPY has been implicated in the stress response, and animal studies suggest differing roles for the different Y receptors. In particular, Y1 receptor stimulation appears to have an anxiolytic effect while Y2 receptor stimulation may have an anxiogenic effect [110]. The role of NPY has been particularly studied in PTSD and a recent RCT compared intranasal NPY *vs.* placebo treatment in patients with this condition [111]. Treatment was generally well tolerated, however no significant effect was noted on either anxiety scale used, although higher doses were associated with greater improvements in anxiety symptoms [111]. To date, NPY-modulating treatment has not been investigated in clinical populations with GAD. Nor have selective Y receptor agonist/antagonists, which could hold promise in the treatment of anxiety disorders, been investigated in clinical populations.

The tachykinin system is a neuropeptide system involved in a variety of physiological functions [112]. It consists of several neuropeptides and three neurokinin receptors (1-3) [112]. Substance P (SP) is widely expressed throughout the brain and preferentially binds the neurokinin 1 receptor (NK1R) [113]. SP and NK1R have been implicated in the stress response and anxiety in animal studies [113]. NK1R antagonists have been developed and showed promise in animal models of anxiety and were translated into clinical populations, but without success. One RCT compared the NK1R antagonist L-759274 with lorazepam and placebo treatment over 6 weeks in patients with GAD [114]. No difference in HAM-A score was noted between L-759274 and placebo at the end of the treatment period [114]. The additional NK1R antagonists LY686017 and GR205171 did not differentiate from placebo treatment in the treatment of SAD and PTSD respectively [115,116]. To our knowledge, no further studies using tachykinin-modulating agents in anxiety disorders, are currently ongoing.

Corticotropin-releasing factor/hormone (CRF/CRH) is a peptide hormone secreted by the hypothalamus in response to stress. It stimulates secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary and is a component of the hypothalamic-pituitary-adrenal (HPA) axis. CRF binds two different GPCR (CRF1 and CRF2 receptors) which are expressed in the hypothalamus and other brain regions [117]. An anxiogenic (and pro-depressive) role of CRF1 receptors was identified in animal studies, leading to the development of several CRF1 receptor antagonists [117,118]. However, clinical studies of CRF1 receptor antagonists have not shown promise in anxiety disorders [118]. To date, only one RCT has been published in GAD, which showed that the CRF1 receptor antagonist pexacerfont did not differentiate from placebo treatment after 8 weeks of treatment [119].

The neuropeptide oxytocin (OT) is a hormone secreted by the posterior pituitary gland with physiological (milk ejection, uterine contraction during labour) and behavioural roles (maternal behaviour, pair bonding). OT exerts these actions through binding at the oxytocin receptor (OXTR) which is expressed widely throughout the mammalian brain [120]. An anxiolytic effect of oxytocin has been identified in rodent models and several translational human studies have been conducted, with exogenous OT usually administered intranasally [121,122]. While the focus of these human studies has been in SAD, one small pilot study has been conducted in GAD [123]. This cross-over trial randomised 13 patients with GAD to receive 3 weeks of intranasal OT (titrated up to 40 international units [IU] twice daily) and 3 weeks of placebo treatment. A significant decrease in anxiety symptoms (on the HAM-A) was noted for male but not female patients. To our knowledge, there have been no further studies of oxytocin in GAD.

The orexin neurotransmitter system comprises two neuropeptides (orexin-A and orexin-B) and two G-protein coupled receptors (types 1 and 2) [124]. The orexin system has an important regulatory role in the sleep-wake cycle, the stress response, motivation, reward processing and arousal [124–126]. Animal models of anxiety implicate the orexin system, as do a limited number of human studies in clinical populations with anxiety disorders [127–130]. Translational studies utilising orexin receptor antagonists (ORAs) in healthy volunteers have demonstrated a potential anxiolytic effect in experimental medicine models of anxiety, including carbon dioxide inhalation and a unpredictable threat paradigm [131–133]. Multiple ORAs have entered clinical practice for the treatment of insomnia, and there is evidence of a reduction in anxiety symptoms when used for this purpose in clinical practice [134]. To date, no study has investigated the effect of an orexin modulating agent in a clinical population with anxiety disorders. A limited number of clinical studies have considered the efficacy of ORAs in the treatment of depression without consistent evidence of benefit [135].

The endocannabinoid system is a widespread neurotransmitter system, consisting of endogenous ligands (anandamide and 2-AG) and two cannabinoid receptors (CB1 and CB2). Exogenous ligands for cannabinoid receptors are produced by the cannabis plant (*Cannabis sativa)* and these phytocannabinoids have been widely used throughout human history [136]. Identified phytocannabinoids include Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) [137]. Several synthetic cannabinoids have also been produced. CBD lacks the psychotomimetic effects of Δ9-THC and animal studies indicate a potential anxiolytic effect [138]. However, to date, there are limited clinical studies on the effect of cannabinoids in anxiety disorders [139]. No RCT has considered the effect of cannabinoids in GAD, although one small RCT demonstrated a single dose of CBD (600mg) reduced anxiety induced by public speaking in patients with SAD [140]. In addition, a crossover RCT demonstrated the efficacy of 7 weeks of treatment with the synthetic cannabinoid nabilone on frequency of nightmares and quality of life in PTSD (albeit with a small sample size of 10 participants) [141].

4.5 Immunological treatments

Interactions between the immune system and central nervous system have been implicated in several psychiatric illnesses, including anxiety disorders [142]. Multiple studies have measured peripheral inflammatory markers in GAD, with elevated serum levels of the pro-inflammatory cytokines C reactive protein (CRP), interferon-γ, and tumour necrosis factor-α (TNF-α) seen in two or more studies [143]. Patients treated for ‘first episode’ GAD with SSRIs, show a reduction in serum levels of pro-inflammatory cytokines suggesting an anti-inflammatory effect of anxiolytic treatments in current practice [144]. To date, only one RCT has been conducted to investigate the effect of a specific anti-inflammatory treatment in GAD [145]. This study compared adjuvant treatment with the statin simvastatin (20mg/day) to placebo over 8 weeks. Statins are widely used in the treatment of hypercholesterolaemia and additional anti-inflammatory effects have been identified [146]. However, no significant difference in HAM-A score was observed in the simvastatin group [145]. No further trials have investigated anti-inflammatory agents in the treatment of GAD, to date.

5. Conclusion

GAD is a common psychiatric illness associated with considerable disability and much comorbidity. RCTs and meta-analyses support the efficacy of a number of different pharmacological treatments in adults, including SSRIs, SNRIs, agomelatine, mirtazapine, bupropion, buspirone, pregabalin, hydroxyzine, quetiapine and benzodiazepines. However, quetiapine, benzodiazepines and paroxetine are less well tolerated than placebo (based on trial dropout rates). Current treatment guidelines generally support the use of SSRIs as a first line pharmacological treatment, with SNRIs and pregabalin suggested if SSRIs are not effective or tolerated.

A wide range of different neurotransmitter and hormone systems are under investigation as potential targets for novel anxiolytic treatments, several of which have been investigated in clinical trials in GAD. These include the azapirone tandospirone, the psychedelics psilocybin and LSD, several α2/α3-GABAA receptor positive allosteric modulators, ketamine, mGluR2/3 agonists, NK1R antagonists, CRF1 receptors, oxytocin, and simvastatin. Most of these trials have not demonstrated efficacy, however trials in psilocybin, ketamine, and oxytocin showed promise. However, larger scale clinical trials are needed to determine the efficacy of these agents in GAD.

6. Expert Opinion

Epidemiological data consistently demonstrate that GAD is common, persistent, associated with significant disability, and in most cases, comorbid with other psychiatric illnesses. Despite a large number of effective anxiolytic treatments, a substantial minority of patients have limited benefit from current pharmacological treatment.

Most randomised controlled trials in GAD have been relatively short (median 8 weeks) and are focussed on the efficacy of first line pharmacological treatment. Although longer-term relapse prevention studies have been conducted to guide maintenance treatments, these are limited to single studies for a small number of medications with most only lasting up to 6 months. Therefore, current guidelines recommend continuing pharmacological treatments for several or 6 months, but it is unclear how much further the benefit of treatment could extend beyond this. In addition, the epidemiology and management of treatment resistance in GAD has not been explored in detail in the current literature, reflected by the fact that no agreed consensus definition is in use. Developing a clear definition of treatment-resistant GAD would allow further study of this area, and sequential stepped randomised controlled trials (in the manner of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial in MDD) could be conducted to provide an greater evidence base for the management of treatment resistance [147].

Historically, effective pharmacological treatments in GAD were largely discovered serendipitously or repurposed from treatments for other psychiatric or medical conditions, chiefly MDD. In recent decades, knowledge of the neurobiology of anxiety has increased markedly with the implication of many new neurotransmitter systems and potential drug targets. However, translation from animal models of anxiety into clinical populations with GAD has not been smooth. The failures in clinical trials of two α2/α3-GABAA receptor positive allosteric modulators (AZD7325 and PF-06372865), an mGluR2/3 agonist, a NK1R antagonist and a CRF1 receptor antagonist reflect these challenges, which have been noted across the field of psychopharmacology [148]. Many of the core subjective symptoms of GAD such as excessive worrying and general apprehensiveness, are challenging, if not impossible to study in animal models. The further development of experimental medicine models of anxiety disorders in healthy humans could aid the translation process, assessing novel anxiolytics before large scale clinical trials are conducted [149,150]. Currently used experimental models include 7.5% CO2 inhalation, the unpredictable shock paradigm, the Trier social stress test (TSST) or the display of anxiogenic stimuli using virtual reality techniques [151–154]. Changes could also be made to the design of clinical trial programmes, for example through the judicious use of pilot studies, *a priori* adaptive trial designs (for example for medication dosage), increasing the representativeness of patients recruited to trials, and trial protocols designed to curtail the high placebo responses seen in studies of anxiolytic medications.

Alongside the recent translation failures, several clinical trials of novel anxiolytics in GAD have generated encouraging findings. Of particular interest were the 3 small trials using psilocybin, although the majority of included patients were suffering from anxiety symptoms in the context of a physical health condition (usually cancer) rather than an anxiety disorder *per se.* In addition, the full potential of several other agents including ketamine, oxytocin and agents modulating the orexin and endocannabinoid systems, and immune modulating treatments, has not been adequately explored in GAD and could translate into effective treatment strategies.

7. References

Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*) to readers.

[1] Crocq MA. The history of generalized anxiety disorder as a diagnostic category. Dialogues Clin Neurosci. 2017;19:107–116.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed. Washington DC: American Psychiatric Association; 1980.

[3] World Health Organization (WHO). The ICD-10 Classification of Mental and Behavioural Disorders. Genève, Switzerland: World Health Organization (WHO); 1993.

[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

[5] World Health Organization (WHO). ICD-11: International Classification of Diseases. 11th ed. Genève, Switzerland: World Health Organization (WHO); 2022

[6] Kessler RC, Chiu WT, Demler O, et al. Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry. 2005;62:617–627.

[7] Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol. 2005;15:357–376.

[8] Ruscio AM, Hallion LS, Lim CCW, et al. Cross-sectional Comparison of the Epidemiology of DSM-5 Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017;74:465–475. \*A recent detailed cross-sectional epidemiological study of GAD covering 26 high-, middle- and low-income countries.

[9] COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398:1700–1712.

[10] Moreno-Peral P, Conejo-Cerón S, Motrico E, et al. Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. J Affect Disord. 2014;168:337–348.

[11] Solmi M, Radua J, Olivola M, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry. 2022;27:281–295.

[12] Munjack DJ, Baltazar PL, DeQuattro V, et al. Generalized anxiety disorder: some biochemical aspects. Psychiatry Res. 1990;32:35–43.

[13] Abelson JL, Glitz D, Cameron OG, et al. Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. Arch Gen Psychiatry. 1991;48:157–162.

[14] Garvey MJ, Noyes R, Woodman C, et al. Relationship of generalized anxiety symptoms to urinary 5-hydroxyindoleacetic acid and vanillylmandelic acid. Psychiatry Res. 1995;57:1–5.

[15] Schienle A, Wabnegger A. Chapter 8- Structural and Functional Neuroanatomy of Generalized Anxiety Disorder. In: Gerlach AL, Gloster AT, editors. Generalized Anxiety Disorder and Worrying: A Comprehensive Handbook for Clinicians and Researchers. Hoboken (NJ): John Wiley & Sons; 2020. p 151-171.

[16] Baxter AJ, Scott KM, Vos T, et al. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013;43:897–910.

[17] Revicki DA, Travers K, Wyrwich KW, et al. Humanistic and economic burden of generalized anxiety disorder in North America and Europe. J Affect Disord. 2012;140:103–112.

[18] Slee A, Nazareth I, Bondaronek P, et al. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393:768–777. \*\*A systematic review and meta-analysis of all randomised controlled trials in adults with GAD, published between 1994 and 2017.

[19] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50–55.

[20] Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2015;29:459–525.

[21] Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28:403–439. \*These 2014 guidelines from the British Association for Psychopharmacology provide evidence-based recommendations for the treatment of GAD.

[22] Carvalho AF, Sharma MS, Brunoni AR, et al. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom. 2016;85:270–288.

[23] Rothmore J. Antidepressant-induced sexual dysfunction. Med J Aust. 2020;212:329–334.

[24] Andrade C, Sandarsh S, Chethan KB, et al. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry. 2010;71:1565–1575.

[25] Beach SR, Celano CM, Sugrue AM, et al. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. Psychosomatics. 2018;59:105–122.

[26] Harvey BH, Slabbert FN. New insights on the antidepressant discontinuation syndrome. Hum Psychopharmacol. 2014;29:503–516.

[27] Buoli M, Grassi S, Serati M, et al. Agomelatine for the treatment of generalized anxiety disorder. Expert Opin Pharmacother. 2017;18:1373–1379.

[28] Croom KF, Perry CM, Plosker GL. Mirtazapine: a review of its use in major depression and other psychiatric disorders. CNS Drugs. 2009;23:427–452.

[29] Dawson LA, Watson JM. Vilazodone: a 5-HT1A receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders. CNS Neurosci Ther. 2009;15:107–117.

[30] Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther. 2015;145:43–57.

[31] Dhillon S, Yang LPH, Curran MP. Bupropion: a review of its use in the management of major depressive disorder. Drugs. 2008;68:653–689.

[32] Huang X, Yang J, Yang S, et al. Role of tandospirone, a 5-HT1A receptor partial agonist, in the treatment of central nervous system disorders and the underlying mechanisms. Oncotarget. 2017;8:102705–102720.

[33] Ortiz A, Pohl R, Gershon S. Azaspirodecanediones in generalized anxiety disorder: buspirone. J Affect Disord. 1987;13:131–143.

[34] Micó JA, Prieto R. Elucidating the mechanism of action of pregabalin: α(2)δ as a therapeutic target in anxiety. CNS Drugs. 2012;26:637–648.

[35] Frampton JE. Pregabalin: a review of its use in adults with generalized anxiety disorder. CNS Drugs. 2014;28:835–854.

[36] Evoy KE, Sadrameli S, Contreras J, et al. Abuse and Misuse of Pregabalin and Gabapentin: A Systematic Review Update. Drugs. 2021;81:125–156.

[37] Baldwin DS, Masdrakis V. Non-prescribed use of gabapentinoids: Mechanisms, predisposing factors, associated hazards and clinical management. Eur Neuropsychopharmacol. 2022;63:6–8.

[38] Zaccara G, Gangemi P, Perucca P, et al. The adverse event profile of pregabalin: A systematic review and meta-analysis of randomized controlled trials. Epilepsia. 2011;52:826–836.

[39] Schjerning O, Rosenzweig M, Pottegård A, et al. Abuse Potential of Pregabalin. CNS Drugs. 2016;30:9–25.

[40] Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol. 2017;27:1185–1215.

[41] Molero Y, Larsson H, D’Onofrio BM, et al. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. BMJ. 2019;365:l2147.

[42] Llorca PM, Spadone C, Sol O, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002;63:1020–1027.

[43] Lader M, Scotto J-C. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology (Berl). 1998;139:402–406.

[44] Snowman AM, Snyder SH. Cetirizine: actions on neurotransmitter receptors. J Allergy Clin Immunol. 1990;86:1025–1028.

[45] Meldrum BS, Chapman AG. Basic mechanisms of gabitril (tiagabine) and future potential developments. Epilepsia. 1999;40 Suppl 9:S2-6.

[46] Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. J Clin Psychiatry. 2002;63 Suppl 13:5–11.

[47] Garver DL. Review of quetiapine side effects. J Clin Psychiatry. 2000;61 Suppl 8:31–33; discussion 34-35.

[48] López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. J Anxiety Disord. 2011;25:554–562.

[49] Baldwin DS, Aitchison K, Bateson A, et al. Benzodiazepines: risks and benefits. A reconsideration. J Psychopharmacol. 2013;27:967–971.

[50] Soyka M. Treatment of Benzodiazepine Dependence. N Engl J Med. 2017;376:1147–1157.

[51] Baldwin DS. Clinical management of withdrawal from benzodiazepine anxiolytic and hypnotic medications. Addiction. 2022;117:1472–1482.

[52] Czobor P, Skolnick P, Beer B, et al. A multicenter, placebo-controlled, double-blind, randomized study of efficacy and safety of ocinaplon (DOV 273,547) in generalized anxiety disorder. CNS Neurosci Ther. 2010;16:63–75.

[53] Bandelow B, Allgulander C, Baldwin DS, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders - Version 3. Part I: Anxiety disorders. World J Biol Psychiatry. 2022;1–39. \*These 2022 guidelines from the World Federation of Societies of Biological Psychiatry provide evidence-based recommendations for the treatment of GAD.

[54] Baldwin D, Woods R, Lawson R, et al. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011;342:d1199.

[55] Bech P. Dose-response relationship of pregabalin in patients with generalized anxiety disorder. A pooled analysis of four placebo-controlled trials. Pharmacopsychiatry. 2007;40:163–168.

[56] Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. Dialogues Clin Neurosci. 2015;17:191–206.

[57] Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. 2022;27:58–72.

[58] Bokma WA, Wetzer GAAM, Gehrels JB, et al. Aligning the many definitions of treatment resistance in anxiety disorders: A systematic review. Depress Anxiety. 2019;36:801–812. \*This 2019 systematic review surveys the literature for currently used definitions of treatment resistance in anxiety disorders and proposes a new definition of treatment resistance.

[59] Pollack MH, Simon NM, Zalta AK, et al. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. Biol Psychiatry. 2006;59:211–215.

[60] Rickels K, Shiovitz TM, Ramey TS, et al. Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. Int Clin Psychopharmacol. 2012;27:142–150.

[61] Chen TR, Huang HC, Hsu JH, et al. Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis. J Psychiatr Res. 2019;118:73–83.

[62] Newman MG, Basterfield C, Erickson TM, et al. Psychotherapeutic treatments for generalized anxiety disorder: cognitive and behavioral therapies, enhancement strategies, and emerging efforts. Expert Rev Neurother. 2022;22:751–770.

[63] Sala R, Goldstein BI, Morcillo C, et al. Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population. J Psychiatr Res. 2012;46:865–872.

[64] Ross LE, McLean LM. Anxiety disorders during pregnancy and the postpartum period: A systematic review. J Clin Psychiatry. 2006;67:1285–1298.

[65] McAllister-Williams RH, Baldwin DS, Cantwell R, et al. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. J Psychopharmacol. 2017;31:519–552.

[66] Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: Methodological issues and a review of the literature. J Affect Disord. 2008;109:233–250.

[67] Lenze EJ, Mulsant BH, Shear MK, et al. Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. Am J Psychiatry. 2005;162:146–150.

[68] Montgomery S, Chatamra K, Pauer L, et al. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. Br J Psychiatry J Ment Sci. 2008;193:389–394.

[69] Mezhebovsky I, Mägi K, She F, et al. Double-blind, randomized study of extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder. Int J Geriatr Psychiatry. 2013;28:615–625.

[70] Hall J, Kellett S, Berrios R, et al. Efficacy of Cognitive Behavioral Therapy for Generalized Anxiety Disorder in Older Adults: Systematic Review, Meta-Analysis, and Meta-Regression. Am J Geriatr Psychiatry. 2016;24:1063–1073.

[71] Green, H. editor. Mental health of children and young people in Great Britain. Basingstoke: Palgrave Macmillan; 2005.

[72] Gale CK, Millichamp J. Generalised anxiety disorder in children and adolescents. BMJ Clin Evid. 2016;2016:1002.

[73] Strawn JR, Geracioti L, Rajdev N, et al. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expert Opin Pharmacother. 2018;19:1057–1070.

[74] Batelaan NM, Bosman RC, Muntingh A, et al. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. BMJ. 2017;358:j3927. \*This 2017 systematic review and meta-analysis reviews all relapse prevention trials conducted in GAD.

[75] Stocchi F, Nordera G, Jokinen RH, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry. 2003;64:250–258.

[76] Allgulander C, Florea I, Huusom AKT. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. Int J Neuropsychopharmacol. 2006;9:495–505.

[77] Davidson JRT, Wittchen HU, Llorca PM, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. Eur Neuropsychopharmacol. 2008;18:673–681.

[78] Rickels K, Etemad B, Khalid-Khan S, et al. Time to relapse after 6 and 12 months’ treatment of generalized anxiety disorder with venlafaxine extended release. Arch Gen Psychiatry. 2010;67:1274–1281.

[79] Stein DJ, Ahokas A, Albarran C, et al. Agomelatine prevents relapse in generalized anxiety disorder: a 6-month randomized, double-blind, placebo-controlled discontinuation study. J Clin Psychiatry. 2012;73:1002–1008.

[80] Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. Int Clin Psychopharmacol. 2012;27:197–207.

[81] Feltner D, Wittchen H-U, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. Int Clin Psychopharmacol. 2008;23:18–28.

[82] Katzman MA, Brawman-Mintzer O, Reyes EB, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2011;26:11–24.

[83] Martin EI, Ressler KJ, Binder E, et al. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. Psychiatr Clin North Am. 2009;32:549–575.

[84] Garakani A, Murrough JW, Freire RC, et al. Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. Front Psychiatry. 2020;11:595584.

[85] Michopoulos V, Powers A, Gillespie CF, et al. Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. Neuropsychopharmacology. 2017;42:254–270.

[86] Pecknold JC, Luthe L, Scott-Fleury MH, et al. Gepirone and the treatment of panic disorder: an open study. J Clin Psychopharmacol. 1993;13:145–149.

[87] Lin J, Su Y, Wang C, et al. Effects of tandospirone augmentation in major depressive disorder patients with high anxiety: A multicenter, randomized, parallel-controlled, open-label study. J Psychiatr Res. 2018;99:104–110.

[88] Li Q, Zhang H, Lin G, et al. Relative Safety and Efficacy of Two Doses of Tandospirone Citrate for Generalized Anxiety Disorder: A Multicenter Randomized Controlled Trial. Neuropsychiatr Dis Treat. 2022;18:1653–1664.

[89] Fabre-Kramer Pipeline [Internet]. Houston (TX): Fabre-Kramer Pharmaceuticals; [cited 2023 Mar 15]. Available from: https://fabrekramer.com/pipeline/#1489503963784-5b2be039-5ceed3eb-d2400966-8526.

[90] Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264–355.

[91] Kelmendi B, Kaye AP, Pittenger C, et al. Psychedelics. Curr Biol. 2022;32:R63–R67.

[92] Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and Psychedelic-Assisted Psychotherapy. Am J Psychiatry. 2020;177:391–410.

[93] Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30:1165–1180.

[94] Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry. 2011;68:71–78.

[95] Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30:1181–1197.

[96] Holze F, Gasser P, Müller F, et al. Lysergic Acid Diethylamide-Assisted Therapy in Patients With Anxiety With and Without a Life-Threatening Illness: A Randomized, Double-Blind, Placebo-Controlled Phase II Study. Biol Psychiatry. 2023;93:215–223.

[97] Skolnick P. Anxioselective anxiolytics: on a quest for the Holy Grail. Trends Pharmacol Sci. 2012;33:611–620.

[98] Maramai S, Benchekroun M, Ward SE, et al. Subtype Selective γ-Aminobutyric Acid Type A Receptor (GABAAR) Modulators Acting at the Benzodiazepine Binding Site: An Update. J Med Chem. 2020;63:3425–3446. \*This 2020 review article provides a detailed summary of the development of subtype selective GABAA receptor modulators and their translation into clinical trials.

[99] Atack JR. Subtype-selective GABA(A) receptor modulation yields a novel pharmacological profile: the design and development of TPA023. Adv Pharmacol. 2009;57:137–185.

[100] NCT00807937. Proof of Concept in Patients With Generalized Anxiety Disorder (GAD)AZD7325 [Internet]. Bethesda (MD): U.S. National Library of Medicine; [cited 2023 Mar 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT00807937.

[101] NCT00808249. AZD7325 Proof of Concept in Patients With Generalized Anxiety Disorder (GAD) [Internet]. Bethesda (MD): U.S. National Library of Medicine; [cited 2023 Mar 17]. Available from: https://www.clinicaltrials.gov/ct2/show/results/NCT00808249?view=results.

[102] Simen A, Whitlock M, Qiu R, et al. An 8-Week, Randomized, Phase 2, Double-Blind, Sequential Parallel-Group Comparison Study of Two Dose Levels of the GABAA Positive Allosteric Modulator PF-06372865 Compared With Placebo as an Adjunctive Treatment in Outpatients With Inadequate Response to Standard of Care for Generalized Anxiety Disorder. J Clin Psychopharmacol. 2019;39:20–27.

[103] McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021;178:383–399.

[104] Dean RL, Hurducas C, Hawton K, et al. Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. Cochrane Database Syst Rev. 2021;9:CD011612.

[105] Glue P, Medlicott NJ, Harland S, et al. Ketamine’s dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. J Psychopharmacol. 2017;31:1302–1305.

[106] Glue P, Neehoff SM, Medlicott NJ, et al. Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders. J Psychopharmacol. 2018;32:663–667.

[107] Whittaker E, Dadabayev AR, Joshi SA, et al. Systematic review and meta-analysis of randomized controlled trials of ketamine in the treatment of refractory anxiety spectrum disorders. Ther Adv Psychopharmacol. 2021;11:20451253211056744.

[108] Dunayevich E, Erickson J, Levine L, et al. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. Neuropsychopharmacology. 2008;33:1603–1610.

[109] Kent JM, Daly E, Kezic I, et al. Efficacy and safety of an adjunctive mGlu2 receptor positive allosteric modulator to a SSRI/SNRI in anxious depression. Prog Neuropsychopharmacol Biol Psychiatry. 2016;67:66–73.

[110] Reichmann F, Holzer P. Neuropeptide Y: A stressful review. Neuropeptides. 2016;55:99–109.

[111] Sayed S, Van Dam NT, Horn SR, et al. A Randomized Dose-Ranging Study of Neuropeptide Y in Patients with Posttraumatic Stress Disorder. Int J Neuropsychopharmacol. 2017;21:3–11.

[112] De Biasi M, McLaughlin I, Klima ML. Chapter 18 - Nicotine and Neurokinin Signaling. In: Preedy VR, editor. Neuropathology of Drug Addictions and Substance Misuse. Volume 1: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids. Cambridge (MA): Academic Press; 2016. p. 189-200.

[113] Ebner K, Singewald N. The role of substance P in stress and anxiety responses. Amino Acids. 2006;31:251–272.

[114] Michelson D, Hargreaves R, Alexander R, et al. Lack of efficacy of L-759274, a novel neurokinin 1 (substance P) receptor antagonist, for the treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2013;16:1–11.

[115] Tauscher J, Kielbasa W, Iyengar S, et al. Development of the 2nd generation neurokinin-1 receptor antagonist LY686017 for social anxiety disorder. Eur Neuropsychopharmacol. 2010;20:80–87.

[116] Mathew SJ, Vythilingam M, Murrough JW, et al. A selective neurokinin-1 receptor antagonist in chronic PTSD: a randomized, double-blind, placebo-controlled, proof-of-concept trial. Eur Neuropsychopharmacol. 2011;21:221–229.

[117] Risbrough VB, Stein MB. Role of Corticotropin Releasing Factor in Anxiety Disorders: A Translational Research Perspective. Horm Behav. 2006;50:550–561.

[118] Spierling SR, Zorrilla EP. Don’t stress about CRF: Assessing the translational failures of CRF1 antagonists. Psychopharmacology (Berl). 2017;234:1467–1481.

[119] Coric V, Feldman HH, Oren DA, et al. Multicenter, randomized, double-blind, active comparator and placebo-controlled trial of a corticotropin-releasing factor receptor-1 antagonist in generalized anxiety disorder. Depress Anxiety. 2010;27:417–425.

[120] Freeman SM, Inoue K, Smith AL, et al. The neuroanatomical distribution of oxytocin receptor binding and mRNA in the male rhesus macaque (Macaca mulatta). Psychoneuroendocrinology. 2014;45:128–141.

[121] Naja WJ, Aoun MP. Oxytocin and Anxiety Disorders: Translational and Therapeutic Aspects. Curr Psychiatry Rep. 2017;19:67.

[122] Neumann ID, Slattery DA. Oxytocin in General Anxiety and Social Fear: A Translational Approach. Biol Psychiatry. 2016;79:213–221.

[123] Serrano V FD MacDonald K, McKinney R, Heisserer N. A randomized, placebo-controlled investigation of intranasal oxytocin in patients with anxiety. Neuropsychopharmacology. 2011;36:S324–S449.

[124] Chieffi S, Carotenuto M, Monda V, et al. Orexin System: The Key for a Healthy Life. Front Physiol. 2017;8:357.

[125] Tsujino N, Sakurai T. Role of orexin in modulating arousal, feeding, and motivation. Front Behav Neurosci. 2013;7:28.

[126] Geiger MJ, Neufang S, Stein DJ, et al. Arousal and the attentional network in panic disorder. Hum Psychopharmacol. 2014;29:599–603.

[127] Flores Á, Saravia R, Maldonado R, et al. Orexins and fear: implications for the treatment of anxiety disorders. Trends Neurosci. 2015;38:550–559.

[128] Johnson PL, Truitt W, Fitz SD, et al. A key role for orexin in panic anxiety. Nat Med. 2010;16:111–115.

[129] Akça ÖF, Uzun N, Kılınç İ. Orexin A in adolescents with anxiety disorders. Int J Psychiatry Clin Pract. 2020;24:127–134.

[130] Gottschalk MG, Richter J, Ziegler C, et al. Orexin in the anxiety spectrum: association of a HCRTR1 polymorphism with panic disorder/agoraphobia, CBT treatment response and fear-related intermediate phenotypes. Transl Psychiatry. 2019;9:75.

[131] Salvadore G, Bonaventure P, Shekhar A, et al. Translational evaluation of novel selective orexin-1 receptor antagonist JNJ-61393215 in an experimental model for panic in rodents and humans. Transl Psychiatry. 2020;10:308.

[132] Kaufmann P, Ort M, Golor G, et al. Multiple-dose clinical pharmacology of the selective orexin-1 receptor antagonist ACT-539313. Prog Neuropsychopharmacol Biol Psychiatry. 2021;108:110166.

[133] Gorka SM, Khorrami KJ, Manzler CA, et al. Acute orexin antagonism selectively modulates anticipatory anxiety in humans: implications for addiction and anxiety. Transl Psychiatry. 2022;12:308.

[134] Nakamura M, Nagamine T. Neuroendocrine, Autonomic, and Metabolic Responses to an Orexin Antagonist, Suvorexant, in Psychiatric Patients with Insomnia. Innov Clin Neurosci. 2017;14:30–37.

[135] Fagan H, Jones E, Baldwin DS. Orexin Receptor Antagonists in the Treatment of Depression: A Leading Article Summarising Pre-clinical and Clinical Studies. CNS Drugs. 2023;37:1–12.

[136] Crocq MA. History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci. 2020;22:223–228.

[137] Izzo AA, Borrelli F, Capasso R, et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30:515–527.

[138] Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics. 2015;12:825–836.

[139] Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: A systematic review and meta-analysis. Lancet Psychiatry. 2019;6:995–1010.

[140] Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. Neuropsychopharmacology. 2011;36:1219–1226.

[141] Jetly R, Heber A, Fraser G, et al. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015;51:585–588.

[142] Hou R, Baldwin DS. A neuroimmunological perspective on anxiety disorders. Hum Psychopharmacol. 2012;27:6–14.

[143] Costello H, Gould RL, Abrol E, et al. Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. BMJ Open. 2019;9:e027925.

[144] Hou R, Ye G, Liu Y, et al. Effects of SSRIs on peripheral inflammatory cytokines in patients with Generalized Anxiety Disorder. Brain Behav Immun. 2019;81:105–110.

[145] Mirzaei E, Mirjalili M, Jahangard L, et al. Influence of Simvastatin as Augmentative Therapy in the Treatment of Generalized Anxiety Disorder: A Pilot Randomized, Placebo-Controlled Study. Neuropsychobiology. 2021;80:242–252.

[146] Kim S-W, Kang H-J, Jhon M, et al. Statins and Inflammation: New Therapeutic Opportunities in Psychiatry. Front Psychiatry. 2019;10:103.

[147] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. Am J Psychiatry. 2006;163:1905–1917.

[148] Correll CU, Solmi M, Cortese S, et al. The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents. World Psychiatry. 2023;22:48–74.

[149] Baldwin DS, Hou R, Gordon R, et al. Pharmacotherapy in Generalized Anxiety Disorder: Novel Experimental Medicine Models and Emerging Drug Targets. CNS Drugs. 2017;31:307–317.

[150] Grillon C, Robinson OJ, Cornwell B, et al. Modeling anxiety in healthy humans: a key intermediate bridge between basic and clinical sciences. Neuropsychopharmacology. 2019;44:1999–2010.

[151] Bailey JE, Dawson GR, Dourish CT, et al. Validating the inhalation of 7.5% CO(2) in healthy volunteers as a human experimental medicine: a model of generalized anxiety disorder (GAD). J Psychopharmacol. 2011;25:1192–1198.

[152] Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nat Protoc. 2012;7:527–532.

[153] Kirschbaum C, Pirke KM, Hellhammer DH. The ’Trier Social Stress Test’--a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28:76–81.

[154] Biedermann SV, Biedermann DG, Wenzlaff F, et al. An elevated plus-maze in mixed reality for studying human anxiety-related behavior. BMC Biol. 2017;15:125.