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Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

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To cite this article: Harry A. Fagan & David S. Baldwin (2023): Pharmacological Treatment of Generalised Anxiety Disorder: Current Practice and Future Directions, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2023.2211767

To link to this article: https://doi.org/10.1080/14737175.2023.2211767

Published online: 15 May 2023.

EXPERT REVIEW OF NEUROTHERAPEUTICS
https://doi.org/10.1080/14737175.2023.2211767

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REVIEW

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

Harry A. Fagan[a,b] and David S. Baldwin[a,b,c]

[a]Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK; [b]College Keep, Southern Health NHS Foundation Trust, Southampton, UK; [c]Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

ABSTRACT

Introduction: Generalized Anxiety Disorder (GAD) is a common psychiatric condition, characterized 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, the authors 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 HISTORY
Received 31 March 2023
Accepted 4 May 2023

KEYWORDS
Generalized Anxiety Disorder; GAD; novel anxiolytics; pharmacological treatment; pharmacotherapy

1. Introduction

Generalized Anxiety Disorder (GAD) is a common psychiatric condition and is one of the small number of anxiety disorders recognized in modern classification systems. The concept of GAD was developed from earlier concepts of 'neurasthenia' and 'anxiety neurosis' introduced in the late nineteenth and early twentieth 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 emphasizes 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

CONTACT Harry A. Fagan h.fagan@soton.ac.uk College Keep, Southern Health NHS Foundation Trust, 4-12 Terminus Terrace, Southampton SO14 3DT, UK

Article highlights

- Generalized Anxiety Disorder (GAD) is a psychiatric condition, characterized by the presence of general apprehensiveness and excessive worry.
- A range of pharmacological treatments are available for GAD, with the 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.

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 etiological factors associated with the development of GAD, although these studies are predominantly based on the 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 etiological 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 the 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 particular 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 is suggestive of increased α_2-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 amygdala and decreased hippocampal gray 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 the 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 an 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 generalized 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 randomized 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-HT_3 stimulation and sexual dysfunction from postsynaptic 5-HT_{2A} stimulation, while the increased bleeding risk results from impaired platelet-mediated hemostasis [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 α_1-adrenoceptors, 5-HT_{2A}, and 5-HT_{2C} receptors, H_1 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-HT_{2C} 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 α_2-adrenergic, 5-HT_2, 5-HT_3, and H_1 receptors) [28]. The principal adverse effects of mirtazapine are weight gain and sedation (secondary to H_1 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-HT_{1A} partial agonism and vortioxetine demonstrating 5-HT_{1A} full agonism, 5-HT_{1B} partial agonism, and 5-HT_{1D}, 5-HT_3, and 5-HT_7 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, gastrointestinal 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 contraindicated) and appetite suppression [31].

2.7. Azapirones

Azapirones act as anxiolytics through 5-HT_{1A} 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 than that with benzodiazepine use [35]. In recent years, gabapentinoids have been increasingly recognized 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 the patients describe euphoria, with a greater prevalence at higher doses (≥450 mg/day) [38]. Non-prescribed use of pregabalin is increasingly recognized, often through supratherapeutic 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 behavior, 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 H_1 receptor inverse agonism; however, hydroxyzine shows weak antagonism at the 5-HT_{2A} receptor, not seen with other antihistamines [44]. The principal adverse effect noted in RCTs for GAD is daytime somnolence (due to H_1 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 five 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 four RCTs using extended-release dosages of 50–300 mg 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 H_1, α_1 and α_2-adrenocepter, 5-HT_{2A} and 5-HT_{2C} receptors, alongside a comparably low affinity to the D_2 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 H_1 receptor blockade), dizziness (secondary to adrenergic blockade), and weight gain (secondary to H_1 and 5-HT_{2C} receptor blockade) [47]. Unlike most other antipsychotics, it is rarely associated with extra-pyramidal side effects or hyperprolactinemia [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 2.14).

2.12. Benzodiazepines and non-benzodiazepines

Benzodiazepines are among the oldest anxiolytic agents that 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 $GABA_A$ 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 extent this occurs for the anxiolytic effects [49]. Dependence on benzodiazepines can also occur with an associated withdrawal syndrome, usually characterized 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 $GABA_A$ receptor positive allosteric modulators that fall within one of the several different chemical classes to benzodiazepines. Several have specific affinity to particular sub-units of the $GABA_A$ 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 that 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 generalized anxiety disorder.

Current consensus guidelines summarize 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 summarize 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 advice, if a pharmacological treatment is preferred, to offer 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 advice 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 the 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-behavioral 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 hemorrhage [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 characterized by irritability, jitteriness, vomiting, 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 a broadly similar use of pharmacological agents, while recognizing the increased sensitivity to adverse effects in this patient group [21,53]. Of particular importance is the increased risk of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), increased sensitivity to extrapyramidal symptoms, increased risk of QT_C 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 the 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 previously 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 generalized 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 the most effective treatments. Anxiolytic forms of serotonergic modulation include serotonin transporter (SERT) inhibition, 5-HT_{1A} receptor partial agonism or 5-HT_2/5-HT_3 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 $GABA_A$ 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 developments 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-HT_{1A} 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 azapirone tandospirone improved both depressive and anxiety symptoms [87]. A multicentre RCT conducted in China compared 60 mg *vs.* 30 mg/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-HT_{1A} partial agonist with 5-HT_2 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 that 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-HT_{2A} 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 crossover RCT, patients with cancer and associated anxiety showed significant improvements in anxiety symptoms after a single dose of psilocybin (0.3 mg/kg) [93]. Two other crossover 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 to placebo-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 focused 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 ($GABA_A$ and $GABA_B$) stimulated the desire to develop a non-sedating GABAergic anxiolytics, described as a 'Holy Grail' of psychopharmacology [97,98]. The $GABA_A$ 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 $GABA_A$ receptor subtypes are expressed selectively throughout the mammalian brain and appear to have different functions [98]. The α subunit present in the $GABA_A$ receptor has been found to be of particular importance, with $GABA_A$ receptor subtypes containing α1 subunit mediating sedative effects of BZDs while those containing α2/3 subunits mediating anxiolytic effects [98].

Several α2/α3-$GABA_A$ 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 difference 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 an RCT in patients with GAD, not responding to initial pharmacological treatment [102]. This study was terminated early (due to a change in portfolio prioritization) 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 anesthetic 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 two 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 trialed 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 trialed 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 (CRF_1 and CRF_2 receptors) which are expressed in the hypothalamus and other brain regions [117]. An anxiogenic (and pro-depressive) role of CRF_1 receptors was identified in animal studies, leading to the development of several CRF_1 receptor antagonists [117,118]. However, clinical studies of CRF_1 receptor antagonists have not shown promise in anxiety disorders [118]. To date, only one RCT has been published in GAD, which showed that the CRF_1 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 labor) and behavioral roles (maternal behavior, 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 randomized 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

utilizing orexin receptor antagonists (ORAs) in healthy volunteers have demonstrated a potential anxiolytic effect in experimental medicine models of anxiety, including carbon dioxide inhalation and an 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 (CB_1 and CB_2). 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 Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) [137]. Several synthetic cannabinoids have also been produced. CBD lacks the psychotomimetic effects of Δ^9-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 (600 mg) 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 the 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 cytokine C reactive protein (CRP), interferon-γ, and tumor 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 the 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 (20 mg/day) to placebo over 8 weeks. Statins are widely used in the treatment of hypercholesterolemia 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-$GABA_A$ receptor positive allosteric modulators, ketamine, mGluR2/3 agonists, NK1R antagonists, CRF_1 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 randomized controlled trials in GAD have been relatively short (median 8 weeks) and are focused 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 benefits 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 randomized controlled trials (in the manner of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial in MDD) could be conducted to provide a 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-$GABA_A$ receptor positive allosteric modulators (AZD7325 and PF-06372865), an mGluR2/3 agonist, a NK1R antagonist, and a CRF_1 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% CO_2 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 programs, for example through the judicious use of pilot studies, *a priori* adaptive trial designs (e.g. 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 three 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, 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.

Funding

This paper was not funded.

Declaration of interest

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) program. At the time of submission, no decision had been made. DS Baldwin has acted as an advisor to Idorsia Pharmaceuticals Ltd (no honorarium sought or paid) and is a Medical Patron of Anxiety UK. He is also the current president of the British Association for Psychopharmacology. HA Fagan is also supported to carry out this work through an Academic Clinical Fellowship, funded by the National Institute of Health and Care Research (NIHR), the United Kingdom (Award reference: ACF-2022-26-003).

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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